CHAPTER-1

INTRODUCTION
General Introduction

Human ailments are as old as human being. So is the search for drugs to combat them. Most of the drugs used in the primitive system of medicine, were from the natural sources. From about the 3rd century BC to the early 20th century most useful drugs, e.g., morphine, quinine, digitalis, ergot, atropine, to name a few, were derived from plant sources and their therapeutic uses were based on ancient serendipitous discoveries. As the abilities of the chemists to synthesize, isolate and characterize new compounds grew and as biologists learned more about the action of drugs and about biological mechanism in health and disease, the search for new drugs became more rational.

In the development of organic therapeutic agents, Pharmaceutical scientists have explored numerous approaches for finding the developing organic compounds that are now available to us in dosage forms, suitable for the treatment of our ills and often for the maintenance of our health.

Pure organic compounds natural or synthetic are the chief source of agents for the cure, the mitigation or prevention of disease today. These remedial agents have had their origin in a number of ways,

(1) From naturally occurring materials of plants and animal origin and latter from micro-organisms and their fermentation products,
(2) From the synthesis of organic compounds whose structure are closely related to those of naturally occurring compounds (e.g. morphine, atropine, steroids and cocaine) that have been shown to possess useful medicinal properties.

Although, these first two approaches have led to the development of useful medicinal agents a third approach, that of pure synthesis has provided significant discoveries of medicinal agents. A few of them are-

(i) Ehrlich’s outstanding synthetic efforts to develop antiparasitic drugs which yielded the useful organoarsenicals and various antimicrobial drugs,
(ii) Development of the active sulfanilamide as a study of the metabolic products of the azo dye prontosil;
(iii) The discovery of the diuretic and anti-diabetic properties of certain analogs of sulfanilamide during a study of their biological properties other than anti-microbial.

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(iv) The discovery of the outstanding analgesic properties of Demerol (meperidine) as an observation is connection with its biological testing as an antispasmodic agent. These discoveries gave an outstanding lead to the development of other important medicinals.¹

The development of new drugs has been responsible for decreasing human morbidity and mortality more than any other scientific endeavor. These products have dramatically improved the quality of life across all ages. They can prevent illness or when illness occurs, speed recovery, reduces hospital stays and decreases the need for surgery.

The search for new drugs still involves a generous measure of serendipity, but a more rational approach has gradually developed. For example, a discovery in basic biological research may lead to a hypothesis that a certain chemical mediator, a particular enzyme or perhaps a specific receptor plays a key role in a pathological condition. Candidate drugs designed and synthesized partly on the basis of such known mediators, hormones, metabolites or substrates. Initial screening of hundreds or perhaps thousands of compounds may be rapidly accomplished by using in-vitro enzymatic or receptor test systems. Typically, several unique active lead compounds emerge, which are studied in a variety of biological systems, either confirming or refuting the original hypothesis. Whether or not a promising new drug is born, the extensive biological characterization often reveals an unexpected action for one or more of the new biological concepts.²

The search for chemical structures, which exhibit physiologic activity is a difficult goal or organic chemical research. Compounds are submitted to screening for numerous types of biological and pharmacological action. Observations of interesting repeatable biological activity open pathways for additional chemical research effort in the expansion of the series and often leads to significant new medicinal products.

The pharmacological activity of a compound is an involved function of the structure, and a very small change may profoundly modify the pharmacological effect. These structure modifications may involve replacing one group with another at a specific point in the molecule, shifting the same group from place to place in the parent molecule, saturating valence bonds or modifying the acidity or basicity.
Slight change sometime completely reverse the action of the compound, as is the case when the terminal methyl group of 5-(1-methyl amyl)-5 ethyl barbituric acid (1) is moved one carbon atom nearer the nucleus to forms 5- (1,3-dimethyl butyl)- 5- ethyl barbituric acid (2). The latter compound produces convulsion and is fatal in small dose. This effect can be neutralized and the animal life saved by a dose of the sedative isomer (1).

Many of the currently used antispasmodics, anti-convulsants, local anaesthetics, non-narcotic analgesics, chemotherapeutic agents and hypnotics have been products of this approach.

Another style of research is to identify, isolate and purify compounds from biologically active mixtures. The determination of the structure of a biologically active molecule provides a two-fold benefit to pharmacy and medicine. It makes possible research leadings to synthesis and modification of the structure. A change in structure usually accompanies with changes in biological activity and occasionally vast improvement is accomplished.

Total synthesis is made possible by knowledge of chemical structures and is important economically in reducing the cost of the drug. viz., chloramphenicol which can be obtained from cultures of Streptomyces venezuelae, combats bacteria producing typhoid dysentery and Rocky Mountain spotted fever is now a days synthesized commercially. Many of the water- soluble vitamins are produced commercially in large amounts by chemical synthesis. In addition, the total synthesis of compounds such as penicillin, tetracycline, insulin and lysergic acid although not economical, nevertheless represents outstanding contribution to the science of organic chemistry.

Occasionally new drugs are found by accident. More frequently they are developed as part of an organized effort to discover new ways to treat specific disease. The discovery of new pharmaceutical agents has gone through an evolution over the
years and has been adding new technologies to this increasingly complex process. Discovery of drugs can be summarized as follows.

(a) Screening for new drugs

The traditional way to discover new drugs has been to screen a large number of synthetic chemical compounds or natural products for desirable effects. The major advantage of screening is that the large amount of information is not needed to carry out the process. One does not need to know the structure of the drug being sought. Nor does one need to know the structure of the target upon which the drug will act. Most importantly, one does not need to know the underlying mechanism of the disease process itself.

Although this approach for the development of new pharmaceutical agents has been successful, but it is inherently repetitious, time consuming and random in nature.

(b) Modifications for improvement

Once an active (lead) compound has been identified and its chemical structure determined, it is usually possible to improve this activity and/or to reduce the side effects by making modifications to the basic chemical structure. Modifications to improve performance are often carried out using chemical or biofermentive means to make changes in the lead structure or its intermediates. Alternatively, for some natural products, the gene itself may be engineered so that the producer organism synthesizes the modified compound directly. A prime example of the power of this approach is in the anti-infective area where modifications of the original first generation cephalosporins have led to second and now third generation off springs with substantially improved characteristics.

(c) Mechanism based drug design

As still information becomes available about the biological basis of a disease, it is possible to begin to design drugs using a mechanistic approach to the disease process. When the disease process is understood at the molecular level and the target molecule(s) are defined, drugs can be designed specifically to interact with the target molecule in such a way as to disrupt disease.

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(d) Combining techniques

Drug discovery is both a cumulative and reiterative process. Potential drugs developed by modifying a lead structure are certain to be sent through selective screening process to confirm activity and select for the best candidate to go on for further development. Likewise, drugs developed mechanistically will likely be both screened and later modified in other to produce the best candidate drug.

Out of millions of compounds recorded in Chemical Abstract, approximately half of these contain heterocyclic ring structures. Heterocyclic compounds have a cyclic structure with two or more different kind of hetero atoms in the ring. Since the ring can be of any size, from three member upwards, and since the hetero atoms can be drawn in almost any combination from a large number of the elements (nitrogen, oxygen and sulfur are the most common), the number of possible heterocyclic systems is almost limitless. An enormous number of heterocyclic compounds are known and this number is increasing very rapidly.

Heterocyclic compounds are very widely distributed in nature, and are essential to life in many ways. They play a vital role in the metabolism of all living cells. Thus, for example: the pyrimidine and purine bases of genetic material DNA; the essential amino acids proline, histidine and tryptophan; the vitamins and coenzyme precursors thiamine, riboflavin, pyridoxine, folic acid and biotin; the B₁₂ and E families of vitamins; the photosynthesizing pigment chlorophyll; the oxygen transporting pigment hemoglobin, and its breakdown products the bile pigments; the hormone kinetin, heterauxin, serotonin, histamine and methoxatin; most of sugars and their derivatives including vitamin C exist largely in the form of five-member (furan) or six member (pyran) rings containing one oxygen atom.

There are vast numbers of pharmacologically active heterocyclic compounds in regular clinical use. Some of these are natural products, for example vincristine, vinblastine, streptomycin and actinomycin D as anticancer agents; salicylic acid, salicin and morphine as analgesics; penicillins and cephalosporins as anti-infective agents; strychnine and picrotoxin as analeptics; atropine and hyoscine as anticholinergic drugs; emetine as expectorant (emetic and diaphoretic); reserpine as antihypertensive and tranquilizer; papaverine as coronary vasodilator and quinine as anti-malarial.
The presence of heterocyclic structures in such diverse types of compounds is strongly indicative of the profound effects such structures exert on physiologic activity, and recognition of this is abundantly reflected in efforts to find useful synthetic drugs. Examples include researches leading to a wide variety of modern drugs such as acetazolamide and methazolamide (carbonic anhydrase inhibitors); chloroquine and primaquine (antimalarials); dapsone (leprotic); cyclophosphamide and 5-fluorouracil (antineoplastics); guanethidine, diazopoxide, hydralazine, prazosin and clonidine (antihypertensive), nicotinic acid (antihyperlipidemic); imipramine (antidepressant); chlordiazepoxide (tranquilizer); indomethacin, mefenamic acid, tolnmetin, zomepirac, piroxicam and phenylbutazone (anti-inflammatory, analgesics); and many others. A few of the heterocycles presents in drugs are shown in Table 1.1

Table 1.1: List of Some Heterocyclic Rings Present in Drugs

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Heterocycle</th>
<th>Ring’s Name</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td><img src="image" alt="Quinazoline" /></td>
<td>Quinazoline</td>
<td>Methaqualone</td>
</tr>
<tr>
<td>02</td>
<td><img src="image" alt="1,3,4-Thiadiazole" /></td>
<td>1,3,4-Thiadiazole</td>
<td>Acetazolamide, Methazolamide</td>
</tr>
<tr>
<td>03</td>
<td><img src="image" alt="Isoxazole" /></td>
<td>Isoxazole</td>
<td>Isocarboxazidine, Sulfisoxazole</td>
</tr>
<tr>
<td>04</td>
<td><img src="image" alt="Thiazole" /></td>
<td>Thiazole</td>
<td>Thiabendazole</td>
</tr>
<tr>
<td>05</td>
<td><img src="image" alt="Imidazole" /></td>
<td>Imidazole</td>
<td>Histamine, Pilocarpine</td>
</tr>
<tr>
<td>06</td>
<td><img src="image" alt="Pyrimidine" /></td>
<td>Pyrimidine</td>
<td>Pyrimethamine, Sulfadiazine</td>
</tr>
</tbody>
</table>

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</thead>
<tbody>
<tr>
<td>07.</td>
<td><img src="image" alt="Piperidine" /></td>
<td>Piperidine</td>
<td>Glutethimide, Meperidine</td>
</tr>
<tr>
<td>08.</td>
<td><img src="image" alt="4-Thia-1-azabicyclo [3.2.0]-heptane" /></td>
<td>4-Thia-1-azabicyclo [3.2.0]-heptane</td>
<td>Penicilline</td>
</tr>
<tr>
<td>09.</td>
<td><img src="image" alt="Benzimidazole" /></td>
<td>Benzimidazole</td>
<td>Thiabendazole, Droperidol, Cyanocobalamin</td>
</tr>
<tr>
<td>10.</td>
<td><img src="image" alt="Quinoline" /></td>
<td>Quinoline</td>
<td>Chloroquine, Quinine</td>
</tr>
<tr>
<td>11.</td>
<td><img src="image" alt="1,4(3H)-Benzodiazepine" /></td>
<td>1,4(3H)-Benzodiazepine</td>
<td>Chlordiazepoxide</td>
</tr>
<tr>
<td>12.</td>
<td><img src="image" alt="Phenothiazine" /></td>
<td>Phenothiazine</td>
<td>Chlorpromazine</td>
</tr>
</tbody>
</table>

There are also a large number of heterocyclic compounds with other important practical applications, as dyestuffs, copolymers, solvents, photographic sensitizers and developers, as anti-oxidants and as vulcanization accelerators in the rubber industry and many valuable intermediates in synthesis.

The successful application of heterocyclic compounds in these and many other ways, and their appeal as materials in applied chemistry and in more fundamental and theoretical studies, stems from their very complexity, which ensures a virtually limitless series of structurally novel compounds with a wide range of physical, chemical and biological properties, spanning a broad spectrum of reactivity and stability. Another consequence of their varied chemical reactivity including the possible destruction of the heterocyclic ring, is their increasing use in the synthesis of specifically functionalized non-heterocyclic structures e.g., Indomethacin (3) and Sulindac (4).
During the past decade novel approaches have been innovated for the synthesis and pharmacological/biological properties of azoles.

As the present work is on 4(3H)-quinazolinone, the same heterocyclic nucleus has been taken up for discussion.
Quinazolin 4(3H)-one

Quinazolin 4(3H)-one consists of a benzene and a pyrimidine ring.

An example of commercially important quinazolin 4(3H)-one is 2-methyl -3- o-tolyl 4(3H)-quinazolinone known a methaqualone is a sedative-hypnotic introduced in 1965. The market products of this quinozolinone in U.S.A. are Quaalude®, Parset®, and Sopor® in the form of HCl salt.

The compound methaqualone has been reported to have anticonvulsant activity also.

Methaqualone

Reaction and Properties

Chemistry of Quinazoline resemble closely with pyrimidine. Quinazoline as a base has an ionization constant of the order of 2x10⁻¹¹ (pka=3.3). Quinazolines are generally stable to oxidation, but vigorous oxidation breaks the benzene ring to give pyrimidine carboxylic acid.

Sodium and sodium amalgam in alcohol reduce the pyrimidine ring completely to give 1,2,3,4-tetrahydroquinazoline.
Quinazolines having hydroxy group in the compound 5 at 2\textsuperscript{nd} and compound 6 at 4\textsuperscript{th} position are tautomeric with the 2- and 4-oxodihydroquinazolines (Quinazolones) and 2:4-dihydroxyquinazoline (Compound 7) with 2:4-dioxo-1,2,3,4-tetrahydroquinoxaline (Benzoyleneurea).

![Chemical structures of 2(1H)-Quinazolone and 4(3H)-Quinazolone]

Quinazolones are high melting crystalline solids, insoluble in water and most organic solvents but soluble in aq. alkali. They are stable to oxidation, reduction and hydrolysis.

Oxidation of a 2- or 4-quinazolone with permanganate or chromic acid gives benzoyleneurea (2, 4-dioxo-1,2,3,4-tetrahydroquinoxaline).

![Chemical reaction with KMnO₄ or CrO₃]

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Alkylation of 4-quinazolone sodium salts with ethyl iodide gives mixture of the N-ethyl quinazolones and the ethoxy quinazolines (Major product) and with the silver salts the ethoxy quinazoline is the predominant product.

Phosphorous pentachloride in phosphorus oxychloride sodium converts 2-or 4-quinazolone or benzylene urea to the corresponding chloro- or dichloroquinazoline.

2-Methylquinazoline undergoes a Claisen condensation with diethyl oxalate.\textsuperscript{11-14}

Quinazolinone gives Mannich reaction when it is refluxed with formaldehyde and an imide (succinimide).\textsuperscript{15}