CHAPTER I

GENERAL INTRODUCTION

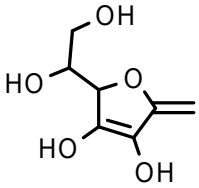
General Introduction of Heterocyclic Compound:

Heterocyclic compounds are acquiring more importance in recent years as their have found more importance in biological activity [(1)]. Heterocyclic compounds are one hetero atom in a ring such as oxygen; nitrogen, sulphur etc. are the most common hetero atoms [(2)]. Heterocyclic compounds occur widely in nature and in a variety of non naturally occurring compounds, a large number of heterocyclic compounds are essential to life to life such as alkaloids, antibiotics, amino acids, vitamins, hemoglobin, hormones and a large number of synthetic drugs and dyes [(3)] .

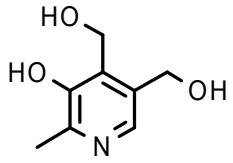
The biological activity of the heterocyclic compounds is mainly due to their molecular structures [[4])]. Heterocyclic compounds particularly five and six membered heterocyclic gained loss of attention of pharmaceutical industries due to their therapeutic values [[5].] Similarly polyfunctionalised the heterocyclic compounds which contain nitrogen, sulphur, and oxygen as hetero atoms play an important role in the discovery of drug [[6]].

Heterocyclic compounds with five membered rings such as triazole. These may be structural types 1, 2, 3-triazole. Heterocyclic compounds such as furan a five membered of pyran a six membered ring contain oxygen atom in a ring system. Most members of vitamin B group possess

heterocyclic ring containing nitrogen as vitamin B_6 (pyridoxine) which is a derivative of pyridine, essential in amino acid metabolism [7].

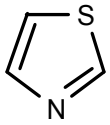


2-(1,2-Dihydroxy-ethyl) -5-methylene-2,5-dihydro-furan-3,4-diol

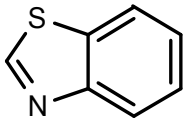


4,5-Bis-hydroxymethyl-2-methyl-pyridin-3-ol

The five membered ring in which two hetero atoms are such as nitrogen and sulphur.

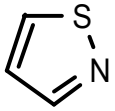


thiazole



benzothiazole

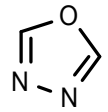
Simple thiazole nucleus was first reported by Hantzsch and Weber they are thiazole and isothiazole.



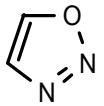
isothiazole

Oxadiazole is important heterocyclic ring present in variety of biological active molecule inclusive of fungicidal, bactericidal anticancer, activities. [8] Oxadiazole is a heterocyclic nucleus which gains interests by many researchers regarding inventions of novel remedial molecules. There

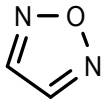
are possibly 4- isomers of oxadiazole in which 1,3,4 oxadiazoles have enormous importance.



[1,3,4]oxadiazole

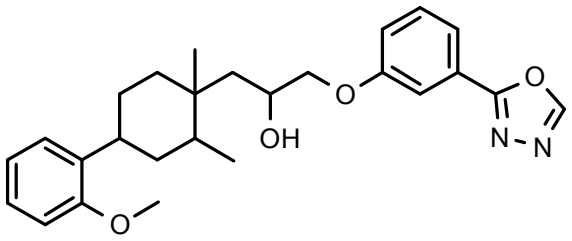


[1,2,3]-oxadiazole



[1,2,5]-xadiazole

Variety of theraptically active agents e.g. raltagravir as HIV-integrase inhibitor, furamizole as antibacterial, antimicrobial, anti cancer activity etc. are based on 1,3,4-oxadiazole.

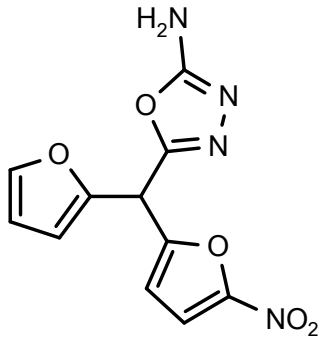


1-[4-(2-Methoxy-phenyl) -1,2-dimethyl-cyclohexyl]-3-(3-[1,3,4]oxadiazol-2-yl-phenoxy) -propan-2-ol

Nesapidil (antihypertensive agent)

The 1,3,4-oxadiazole exhibits variety of reactions such as electrophilic substitution, nucleophilic substitution, thermal and photochemical reaction [9].Oxadiazole is a very weak base because there is an inductive effect of extra hetero atom. Oxadiazole consists of 2-pyridene type nitrogen (-N=) hence there is reduction in aromaticity of oxadiazole ring and which in turn leads the oxadiazole ring to exhibits the conjugated diene.

The –N= containing heterocycles especially five membered rings are if great interest as they are found in natural products[10] and used frequently in medicinal chemistry amongst these heterocycles, the 1,3,4-oxadiazole nucleus is a particular value in material science, agrochemical, and in pharmaceutical chemistry as it can be used as a bioisosteric replacement of acid ,esters and amides functionalities.



5-[Furan-2-yl-(5-nitro-furan-2-yl) - methyl]-[1,3,4]oxadiazol-2-ylamine

Furamizole

A number of synthetic methods for the preparation of 1,3,4-oxadiazole have been hence developed over the years. As 1,3,4-oxadiazole are associated with diverse biological activities like antimicrobial, anti-inflammatory, ant tubular, anticonvulsants, hypnotic anaesthetic activity.1,3,4-oxadiazole showed antibacterial properties similar to those of well known sulfonamides drugs[11].

As oxadiazole are cyclic compounds containing one oxygen and 2-nitrogen atoms in a five membered ring [12, 13]. Different substituted

oxadiazole nucleus posses interesting properties such as anthelmentics [14] anticancer [15] antiviral [16] antioxidant [17] analgesics [18] etc.

Tuberculosis is currently the leading killer of the youth, woman, and AIDS patient throughout the world. Although many active anti tubercular agents have been developed, the use of present drugs as single agent has developed drugs resistant [19, 20]. The development of this resistance can be forestalled through the use of combination regiments it is clear that drug resistance will continue to be a problem [21] .Therefore, there is a clear need for the discovery of new derivatives with antitubercular activity for the management of tuberculosis.

It was observed from literature that certain five membered heterocyclic compounds possess interesting biological activity. Among them the compounds bearing 1,3,4-oxadiazole nucleus have wide application in medicinal chemistry. These compounds also have been reported to have significant anti tubercular activity [21, 22)]. Nowadays the development of ecofriendly synthetic method has great importance and is the need of the hour [23, 24]. A large number of 1,3,4-oxadiazole has been discussed in the literature because of its application. Organic synthesis involving electrochemical techniques using suitable solvent & electrolytes are basic to clean synthesis while multi-step conventional synthesis

produces considerable amounts of environmentally hazardous waste due to a series of complex isolation procedures involving expensive and toxic solvents after each step. In recent year's multicomponent reaction have appeared as an efficient and powerful tool in modern synthetic organic chemistry due to their valuable feature such as atom economy design of reaction.

All the organic reagents used are consumed and reacted to give the target molecule, purification of products resulting from multi component reaction is also simple –MCR , leading to interesting heterocyclic especially useful for the construction of drug like molecule. The isocyanides base MCR is very important in this area [25, 26]. Isocyanides base reactions due to their synthesis potential, their inherent atom efficiency, convergent nature, ease of implementation and the generation of molecular diversity have attracted considerable attention because of the advantages that they offer to the field of combinatorial chemistry [27, 28]. But in recent years compounds containing particularly 1,3,4-oxadiazole nucleus have been shown to possess a wide range of pharmacological and therapeutic activities.

Heterocyclic chemistry is very important branch of chemistry. A cyclic compound containing all carbon atoms in ring formation is usually

called as carbocyclic compound. According to the literature survey reveals that enormous member of heterocyclic compounds are known. The aromatic the aromatic heterocyclic compounds which have hetero atom in a ring system and behaves in a similar manner as that of benzene in some of its properties the vast distribution of heterocyclic in natural products, they are also the major components of biological molecules such as DNA and RNA. DNA is no doubt the most important class macromolecules of life [29, 30]. Nucleotides the building blocks of our genes are derivatives of Pyrimidines and purine ring structure chlorophyll and hence the oxygen carriers in plants and animals respectively are derivatives of large porphyrin rings.

Heterocycles are an important class of compounds making up more than half of all known organic compounds. Heterocycles are presents in a wide variety of drugs, mostly vitamins, some natural products, biomolecules, biologically active compounds which includes antitumor, antibiotics, anti-inflammatory, antidepressant, antimalarials, anti HIV anti microbial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal fungicidal and insecticidal agent. They are also found in as key structural unit in synthetic pharmaceutical and agrochemicals [31, 32].

Majority of heterocyclic compounds shows important application in material science such as dyestuff, fluorescent sensor, brightening agents, information storage plastic and analytical reagents. They have also show application in supra molecular and polymer chemistry, especially in conjugated polymers they act as organic conductor, semiconductor, molecular wires photovoltaic cells and organic light harvesting system, optical data carriers chemically controllable switches and liquid crystalline compounds. Heterocyclic compound are also of interest in synthetic utility as synthetic intermediates protecting groups chiral auxiliaries. Organo catalyst and metal ligands in asymmetric catalyst in inorganic synthesis therefore it gains attention to develop efficient new methods to synthesize new and new heterocycles.

The alkaloids form a major group of naturally occuring heterocyclic compounds having varied biological activity host of the alkaloids contains basic nitrogen atoms. Such as ergotamine, the Indole based alkaloid exhibits anti migraine activity.

A widely variety of benzimidazole derivatives have been described for their chemotheraptic importance. Oxadiazole compounds have shown biological activity against parasites and bacteria. Also the presence of basic Mannich side chain in a drug may overcome the water insolubility problem

through the formation of hydrochlorides. Some heterocyclic moieties such as triazole nucleus are known to possess antibacterial and antifungal properties. Furthermore the Schiff bases are having anticancer activity, pyrazole pyrazolone and alkyl pyrazole having pharmacological activities and microbial activities.

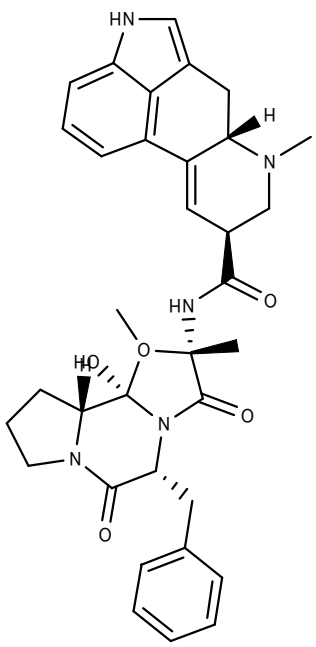
Benzimidiazole and its derivative are of great importance in medicinal chemistry because of their wide variety of biological and pharmacological application. A large number of benzimidiazole derivative have been found to exhibit various biological activities such as anti inflammatory anthelmentics fungicide etc.

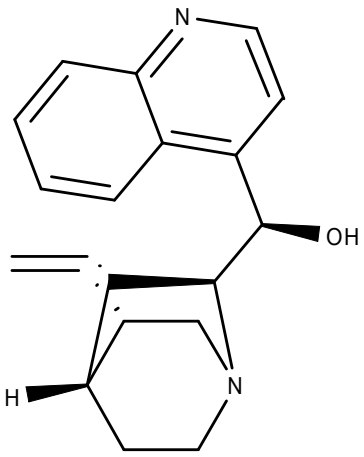
Benzimidiazole and oxadiazole derivatives it was contemplated to synthesized a new series of 1,3,4-oxadiazole carrying benzimidiazole moiety. There is very scarce recent literature data on antimicrobial potential of benzimidiazole containing azomethine linkage that should combine favorable structural properties of both azomethine and benzimidiazole. Benzimidiazole nucleus is also found variety of naturally occuring compounds such as vitamiB_{12} and its derivative and it is structurally similar to purine bases. Benzimidiazole are widely used as drug such as Omperzole, Pantoprazole, Albendazole Mebendazole, Thiabendazole, etc. shows antimicrobial and anthelmentics activity.

1,3,4-Oxadiazole, it is an important class of compounds having a wide spectrum of biological activities. In the past years it is an antibacterial, antifungal, antimalarials, anticonvulsant, and insecticide compounds. The 1,3,4-Oxadizole derivatives which contain substitution group in the 2-and 5- position and specially in the 2-marcapto oxadiazole which contain thioamide group –N-C=S, its important lies in removing the poisons in much of the medicine used by human beings.

Cinchona is a quinoline class of alkaloid shows anti malarial activity.

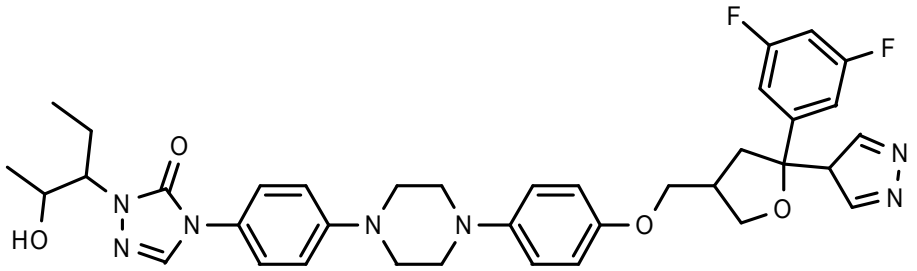
ergotamin





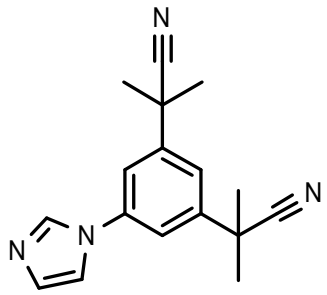
cinchonine

Posaconazole is a triazole antifungal drug.[3] it is active against micro-organism such as Candida, Asperigillus, Zyagomycetes.



4-[4-(4-{ 4-[5-(3,5-Difluoro-phenyl) -
5-(4H-pyrazol-4-yl) -tetrahydro-furan-
3-ylmethoxy]-phenyl} -piperazin-1-yl) -phenyl]-
2-(1-ethyl-2-hydroxy-propyl) -2,4-dihydro-[1,2,4]triazol-3-one

Anstrozole is anaromatize inhibiting drug approved for the treatment of breast cancer after surgery as well as for metastasis in both pre and post menopausal women. Anastrozole works by inhibiting the synthesis of estrogen.

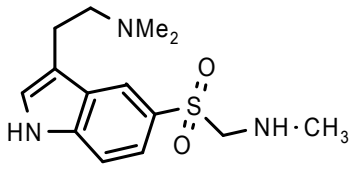


2-[3-(Cyano-dimethyl-methyl) -
5-imidazol-1-yl-phenyl]-2-methyl-propionitrile

Anastrozole

Out of 20 amino acid three are heterocyclic contains essential vitamins. Heterocyclic compounds are having wide range of applications such as shows physiological activites also.

Sumatriptan a heterocyclic compounds is first anti-migrain drugs.



C-[3-(2-Dimethylamino-ethyl) -
1H-indol-5-yl]-N-methyl-methanesulfonamide

Sumatriptan

A new route for the synthesis of Schiff bases was developed by eco-friendly reactions to Increase the yield of products by maintaining the purity of them. By considering this a novel and green synthesis of salicylaldimine Schiff bases were successfully carried out by irradiating salicylaldehyde with substituted aryl amines respectively without using any solvent and catalysts. The justification and identification of the structure of these newly synthesized compounds have been established on the basis of elemental analysis and through spectral data.

A mixture of respective anilines and salicylaldehyde was taken in a 50 mL beaker and mixed well. The mixture was irradiated in a microwave oven at a power of 160 W for the specified time. The reaction was monitored by thin layer chromatography (TLC) and spots were visualized in iodine chamber. After completion of the reaction, the reaction mixture was poured into ice water. The yellow solid obtained was filtered, washed, dried and recrystalised from ethanol.

A series of salicylaldimine Schiff bases are prepared from salicylaldehyde and substituted aniline by microwave irradiation in appropriate time. It is observed that the condensation between a carbonyl compound and an amine leading to the formation of Schiff bases should be a facile reaction due to the good electrophilic and nucleophilic characteristic properties of the carbonyl and amine groups respectively [33].

Azoles have played a crucial part in the history of heterocyclic chemistry and also been used extensively as important synthons in organic synthesis. Owing to the versatile chemotherapeutical activities of azoles especially imidiazole and benzimidazole, a significant amount of research activity and efforts has been directed towards this class of compounds. Benzimidazoles, its aryl and alkyl substituted derivatives have evoked considerable attention in last three decades as these are endowed with a wide range of pharmaceutical activities like antifungal, antihypertensive, antioxidant, cardio-tonic, antithrombotic, HIV-IPR inhibitor, IL-1 inhibitor, anticonvulsant, anti-hepatitis B and C virus activity, antitubercular ,antiulcer activities etc.

The cytotoxicity of 2-methyl benzimidazole derivatives was investigated against a variety of cell lines where, introduction of various heterocyclic rings stirred at room temperature for 1 hr. and left overnight.

It was then poured on crushed ice. The resulting suspension was kept in ammoniacal water for 2 hr., solid obtained was filtered and recrystalised from ethanol [34].

A survey covering the synthetic strategies leading to benzimidazole based fused poly heterocyclic systems utilizing simple reactive benzimidazole synthons since 1980. The poly heterocyclic systems are classified based on the number of rings; tetra-, penta- , hexa- and hepta-fused ring systems. Among each poly heterocyclic system, further classification according to the number of hetero atoms; two-, three-, four-, five-, six- and seven hetero atoms is considered [35].

Epilepsy, a neurological disorder, has been found to affect around 1% of total world's population. Several new compounds such as zonisamide, vigabatrin, lamotrigine, gabapentin have emerged following the widely used classical antiepileptic drugs such as phenytoin, Phenobarbital, carbamazepine, valproic acid and various benzodiazepines. The need to synthesize newer molecules persists to treat those cases that have developed resistance to the available medication and to minimize the side effects to the lowest possible level.

The isoindoline-1,3-dione ring system has been widely used to synthesize various derivatives having diverse Pharmacological properties

such as hypo-lipidemic, antimalarials, hypoglycemic, anti-androgenic, sedative hypnotic, antiangiogenic, anti-viral and antiepileptic. The anticonvulsant properties of isoindoline-1,3-dione ring system surfaced as a consequence of pioneering discovery of the anticonvulsant properties of Thalidomide. Thalidomide was first marketed in 1954 as an anticonvulsant [36].

Depression, especially major depression, is an extremely serious disease affecting about 121 million people and is one of the leading causes of disability worldwide. And unipolar depression is predicted to be the second main cause of disability in 2020 by the World Health Organization. Over the past several decades, the synaptic actions of monoamine neurotransmitters such as norepiephrine (NE) and serotonin (SER, 5-HT) were considered as important indications to psychiatric disease, including anxiety and depression.

Various psychotropic drugs which are associated with these neurotransmitters have been individually developed. Selective serotonin reuptake inhibitors (SSRIs) are a relatively newer class of antidepressants for treating depression. SSRIs such as fluoxetine, sertraline, paroxetine, and citalopram have been the most widely prescribed antidepressants since

1980s. All SSRIs strongly and selectively inhibit 5-HT reuptake by the pre synaptic neuron, thus increasing 5-HT concentration at the synapse.

Although SSRIs offer a more favorable profile, they also have some side adverse effects including anxiety, sedation, headache, tremor, insomnia, and sexual dysfunction. More importantly, there are troublesome facts that SSRIs are generally effective only for less than two-third patients and have undesirably long therapeutic onset time. Recently there has been the achievement of an important development of an antidepressant which interacts with dual or multiple targets. 5-HT1 auto receptors are widely distributed in the brain, and also serotonin transporters (SERT) are known to have a major role in the control of synaptic. Their general chemical structure contains an alkyl chain attached to the N4 atom of the piperazines moiety and a terminal amide or an imides fragment because numerous side effects are associated with nonselective binding at postsynaptic 5-HT receptors [37].

Synthesis of five-membered hetero aromatic compounds such as pyrazoles, isoxazoles and 1,2,4-oxadiazoles are important for pharmaceutical industry and material science due to their applications. Although there are many methods to prepare such compounds, new

variants continue to appear since they exhibit a wide range of biological and medicinal activities.

The synthesis of 4-iodopyrazoles, pyrazoles, isoxazoles, 1,2,4-oxadiazoles and/or 1,2,4-oxadiazepines. In the first part of the study, electrophilic cyclization of α,β-alkynic hydrazones by molecular iodine and copper iodide were investigated as new ways for the synthesis of 4-iodopyrazoles and pyrazoles, respectively. Initially, α, β-alkynic hydrazones were prepared by the reactions of propargyl aldehydes and ketones with hydrazines. Then α, β-alkynic hydrazones were treated with molecular iodine in the presence of NaHCO3, which afforded 4-iodopyrazoles in good to excellent yields. Subsequently, the same reactions were carried out with CuI in the presence of NEt3, which furnished corresponding pyrazoles in good yields. Moreover, ferrocenyl-substituted 4-iodopyrazoles and pyrazole derivatives were synthesized from corresponding alkynic hydrazones by using such electrophilic cyclization.

In the second part of the study, the reactions between propargyl aldehydes and amidoximes were investigated. These reactions produced exclusively conjugate addition products. In one reaction, a new product was isolated in low yield and tentatively characterized as 7-pentyl-3-phenyl-1,2,4-oxadiazepine. Interestingly, under acidic and basic

conditions, conjugate addition products afforded isoxazoles and 1,2,4-oxadiazoles, respectively. When conjugate addition products were treated with HCl, they afforded isoxazoles in good yields. On the other hand, when treated with bases such as KOH and NaOH, conjugate addition products furnished 1,2,4- oxadiazoles in good to excellent yields.

Reaction mechanism for the formation of isoxazoles and 1,2,4-oxadiazoles from conjugate addition products was also proposed. In the last part of the study, one-pot reactions between propargyl aldehydes and amidoximes in the presence of KOH were investigated for the synthesis of 1,2,4-oxadiazoles. As anticipated, these one-pot reactions provided corresponding 1,2,4-oxadiazoles. One-pot reactions afforded oxadiazoles in slightly lower yields as compared to their two-step syntheses but they saved time and chemicals due to easy purification. More importantly, the synthesis of 5-ferrocenyl-1,2,4-oxadiazoles was achieved by one-pot procedure since the reaction of 3-ferrocenylpropanal with amidoximes did not yield corresponding conjugate addition products.

In summary, a variety of pyrazoles, 4-iodopyrazoles, isoxazoles, 1,2,4-oxadiazoles and/or 1,2,4-oxadiazepines were synthesized by new methods, which may have useful biological and medicinal activities[38]. Polysubstituted furans are important heterocyclic molecules as well as

having practical utility as recurring unit in many natural and medicinal molecules. Many of the naturally occurring furans have shown interesting biological activities, such as cytotoxic and antitumor properties well as antispasmodic, antimicrobial and several other potentially useful activities.

Motivated by these facts, and as a part of our program directed to synthesize new bioactive heterocycles, the present investigation deals with the use of 2-arylideneamino-4,5-diphenylfyran- 3-carbonitrile in the synthesis of some new interesting heterocyclic compounds of expected biological activities [39].

Benzimidazole and its derivatives are a very important class of compounds due to their pharmacological and biological activities.1,2-Disubstituted benzimidazoles represent an important branch of this family. These structures are valuable bioactive structures and have been reported as specific angiotensin II receptor type 1 selective antagonists, hepatitis C virus NS5B polymerase inhibitors. Furthermore, they exhibit several other pharmacological activities and have been used in antidiabetic, antihistamine, analgesic, antiviral, antifungal, and anti-parasitic applications.

Although a number of methods for the synthesis of 1- or 2-monosubstituted benzimidazoles have been reported, the assembly of 1,2-

disubstituted benzimidazoles still encounters challenges in controlling regioisomeric selectivity, increasing efficiency, and improving generality. Most of the methods toward 1,2-disubstituted Benzimidazoles such as the condensation of carboxylic acids with N-substituted 1,2-diaminoarenes and N-arylation/alkylation reactions of 1H-benzimidazoles have often suffered from a limited scope and led to a mixture of two regioisomers because of the difficulty of differentiating the two N-atoms. Alternatively, the palladium-, copper-, indium-, ruthenium-, and cobalt-5e, catalyzed intramolecular N-arylation starting from o-halo anilines/ o-halo nitrobenzene has been used. However, most of these protocols involve multistep synthetic transformations and engage a complex isolation process leading to a high cost and/or they suffer from poor availability of starting materials.

In some cases the use of strong acid-catalyzed conditions also limits the functional group tolerance. In addition, the employed metals are not environmentally friendly and are not attractive for commercial adoption due to a low catalyst activity and the generation of corrosive waste. These drawbacks prompted us to investigate a more practical access to the 1,2-disubstituted benzimidazole scaffold. Herein, we wish to describe a simple

one-pot multicomponent reaction sequence to access these ring systems under metal-free neutral conditions [40].

Infectious microbial diseases remained pressing problems worldwide, because of resistance to a number of antimicrobial agents among variety of clinically significant species of microorganisms and has become an important global health problem. One way to battle with this challenge is the conscious usage of the currently marketed antibiotics the other is the development of novel antimicrobial agents.

Hence, there will always be a vital need to discover new chemotherapeutic agents to avert the emergence of resistance and ideally shorten the duration of therapy. Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications. They have is an important pharmacophore and privileged structure in medicinal chemistry both with respect to their inhibitory activity and their favorable selectivity ratio.

Literature survey revealed that amongst the benzimidazole derivatives, 2-substituted are found to be pharmacologically more potent and hence the design and synthesis of 2-substituted benzimidazoles are the potential area of research. Extensive biochemical and pharmacological studies have confirmed that these derivatives are effective against various

strains of microorganisms. Thus, benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibited the immense potential and varied bioactivities; therefore, efforts have been made from time to time to generate libraries of these compounds and screened them for potential biological activities. Therefore, seeing the importance of benzimidazole nucleus, it was thought that it would be worthwhile to design and synthesize some new 2-substituted benzimidazole derivatives and screen them for potential biological activities [41].

Amino acids have been repeatedly shown to produce wide complexes with transition metals repeatedly in the literature. All of naturally occurring α-amino acids bind in what is known as the glycinate way. This means that a five-membered ring is formed with the metal, amine nitrogen and the carboxylic oxygen. This arrangement is always present for the natural human amino acids even when the side chain has a legating group. If there is a ligating group on the side chain, it well typically binds apically in place of a solvent molecule.

The N-protected amino acids are used for the synthesis of peptide bonds in solid phase syntheses. The Phthalimide group acts as a protecting group for amines and amino acids .Several Phthalimide derivatives have

importance in medicinal chemistry and are used as antimicrobial reagents. Amino acid complexes are important in biology. The metal complexes of N-protected α-amino acids are of great interest because they may be used as a basis for understanding metal-protein interactions.

Coordination chemistry of these amino acids with metals can give a basis for understanding the coordination chemistry for the protein at large. Much kind of proteins within the body need metal ions to work, that can also be activated or deactivated by metal ions. These reversible effects are caused by ligation of the metal ions and the protein. If one has an understanding of the basic metal ion N-protected α-amino acid complexation, then one could better identify the coordination site within the protein much more easily. Then one could simply use the N-protected α-amino acids as models of the binding sites of various proteins[42].

2-Pyrazolines display a broad spectrum of potential pharmacological activities and are present in a number of pharmacologically active molecules such as phenazone/ amidopyrene/ methampyrone (analgesic and antipyretic), azolid/ tandearil (anti-inflammatory), indoxacarb (insecticide) and anturane. Changes in their structure have offered a high degree of diversity that has proven useful for the development of new therapeutic agents having improved potency and lesser toxicity. In this context, the

recently synthesized 2-pyrazoline derivatives possessing important pharmacological activities have been highlighted.

As follows from the X-ray analysis, it has the structure of the five-membered dihydropyrazole ring, has an envelope conformation C5 atom is deviated from the almost planar system of the other four atoms of the heterocyclic ring. It plays a crucial role in the development of theory in heterocyclic chemistry and is also extensively used as useful synthons in organic synthesis. Single crystal X-ray structure of 1-Carboxamido-2-pyrazoline (ORTEP representation) 2-pyrazoline is insoluble in water but soluble in propylene glycol because of its lipophilic character. It is known that the compounds of the 2-pyrazoline group that do not contain a substituent at the 1-position of the hetero ring can react with benzaldehyde at high temperature (200°C) and in an inert atmosphere to give 4-benzylidine derivatives.

Pyrazoline derivatives, typical ICT (Intramolecular Charge Transfer) compounds are known as a kind of fluorescent brightening agents because they have strong blue fluorescence in solution. They have a whole transport tendency. An intramolecular conjugated charge transfer process has been reported to exist in it in the excited state. In the conjugated part (–N1–N2–C3–) of the ring, the nitrogen atom at the 1-position and the

carbon atom at the 3-position are, respectively, electron donating and withdrawing moieties. The carbon atoms at 4- and 5-positions do not conjugate with the above conjugated part.

Its fluorescence spectrum exhibits a large red shift with an increase in the polarity of solvents. These compounds show stronger fluorescence because of the double bond hindering which occurred due to cyclization. Bulky groups in both the 4- and 5-positions improved both the fluorescence efficiency and the stability to light of the molecule. It has significance for the design of pyrazoline whitening agents. Aryl group at position-5 is also responsible for spiroconjugated charge transfer quenching of pyrazoline fluorescence[43].

Benzimidazoles are very useful building blocks for the development of molecules that are important in medicinal chemistry. 2-substituted benzimidazole derivatives have found applications as diverse therapeutic agents, including antiulcer, antihypertensive, antivirals, antifungal, anticancer, and antihistaminics. Because of their importance, the methods for their synthesis have become a focus of Synthetic Organic Chemists. However, we failed to locate report in the literature that covers various efforts that have been made for the synthesis of 2-arylbenzimidazoles.

Therefore, in the present review, we have tried to compile some of the important synthetic techniques and methodologies used for its synthesis during the last decade. The synthesis of benzimidazoles has gained importance in recent years, because they exhibit illustrious biological and pharmacological activities and are used as selective Neuropeptide YY1 receptor antagonists, factor Xa inhibitors, smooth muscle cell proliferation inhibitors, antitumor, antiviral, and antimicrobial agents, and for HIV, herpes (HSV-1), RNA, influenza, and human cytomegalovirus (HCMV). They are also used in diverse areas of chemistry and are very important intermediates in various organic reactions.

The structural similarities between benzimidazole nucleus and various biological compounds such as the purine base of the DNA and its presence in vitamin B12 have made it important in pharmaceutical industry. This similarity is believed to help easy recognition of benzimidazole by various biological systems. As a result of this, benzimidazoles have been termed as "privileged structures" for drug design. Moreover, it has been also reported that benzimidazole exhibit high affinity for enzyme and protein receptors. Thus, because of its increasing medicinal importance, great efforts have been made time to time to develop an efficient and economical method for the synthesis of its large

number of new derivatives, in a hope to obtain a potent pharmacophore for the future.

Commonly employed methods for the synthesis of benzimidazoles involve reaction between *o*-phenylenediamines and carboxylic acids or their derivatives (nitriles, amidates, orthoesters) in the presence of strong acids such as Polyphosphoric acid or mineral acids. Other methodologies like thermal or acid promoted cyclization of *N*-(*N*-arylbenzimidoyl)-1,4-benzoquinoneimines or direct *N*-alkylation of an unsubstituted benzimidazole have been also reported. Recently, strategies have been directed toward its synthesis involving cyclo condensation of O-phenylenediamines with aldehydes under oxidative conditions.

Besides above methodologies, many reports have also appeared in the literature, for the synthesis of 2-arylbenzimidazoles, using eco-friendly technologies as well, like use of microwave, sonicator or ultrasound. Some methods were also reported where organic solvents have been replaced by water. In the last ten years, a large number of scientific publications have appeared in the literature describing the synthesis of 2-arylbenzimidazoles. This indicated clearly the importance of 2-arylbenzimidazoles for a Chemist, a Researcher or an Industrialist.

Unfortunately, there is not a single review which describes various synthetic strategies that were developed and reported from time to time in the literature .In fact there are two methods which are generally used for the synthesis of 2-substituted benzimidazoles. One is the coupling of *o*-phenylenediamines with carboxylic acids or their derivatives (nitriles, imidates, or orthoesters). This often requires strong acidic conditions, and sometimes very high temperature. The other involves two-step procedure that includes oxidative cyclo dehydrogenation of aniline Schiff's bases, often generated from the condensation of *o*-phenylenediamines with aldehydes [44].

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