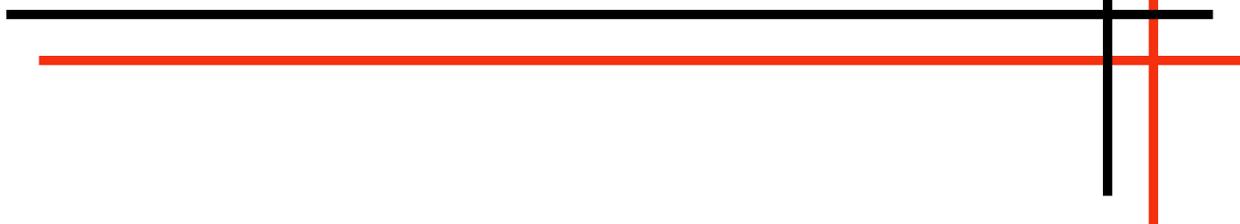


# **CHAPTER-1**

## **INTRODUCTION OF SOME HETEROCYCLIC CHEMOTHERAPEUTIC AGENTS**



## Chapter-1:

# INTRODUCTION OF SOME HETEROCYCLIC CHEMOTHERAPEUTIC AGENTS

### 1.[A] GENERAL

Fighting of diseases with drugs is the timeless struggle. It began with the existence of the mankind. Survival of the mankind on this planet has been depended upon its success.

The great expansion in medicinal research in past has contributed much to the unparalleled progress of medicine during that period. Improved and basically more meaningful biological test procedures and methods of diagnosis have provided better guidance in drug discovery by pointing out suggestive observations which could be used in the design of therapeutic agents. The elucidation of the structure of many metabolites, and of polypeptides, enzymes, polynucleotides and other biopolymers helped in more rational study of the chemical mode of action of such compounds, and their interaction with drugs. Medicinal chemistry has become the acknowledged meeting ground of modern organic, physical and biochemistry and the application of these fields to drugs, with its own literature and procedures.

The molecules of organic chemical compounds are built by a framework of carbon atoms to which hydrogen, oxygen, or other heteroatoms are attached. Carbon atoms can in particular readily join with one another to form chains of atoms. When the ends of the chain are joined together, ring is formed, resulting into cyclic compounds; such compounds often referred as alicyclic or carbocyclic compounds.

Substitution of one or more of the ring carbon atoms in the molecule of carbocyclic compounds by a heteroatom gives a heterocyclic compound. In the biological world, heterocyclic compounds are spread everywhere. Heterocycles form the sites of reaction in many enzymes and co-enzymes.

### Medicinal Chemistry

Medicinal chemistry is defined as a field which applies the principles of chemistry and biology to the knowledge which leads to the introduction of new therapeutic agents. Hence, the medicinal chemist must not only be a competent organic

chemist but he must have a basic background in the biological sciences, especially biochemistry and pharmacology.

The basis of understanding the medicinal chemistry lies in an awareness of the relationship between the chemistry of particular compound or group of compounds and their interaction with body, which is known as structure-activity relationship (SAR), and the mechanism by which the compound influences the biological system, which is known as its mode of action. The objective of these studies is to improve the therapeutic effect of a drug and at the same time minimizing undesirable side effect.

### **Drugs**

The word 'drug' is derived from the French word "drogue", which means a dry herb. In general way, a drug may be defined as a substance used in the prevention, diagnosis, treatment or cure the disease in man or other animals. According to WHO, a drug may be defined as any substance or product which is used or intended to be used for modifying or exploring physiological system or pathological state for the benefit of the recipient.

The earlier sources of drugs were from plants, animals and mineral sources, but due to the lack of potential action and definitive cure and some time more toxicity, the discovery of new drugs that are more potential and less toxic is essential. The synthesis of derivatives has been an important part and is aimed at modifying the action of drugs, particularly to reduce the side effects and to potentiate the drug action. Today more than 60% drugs used in practice are synthesized derivatives, and day-by-day the scope of synthetic medicinal chemistry is broadening.

### **Pharmacophore**

The physiological activity of drugs depends upon the presence of particular functional groups or structural units. This part of the drug causes the actual physiological effect, which is known as phamacophore.

When a phamacophore is introduced in biologically inactive compound, the introduction of it makes the compound biologically more active than the parent compound. Thus, it is possible to make the compounds biologically active but less toxic by introducing various pharmacophores. Some examples of pharmacophores are alkyl, hydroxy, alkoxy, aldehyde or ketone, nitro, nitrile, unsaturated compound, isomerism, halogens and unsaturated lipids.

## Drug design process

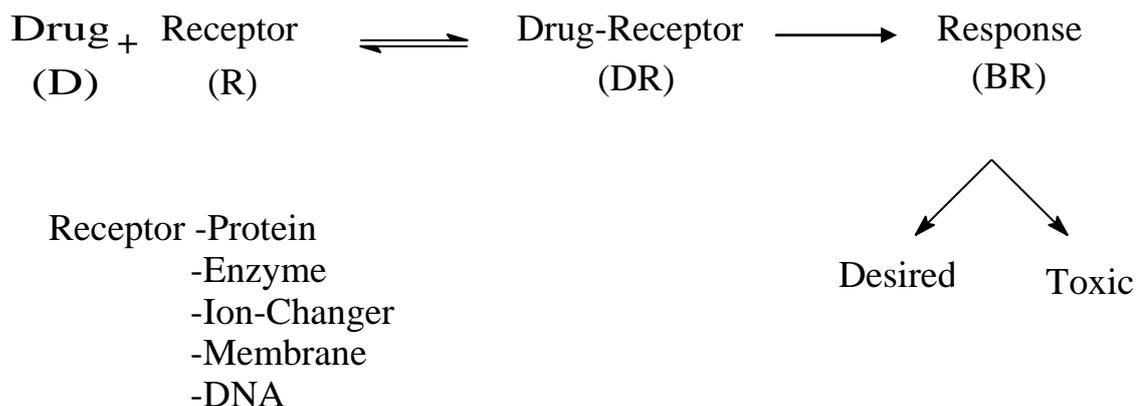
The process of creating or discovering the new chemical entity (NCE), which further develops as a drug is highly innovative and is precisely designed, it is broadly referred as drug discovery process. It involves two distinct interlinked step of identification and optimization of the lead structure. Among different approaches to drug design, the one of based on the identification of substructures (pharmacophores) and their annealation or incorporation on to carrier systems, or building of active molecules into conformationally rigid structures, followed by optimization of the activity. The structure-activity analysis has not only resulted in the discovery of new drugs and lead structures but also added to the knowledge about the contours of receptors and the sites important for interaction with the drugs.

New trends in the field of drug design comprise the combinatorial chemical synthesis of large libraries of compounds and further high through put screening using quick and cost effective assays.

## Drug binding

Extensive drug binding in the body occurs in the blood. Blood contains 6.5% of protein of which 50% is albumin. It is mainly involved in drug binding. It can interact with anions and cations also. The drug-protein binding may be due to ion-ion interactions, hydrogen bonding, hydrophobic and Vander Waal's forces. The protein drug binding is usually reversible reaction.

The drug binding resembles salt formation. The protein binding act as a transport system for the drug, which while bound is hindered in its access to the site of metabolic action and excretion.



## **Chemotherapy**

The treatment of infectious disease by using a chemical agent is called chemotherapy. The substance so employed is referred to as chemotherapeutic agent. These agents are designed in such a way that they kill or destroy the disease-producing organisms without any harmful effect on the cells in which organisms are present.

Paul Ehrlich (1854-1915) did outstanding work in medicinal chemistry and therefore called 'Father of Chemotherapy'. He gave original ideas about the models of action of drugs. According to him, there are some cellular constituents in mammalian cells, which were earlier called *receptors* by Langley (1878). Ehrlich defined chemotherapy "*as the use of drugs to injure an invading organism without causing injury to the host*".

## **Pharmacodynamic agents**

The drugs, which stimulate or depress various functions of body so as to provide relief from symptoms of discomfort, are known as pharmacodynamic agents. Although these agents have a characteristic effect on the animal, they have no specific remedies for particular diseases. These agents are mainly used in the case of non-infectious diseases, to correct abnormal functions. However, they have no action on infective organism, which causes the disease. Examples of pharmacodynamic agents are analgesics, sedatives, anesthetics, antihistamines, etc.

Some differences may be pointed out between chemotherapeutic agents and pharmacodynamic agents; among them are the following:

1. Chemotherapeutic agents are used in the treatment and cure of infectious disease; pharmacodynamic agents are used for relief and correction of abnormal functions.
2. Chemotherapeutic agents usually exert an irreversible action, by attaching strongly, sometimes through a covalent bond, to special moieties of macromolecules of invading organism; pharmacodynamic agents should preferably produce reversible results, by forming weak bonds with pharmacological receptors.
3. Potential chemotherapeutic agents are often easily screened, because in many cases it is very simple to isolate the invading organism and study it separately;

pharmacodynamic agents have been found to be more difficult to test, because it is not yet possible to isolate receptor molecules.

Some therapeutic agents may have one or both of the following effects:

(a) *static*, when they inhibit further growth or multiplication of invading organism or cell; (b) *cidal*, when they kill or destroy it. Static or cidal effects depend on several factors, such as concentration of drug, pH, temperature, duration of action, metabolic phase of the invader, and presence of interfering substance. Thus drug with static effects may exert cidal effects if the doses are increased.

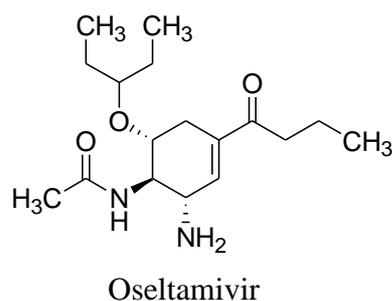
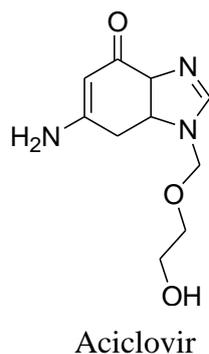
The relative efficiency and safety of chemotherapeutic agents has been indicated by the so-called *chemotherapeutic index*, which may be expressed by the relationship

$$\text{Chemotherapeutic index} = \frac{\text{Maximal tolerated dose by the host}}{\text{minimal curative dose}}$$

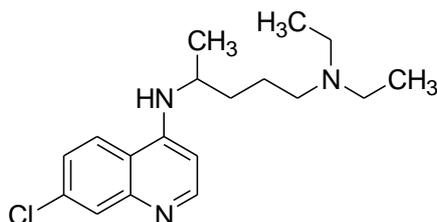
The greater this index, the better the chemotherapeutic agent because of its greater safety to the patient. The progress of drug design is extensively driven in the instincts, introduction and experience of research scientists. It is often instructive to attempt to ‘capture’ these experiences by analyzing the historical record that is successful drug design projects to past. From this analysis the interference draws to play an important role in shaping our on current and future projects.

Some heterocyclic Chemotherapeutic agents are drugs used in the treatment of infectious diseases. These diseases are caused by certain species of metazoa, protozoa, fungi, bacteria, ricketissa and viruses. Drugs active on these pathogenic agents divided into the following type according to their therapeutic activity.

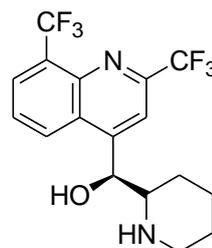
Following Aciclovir and Oseltamivir are heterocyclic antiviral drugs.



Following Chloroquine and Mefloquine are heterocyclic antimalarial drugs.

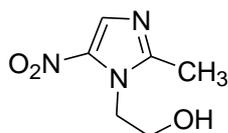


Chloroquine

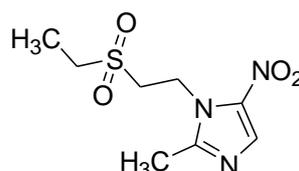


Mefloquine

Following Metronidazole and Tinidazole are heterocyclic Antiprotozoal drugs.

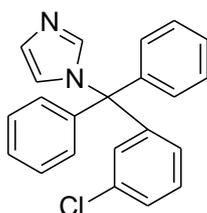


Metronidazole

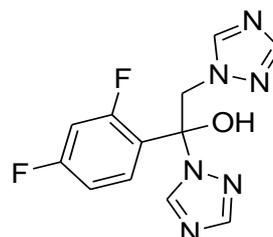


Tinidazole

Following Clotrimazole and Fluconazole are heterocyclic Antifungal drugs.

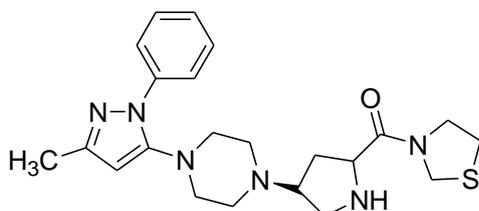


Clotrimazole

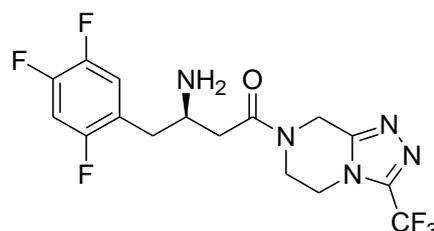


Fluconazole

Following Saxagliptin and Sitagliptin are heterocyclic Antidiabetic drugs.

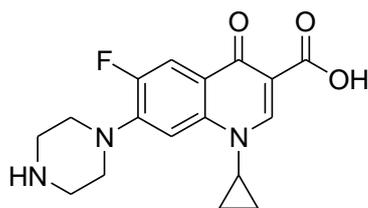


Teneligliptin

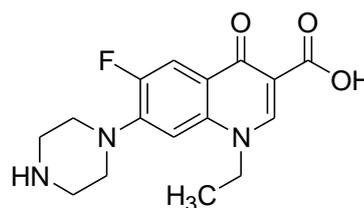


Sitagliptin

Following Ciprofloxacin and Norfloxacin are heterocyclic Antibiotic drugs

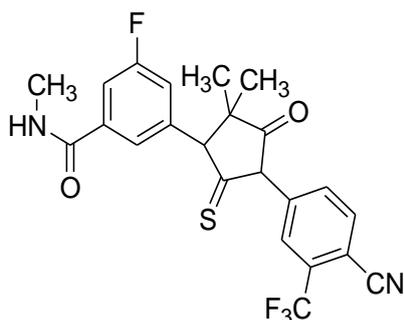


Ciprofloxacin

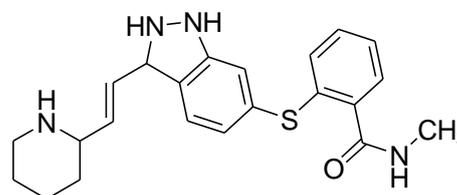


Norfloxacin

Following Enzulatamide and Axitinib are heterocyclic Antineoplastic drugs

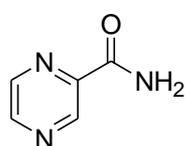


Enzulatamide

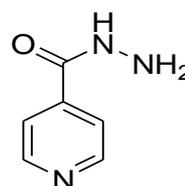


Axitinib

Following Pyrazinamide and Isoniazid are heterocyclic Antituberculosis drugs



Pyrazinamide



Isoniazid

Among all heterocycles, nitrogen based heterocycles have specific and unique identity in the world of pharmaceutical chemistry. Pyridine, oxadiazole, coumarin, pyrimidine, quinazoline, benzimidazole, triazole are some of the examples. The research work described here is humble efforts to synthesize the nitrogen based novel heterocycles and study their pharmaceutical importance.

Our research work is based on the following type of heterocyclic compounds having central moiety of

1.[B]. Quinazoline

1.[C]. Benzimidazole

1.[D]. Triazole

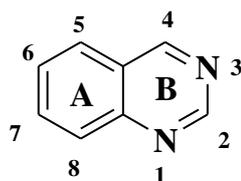
## 1.[B] QUINAZOLINE:

### 1.[B].1. HISTORY OF QUINAZOLINE:

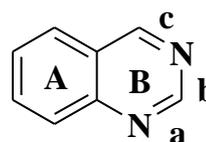
Quinazoline is synthetically versatile substance, where it can be used for the synthesis of a large variety of heterocyclic compounds in pharmaceuticals, such as indoles as raw material for drug synthesis. The advances in the use of quinazoline for organic synthesis during the last twenty-five years, as well as a survey of its biological and pharmacological properties are reported.

Quinazoline derivatives used for the treatment of inflammatory diseases and particular emphasis on potency specified in the screening assays over the last three decades. A growing interest and an absolute need for the discovery of new, selective and promising inhibitors with an improved safety and efficacy profile has stimulated us to present an attractive approach towards design and development of new anti-inflammatory and anti-allergic agents. A couple of reviews in the past appeared in the literature giving a broader perspective of the pharmacological activities of quinazoline derivatives<sup>1,2</sup>.

The quinazoline compounds are classified based on the substituent's present on different positions. The basic skeleton of quinazoline ring system (1) and the face of the fusion on hetero ring in quinazoline ring (2) as cited below.



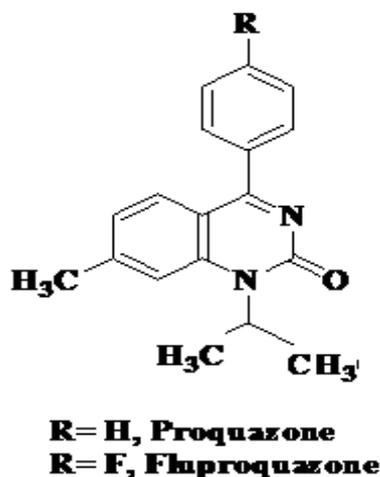
(1)



(2)

## Quinazoline

Earlier in this century, first generation non-steroidal anti-inflammatory drugs (NSAIDs) such as acetylsalicylic acid (ASA) became well established in the treatment of pain and inflammation. Continued research in this area led to a second generation of NSAIDs, such as phenylbutazone. Though this was considered as a significant improvement over the first generation, still it was felt that it is falling short of the desired activities. As a consequence, the third generation NSAIDs emerged and on an average, these agents are superior to the second generation in both; safety and efficacy. Examples of these new agents are 4-aryl-1-alkyl-2(1H)-quinazolinones<sup>3</sup>, particularly proquazone (1-isopropyl-7-methyl-4-phenyl quinazolin-2(1H)-one) and fluproquazone (4-(4-fluorophenyl)-1-isopropyl-7-methyl quinazolin-2(1H)-one)<sup>4</sup>. The overall anti-inflammatory profile of proquazone is comparable with that of indomethacin (1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid). It is very remarkable that proquazone is the first potent anti-inflammatory drug of a non-acidic nature, which is a potent prostaglandin synthesis inhibitor and a collagen-induced platelet aggregation inhibitor. Proquazone is also shown to be a highly effective and well - tolerated drug for the treatment of gout.



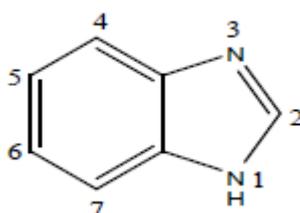
(1)

The synthetic versatility of quinazoline has led to the extensive use of this compound in organic synthesis. Three reviews have been published regarding the chemistry of this compound: the first by Sumpter<sup>5</sup>, a second by Popp<sup>6</sup> and the third on the utility of quinazoline as a precursor for the synthesis of other heterocyclic compounds<sup>7</sup>.

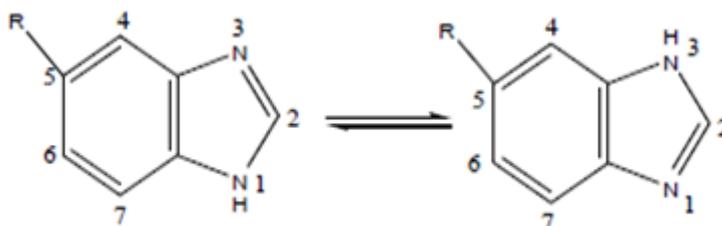
## 1.[C]. BENZIMIDAZOLE:

### 1.[C].1. HISTORY OF BENZIMIDAZOLE:

Benzimidazole is a heterocyclic aromatic organic compound. This bicyclic compound consists of the fusion of benzene and imidazole. The most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B12. Benzimidazole<sup>8</sup>, in an extension of the well-elaborated imidazole system, has been used as carbon skeletons for N-heterocyclic carbenes. They are often prepared by deprotonating an N, N'-disubstituted benzimidazolium salt at the 2-position with a base.<sup>9,10</sup>



Benzimidazole and its derivatives are used in organic synthesis and vermicides or fungicides as they inhibit the action of certain microorganisms. Examples of benzimidazole class fungicides include carbendazim, chlorfenazole, cypendazole, debacarb, fuberidazole, furophanate, mecarbinzid, rabenzazole, thiabendazole, thiophanate. Benzimidazole structure is the nucleus in some drugs such as proton pump inhibitors and anthelmintic agents. Benzimidazole,  $pK_a = 5.68$ , is less basic than imidazole, but with  $pK_a = 12.75$  is more strongly NH-acidic<sup>11</sup>. Like imidazoles, benzimidazoles display annular tautomerism in solution, e.g.:



## 1.[D].TRIAZOLE:

### 1. [D].1. HISTORY OF TRIAZOLE:

Triazoles are the class of heterocyclic compounds<sup>12</sup> which are under study since many years. Its diversity in showing the pharmacological activities is mind blowingly identified well by the medicinal chemists. Triazole, with many a compounds as incorporating with other heterocyclic nucleus, hydrazides<sup>13</sup>, substituted triazoles<sup>14</sup>,  $\beta$ -agonist<sup>15</sup> or incorporated with antibiotics<sup>16</sup> are some of great uses which fascinates the chemists to continue research on it and find out more hidden potentials of this nucleus.



Triazoles nucleus have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatory, CNS stimulants, sedatives, anti-anxiety and antimicrobial agents, Anti fungal activity. They are used as optical brightening agents, as antioxidants, as corrosion inhibitors and as additives with a variety of other functions. Many dye stuffs and pigments have heterocyclic. Many dye stuffs and pigments have heterocyclic. The Triazole derivative poses a wide a range of pharmacological such as antimicrobial, analgesic, anti- Inflammatory, anti convulsant, anti neoplastic, anti malarial, anti viral, anti proliferative, and anti cancer activities.

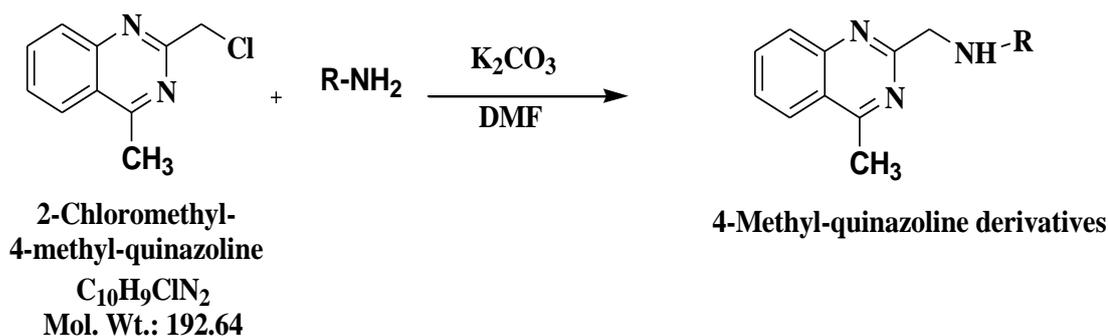
The pharmacological properties shown by this moiety (Fig.1) includes Phosphodiesterases enzyme inhibitor<sup>17</sup>, hepatitis-C<sup>18</sup>, anti-inflammatory<sup>19</sup>, antimicrobials<sup>20</sup>,  $\beta$ -lactamase inhibitors<sup>21</sup>, fungicidal<sup>22</sup>, insecticidal<sup>23</sup>, antitumor<sup>24</sup>, anticonvulsant<sup>25</sup>, antidepressant<sup>26</sup>, plant growth inhibitor<sup>27</sup>. Further synthesis of various compounds as 1,2,4-triazole-C-nucleoside<sup>28</sup>, acyclic C-nucleosides<sup>29</sup>, pyrimidines<sup>30</sup>, D-manno-pentitol-1-yl-1,2,4-triazoles<sup>31</sup>, benzotriazoles<sup>32</sup>, indoles<sup>33</sup>, quinolones<sup>34</sup>, triazolo thymidines<sup>35</sup> are in record.

**1.[E]. PRESENT WORK:**

In present novel works devided in three parts as given below,

**1.[E].1.**

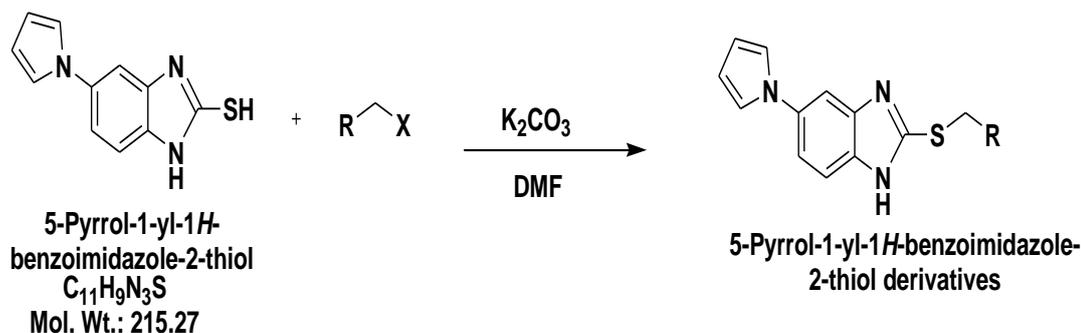
2-chloromethyl-4-methyl-quinazoline reacted with different aliphatic and aromatic amine in presence of base gives novel substituted 4-Methyl quinazoline derivatives. Reaction scheme shown as given below.



R= substituted Piperazine, Piperadine, Morpholine, substituted Morpholine, Phenyl amine, Pyrrolidine, substituted pyrrolidine, aliphatic amine, aromatic amine, substituted pyrrole

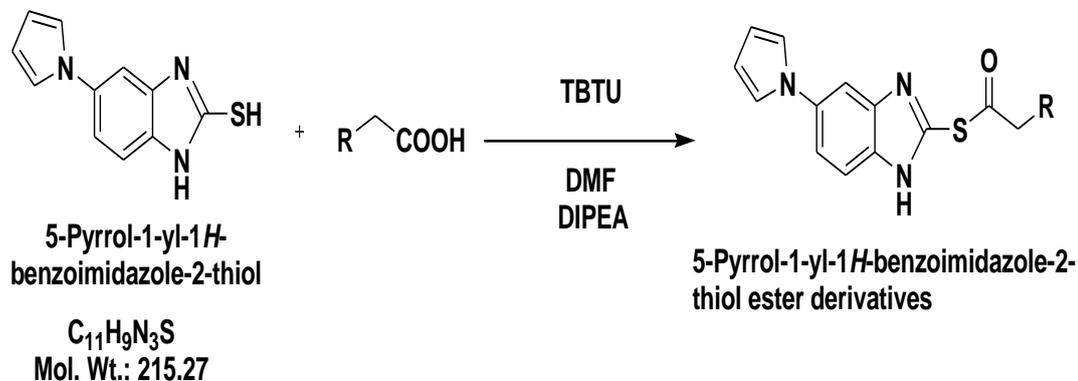
**1.[E].2.**

5-Pyrrol-1-yl-1H-benzoimidazole-2-thiol reacted with different alkyl and aryl halide in presence of base gives novel 5-Pyrrol-1-yl-1H-benzoimidazole-2-thiol derivatives. Reaction scheme shown as given below.



Where R= alkyl halide and aryl halide

5-Pyrrol-1-yl-1H-benzoimidazole-2-thiol reacted with different aliphatic acid substituent in presence of TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate) and base gives novel 5-Pyrrol-1-yl-1H-benzoimidazole-2-thiol ester derivatives. Reaction scheme shown as given below.



#### Where

R= Different aliphatic acid substituent.

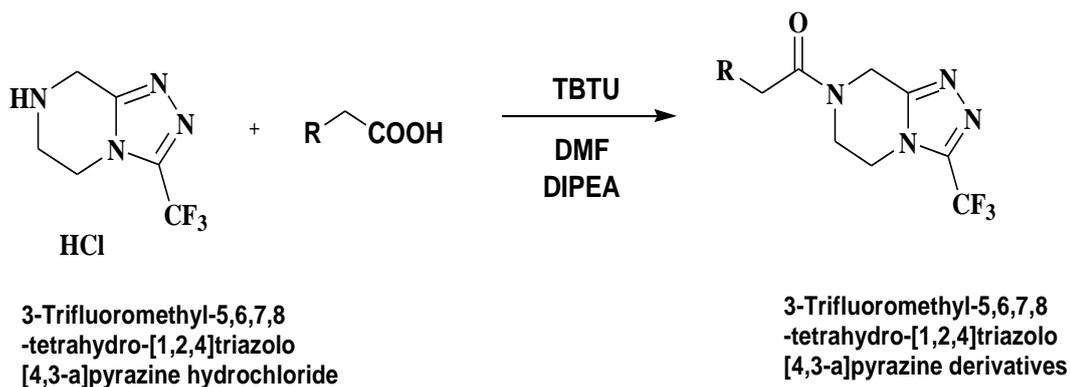
TBTU=2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate.

DIPEA=N,N-Diisopropyl ethyl amine.

DMF=N,N-Dimethyl formamide.

#### 1.[E].3.

3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a] pyrazine Hydrochloride reacted with Different aliphatic and aromatic acid substituent in presence of TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate) and base gives novel 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine derivatives. Reaction scheme shown as given below.



**Where**

R= Different aliphatic and aromatic acid substituent.

TBTU=2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate.

DIPEA=N,N-Diisopropyl ethyl amine.

DMF=N,N-Dimethyl formamide.

Today a large number of diseases can be cured or at least controlled by drug therapy. The fight against bacterial and fungal infections has been largely won and significant progress has been made. It would not be an exaggeration to claim that certain form of cancers can be cured by chemotherapy. However when coupled with other chronic conditions, its still irritates physician even today, because of the resistance offered by acting against various forms of therapy.

Our work studies are presented in following chapters as outlined below:

Chapter [II] Synthesis of novel quinazoline compounds.[DJP/D102-DJP/D125]

Chapter [III] Synthesis of novel Benzimidazole compounds.[DJP/D131-DJP/D155]

Chapter [IV] Synthesis of novel Triazole compounds.[DJP/D156-DJP/D165]

Chapter [V] Characterization and Interpretation of novel compounds.

Chapter [VI] Microbial study of Novel Quinazolin, Benzimidazole and Trizole derivatives.

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