CHAPTER – I

(A) INTRODUCTION
(B) PLAN OF WORK
INTRODUCTION

Fighting disease with drugs is the timeless struggle. It begun with the existence of the mankind. Survival of the mankind on this planet has been depended upon its success. Today the conflict is increasing continuously in the laboratory and the clinic. The scientific approach to this struggle is pharmacology. With the knowledge of cell-biology and biochemistry increasing, the field of pharmacology has also changed substantially. It has become possible through molecular analysis of receptor to design chemical that act on specific cellular metabolic pathway by affecting sites directly on cell-surface receptors.

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 new prophylactic and therapeutic agents. The growth of molecular biology with its chemical insight into experimental biology has contributed to more significant pharmacological theories. 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 taken advantage of these investigations and refined the pertinent chemical theories, to establish itself firmly as an interdisciplinary science. 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.

Organic chemistry has its origin in the study of natural products and this still remains the most important role. Many organic compounds occur naturally and their functions are often of fundamental importance to living organisms. Today, although many compounds of carbon are still most conveniently isolated from plant and animal sources, most of them are synthesized.

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. Carbohydrates are heterocyclic; so are chlorophyll and haemin. Heterocycles form the sites of reaction in many enzymes and co-enzymes.

Among all heterocycles, nitrogen based heterocycles have specific and unique identity in the world of pharmaceutical chemistry. Pyridine, oxadiazole, coumarin, pyrimidine, s-triazine 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.

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, it still irritates physician even today, because of the resistance offered by acting against various forms of therapy.

**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.

For the drug to be most useful, first of all it should not be toxic, but should possess good pharmacokinetic properties. Secondly it should not be rapidly metabolized but should optimally be absorbed after oral administration. Thus, ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties of compounds must be investigated early in the drug discovery path to clarify clinical utility of new genes as targets. Very few drugs satisfy all the above conditions. However, the search for ideal drug continues.

There have been three approaches to the problem of finding a drug to combat a particular disease:

1. The first method is of trial and error. Where all kind of compounds, natural and synthetic is used for trials.
2. In second method, one first requires knowledge of cell system, and then synthesizes the compounds, which would have an action on the cell system.
3. Till today, The third method has proved to be the most fruitful wherein a known compound having some minimum activity has been taken, to further restructure the molecule systematically so as to enhance the activity of the same.

Pharmacophore

The physiological activity of drug 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 pharmacophore.

When a pharmacophore 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 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 throughput 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. Its molecular weight is 69000 and it has net negative charge at blood pH 7.4. 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.

\[
\text{Drug (D) + Receptor (R) } \rightarrow \text{Drug-Receptor (DR) } \rightarrow \text{Response (BR)}
\]

- Desired
- Toxic
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 named as receptors by Langley (1878). Ehrlich defined chemotherapy as the use of drugs to injure an invading organism without causing injury to the host.

Chemotherapeutic drugs

According to Ehrlich chemotherapeutic agents are chemical substances with high parasitotropism and low or no organotropism. In other words, they are selectively toxic, being harmful to as much as possible to the invading organism but innocuous to the host.

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

1. Antimalarial Agents
2. Antiprotozoal Agents
3. Antifungal Agents
4. Antibacterial Agents
5. Antiseptic Agents
6. Antituberculosis and Antilepral Agents
Pharmacodynamic agents

The drug 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, anaesthetics, 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.

**Antibacterial Chemotherapy**

The development of resistance to current antibacterial therapy continues to drive the search for more effective agents. Bacteria are commonly responsible for many diseases, which are continuously increasing their resistance to chemotherapy.

**Bacteria**

These are a group of microorganisms, which are unicellular and surrounded by rigid, complex, protein cell wall. These may be free living, saprophytic or parasitic; some are pathogenic to man, animals and plants.

Bacteria are classified into two types, i.e. gram-positive and gram-negative according to method developed by Christian Gram, which is as follows:

In this method, the fixed bacterial smear is first treated with a solution of crystal violet and then with iodine solution, which reacts with the dye and the cell constituents. The smear is then washed with alcohol (decolourizing agent) and safranine or some other counter stain is added.

The bacteria that retain the colour of crystal violet and appear deep violet (in colour) are called Gram-positive bacteria, whereas those, which lose the violet colour and get counterstained by safranine and appear red in colour, are called Gram-negative bacteria. The followings are some of the disease causing bacteria classified in this manner:
Gram positive bacteria | Gram negative bacteria
--- | ---
*Diphtheria bacillus* | *Coli and Typhoid bacillus*
*Leprosy bacillus* | *Gonococcus*
*Pneumococcus* | *Meningococcus*
*Staphylococcus* | *Plague bacillus*
*Streptococcus* | *Spirochaetes*
*Tubercle bacillus* | *Vibrios (V. Cholerae)*

> **Antibacterial agents**

The history of antibacterial has been dynamic, characterized by the constant emergence of new challenges followed by investigation, discovery and the production of new drugs. A complete review of the various agents employed as antibacterial would be beyond the scope of this work and hence is not attempted. A brief summary of the important classes of antibacterial compounds are given below.

> **Synthetic antibacterial agents**

The synthetic antibacterial agents are comprised of two major classes of compounds:

[A] Topical antibacterial agents

[B] Systematically antibacterial agents

[A] **Topical antibacterial agents**

Antibacterial agents that are employed topically are commonly termed as antiseptics, disinfectants or preservatives depending on how they are employed. Since there is a considerable degree of overlap in usage among these three groups, the more convenient method of classifying them, would be based on the types of structure.

The antiseptics and disinfectants are large and diverse group of chemical compounds that play an important role in the maintenance of human and animal health.
Topical synthetic antibacterial agents are classified as follows:
1. Halogens and Halophors
2. Phenols
3. Alcohols
4. Aldehydes
5. Quaternary Ammonium compounds
6. Dyes
7. Ureas, Biguanides
8. Heavy Metal Compounds

[B] Systematically antibacterial agents

The systematically active antibacterial has been divided into three groups, two of which are the sulfonamides and the antitubercular agents. The remaining compounds are the main agents for the treatment of urinary tract infections.

Except for the sulfonamides and antitubercular drugs, only a few systemically active synthetic antibacterials are commercially important today. The multitudes of highly effective relatively nontoxic antibiotics available for the treatment of bacterial infections have provided stiff competition for the medicinal chemist attempting to synthesize new antibacterial agents.

Systemic synthetic antibacterial agents are classified as follows:
1. Antitubercular agents
2. β-Lactam antibiotics
3. Trimethoprim, Cotrimoxazole
4. Methanamine
5. Nitrofurans
6. Quinolones
7. Sulfonamides

According to the effect produced, antibacterial drugs can be bactericidal (kill the bacteria) or bacteriostatic (inhibit growth of bacteria). Commonly used bactericidal and bacteriostatic drugs are given below.
Mechanism of Action of Antimicrobial Agents

The mechanisms of action of specific chemotherapeutic agents are taken up in more detail when individual drugs and group of drugs are discussed later in this chapter. A few general observations are highlighted at this point (Table–1). It is important to know some basic things about the mechanism of drug action because this information will be useful in explaining the nature and degree of selective toxicity of individual drugs and sometimes aids in the design of new chemotherapeutic agents.

Antimicrobial drugs can damage pathogens in several ways, as can be seen in table-1. The most selective antibiotics are those that interfere with the synthesis of bacterial cell walls (e.g., penicillin, cephalosporin, vancomycin, and bacitracin). These drugs have a high therapeutic index because bacterial cell walls have a unique structure not found in eukaryotic cells.

Streptomycin, gentamycin, spectinomycin, clindamycin, chloramphenicol, tetracycline, erythromycin and many other antibiotics inhibit protein synthesis by binding with the prokaryotic ribosome. Because these drugs discriminate between prokaryotic and eukaryotic ribosome, their therapeutic index is fairly high, but not as favorable as that of cell wall synthesis inhibitors. Some drugs bind to the 30S (small) subunit, while others attach to the 50S (large) ribosomal subunit. Several different steps in the protein synthesis mechanism can be affected: aminoacyl - tRNA binding, peptide bond formation, mRNA reading, and translocation. For example, fusidic acid binds to EF-G and blocks translocation, whereas mucopirocin inhibits isoleucyl-tRNA synthetase.

The antibacterial drugs that inhibit nucleic acid synthesis or damage cell membranes often are not as selectively toxic as other antibiotics. This is because

<table>
<thead>
<tr>
<th>Bactericidal Drugs</th>
<th>Bacteriostatic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin, Aminoglycosides, Cephalosporin, Isoniazid,</td>
<td>Sulfonamides, Nitrofurans, Erythromycin,</td>
</tr>
<tr>
<td>Cotrimoxazole, Ampicillin, Carbenicillin, Methicillin,</td>
<td>Tetracyclines, Chloramphenicol, Lincomycin,</td>
</tr>
<tr>
<td>Vancomycin, Bacitracin, Streptomycin, Gentamycin,</td>
<td>Clindamycin, Rifampin, Dapsone</td>
</tr>
<tr>
<td>Ciprofloxacin, Polymyxin B, Trimethoprim</td>
<td></td>
</tr>
</tbody>
</table>

- 11 -
prokaryotes and eukaryotes do not differ as greatly with respect to nucleic acid synthetic mechanisms or cell membrane structure. Good examples of drugs that affect nucleic acid synthesis or membrane structure are quinolones and polymyxins. Quinolones inhibit the DNA gyrase and thus interfere with DNA replication, repair and transcription. Polymyxins act as detergents or surfactants and disrupt the bacterial plasma membrane.

**Table-1: Mechanism of Antibacterial Drug Action**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell Wall Synthesis Inhibition</strong></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>Inhibit transpeptidation enzymes involved in the cross-linking of the polysaccharide chains of the bacterial cell wall peptidoglycan. Activate cell wall lytic enzymes.</td>
</tr>
<tr>
<td>Ampicillin</td>
<td></td>
</tr>
<tr>
<td>Carbenicillin</td>
<td></td>
</tr>
<tr>
<td>Methicillin</td>
<td></td>
</tr>
<tr>
<td>Cephalosporin</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Binds directly to the D-Ala-D-Ala terminus and inhibits transpeptidation.</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Inhibits cell wall synthesis by interfering with action of the lipid carrier that transports wall precursors across the plasma membrane.</td>
</tr>
<tr>
<td><strong>Protein Synthesis Inhibition</strong></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Binds with the 30S subunit of the bacterial ribosome to inhibit protein synthesis and causes misreading of mRNA.</td>
</tr>
<tr>
<td>Gentamycin</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Bind to the 50S ribosomal subunit and blocks peptide bond formation through inhibition of peptidyl transferase.</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Bind to the 30S ribosomal subunit and interfere with aminoacyl-tRNA binding.</td>
</tr>
<tr>
<td>Erythromycin and Clindamycin</td>
<td>Bind to the 30S ribosomal subunit and inhibit peptide chain elongation.</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>Bind to EF-G and blocks translocation.</td>
</tr>
<tr>
<td><strong>Nucleic Acid Synthesis Inhibition</strong></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin and other Quinolones</td>
<td>Inhibit bacterial DNA gyrase and thus interfere with DNA replication,</td>
</tr>
</tbody>
</table>
transcription and other activities involving DNA.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>Blocks RNA synthesis by binding to and inhibiting the DNA-dependent RNA polymerase.</td>
</tr>
<tr>
<td><strong>Cell Membrane Disruption</strong> Polymyxin B</td>
<td>Binds to the plasma membrane and disrupts its structure and permeability properties.</td>
</tr>
<tr>
<td><strong>Metabolic Antagonism</strong> Sulfonamides</td>
<td>Inhibit folic acid synthesis by competition with p-aminobenzoic acid.</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Blocks tetrahydrofolate synthesis through inhibition of the enzyme dihydrofolate reductase.</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Interferes with folic acid synthesis.</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>May disrupt pyridoxal or NAD metabolism and functioning. Inhibits the synthesis of the mycolic acid “cord factor”.</td>
</tr>
</tbody>
</table>

Several valuable drugs act as **antimetabolites**: they block the functioning of metabolic pathway by competitively inhibiting the use of metabolites by key enzymes. Sulfonamides and several other drugs inhibits folic acid metabolism. Sulfonamides (e.g. sulfanilamide, sulfamethoxazole and sulfacetamide) have a high therapeutic index because humans cannot synthesize folic acid and must obtain it in their diet. Most of the bacterial pathogens synthesize their own folic acid and are therefore susceptible to inhibitors of folate metabolism. Antimetabolite drugs can also inhibit other pathways. For example, isoniazid interferes with either pyridoxal or NAD metabolism.

The work presented in this thesis is an effort in the field of medicinal chemistry. Though very minute, this research work may offer a practical solution to the innumerable problems. Nevertheless, a devoted and sincere effort has been put in to contribute towards a healthier human life. The work deals with some of the most common ailments viz. tuberculosis and bacterial infections though not considered fatal by and large.
References:


Series – 1, 2, 3 & 4

Heterocycles bearing nitrogen, sulphur and oxygen constitute the core structure of a number of biologically interesting compounds. 2-Mercapto analogue of oxadiazole derivatives are one of them and known to possess various pharmacological activities\(^1,2\).

1,3,4-Oxadiazole moiety possess antibacterial\(^3-5\), anti-inflammatory\(^6\), anticonvulsant\(^7\), CNS stimulant\(^8\), antihypertensive\(^9\), hypnotic\(^10\) and sedative activities.

1,3,4-Oxadiazole derivatives constitute an important class of compound possessing diverse pharmacological activities including fungitoxic\(^11,12\), insecticidal\(^13\), herbicidal\(^14\) and anti-inflammatory etc.

Aboraia et al.\(^15\) have synthesized a series of 5-(2-hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives (1) and evaluated for their *in vitro* anti cancer activity, some of the compounds displayed higher anti-cancer activity in primary assay.

\[
\text{R} = (3\text{-Chloroanilino})\text{methyl} \\
(4\text{-Chloroanilino})\text{methyl}
\]

Maslat and co-workers\(^16\) synthesized some bis 1,3,4-oxadiazole derivatives and tested for antibacterial, antifungal and genotoxic activities. Among which compounds (2a-c) exhibited both antibacterial and antifungal activities against *S. aureus* and *B. subtilis*. Rest of all displayed activity against *C. albicans*. 

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- 16 -
Rutavicius and Kuodis\textsuperscript{17} have reported the synthesis of S or N substituted-2-mercapto-5-(4-pyridyl)-1,3,4-oxadiazole (3) and their antibacterial, antitubercular and tranquilizing properties.

Undavia et al.\textsuperscript{18} synthesized oxadiazole derivative of type (4) and studied their antibacterial, antitubercular, anticancer and anti HIV activities. Among which, compounds with nitro and methoxy substitution at para position to phenyl ring showed excellent growth retardation in CNS and colon cancer.

Considering 1,2,4-oxadiazole derivatives (5) as a base compound, new analogue (6) has been derived by Zen et al. as potent sphingosine-1-phosphate-1 ($S_1P_1$) receptor agonists with minimal affinity for the $S_1P_2$ and $S_1P_3$ receptor subtypes\textsuperscript{19}. 
Oxadiazole derivatives (7) have been synthesized as a novel apoptosis inducer through caspase and cell based high throughput screening assay\textsuperscript{20}.

Where, $R = \text{H, 4-CF}_3$.

Rajanarendar et al.\textsuperscript{21} have synthesized imidazole, coumarin, isoxazole containing triheterocyclic compounds and their derivatives (8).
Encouraged by these reports, it was thought to keep 2-mercapto-1,3,4-oxadiazole as a principle nucleus and linked with substituted thiosemicarbazide and semicarbazide motif through thioether linkage.

Semicarbazide and thiosemicarbazide derivatives (9) of pyrimidine analogues have been synthesized and studied their antimicrobial activity.\(^{22}\)

\[ \text{X} = \text{O, Semicarbazide derivatives.} \]
\[ \text{X} = \text{S, Thiosemicarbazide derivatives.} \]

Thomas et al.\(^{23}\) synthesized 2-\{[4-hydroxy-8-(trifluoromethyl)quinolin-3-yl]carbonyl\} hydrazinecarboxamide and 2-\{[4-hydroxy-8-(trifluoromethyl)quinolin-3-yl]carbonyl\} hydrazinecarbothioamide derivatives which shows good antimicrobial and antitubercular activities.
Randhavane et al.\textsuperscript{24} synthesized thiosemicarbazide derivatives (12) by condensing compound (11) with aryl isothiocyanates using conventional and ultrasound method, and studied their antibacterial, antifungal, and antiviral HIV activities.

Ismail et al.\textsuperscript{25} have synthesized semicarbazide and thiosemicarbazide derivatives (13) and evaluated their antimicrobial activity.

\begin{align*}
\text{(11)} & \quad \text{Aryl isothiocyanate} \\
\text{1. conventional} & \quad \text{2. ultrasound}
\end{align*}

\begin{align*}
\text{(12)} & \\
\text{(13)} & \\
R = \text{H, o,m,p-CH}_3, \text{p-OCH}_3 \\
X = \text{O, Semicarbazide derivatives.} \\
X = \text{S, Thiosemicarbazide derivatives.}
\end{align*}
After an extensive literature survey it was thought to undertake the synthesis of 5-(3-pyridinyl)-1,3,4-oxadiazol-2-thiol, and condense it with chloroacetyl chloride in DMF/Ethanol and then with hydrazine hydrate to get intermediate 2-\{[5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl]sulfanyl\}acetohydrazide, which on further condensation with different aryl isocyanates and aryl isothiocyanates gave compounds of **series-1** and **series-2**. 5-(3-Pyridinyl)-1,3,4-oxadiazol-2-thiol condense with chloroacetyl chloride in DMF and then with hydrazine hydrate to get intermediate S-[5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl]hydrazinylethanethioate. Finally the resulted intermediate upon condensation with different aryl isocyanates and aryl isothiocyanates gave compounds of **series-3** and **series-4**.

**SERIES-1**

![Chemical structure](image)

N-aryl-2-\{[5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl]sulfanyl\} acetyl)hydrazinecarboxamide

**(VBA-1 to VBA-10)**
SERIES-2

N-aryl-2-({[5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}\nacetyl)hydrazinecarbothioamide

(VBB-1 to VBB-10)

SERIES-3

S-[5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl][2-(arylcarbamoyl)\nhydrazinyl]ethanethioate

(VBC-1 to VBC-10)

SERIES-4

S-[5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl][2-(arylcarbamothioyl)\nhydrazinyl]ethanethioate

(VBD-1 to VBD-10)
The synthesis of heterocyclic compound draws attention of chemist over the years mainly because of their important biological properties. Particularly, the role of β-lactam which are endowed with unique structure and potent antibacterial activity.

2-Azetidinone derivatives have been reported to possess anti-inflammatory\textsuperscript{26}, anticonvulsant\textsuperscript{27}, fungicidal\textsuperscript{28}, antibiotic\textsuperscript{29}, anticancer\textsuperscript{30-31}, antielastase\textsuperscript{32}, antiviral\textsuperscript{33}, antimicrobial\textsuperscript{34-35}, antitumor\textsuperscript{36}, anti-HCMV\textsuperscript{37} (Human cytomegalovirus inhibitor), antibacterial\textsuperscript{38} activities and their pharmacological interest.\textsuperscript{39}

Kumar et al.\textsuperscript{40} synthesized and characterized 2-azetidinone derivatives of type (14). These compounds have shown better anti-inflammatory and analgesic activities to the known β-lactam derivatives.

\begin{center}
\begin{tikzpicture}
\node[below left] at (0,0) {R = H, o-Cl, p-Cl, o-OCH\textsubscript{3}, p-OCH\textsubscript{3}, p-N(CH\textsubscript{3})\textsubscript{2}, p-OH, p-CH\textsubscript{3}, p-NO\textsubscript{2}};
\end{tikzpicture}
\end{center}

Desai et al.\textsuperscript{41} have synthesized some novel 2-azetidinone derivatives (15) by both microwave and conventional condensation method. The synthesized derivatives were screened for their \textit{in vitro} antibacterial activities and antifungal activities. The substitution of methoxy, chloro and polar group (phenolic or nitro moiety) at C-4 position of phenyl ring seems to be very important for antifungal activity.
Where, $R = 4\text{-NO}_2, 3,4,5\text{-}(\text{OCH}_3)_3, 2\text{-OH, 3-OH, 4-OH}$,

$2\text{-OCH}_3, 4\text{-OCH}_3, 2\text{-Cl, 3-Cl, 4-Cl}$,

Equation (15)

Singh et al.\textsuperscript{42} have synthesized a series of some novel 2-azetidinone derivatives by the reactions of N-salicylideneamines with diarylketenes generated from thermal decomposition of 2-diazo-1,2-diarylethanones, among which 4-chlorophenyl group on $\beta$-lactam ring nitrogen and 4-methylphenyl groups on $\beta$-lactam ring C-3 position (16) was found most active compound.
Kagthara et al.\textsuperscript{43} have synthesized some 2-azetidinone derivatives which showed a potential antitubercular activity. The synthesized compounds were tested \textit{in vitro} for their antitubercular activity against Mycobacterium tuberculosis H37RV. Orthochlorophenyl and 2,4-dichlorophenyl substituents with \( \text{2-}(1\text{H}-\text{Benzoimidazol-2-yl})-\text{N-}[3\text{-chilo-2-(substitutedphenyl)}-\text{4-oxo-azetidin-1-yl]}-\text{benzamide(17)} \) showed the highest activity against \textit{M. tuberculosis}.

![Chemical structure of compound 17](image)

Burnett et al.\textsuperscript{44} have synthesized a series of various C-3 mono- and disubstituted 2-azetidinones and tested for their cholesterol absorption inhibitory activity. The compound (3R,4S)-1,4-bis(4-methoxyphenyl)-3-ethyl-3-(3-phenyl propyl)-2-azetidinone (-)\text{SCH48461 (18)} showed very good activity in both \textit{in vivo} and \textit{in vitro} assay.
Based on the metabolism of the potent cholesterol absorption inhibitor (-) SCH48461 and structure-activity relationship information, Duger et al. have designed and evaluated (-) SCH53079. This compound was found to be equipotent to (-) SCH48461 in both the cholesterol-fed hamster and rhesus monkey assays. Importantly, (-) SCH 53079 was metabolically more stable than (-) SCH48461 and as desired had very low plasma levels and did not cause hepatic enzyme induction.

Aoyama et al. have designed a novel series of 3-Benzylazetidine-2-one derivatives and evaluated for their activity as chymase inhibitors.
Goel synthesized a novel series of 2-azetidinone (21) compounds via \( \{2 + 2\} \) cycloaddition (Staudinger) reaction of imines with ketenes. The synthesized compounds were evaluated for antihyperglycemic activity.

2-(1-Isopropyl-2-oxo-4-styryl-azetidin-3-yl)-isoindol-1,3-dione.

(21)
To search for other β-lactam lead compounds (22) as inhibitors of HIV-1 PR, Sperka et al.\textsuperscript{47} have applied a colorimetric micro titer plate method to screen a 126-member combinatorial monocyclic β-lactam library for inhibition of the enzyme. Using this high throughput screening method several of the inhibitors provided greater than 60% inhibition.

\[
\text{\begin{align*}
\text{CH}_2(C_2N_3H_4) & \text{CONH} \\
\text{C} & \text{N} \\
\text{N} & \text{C} \\
\text{C} & \text{O} \\
\text{COOBn} & \\
\text{O} & \text{H} \\
\text{C} & \text{N} \\
\text{C} & \text{R} \\
\text{O} & \text{H} \\
\text{N} & \text{S} \\
\text{N} & \text{CONH} \\
\text{CH}_3 & \text{Ar} \\
\text{Cl} & \end{align*}}
\]

1-[(4-Azido-benzylcarbamoyl)-phenyl-methyl]-4-oxo-azetidine-2-carboxylic acid benzyl ester.

\textbf{(22)}

Dighe et al.\textsuperscript{48} have synthesized a novel series of 2-azetidinone compounds (23) which showed a potential antitubercul ar activity. The synthesized compounds were tested \textit{in vitro} for their antitubercular activity against \textit{Mycobacterium tuberculosis} H37Rv.

\[
\text{\begin{align*}
\text{Ar} & \text{CONH} \\
\text{N} & \text{C} \\
\text{C} & \text{N} \\
\text{R} & \text{H'} \\
\text{H'} & \text{C} \\
\text{CO} & \text{N} \\
\text{CH}_3 & \text{Ar} \\
\text{Cl} & \end{align*}}
\]

Where, \(R = C_6H_5, 4\text{-FC}_6H_4, 3,4,5\text{-}(\text{CH}_3O)_2C_6H_2, 4\text{-}(\text{CH}_3)_2NC_6H_4, 2\text{-FC}_6H_4, 4\text{-ClC}_6H_4\)
Naphthalene containing drugs are available, such as Naftacillin, Naftifine, Tolnaftate, Terbinafine, etc. which play vital role in the control of microbial infection\textsuperscript{49}. Rokade et al\textsuperscript{50} has synthesized a novel series of 2-azetidinone derivatives (24). The synthesized derivatives were screened for their antimicrobial activities.

\begin{center}
\includegraphics[width=0.5\textwidth]{image1}
\end{center}

(24)

Ar = Phenyl, 2-Hydroxy Phenyl, 4-Methoxy Phenyl, 4-Methyl Phenyl, 3-Nitro Phenyl, 4-Chloro Phenyl, 4-Dimethylamino Phenyl, Fural.

Several pyrimidine based 2-azetidinones (25) have been synthesized and studied their antibacterial, antifungal, and antituberculosis against different microorganism\textsuperscript{51}.

\begin{center}
\includegraphics[width=0.5\textwidth]{image2}
\end{center}

(25) Where, R = 2-NO\textsubscript{2}, 3-NO\textsubscript{2}, 2-Cl, 3-Cl etc.
From the literature survey it has been observed that 2-azetidinone nucleus is biologically very active, hence various azetidinone based heterocycles have been synthesized with pyridinyl-oxadiazole with anticipation of augmented antimicrobial activities. First the Schiff’s bases were prepared by reacting the 2-{[5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetohydrazide with different aromatic aldehydes. Which was then cyclised with chloroacetyl chloride in the presence of triethylamine to afford azetidinones (series-5) and evaluated for their antimicrobial activities.

**SERIES-5**

![Chemical Structure](image)

N-(3-chloro-2-oxo-4-arylazetidin-1-yl)-2-{{5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetamide

*(VBE-1 to VBE-10)*
Series – 6

4-Thiazolidinones are always being an attraction for researchers because of its wide range of biological activities and industrial importance. The derivatives of 4-thiazolidinone nucleus have occupied a unique place in the field of medicinal chemistry due to wide range of pharmacological activities like antibacterial, antitubercular, anticancer, anticonvulsant and antifungal\textsuperscript{52}. 4-thiazolidinone also possesses good inhibiting activity towards COX-II and HIV Reverse transcriptase enzymes\textsuperscript{53}.

4-Thiazolidinone derivatives have been found to possess potent wide spectrum of activities like antibacterial\textsuperscript{54,55}, antifungal\textsuperscript{56-58}, anticonvulsant\textsuperscript{59}, anti-inflammatory\textsuperscript{60-63}, antituberculosis\textsuperscript{64-66}, antiviral\textsuperscript{67-72} and anticancer\textsuperscript{73-76}.

Rao et al.\textsuperscript{77} have synthesized some novel thiazolidinone derivatives (26), (27) and studied their anti HIV activity.

Where, $R_1=H, 5,6,8$-CH$_3$, $R_2=H,7$-CH$_3$, $R_3=2F,3$-NO$_2$, $R_4=6F$,
Where, $X = \text{N, CH,}$  
$Y = \text{N, CH,}$  
$R_1 = \text{Br,CH}_3\text{OCH}_3$  
$R_2 = \text{H, CH}_3,$  
$R_3 = \text{Cl,F},$  
$R_4 = \text{H, CH}_3,$  
$R_5 = \text{Cl,F},$

Shah et. al.\textsuperscript{78} have described a series of 2-(substituted phenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl-ureido]-5H/methyl/carboxy methyl -4-thiazolidinones \textsuperscript{(28)} and screened against different strains of bacteria and fungi.

\textsuperscript{(28)} Where, $R = \text{aryl,}$  
$X = \text{H, CH}_3\text{CH}_2\text{COOH}$
Kumar et al.\textsuperscript{40} have synthesized 3-[4’-(p-chlorophenyl)-thiazol-2-yl]-2-[(substituted thiazolidinone)-aminomethyl]-6-bromoquinazolin-4-ones (29). Some of the compounds have shown satisfactory anti-inflammatory activity.

![Chemical structure](image)

(29) Where, R = H, o,p-Cl, p-OH, p-CH\textsubscript{3}, p-N(CH\textsubscript{3})\textsubscript{2}, o,p-OCH\textsubscript{3},

Some researchers reported 2-(2,6-dibromophenyl)-3-heteroaryl-1,3-thiazolidin-4-one derivatives as shown in the (30). A positive correlation between size of the halogen substituent and HIV-RT inhibitory activity was taken as logic for the synthesis\textsuperscript{79}.

![Chemical structure](image)

(30)
Solomon et al. synthesized chloroquine analogues having a 1, 3-thiazolidin-4-one nucleus at the terminal side chain amino group of 4-aminoquinoline (31) shows antimalarial activity against *P. falciparum* in-vitro and some compounds have shown their activity comparable to standard drug were also evaluated against *P. yoelli* in vivo.

Upadhyay et al. have synthesized N-[(4-oxo-2-substituted aryl-1,3-thiazolidine)-acetamidyl]-5-nitroimidazoles from N-(arylidene amino acetamidyl)-5-nitroindazoles. The reactions were carried out by both conventional as well as microwave methods.

The compound (32) and (33) shows the maximum antibacterial activity against *Escherichia coli* and antifungal activity against *Fusarium oxysporum*.
Sparatore et al.\textsuperscript{82} has synthesized aromatic Schiff bases and 2,3-disubstituted-1,3-thiazolidin-4-one derivatives (34) as anti-inflammatory agents.

\[
\begin{align*}
\text{R} & \quad \text{N} \quad \text{C} \quad \text{O} \\
\text{Z} \quad \text{Y} \quad \text{X} \\
\text{Where, X = N; Y,Z = CH} & \quad \text{Z = CF; X,Y = CH} \\
\text{R = 3-CF}_3\text{,4-SO}_2\text{NH}_2,4-\text{SO}_2\text{CH}_3 \\
\end{align*}
\]

Desai et al.\textsuperscript{83} have carried out the microwave assisted synthesis of thiazolidinone from the Schiff’s bases (35) using thiolactic acid.

\[
\begin{align*}
\text{O} & \quad \text{C} \\
\text{N} \quad \text{S} \\
\text{H}_3\text{C} \\
\text{Cl} \quad \text{Cl} \\
\end{align*}
\]

Upendra et al.\textsuperscript{84} have synthesized 3-\{[(1E)-1-(5-chloro-3-methyl-1-benzofuran-2-yl) ethyldiene] amino\}-2-substituted phenyl-1,3-thiazolidin-4-one (36). Synthesized derivatives were evaluated for their antitubercular activity against \textit{mycobacterium tuberculosis} H37RV.
Where, \( R = \text{C}_6\text{H}_5, \text{C}_6\text{H}_4\text{OH}(\text{p}), \text{C}_6\text{H}_4\text{Cl}(\text{p}), \text{C}_6\text{H}_4\text{OCH}_3(\text{p}) \).

From literature survey it has been observed that 4-thiazolidinone nucleus is biologically very active, hence various thiazolidinone based heterocycles have been synthesized with pyridinyl-oxadiazole with anticipation of augmented antimicrobial activities. First the Schiff’s bases were prepared by reacting the 2-\{5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl\}sulfanylacetohydrazide with different aromatic aldehydes. Which was then cyclised with thioglycolic acid in the presence of anhydrous zinc chloride using Dean stark apparatus to get various thiazolidinones (series-6) and evaluated their antimicrobial activities.

SERIES-6

\[
\text{N-(4-oxo-2-aryl-1,3-thiazolidin-3-yl)-2-\{5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl\}sulfanylacetamide} \\
(VBF-1 \text{ to } VBF-10)
\]
Series – 7 & 8

The quinazoline ring skeleton is widely found in alkaloids and many biologically active compounds\textsuperscript{85}. Quinazoline a nitrogenous heterocycle, proved to possess a multitude of biological potency including anticancer\textsuperscript{86}, antitubercular\textsuperscript{87}, antiinflammatory\textsuperscript{88}, anticonvulsant, CNS depressant and anti-HIV agents\textsuperscript{89}.

Domarkas et al.\textsuperscript{90} synthesized quinazolinone derivatives of type (37) based on combi-targeting concept and their EGFR (epidermal growth factor receptor) inhibitory activities have been studied.

\[
\begin{align*}
\text{R}_1 & = \text{H, CH}_3 \\
\text{R}_2 & = \text{H,ClEtNHCO,ClEtN(NO)CO} \\
\text{X} & = \text{CH}_3, \text{Cl, Br}
\end{align*}
\]

(37)

A series of C-6 alkynyl-substituted 4-anilinoquinazoline derivatives have been prepared and bioactive assay for \textit{in vitro} EGFR kinase inhibition demonstrated that compound (38) was found potent with an IC\textsubscript{50} of 14 nM\textsuperscript{91}.

\[
\begin{align*}
\text{F} \\
\text{Cl} \\
\text{HO} \\
\text{N} \\
\text{N}
\end{align*}
\]

(38)

A series of N9-substituted 2,4-diaminoquinazolines (39) were synthesized and evaluated as inhibitors of \textit{pneumocystis carinii} (pc) and \textit{Toxoplasma gondii} (tg) dihydrofolate reductase (DHFR)\textsuperscript{92}.
Previous studies with the anilinoquinazoline epidermal growth factor receptor (EGFR) irreversible inhibitor $[^{11}\text{C}]$-MLo3 demonstrated a rapid metabolism of the traces, which led to its low in vivo accumulation in EGFR over expressing tumors. To enhance tumor uptake the chemical structure of the compound was modified and novel group of EGFR inhibitors of type-(40a-c) with a wide range of chemical reactivity’s have been synthesized.

A novel series of 2-styrylquinazoline-4(3H)-ones type (41), (42) which inhibited tubulin polymerization and the growth of L1210 murine leukemia cells were observed. Its extensive SAR study suggests that the entire quinazolinone structure is required for antitumor activity against murine solid tumors as well as human tumor xenografts.
Saleh et al.\textsuperscript{95} have synthesized novel 3H-quinazoline-4-one derivatives containing a pyrazolinone, pyrazole and pyrimidone ring with the aim of obtaining some novel heterocyclic systems with potentially enhanced biological properties.

\[
\text{N-\{4-[(3-Iodophenyl)amino]quinazoline-6-yl\}-2-chloro acetamide (43)}
\]

derivatives have been synthesized, their potencies toward the EGFR were studied and established their potential as positron emission tomography (PET) against for molecular imaging of EGFR positive tumor\textsuperscript{96}.

\[
\text{(43)}
\]

Foote et al.\textsuperscript{97} synthesized 1-acetanilide-4-aminopyrazole substituted quinazolines as selective inhibitors of Aurora A kinase with anti-tumor activity.

Quinazoline derivatives (44) have been launched for the treatment of a non small cell lung cancer (NSCLC) and also its analogues inhibiting tyrosine kinase activity & restrictive receptor catalytic activity, auto phosphorylation and its engagement with signal transducers\textsuperscript{98}. Its novel route of synthesis has also been reported\textsuperscript{99}.

- 39 -
US FDA approved the first EGFR inhibitor Iressa, for the treatment of lung cancer, highlighting the importance of 4-anilinoquinazolines in medicine\textsuperscript{100}.

A series of 4-dimethylamino-butenoic acid [4-(3,6-dioxo-cyclohexa-1,4-dienylamino)-7-ethoxy-quinazolin-6-yl]-amide derivatives (45) were prepared. These compounds have two independent reactive centers and were designed to function as dual irreversible inhibitors of the kinase domains of both epidermal growth factor receptor (EGFR) and Vascular endothelial growth factor receptor-2 (VEGFR-2) where each reactive center targets a different, non-conserved, cysteine residue located in the ATP binding pocket of these enzymes. The compounds contain a 6-(4-(dimethylamino) crotonamide) Michael acceptor group that targets Cys-773 in EGFR and a 4-(amino-[1,4] benzoquinone) moiety that targets Cys-1045 in VEGFR-2. \textit{In vitro} studies indicated that most of these compounds are relatively potent inhibitors of each enzyme.\textsuperscript{101}
A series of 4-aminoquinazoline derivatives have been synthesized, characterized and evaluated for their ability to inhibit tumor cells by MTT assays. Among them, compounds (46) and (47) were found as potent inhibitors, with IC₅₀ values ranging from 5.8 to 9.8 µM, in *in vitro* assay¹⁰².

Quinazoline derivatives (48) including urea, thiourea, urethane and acylthiourea groups were found highly potent compounds as the PDFG receptor autophosphorylation inhibitor. Further synthesis and biological evaluation of these derivatives showed receptor selectivity between PDGF receptor and e-kit receptor¹⁰³,¹⁰⁴.
Where X = N, CH
Y = O, S
Z = NH
R = OCH₃, C₆H₅, Cyclohexyl etc.

(48)

3-phenethyl-2-furan-2-yl-3H-quinazolin-4-one, NPS 53574 (49) has been prepared and its SAR study led to the discovery of novel potent CaR antagonists¹⁰⁵,¹⁰⁶ with acceptable pharmacokinetic properties. In this context structure-activity relationship studies¹⁰⁷, focused on identification of the active pharmacophore fragments in a single high throughput screening calcilytic hit, resulted in the discovery of potent calcium receptor antagonists, substituted 3H-quinazolin-4-ones (50).

(49)                                                      (50)

Where, R₁ = 6,7-F, 6,7-Cl, 5-Me
R₂ = H, 3-Cl, 3-F
R₃ = OH,

Al-Rashood et al.¹⁰⁸ synthesized novel series of quinazoline analogs as new leads for anticancer drugs.
Despite being withdrawn from clinical studies because of unpredictable nephrotoxicity, the quinazolinone based antifolate CB 3717 established the principle of antitumor chemotherapy with a specific inhibitor of thymidylate synthesis (TS) by showing responses in phase I/II clinical trials against breast, ovarian and liver cancer. A search for more soluble analogues devoid of renal toxicity and the decrease in aqueous solubility observed with lipophilic quinazoline antifolates led to the discovery of 2-methyl quinazoline analogue.

Quinazoline derivatives of type (51) have been synthesized and studied for their insecticidal and antimicrobial activities. Among the synthesized compounds bearing naphthyl substituents showed mortality of insect at 190 minutes while standard compounds exhibited at 280 minutes at a concentration of 5 g/L. The other compounds of this series also shows antibacterial and antifungal activity in moderate to its properties.

\[
\text{Where, } R = \text{Different heterocycles}
\]

Blum et al. designed, synthesized, studied and found aminoquinazolines (52) as TRPV1 antagonist.

\[
\text{Where } R = \text{H, Me, CH}_2\text{OH etc.}
\]
Quinazolone bearing imidazoline, thiourea and amido moieties at their position-3 have been synthesized and studied their antibacterial, antitubercular, anticancer and anti-HIV activities\textsuperscript{117}.

4-[4-(N-Substituted(thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives (53) were synthesized as potent inhibitors of the phosphorylation of platelet derived growth factor receptor (PDGFR). Structure activity relationships in the (thio) urea moiety, the phenyl ring itself, the linker between these two moieties, and the piperazine moieties were investigated\textsuperscript{118}.

\[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{H}_3\text{CO} \\
\text{NH} & \quad \text{R} \\
(\text{53}) & \\
\text{Where } X = \text{S or O}
\end{align*}
\]

Urea derivatives possess wide therapeutic activities such as antithyroidal\textsuperscript{119}, hypnotic and anaesthetic\textsuperscript{120}, antibacterial\textsuperscript{121}, diuretic\textsuperscript{122} and anthelmintics.

2-Substituted amino pyrido [2,3-d] pyrimidin-7-y1 ureas (54) have been found as a novel class of soluble, potent, broadly active tyrosine kinase (TK) inhibitors\textsuperscript{123}.

\[
\begin{align*}
\text{Cl} & \\
\text{R}_1\text{NH} & \\
\text{N} & \\
\text{N} & \\
\text{O} & \quad \text{NH} \\
(\text{54}) & \\
\text{Where } R_1 = (\text{CH}_2)_3\text{NEt}_2, (\text{CH}_3)_3\text{NEt}_2 \\
\text{R} = \text{t-Bu}
\end{align*}
\]
Khadse et al.\textsuperscript{124} have prepared following type (55) of thiourea derivatives possessing antituberculosis activity at 1.56 $\mu$g/ml against \textit{M. tuberculosis}.

\begin{equation}
\text{(55)}
\end{equation}

Hazarika et al.\textsuperscript{125} synthesized biologically active thiourea based (56) heterocycles.

\begin{equation}
\text{(56)}
\end{equation}

Where, $X = O, S$

$Ar = C_6H_5$

From the above it is found that 4-chloroquinazoline is important synthetic intermediate as it can be further explored through nucleophilic attack at C-4 position. For example compound (57) and intermediate in the synthesis of AX7593 a quinazoline derived photo affinity probe for EGFR\textsuperscript{126}.

\begin{equation}
\text{(57)}
\end{equation}

Marvania et al.\textsuperscript{127} have synthesized a series of quinazoline compounds (58) bearing a urea or hydrazinecarboxamide linker for antitumor evaluation.
Madapa et al.\textsuperscript{128} have synthesized a 6-ureido-4-anilinoquinazolines (59) and their \textit{in vitro} antimalarial activity against chloroquine-sensitive \textit{P. falciparum} have been examined.

Encouraged by these observations it was tempted to synthesize various urea, thiourea derivatives of sulphur bridged quinazoline-oxadiazole motif. 4,7-Dichloro-6-nitro-quinazoline was condensed with 5-(3-pyridinyl)-1,3,4,-oxadiazol-2-thiol and N-methylpiperazine sequently, the resultant motif was then reduced and condensed with various aryl isocyanates / isothiocyanates to get the compounds of \textbf{series-7 & series-8} which were screened for their antimicrobial activities.
SERIES-7

![Chemical Structure](image1)

1-(7-(4-Methylpiperazin-1-yl)-4-\{5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yI\}sulfanyl)quinazolin-6-yl)-3-arylurea

(VBG-1 to VBG-10)

SERIES-8

![Chemical Structure](image2)

1-(7-(4-Methylpiperazin-1-yl)-4-\{5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yI\}sulfanyl)quinazolin-6-yl)-3-arylthiourea

(VBH-1 to VBH-10)
**Series – 9 & 10**

s-Triazine derivatives are an important class of compounds having anticancer\textsuperscript{129}, antitumor\textsuperscript{130}, antiviral\textsuperscript{131} and antifungal\textsuperscript{132} activities. These compounds have been used in the treatment of depression\textsuperscript{133} and hence received a considerable therapeutic importance. These are valuable bases for estrogen receptor modulators\textsuperscript{134} and also used as bridging agents to synthesize herbicides.\textsuperscript{135} Further substituted s-triazines have been used as NLO materials, which have a wide range of applications in optoelectronics and telecommunications\textsuperscript{136}. It has been reported that substituted s-triazine derivatives possess antibacterial activity\textsuperscript{137} and nowadays, research on new substances possessing antibacterial activity has considerable attention owing to the continuous increase in bacterial resistance\textsuperscript{138}.

s-Triazine derivatives of type (60, 61, 62) have been synthesized and their MIC values were carried out for three representative against Gram positive and Gram negative microorganisms\textsuperscript{139}.

Where, R = H, Cl, F, CH\textsubscript{3}, OCH\textsubscript{3}  
**(60)**

Where, R = H, Cl, OCH\textsubscript{3}  
**(61)**
A new series of aromatic benzene sulfonamides incorporating 1,3,5-triazine moieties in their molecule have been synthesized (63, 64, 65) and tested for the inhibition of three physiologically relevant Carbonic Anhydrase (CA) isozymes. SAR has also been discussed\textsuperscript{140}.

Menicagli et al.\textsuperscript{141} have synthesized s-triazines (66, 67, 68), studied its \textit{in vitro} cytotoxic activities and concluded that synthesized derivatives are lead entities for anti cancer research.
1,3,5-Triazines are known for their applications in different fields, including the production of herbicides and polymer photostabilizers\textsuperscript{142}. Some s-triazines display important biological properties, for example hexamethyl melamine (HMM) \textsuperscript{(69)} and 2-amino-4-morpholino-s-triazine \textsuperscript{(70)} are used clinically due to their antitumor properties to treat lung, breast and ovarian cancer respectively\textsuperscript{143}. Hydroxymethyl pentamethyl melamine \textsuperscript{(71)} is also the hydroxylated metabolite which corresponds to the major active form of HMM\textsuperscript{144}. Recently, significant aromatase inhibitory activities were observed for s-triazines of general structure \textsuperscript{(72)}. For the similar general structure \textsuperscript{(73)} antitumor activity in human cancer and murine leukaemia cell lines were also observed\textsuperscript{144}.
Gilbert et al.\textsuperscript{145} designed and synthesized a series of melamine based nitro heterocycles (74) with aim of selectively delivering compounds to the parasites. Some of the compounds were also evaluated \textit{in vivo} in Rodent models Tryparosoma brucei. T. brucei rhodesiense which showed pronounced activity and in two cases were found curative without overt signs of toxicity.

\[
\begin{align*}
\text{NH}_2 \\
\text{H}_2\text{N} & \quad \text{N} \\
\text{N} & \quad \text{NH} \\
\text{N} & \quad \text{N} \\
\text{NO}_2 & \quad \text{Cl} \\
\end{align*}
\]

\textbf{(74)}

Where \(X=\text{O, S}\)

Mulwad et al.\textsuperscript{146} have synthesized, characterized and studied antibacterial activity of s-triazine based heterocycles type (75a&b).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{NH} & \quad \text{NH} \\
\text{S} & \quad \text{S} \\
\end{align*}
\]

\textbf{(75a)}

Where \(R = R_1 = \text{CH}_3\)
Several specific synthetic protocols were developed for the preparation from cyanuric chloride derivative of a range of symmetrical and unsymmetrical di and tri-substituted 1,3,5-triazine containing alkyl, aromatic, hindered, chiral and achiral hydroxyalkyl, ester and imidazole groups via sequential nucleophilic substitution at the C-Cl bond by C-O, C-N and C-S bonds (76, 77, 78). 

\[ \text{(76)} \quad \text{(77)} \quad \text{(78)} \]

Where \( R_1 = \text{PhS} \)  
\( R = \text{PhCH}_2\text{S, Ph} \)  
\( R_2\text{N} = \text{CH}_3\text{CH}_2\text{N}^- \)

s-Triazine derivatives of type (79) have been synthesized and studied for their inhibition Ki values (nm) in stable cell lines transacted with human CRF\textsubscript{1} receptors. \cite{148}
Where $R = \text{Me, Et, } \text{NR}_1\text{R}_2 = \text{PhCH}_2\text{CH}_2\text{NMe, (nBu)}_2\text{N}$.  
$X = 2,4,6$-$\text{Me}_3$, $2,4$-($\text{OMe}$)$_2$ etc.

Nishikagi et al.\textsuperscript{149} synthesized several 2,4-diamino-6-(5-nitro-2-furyl)-s-triazines \textsuperscript{(80)} and 2,4-disubstituted 6-[(5-nitro-2-furyl)-vinyl]-s-triazine \textsuperscript{(81)} and studied their \textit{in vitro} antibacterial activity against Gram +Ve and Gram −Ve organisms.

As 1,3,5-triazine based estrogen receptor (ER) modulators are modestly selective for ER$\beta$ subtype among which Henke et al.\textsuperscript{150} synthesized compound \textsuperscript{(82)} which displayed modest potency and selectivity for ER$\beta$ vs ER$\alpha$. 

\textsuperscript{(80)}
\textsuperscript{(81) where } R_1, R_2 = \text{NH}_2
\textsuperscript{(82)}

\textsuperscript{- 53 -}
3,4-Dimethoxyphenylethyl-1,3,5-triazinyl thiourea derivatives (83) were prepared by condensation of 2,4,6-trichloro-1,3,5-s-triazine with 4-hydroxy coumarin, 3,4-dimethoxy phenyl ethyl thiourea and various substituted phenyl urea/thiourea and tested for their antibacterial and anti-HIV activities against different microorganisms\textsuperscript{151}.

![Diagram of 3,4-Dimethoxyphenylethyl-1,3,5-triazinyl thiourea derivatives (83)](image_url)

\[ X = O \& S; \text{Ar} = \text{C}_6\text{H}_5 \]

Parekh et al.\textsuperscript{152} have prepared compounds of type (84). These derivatives exhibited antimicrobial activity against the various strains of bacteria and fungi.

![Diagram of Parekh's compounds (84)](image_url)

\[ \text{Where } R = \text{Aryl} \]

Parikh et al.\textsuperscript{153} have prepared s-triazine derivatives of type (85), which exhibited antibacterial and antifungal activity.
Regarding “traditional” industrial applications 1,3,5-triazines have been used as versatile intermediates to build up agrochemical (86) as well as pharmaceutical (87).

In addition, 1,3,5-triazines are building blocks for the manufacturing of performance chemicals, e.g. reactive dyes (86), polymers and optical brighteners (87).

Kavash et al. (88) have prepared s-triazine of type (88) anticipating anti-HIV activity.
Kuo-Yi Chen and Chin-The Huang have synthesized and studied phenoxy propionic acid derivatives (89) based on the 1,3,5-triazine with certain biological activity in agricultural applications such as a herbicide and growth regulator.

\[
\text{Cl} \quad \text{N} \quad \text{N} \\
\text{Cl} \quad \text{O} \quad \text{O} \\
\text{CH}_3 \quad \text{OMe} \\
\text{(89)}
\]

Paquin et al. have designed and synthesized s-triazine derivatives of type (90) as a novel class of histone deacetylase inhibitors. Some of the compounds among this series showed IC\textsubscript{50} values below \(\mu\text{M}\) range, also significantly reduce tumour growth in human tumour xenograft models in mice.

\[
\begin{aligned}
\text{N} & \quad \text{N} \\
\text{R}_1 & = \text{R}_2 = \text{NH}_2 \\
\text{(90)}
\end{aligned}
\]

Where \(\text{R}_1 = \begin{array}{c}
\text{NH} \\
\text{O} \\
\text{N}
\end{array}\), \(\text{R}_2 = \begin{array}{c}
\text{NH}_2 \\
\text{N}
\end{array}\).

A. Gopalsamy and Hui Yang have synthesized 6-amino-2,4-dioxo-3,4-dihydro-1,3,5-triazine derivatives for their herbicidal activities.

Sareen et al. synthesized some fluorinated s-triazine derivative (91) and evaluated their antimicrobial activity.
Gupta et al.\textsuperscript{163} have synthesized s-triazine derivatives (92) and studied their antimicrobial activity.

Gupta et al.\textsuperscript{163} have synthesized s-triazine derivatives (92) and studied their antimicrobial activity.

Srinivas et al.\textsuperscript{164} incorporated various groups on s-triazine to understand their role towards antibacterial activity and derived conclusion.

A series of 2,4,6-trisubstituted 1,3,5-triazines (93) were synthesized and evaluated for their \textit{in vitro} antimalarial activity against \textit{P. falciparum}. Some of the compound showed MIC in the range of 1 to 2 $\mu$g/mL, which is comparable to cycloguanil\textsuperscript{165}.

\textbf{(91)}  
\textbf{(92)} Where R = substituted phenyl

\textbf{(92)} Where R = substituted phenyl

\textbf{(93)} Where R = various heterocycles
Player et al.\textsuperscript{166} have synthesized 4-(benzothiazol-6-yl-amino)-6-(benzyl-isopropyl-amino)-1,3,5-triazin-2-ol, which exhibited low nanomolar potency in the \textit{in vitro} enzyme inhibition essay (IC\textsubscript{50} = 18 nM) and submicromolar inhibitor activity also demonstrated good \textit{in vitro} activity against a panel of growth factor receptor tyrosine kinases.

Aminoxy containing 2,4,6-trisubstituted-s-triazines (94) have been synthesized and studied their antibacterial and antifungal activity\textsuperscript{167}.

\begin{equation}
\begin{array}{c}
\text{R, R' = succinimidoxy} \\
\end{array}
\end{equation}

Alterations of the Imidoyl thiourea (ITU)\textsuperscript{168} complexes serendipitously led to the synthesis of a new diaryltriazine (DATA) class of compounds\textsuperscript{169,170}. Potent DATA NNRTIs inhibited wild-type HIV-1 RT at nanomolar concentrations EC\textsubscript{50}.

\begin{equation}
\begin{array}{c}
\text{DATA derivative} \\
\text{Triazinyl amine analogue} \\
\end{array}
\end{equation}
Based on these surveys, it was planned to consider s-triazine as a basic pharmacophore using the most practical method based on the less expensive reagent cynuric chloride by successive, controlled nucleophilic substitution of each chloride, taking advantage of decreasing reactivity with number of substituents which led us to consider s-triazine nucleus as a principle moiety.

Recently the focal point has been on the motif Het–NH–Ph–U, where Het is an aromatic heterocycle and U is an unsaturated, hydrophobic group including investigations with triazinyl derivatives. The result is several NNRTIs in the 2–20nM range with negligible cytotoxicity and auspicious predicted pharmacological properties. Some specific HIV-1 RT inhibitory profile have been described including urea analogues of PETT (Phenyl Ethyl Thiazolyl Thiourea) derivatives and the series includes derivatives with thiourea and an ethyl linker and conformationally restricted analogues.

\[
\begin{align*}
\text{PETT analogues} \\
\text{A series of novel 1-phenyl-3-\{4-[(2e)-3-phenylprop-2-enoyl] phenyl\}-thiourea and urea derivatives (95) were synthesized and their anti-nociceptive activities were determined.}
\end{align*}
\]

Where X = S, O
Y = H, 4-Cl, 4-OMe etc.
Urea derivatives of type (96) have been synthesized and studied their insecticidal activity against *mythimna separata*[^176].

![Diagram of molecule 96](image)

Where $R^1 = H, \text{CH}_3, \text{CN}$, etc.
$R^2$ = various heterocycles

1,3 Diaryl ureas (97) have been designed, synthesized as COX-1 and COX-2 inhibitors[^177].

![Diagram of molecule 97](image)

Where $X = H, \text{F}, \text{Cl}, \text{Me}, \text{OMe}$, etc

A novel series of potent scientific HIV-1 inhibitory compounds were described. Among which N-(2-phenethyl)-N’-(2-thiazolyl)-thiourea (98) was found to inhibit HIV-1 RT using rCdG as the template with an IC$_{50}$ of 0.9 µM[^178].

![Diagram of molecule 98](image)

A novel thiourea compound of type (99) targeting the non-nucleoside inhibitors binding pocket (NNIBP) of HIV-1 reverse transcriptase (RT) was rationally designed using a computer model of the NNI binding pocket[^179].

![Diagram of molecule 99](image)

Where, $R = 2-\text{OCH}_3, 5-\text{OCH}_3, 2-\text{F}$ etc.
Solankee et al.\textsuperscript{180} have synthesized s-triazine based derivatives (100) which were screened for their antibacterial activity by using the disc-diffusion method.

\[
\text{Where, } R = \begin{array}{c}
\text{NH}_2 \\
\text{R' - Diff. sub. phenyl}
\end{array}
\]

(100)

Kumar et al.\textsuperscript{181} have synthesized hybrid 4-anilinoquinoline triazine derivatives (101), (102) and evaluated in vitro for their antimalarial activity against the CQ-sensitive 3D7 strain of \textit{P. falciparum}.

\[
\begin{array}{c}
\text{R}_1 = \text{piperidino, anilino, o,m,p-toluidino,} \\
\text{R}_2 = \text{diff. sub. arylamine & aliphatic amines}
\end{array}
\]

(101) (102)

Kumar et al.\textsuperscript{182} have synthesized a new series of hybrid 9-anilinoacridine triazines (103) using the cheap chemicals 6,9-dichloro-2-methoxy acridine, cyanuric chloride and evaluated in vitro for their antimalarial activity against CQ-sensitive 3D7 strain of \textit{Plasmodium falciparum}.
Ravichandran et al.\textsuperscript{183} studied and showed comfa approach for predicting anti HIV activity of thiourea analog PETT.

Chikhalia et al.\textsuperscript{184} incorporated various thioureas on s-triazinyl coumarin motif, studied their anti HIV against mutant strains and derived conclusion.

It is very much significant to have a close view on the structural parts of proposed compound which contains three substitutions. One with single atom (oxygen) linker ring their by mimicking butterfly model as coumarin ring and triazine core itself positioned as two different wings as NNRT1.

Another important structural feature is the incorporation of 5-(3-pyridinyl)-1,3,4-oxadiazole-2-thiol at 6\textsuperscript{th} position of triazine through thioether linkage and various aryl urea/thioureas as it is very much acceptable that this scaffold may be represented as NNRTIs (tight binding thioureas/urea part) as well as antibacterial agents. Considering these findings we were tempted to synthesize novel s-triazine based heterocycles. The representative compounds are shown in \textbf{series-9} and \textbf{series-10}.  

2-(N,N-dimethylamino)-4-[4-{1-(aryl)carboxamido}-piperazinyl]-6-
[5-(3-pyridinyl)-1,3,4-oxadiazolyl]-2-thio] -s-triazine

(VBI-1 to VBI-10)

2-(N,N-dimethylamino)-4-[4-{1-(aryl)carbothioxamido}-piperazinyl]-6-
[5-(3-pyridinyl)-1,3,4-oxadiazolyl]-2-thio] -s-triazine

(VBJ-1 to VBJ-10)
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