SECTION-1.1 INTRODUCTION AND SIGNIFICANCE OF THE HETEROCYCLIC COMPOUNDS

Heterocycle compounds possess a cyclic structure with two or more different kinds of atoms in the ring. Organic heterocyclic compounds contain at least one carbon atom; all atoms other than carbon are considered heteroatom. Carbon is still by far the most common ring atom in heterocyclic compounds, but as the number and variety of heteroatom in the ring increase there is a steady transition to the expanding domain of inorganic heterocyclic systems. The rings can be of any size, from three members upwards and the heteroatom can be drawn in almost any combination from a large number of elements. The number of possible heterocyclic system are limitless. An enormous number of heterocyclic compounds are known and this number is increasing rapidly.

Heterocycles, a classical divisions of organic chemistry, are of immense importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are heterocyclic in nature. One striking structural features inherent to heterocycles, which continue to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in defined three dimensional representations. For more than a century, heterocycles have constituted one the largest areas of research in organic chemistry. They have contributed to the development of society from a biological and industrial point of view as well as to the understanding of life processes and to the efforts to improve the quality of life. Among the approximately 20 million chemical compounds identified by the end of the second millenium, more than two-thirds are fully or partially aromatic, and approximately half are heterocyclic. The presence of heterocycles in all kinds of organic compounds of interest in biology, pharmacology, optics, electronics, material sciences, and so on is very well known. Between them, sulfur and nitrogen-containing heterocyclic compounds have maintained the
interest of researchers through decades of historical development of organic synthesis.\textsuperscript{1} However, heterocycles with other heteroatoms such as oxygen\textsuperscript{2}, phosphorus\textsuperscript{3} and selenium\textsuperscript{4} also appears.

Many natural drugs\textsuperscript{5-8} such as quinine, papaverine, emetine, theobromine, theophylline, atropine, procaine, codeine, morphine and reserpine are heterocycles. Almost all the compounds we know as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole, azidothymidine, barbiturates, antipyrine, captopril and methotrexate are also heterocycles. Some dyes (e.g. mauveine), luminophores, (e.g. acridine orange), pesticides (e.g. diazinon) and herbicides (e.g. paraquat) are also heterocyclic in nature. All these natural and synthetic heterocyclic compounds can and do participate in chemical reactions in the human body. Furthermore, all biological processes are chemical in nature. Such fundamental manifestations of life as the provision of energy, transmission of nerve impulses, sight, metabolism and the transfer of hereditary information are all based on chemical reactions involving the participation of many heterocyclic compounds, such as vitamins, enzymes, coenzymes, ATP, nucleic acids and serotonin.\textsuperscript{9}

Why does nature utilize heterocycles? The answer to this question is provided by the fact that heterocycles are able to get involved in an extraordinarily wide range of reaction types depending on the pH of the medium, they may behave as acids or bases, forming anions or cations. Some interact readily with electrophilic reagents, others with nucleophiles, yet others with both. Some are easily oxidized, but resist reduction, while others can be readily hydrogenated but are stable toward the action of oxidizing agents. Certain amphoteric heterocyclic systems simultaneously demonstrate all of the above-mentioned properties. The ability of many heterocycles to produce stable complexes with metal ions has great biochemical significance. The presence of different heteroatoms makes tautomerism ubiquitous in the heterocyclic series. Such versatile reactivity is linked to the electronic distributions in heterocyclic molecules. Evidently, all the natural products and the synthetic drugs mentioned above are good
examples of nature’s preference for heterocycles whose biological activity cannot be determined by one or a combination of two or three of the above-mentioned properties.

The following is a good example of how man learnt to imitate nature by incorporating heterocycles into drug molecules to enhance their biological activity: Red sulfanilamide and the less toxic white sulfanilamide (second generation) were the first sulfa drugs, and these contained no heterocyclic fragments. However, the intensive research work that followed their discovery demonstrated that modification of the \( p \)-amino benzene sulfonamide structure by the introduction of heterocyclic substituents into the amide markedly enhanced their biological activity. Many derivatives of this type, including the well-known sulfathiazole, sulfadimidine, sulfadimethoxine and others, were gradually introduced into clinical treatment. Sulfa drugs are highly efficient against many bacterial species fever and other diseases have been successfully treated by such preparations. With the passage of time, however the increasing evidence of clinical toxicity of these drugs has led to a diminution in their use, and they have been replaced by penicillin, cephalosporin and, more recently, quinolone drugs which are all heterocyclic in structure. The role played by the heterocycle imidazole in the interaction of enzymes with substrates is perhaps the most illustrative example of the importance of heterocycles in biochemical systems.

Synthetic heterocycles have widespread therapeutic uses such as analgesics, antiinflammatory, antibacterial, antifungal, hypnotics, anticancer, anticonvulsant, antidepressant, antimalarial, antitumor, antiviral, anthelmintic, trypanocidal and insecticidal agents.\(^{10-16}\)

The are larger number of synthetic heterocyclic compounds with other important applications such as fungicides, herbicides, anticorrosive agents, photostabilizers, agrochemicals, dyestuff, copolymer, photographic developers, sensitizers, booster agent, antioxidant in rubber and flavouring agent.\(^{17-22}\)

Pyrimidine (cytosine, thymine, and uracil) and purine (adenine and guanine) derivatives are monocyclic and bicyclic heterocycles with two and
four nitrogen atoms, respectively. They are key components of the deoxyribonucleic acid (DNA) molecules and participate directly in the encoding of genetic information. They also pass information to the related ribonucleic acid (RNA) molecules that control, in protein synthesis, the sequence of amino acids.\textsuperscript{23,24} The need for minute quantities of accessory dietary factors, the vitamins is well-known. Vitamins in the B group thiamine, folic acid, riboflavin, cyanocobalamine, are nitrogen-containing heterocycles and function either as coenzymes or their precursors. Other vitamins such as ascorbic acid (vitamin C) and α-tocopherol (vitamin E) are oxygen heterocycles.\textsuperscript{25-27}

The essential amino acid proline, histidine and tryptophan, photosynthesizing pigment chlorophyll; the oxygen transporting pigment haemoglobin, the hormones kinetin, heteroauxin, neurotransmitter serotonin, histamine respectively are successful application of heterocyclic compounds.\textsuperscript{28-30}

In conclusion, it can be questioned why it is specifically appropriate to emphasize the role of heterocycles, since analogies to the roles of other classes of organic compounds are easily found. In fact, dyes, luminophores, pesticides, herbicides and drugs do not necessarily have to be heterocyclic in structure. In a similar fashion there are many common features in chemistry and physics between such related compounds as pyrrole and aniline, or between pyridine and nitrobenzene. Nevertheless, nature selected the heterocycles pyrrole and pyridine, and not the homocycles aniline and nitrobenzene, as the basis of most essential biological systems. We now know the reason for this: the introduction of a heteroatom into a cyclic compound imparts new properties. Heterocycles are chemically more flexible and better able to respond to the many demands of biochemical systems. The constantly accelerating rate of research and development in heterocyclic chemistry suggested that enormous numbers of heterocyclic systems are well known and this number is increasing very rapidly.
Significance of the heterocyclic compounds

Everything of the creation has its own significance and nothing is useless. However, some of products have more importance than others and also, these important things are produced in large amount and with varieties. Heterocyclic compounds are such type of important things of creation. It has a great importance in various fields. Some of the importance in various areas are summarized below.

**Antibiotics**

The word *antibiotics* comes from the Greek anti (against) and bios (life). Antibiotics are drugs that either destroy bacteria or prevent their reproduction. Antibiotics that kill bacteria are called *bactericidal* and the ones that stop the growth of bacteria are called *bacteriostatic*.

Antibacterial antibiotics can be categorized on their target specificity:

- Narrow-spectrum antibiotics target particular types of bacteria, such as Gram-negative or Gram-positive bacteria.
- Broad-spectrum antibiotics affect a wide range of bacteria.
- Antibiotics which target the bacterial cell wall\(^{31}\) (penicillins and cephalosporins), or cell membrane\(^ {32}\) (polymixins), or interfere with essential bacterial enzymes (quinolones and sulfonamides) usually are bactericidal in nature.
- Antibiotics which target protein synthesis such as the aminoglycosides, macrolides and tetracyclines are usually bacteriostatic.\(^ {33}\)

**β-Lactam antibiotics**

β-Lactam antibiotics are a broad class of antibiotics that include penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems,\(^ {34}\) i.e. any antibiotic agent that contains a β-Lactam nucleus in its molecular structure. They work by attacking the cell walls of bacteria. They are the most widely used group of antibiotics. Bacteria often develop resistance to β-Lactam antibiotics by synthesizing Beta-Lactamase, an enzyme that attacks the β-Lactam ring. To overcome this resistance, β-
Lactam antibiotics are often given with β-Lactamase inhibitors such as clavulanic acid.

β-Lactam antibiotics are useful and frequently prescribed an antimicrobial agent that shares a common structure and this class includes penicillins G (1) and V (2), which are active against susceptible gram-positive cocci. Penicillins work by binding to specific penicillin-binding proteins (PBPs) in the bacterial cell wall and inhibiting the final stage of bacterial cell wall synthesis, resulting in autolysis of the bacterial cells by autolysin enzymes.

![Chemical structures of penicillin G (1) and penicillin V (2)]

β-Lactam antibiotics are indicated for the prophylaxis and treatment of bacterial infections caused by susceptible organisms. At first, β-lactam antibiotics were mainly active only against Gram-positive bacteria, yet the recent development of broad-spectrum β-lactam antibiotics active against various Gram-negative organisms has increased their usefulness.

β-Lactam antibiotics are bactericidal, and act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity, especially in Gram-positive organisms. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by transpeptidases known as penicillin-binding proteins. β-Lactam antibiotics block not only the division of bacteria, including cyanobacteria, but also the division of cyanelles, the photosynthetic organelles of the glaucophytes, and the division of chloroplasts of bryophytes. In contrast, they have no effect on the plastids of the highly developed vascular plants. This is supporting the endosymbiotic theory and indicates an evolution of plastid division in land plants.35

β-Lactam antibiotics are analogues of D-alanyl-D-alanine. The structural similarity between β-Lactam antibiotics and D-alanyl-D-alanine
facilitates their binding to the active site of penicillin-binding proteins. The β-
lactam nucleus of the molecule irreversibly binds to (acylates) the Ser\textsubscript{403}
residue of the PBP active site. This irreversible inhibition of the PBPs
prevents the final crosslinking (transpeptidation) of the nascent peptidoglycan
layer, disrupting cell wall synthesis. Some examples of β-lactam antibiotics
are Clavulanic acid (3), Amoxicillin (4), Ampicillin (5) Flucloxacillin (6) and
Methicillin (7).

![Chemical structures of β-lactam antibiotics and glycopeptides](image)

**Glycopeptides Antibiotics:**

Glycopeptides for example vancomycin (8) and lipopeptides for
example daptomycin (9)\textsuperscript{36} inhibits the synthesis of the cell wall by binding
with high affinity to the acyl-D-alanine terminus of cell wall precursor units
and active only against gram positive bacteria.
Quinolone Antibiotics

The quinolones are a family of synthetic broad-spectrum antibiotics. The quinolones are divided into generations based on their antibacterial spectrum. The first generation of the quinolones begins with the introduction of nalidixic acid (10) in 1962 for treatment of urinary tract infections in humans.\(^{37}\) Nalidixic acid was discovered by George Lesher and coworkers in a distillate during an attempt at chloroquine synthesis.\(^{38}\) The drugs most frequently prescribed today consist of ciprofloxacin (11), levofloxacin (12) and trovafloxacin (13).
Macrolide Antibiotics

The macrolides are a group of drugs (typical antibiotics) whose activity stems from the presence of a macrolide ring, a large macrocyclic lactone ring to which one or more deoxy sugars, usually cladinose and desosamine, may be attached. The lactone rings are usually 14, 15 or 16-membered. Macrolides belong to the polyketide class of natural products. Among the antibiotics azithromycin (14), clarithromycin (15), erythromycin (16) and roxithromycin (17) are macrolide antibiotics.

Antibiotic macrolides are used to treat infections caused by Gram positive bacteria, Streptococcus pneumoniae and Haemophilus influenzae infections such as respiratory tract and soft tissue infections. The antimicrobial spectrum of macrolides is slightly wider than that of penicillin, and, therefore, macrolides are a common substitute for patients with a penicillin allergy. Beta-hemolytic streptococci, pneumococci, staphylococci, and enterococci are usually susceptible to macrolides. Unlike penicillin, macrolides have been shown to be effective against mycoplasma, mycobacteria, some rickettsia, and chlamydia.
Sulfonamide Antibiotics

The sulfonamides are a large family of compounds, all of which are derived from the original hydrolysis product of prontosil red, sulfanilamide. They differ in the nature of the substitution on the amino group of sulfonamide (-SO\(_2\)NH\(_2\)) moiety. The antileprosy drug, dapsone and the tuberculostatic \(\rho\)-amino salicylic acid are related substances that are thought to act in a similar way.\(^\text{42}\)

Sulfonamides are synthetic antibiotics also called sulpha drug that inhibit multiplication of bacterial cell growth by activity as competitive inhibition of \(\rho\)-aminobenzoic acid in the folic acid metabolism cycle.\(^\text{43}\)

Sulfa drugs are used to treat some types of bacterial infection such as urinary tract infections, shigellosis, \textit{Nocardia} infections and specific protozoal infections.

Resistance to sulfonamide antibiotics is also common and they are frequently used in combination with trimethoprim which blocks two steps in folic acid metabolism and thus helps to prevent the emergence of strains of bacteria resistant to sulfa drugs. These compounds include sulfadiazine (18), sulfamethazine (19), sulfamethoxazole (20), sulfamethizole (21), sulfa
and sulfafurazole (23). They have a common core chemical structure, $p$-amino benzenesulfonamide.

\[
\begin{align*}
\text{(18)} & \quad \text{H}_2\text{N} & \quad \text{SO} & \quad \text{N} & \quad \text{H} & \quad \text{O} \\
\text{(19)} & \quad \text{H}_2\text{N} & \quad \text{SO} & \quad \text{N} & \quad \text{H} & \quad \text{O} \\
\text{(20)} & \quad \text{H}_2\text{N} & \quad \text{SO} & \quad \text{N} & \quad \text{H} & \quad \text{O} \\
\text{(22)} & \quad \text{H}_2\text{N} & \quad \text{SO} & \quad \text{N} & \quad \text{H} & \quad \text{O} \\
\text{(23)} & \quad \text{H}_2\text{N} & \quad \text{SO} & \quad \text{N} & \quad \text{H} & \quad \text{O}
\end{align*}
\]

**Vitamins:**

Vitamins are non energy producing organic compounds essential for normal human metabolism, that must be supplied in small quantities in the diet. The importance of vitamin as drugs is primarily in the prevention and treatment of deficiency diseases for example thiamine (24), folic acid (25) and riboflavin (26) etc.

\[
\begin{align*}
\text{24} & \quad \text{NH}_2 & \quad \text{N} & \quad \text{S} & \quad \text{H}_3 & \quad \text{C} & \quad \text{H}_3 & \quad \text{C} & \quad \text{H}_3 & \quad \text{C} & \quad \text{H}_3 & \quad \text{OH} \\
\text{25} & \quad \text{H}_3 & \quad \text{C} & \quad \text{N} & \quad \text{H}_3 & \quad \text{C} & \quad \text{NH} & \quad \text{OH} & \quad \text{OH} & \quad \text{OH} \\
\text{26} & \quad \text{H}_3 & \quad \text{C} & \quad \text{N} & \quad \text{H}_3 & \quad \text{C} & \quad \text{NH} & \quad \text{OH} & \quad \text{OH} & \quad \text{OH} & \quad \text{OH}
\end{align*}
\]
Anticonvulsants

The anticonvulsants are a diverse group of pharmaceuticals used in the treatment of epileptic seizures. Anticonvulsants are also increasingly being used in the treatment of bipolar disorder, since many seem to act as mood stabilizers.\(^{47}\) The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure. Failing this, an effective anticonvulsant would prevent the spread of the seizure within the brain and offer protection against possible excitotoxic effects that may result in brain damage. Some studies have site that anticonvulsants themselves are linked to lowered IQ in children.\(^ {48}\)

Some important examples of anticonvulsants are given below.

Phenytoin (27) is the first anticonvulsant. It is often cities as the prime example of an anticonvulsant acting as a sodium channel blocker.\(^ {49,50}\) One effect of neuronal sodium channel block is to decrease presynaptic glutamic acid release, giving anticonvulsant activity.\(^ {50,51}\)

\[
\text{(27)}
\]

Trimethadione (28) was the first drug introduced specifically for treating absence seizures. The drug is metabolized by N-demethylation to putative the active metabolite dimethadione.\(^ {52}\)

\[
\text{(28)}
\]
Carbamazepine (29) is effective drug in partial and generalized convulsions and or in mixed type. Primidone (30) is a 2-deoxybarbiturate which is converted by liver to phenobarbital and phenylethyl malonyldiamide having antiepileptic efficacy.

\[ \text{Carbamazepine} (29) \]

\[ \text{Primidone} (30) \]

Nonsteroidal anti-inflammatory agents:

Inflammatory is a complex process that is mediated by a number of different agents. It is primarily required as a defence mechanism against infection or other injury, but it is readily produced by endogenous causes particularly immunological reactions which lead to tissue damage and chronic disability. A number of agents having anti-inflammatory, antipyretic and mild analgesic activity are as under.

Indomethacin (31) has a prominent anti-inflammatory and analgesic-antipyretic properties. Clinical trials of indomethacin as an anti-inflammatory agent are well established.
Tolemetin (32) is used as an anti-inflammatory, analgesic and antipyretic agents.\textsuperscript{56,57}

\[
\begin{array}{c}
\text{H}_3\text{C}\quad\text{O} \\
\text{CH}_3 \\
\text{CH}_2\text{COOH} \\
\end{array}
\]

(32)

Tenoxicam (26) is effective as an anti-inflammatory agent and has been used in the management of rheumatic osteoarthritis.\textsuperscript{58}

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{CH}_3 \\
\text{CONH} \\
\end{array}
\]

(33)

**Anthelmintics**

Helminth (worm) infections in domestic animal cause enormous damage. In animals, roundworms are by far the greatest problem, followed by liver fluke, lungworm, tapeworm and heart worm. Some examples of anthelmintic drug are Mebendazole (34), Albendazole (35), Thiabendazole (36) and Fenbendazole (37) which are broad spectrum agents and constitute one of main groups of antihelminthics used clinically.\textsuperscript{59-61}

\[
\begin{array}{c}
\text{O} \\
\text{H}_2\text{C} \\
\text{O} \\
\end{array}
\]

(34)

\[
\begin{array}{c}
\text{O} \\
\text{H}_2\text{C} \\
\text{O} \\
\end{array}
\]

(35)

\[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\end{array}
\]

(36)

\[
\begin{array}{c}
\text{O} \\
\text{H}_2\text{C} \\
\text{O} \\
\end{array}
\]

(37)
Antiprotozoals

Trypanosomiasis, leishmaniasis, amebiasis, giardiasis and trichomoniasis are various protozoal infection caused by the parasites which can be transmitted by insect vectors, directly from mammalian reservoirs or from one person to another. Most antiprotozoal drug with heterocyclic moiety have been in used for years because they have not been replaced by better agents. for e.g. Melronidazole (38) and Tinidazole (39).

\[ \text{(38)} \]

\[ \text{(39)} \]

Anti-Histamine

Antihistamine can be used to describe any histamine antagonist that act upon the H\(_1\) histamine receptor. It has been discovered that these H\(_1\)-antihistamines are actually inverse agonists at the histamine H\(_1\)-receptor and are used to treat urticaria, anaphylaxis, asthma and allergic rhinitis. The heterocyclic compounds most used as histamine antagonist are phenothiazine derivatives such as promethazine (40), methdilazine (41) and mequitazine(42). \(^{62,63}\)

\[ \text{40} \]

\[ \text{41} \]

\[ \text{42} \]
Piperazine analogues such as levocetirizine (43), hydroxyzine (44) and niaprazine (45) acts as a sedating antihistamine.\[^{64,65}\]

\[
\begin{array}{c}
\text{43} \\
\text{44} \\
\text{45}
\end{array}
\]

### Diuretics

Some pathological conditions, fluid is retained in the body and diuretic agents are needed to enhance excretion. Some heterocyclic produced clinically effective diuretic for example furosemide, benetanide, torsemide etc.

Both diuretics (46, 47) have fast action often oral therapy. Furosemide (46) shows action in slightly longer duration than bumetanide.\[^{66-70}\] A small percentage of furosemide is converted to the corresponding glucuronide and 88% administered drug which excreted by the kidney. Bumetanide (47) undergoes more extensive biotransformation in the human which is excreted by the urine.

\[
\begin{array}{c}
\text{46} \\
\text{47}
\end{array}
\]
Agrochemicals

Enormous number of heterocycles and their derivatives are claimed to have beneficial agricultural effects. However, only a relatively small number have the high level of biological activity combined with the safe toxicological and environmental properties that are required for use in agriculture. Some of the examples with heterocyclic ring are described as below for agrochemicals.

Herbicides

The production and use of chemicals for destruction of noxious weeds have increased markedly in the past two decades. There is an increased concern about the health effects of herbicides because of run-off from agricultural application and entrance into the drinking water supply.

Atrazine (48) and simazine (49) are still some of the most widely used herbicides and probably from the single most important class of heterocycles in agriculture. Both are used in two ways. At high concentration they act as total herbicides, while at much lower concentration they are used for selective pre-emergence weed controls.\(^\text{71}\)

\[
\begin{align*}
\text{(48)} & \quad \text{Cl} \\
& \quad N = N \\
& \quad \text{H}_2\text{N} \quad \text{NHC}_2\text{H}_5 \\
\text{(49)} & \quad \text{Cl} \\
& \quad N = N \\
& \quad \text{H}_5\text{C}_2\text{NH} \quad \text{NHC}_2\text{H}_5 
\end{align*}
\]

Pesticides

Pesticide is general classification that includes insecticides, rodenticides, fungicides, herbicides and fumigants. Some of the examples of these classes are given below.

Quiniconazole, subthylazine, fluquinconazole and nicotine derivative of quinazolinone triazine, triazole and pyridine respectively have used as
pesticidal agent. The quinozolinone moiety (50) is associated with a broad spectrum of biological activity viz pesticidal, antifungal, insecticidal, antibacterial, anticonvulsant etc. Furthermore derivatives of triazine, naphthalene, pyridine, triazole etc. have found to exhibit promising insecticidal activity.

![Chemical Structure](image)

(50) : R= Phenothiazine/pyridine-2-phenyl-5-marcapo-triazole

2-([2’-2’’-o-Hydroxyphenyl-4”-thiazolidinon-3”-yl]-1’,3’-thiazol-4’-yl]-aminopyridine (51) and 2-[2’(1”-phenyl-3”-o-hydroxyphenyl-formazan-4”-yl]-1’,3”-thiazole-4’-yl]-aminophridin (52) show pivotal role in the development of different medicinal agents and in the field of agrochemicals. Both showed pesticidal, insecticidal and fungicidal activities.
Table-1.1: Pharmacological activity of some heterocycles\textsuperscript{87-95}

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name of drug</th>
<th>Activity</th>
<th>Chemical structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Sitagliptin</td>
<td>Antidiabetic</td>
<td><img src="image1" alt="Chemical structure" /></td>
</tr>
<tr>
<td>2.</td>
<td>Sildenafil</td>
<td>Erectile dysfunction</td>
<td><img src="image2" alt="Chemical structure" /></td>
</tr>
<tr>
<td>3.</td>
<td>Tenonitroazole</td>
<td>Antiprotozoal</td>
<td><img src="image3" alt="Chemical structure" /></td>
</tr>
<tr>
<td>4.</td>
<td>Fomepizole</td>
<td>Antidote</td>
<td><img src="image4" alt="Chemical structure" /></td>
</tr>
<tr>
<td>5.</td>
<td>Pramipexole</td>
<td>Antiparkinson</td>
<td><img src="image5" alt="Chemical structure" /></td>
</tr>
<tr>
<td>6.</td>
<td>Ondansetron</td>
<td>Antiemetic</td>
<td><img src="image6" alt="Chemical structure" /></td>
</tr>
<tr>
<td>7.</td>
<td>Nitazoxanide</td>
<td>Antidiarrhoeal</td>
<td><img src="image7" alt="Chemical structure" /></td>
</tr>
<tr>
<td></td>
<td>Drug Name</td>
<td>Category</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----------------------</td>
<td>-------------------------------</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Lysergic acid diethylamide</td>
<td>Psychedelic drug</td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image1.png" alt="Lysergic acid diethylamide structure" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Cilostazol</td>
<td>Antiplatelet drug</td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image2.png" alt="Cilostazol structure" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Anastrozole</td>
<td>Aromatase inhibitor</td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image3.png" alt="Anastrozole structure" /></td>
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</tr>
</tbody>
</table>
SECTION-1.2: GENERAL REVIEW AND BIOLOGICAL SIGNIFICANCE OF PHENOTHIAZINE AND THEIR RELATED DERIVATIVES

Phenothiazine (53) form an important class of heterocyclic compounds possessing wide spectrum diverse of biological activities.\(^{96-98}\) The phenothiazine contain a heterocyclic ring skeleton with two carbocyclic aromatic rings connected to each other via a sulfide and an imino bridge which facilitates several types of reactions such as substitution at the nitrogen, electrophilic substitution on the aromatic rings, N-oxidation and photochemical reactions.\(^{99-101}\)

![Chemical structure of phenothiazine (53)](image)

In 1950’s its actual medicinal importance was realized when their 10-dialkylaminoalkyl derivatives came into existence. Delay, Pishot, Lamperiare and Elissade reported its beneficial effects in treating psychomotor excitement in 1952.

One of the most widely used phenothiazine i.e. chlorpromazine [2-chloro-10-{(3-dimethylamino) propyl} phenothiazine hydrochloride] with trade name Thorazine was introduced in 1953 by Charpentier\(^{102}\) and possess many therapeutic properties and used to treat overactive schizophrenia. Its introduction into psychiatric practice marked the beginning of psychopharmacology. An article “Progress in Drug Research”\(^{103}\) on various aspects of phenothiazines was published in 1963 with more than thousand references. In 1968, chemistry of phenothiazine was reviewed\(^{104-116}\) in detail by Bodea and Silberg.\(^{117}\) In 1988, a treatise edited by Gupta\(^{118}\) was appeared which comprises of several hundred of pages dealing with several aspects of phenothiazines.
SYNTHESIS

Synthesis of phenothiazine was first time published in 1883 by Bernthsen, however phenothiazine nucleus was reported for the first time in a purple dye (54) (3,7-diamino phenothiazonium chloride, discovered by Lauth) and later on another dye of this class, methylene blue (55) was synthesized which was found to possess antimicrobial activity.

![Purple dye and Methylene blue](image)

Phenothiazines are prepared by heating diphenylamine with sulphur in xylene or o-dichlorobenzene in the presence of catalyst iodine or aluminium chloride at about 180°C. Hydrogen sulphide is evolved and the crude phenothiazine is purified by washing with carbon tetrachloride.

![Phenothiazine synthesis](image)

Biological Significance

Some new N-acyl substituted phenothiazines (56) were synthesized and evaluated for their antibacterial activity against *B.subtilis, E.coli, S.aureus* and *P.aeruginosa* and antifungal activity against *A.niger, A.fumigatus, A.flavus* and *C.albicans*. Some compounds showed promising antibacterial and antifungal activities.
Some new triazolopyridinyl phenothiazines (57) have synthesized and evaluated for their antimicrobial activity. Some of these compounds have shown significant antibacterial and antifungal activities.125

A new series of 5-((10 N-phenothiazin-yl) methyl)-4-(arylideneamino)-3-mercaptotriazoles (58) have been synthesized and screened for their antibacterial and antifungal activities.126
A new series of 2-azetidinone derivatives of phenothiazine (59) were synthesized and evaluated for their antitubercular, antibacterial, antifungal and anti-inflammatory activities by Lowenstein-Jensen medium method, cup plate method, disc diffusion method and carrageenan induced paw edema respectively.¹²⁷

![Chemical structure of 2-azetidinone derivatives of phenothiazine](image)

(59) : \( R = \text{aryl / substituted aryl groups} \)

Some new 2-chloro-phenothiazinothiadiazol-2-oxoazetidines (60) have been synthesized and tested for their antibacterial, antifungal and anti-inflammatory activities.¹²⁸

![Chemical structure of 2-chloro-phenothiazinothiadiazol-2-oxoazetidines](image)

(60): \( \text{Ar} = \text{aryl/substituted aryl groups} \)

A series of phenothiazine-4-one derivatives (61) and phenothiazine-4-one-5,5-dioxide derivatives (62) have been found to possess antimalarial activity.¹²⁹

![Chemical structures of phenothiazine-4-one and phenothiazine-4-one-5,5-dioxide derivatives](image)

Where \( R, R_1, R_2 = \text{H/F/Cl/CH}_3/\text{aryl/ substituted aryl groups} \)
2-Heterocycle-substituted phenothiazines (63) have been synthesized and screened for their antitubercular activity against Mycobacterium tuberculosis H$_{37}$Rv.$^{130}$

![Image of 2-Heterocycle-substituted phenothiazines](image)

(63) : $R = H/OH/Cl/NO_2/OCH_3$

A series of 5-arylidene-2-aryl-3-(phenothiazinoacetamidyl)-1,3-thiazolidine-4-ones (64) have been synthesized and evaluated for their biological activities such as anti-inflammatory, anticonvulsant, analgesic and antimicrobial.$^{131}$

![Image of 5-arylidene-2-aryl-3-(phenothiazinoacetamidyl)-1,3-thiazolidine-4-ones](image)

(64) : $R, R_1, R_2, R_3 = H/aryl/substituted aryl groups$

Phenothiazino acetyl / prpionyl morpholines (65) and Phenothiazino acetyl / prpionyl benzotriazoles (66) were synthesized and evaluated for their antihelminthic activity.$^{132}$

![Image of Phenothiazino acetyl / prpionyl morpholines](image)

(65) : HET = Phenothiazine; $R = H$

(66) : HET = Phenothiazine; $R = H$
1-Nitro-10H-phenothiazine sulfones (67) were synthesized and screened for their antioxidant and antimicrobial activities.\textsuperscript{133}

\[
\begin{array}{c}
\text{O} \\
\text{S} \\
\text{O} \\
\end{array}
\begin{array}{c}
\text{R}_2 \\
\text{R}_1 \\
\text{R}_3 \\
\text{R}_4 \\
\end{array}
\]

(67): R, R\textsubscript{1}, R\textsubscript{2}, R\textsubscript{3}, R\textsubscript{4} = H/alkyl/NO\textsubscript{2}

A series of phenothiazine derivatives (68) were synthesized and screened for their antimicrobial and diuretic activities.\textsuperscript{134}

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{O} \\
\end{array}
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4 \\
\end{array}
\]

(68) : R = H / CH\textsubscript{3} ; R\textsubscript{1} = aryl/substituted aryl groups
SECTION-1.3: GENERAL REVIEW AND BIOLOGICAL SIGNIFICANCE OF INDAZOLE AND THEIR RELATED DERIVATIVES

Among the heterocyclic compounds available for the preparation of potentially valuable new building-blocks in medicinal chemistry, the indazole nucleus is a pharmaceutically important and emerging heterocycle with a broad spectrum of activities. There is a limited number of publications based on indazole chemistry as compared to indole\textsuperscript{135,136} and benzimidazole,\textsuperscript{137-139} presumably a result of the fact that the indazole moiety is rather scarce in natural products.\textsuperscript{140-142} Even so, a large number of synthetically prepared compounds have displayed biological and pharmacological properties.\textsuperscript{143}

SYNTHESIS

The first compound known to contain the indazole ring system was indazolone (69) and its preparation, by heating o-hydrazinobenzoic acid was reported in 1880 by Fischer.\textsuperscript{144}

\begin{center}
\includegraphics[width=0.5\textwidth]{indazolone.png}
\end{center}

Indazole (70) itself was first prepared a few years later by Fischer and Kuzel.\textsuperscript{145} Since then, several approaches for the preparation of indazole and its derivatives have been developed.\textsuperscript{146} The most frequently used method is the use of o-disubstituted benzene derivatives, where the two substituents reacts to form a pyrazole ring. For example, diazotization and intramolecular cyclisation of o-methylaniline derivatives delivered indazoles.\textsuperscript{147,148}

\begin{center}
\includegraphics[width=0.5\textwidth]{indazole.png}
\end{center}
Diazotization can also be applied to prepare 3-substituted indazoles starting from o-aminoketones. The diazonium salt intermediates are reduced to hydrazines which then undergo the ring closure. Another method for preparation of 3-substituted indazole derivatives involves heating of o-substituted benzophenones with hydrazine.\textsuperscript{149-152}

An additional route involves dehydrogenation of 4,5,6,7-tetrahydroindazoles by palladium on charcoal.\textsuperscript{153} The tetrahydroindazoles are best prepared by the reaction of 2-(hydroxymethylene)cyclohexanone with hydrazine hydrate.\textsuperscript{153}

Due to the fact that there is a wide interest in finding general and efficient methodologies for the synthesis of this class of compounds, new synthetic routs are still being explored. In this context, there are several review articles on indazoles, describing their preparation as well as chemical and pharmacological properties.\textsuperscript{143,146}

**BIOLOGICAL SIGNIFICANCE**

A novel indazole derived Nucleosidase inhibitors (71) have been synthesized and evaluated for their antibacterial activity.\textsuperscript{154}
6-(2-Hydroxy phenyl)-4-(substituted phenyl)-3-oxo-2,3,4,5-tetrahydro-1H-indazoles (72) were synthesized and evaluated for their antibacterial activity against *E.coli, P.valgaris, K.pneumoniae, S.aureus* and *S.albus.*

\[
\text{(72)} : \text{Ar} = \text{aryl/substituted aryl groups}
\]

6-(3,5-Dibromo-4-methoxy-phenyl)-4-aryl-2,3a,4,5-tetrahydro-3H-indazole-3-ones (73) have been synthesized and tested for their antibacterial, antifungal and antitubercular activities.

\[
\text{(73)} : \text{Where R = aryl}
\]

Some new potent 5-nitroindazole derivatives (74) were synthesized and screened for their anti-trypanosoma cruzi activity.

\[
\text{(74)} : \text{R = Methoxy/Benzyloxy}
\]

\[
\text{R}_1 = \text{Piperidino-dimethylamino/morpholino/diethylamino/diisopropylamino}
\]
5-nitroindazole derivative (75) has been synthesized and evaluated for their anti-trypanosoma cruzi activity.\textsuperscript{158}

\[
\begin{align*}
\text{(75): Bn = Benzyloxy}
\end{align*}
\]

Ruthenium complexes with indazole (76, 77) have been found to possess antitumor activity.\textsuperscript{159}

\[
\begin{align*}
\text{(76)} & \quad \text{(77)}
\end{align*}
\]

Some new 5-nitroindazole derivatives (78) have synthesized and evaluated for their cytotoxic activity against three tumour cell lines, human colon adenocarcinoma (HT-29), human mammary adenocarcinoma (MCF-7) and human kidney carcinoma (TK-10) respectively.\textsuperscript{160}

\[
\begin{align*}
\text{(78): } R, R_1 = [\text{CH}_2]_5/\text{Me}
\end{align*}
\]
Indazole N-oxides (79) have been synthesized and tested for their cytotoxic activity against three tumour cell lines, human colon adenocarcinoma (HT-29), human mammary adenocarcinoma (MCF-7) and human kidney carcinoma (TK-10) respectively.\textsuperscript{161}

\begin{center}
\includegraphics[width=0.5\textwidth]{79.png}
\end{center}

(79): \( R = \text{aryl/substituted aryl groups} \)

1,1'-Hydrocarbylenebis (indazol-3-ols) oxide (80) has been reported to possess antimalarial activity.\textsuperscript{162}

\begin{center}
\includegraphics[width=0.5\textwidth]{80.png}
\end{center}

Some new 1-halobenzyl-1H-indazole-3-carboxylic acids (81) were synthesized and evaluated for their antispermatogenic activity.\textsuperscript{163}

\begin{center}
\includegraphics[width=0.5\textwidth]{81.png}
\end{center}

(81) : \( R = \text{aryl/substituted aryl groups}; \ R_1 = \text{COOH}; \ R_2 = \text{AcOH} \)

7-Methoxy indazole (82) and their related substituted indazole (83) have been synthesized and screened for their antinociceptive activity.\textsuperscript{164}

\begin{center}
\includegraphics[width=0.5\textwidth]{82_83.png}
\end{center}
SECTION-1.4: GENERAL REVIEW AND BIOLOGICAL SIGNIFICANCE OF PYRIDINE AND THEIR RELATED DERIVATIVES

Pyridine (84) is the simplest and the best known hetercyclic compound. It is an analog of benzene in which one of the methine (=CH) group is replaced by a nitrogen atom. This change does not affect the aromatic character of the ring. Pyridine is found in coal-tar and bone oil. Pyridine is used as a precursor to agrochemicals and pharmaceuticals and is also an important solvent and reagent. It is a colourless liquid with a distinctive and unpleasant fish-like odour. The pyridine occurs in many important compounds, including the vitamins nicotinamides and pyridoxal.

\[
\begin{align*}
\text{(84)}
\end{align*}
\]

SYNTHESIS\textsuperscript{165}

A number of methods for the synthesis of pyridine have been developed but none of them is suitable for the commercial production of pyridine and hence the commercial pyridine is obtained almost solely from coal-tar. Some of the important synthetic methods of pyridine and its derivatives are mentioned below.

1. From aldehydes or ketones and ammonia: Aldehydes or ketones on reaction with ammonia under suitable conditions (such as high temperature and under pressure) give pyridines.

\[
4\text{CH}_3\text{CHO} + \text{NH}_3 \xrightarrow{230^\circ\text{C}} \text{C}_2\text{H}_5\text{N} + \text{H}_3\text{C}
\]
2. The Hantzsch synthesis: This is very widely used method for the synthesis of symmetrically substituted pyridines. This involves the condensation of a β-ketone ester with an aldehyde in the presence of ammonia.

\[
\begin{align*}
    \text{H}_3\text{C} \underset{\text{CH}_2}{\text{OOC}} \underset{\text{C}}{\text{C}} + \text{RCHO} + \text{CH}_2\text{COOC}_2\text{H}_5 & \rightarrow \text{H}_5\text{C} \underset{\text{COOC}_2\text{H}_5}{\text{C}} \underset{\text{CH}_3}{\text{N}} \underset{\text{CH}_3}{\text{N}}
\end{align*}
\]

3. From glutaric aldehyde and ammonia

\[
\begin{align*}
    \text{HC} \underset{\text{O}}{\text{CCH}} \underset{\text{CH}_2}{\text{CHCH}} \underset{\text{CH}_2}{\text{CH(OH)}} & \rightarrow \text{NH}_3 \rightarrow \text{Pyridine}
\end{align*}
\]

4. From pentamethylene diamine hydrochloride

\[
\begin{align*}
    \text{NH}_2 \underset{\text{CH}_2}{\text{CH}_2} \underset{\text{CH}_2}{\text{CH}_2} \underset{\text{CH}_2}{\text{CH}_2} \underset{\text{CH}_2}{\text{CH}_2} \text{NH}_2 \text{HCl} \rightarrow \text{H}_2\text{SO}_4 \rightarrow \text{Pyridine}
\end{align*}
\]

**BIOLOGICAL SIGNIFICANCE**

A new series of 2-[2'- (3"'-chloro-2"'-oxo-4"'-p-hydroxyphenyl-1"'- azetidinyl)-1',3'-thiazol-4'-yl ]-amino-pyridine (85) have been synthesized and evaluated for their pesticidal activity.\(^{166}\)

\[
\text{Pyridine}; \text{R} = \text{H/OH/OCH}_3/4\text{-OH/3-OCH}_3 \text{ groups}
\]
N-(3-chloro-2-aryl-4-oxazetidin-1-yl) nicotinamide (86) have been synthesized and exhibited significant antibacterial, antifungal and antitubercular activity against the tested bacteria and fungi.\(^{167}\)

\[
\text{(86) ; } R = 2,4-\text{ClC}_6\text{H}_4; 2,4-\text{NO}_2\text{C}_6\text{H}_4; 2, 4-\text{OCH}_3\text{C}_6\text{H}_4
\]

A series of 2,6-diaryl-3-isonicotinamido thiazolo [4,5-c] pyrazolines (87) were synthesized and evaluated for their antibacterial activity against \(E.\text{coli}, B.\text{subtilis}\) and \(S.\text{aureus}\) and antifungal activity against \(A.\text{niger}, P.\text{oryzae}\) and \(F.\text{oxysporum}.\)^{168}

\[
\text{(87): } R, R_1 = 4-\text{Cl/4-CH}_3/4-\text{OCH}_3
\]

A new series of phthalimido [2-aryl-3-(5'-(4”-pyridyl)-1,3,4-thiadiazol-2'-yl)-4-oxothiazolidin-5yl] ethanoates (88) have been synthesized and screened for their antibacterial activity against \(E.\text{coli}, B.\text{subtilis}, K.\text{pneumoniae}, P.\text{auregenosae}\) and \(S.\text{aureus}\) and antifungal activity against \(A.\text{fumigatus}\) and \(C.\text{albicans}.\)^{169}

\[
\text{(88): } R = \text{phthalimidoxy; } Ar = \text{aryl/substituted aryl groups}
\]
3-((Ethylthio)-5-pyridin-4-yl)-1H,2,4-triazole-4-amine (89, 90) have been synthesized and screened for their antimicrobial activity.\(^{170}\)

![Chemical structure of 3-((Ethylthio)-5-pyridin-4-yl)-1H,2,4-triazole-4-amine](image1.png)

A series of pyridinyl thiazolyl formazans (91) have been synthesized and found to possess insecticidal activity.\(^{171}\)

![Chemical structure of pyridinyl thiazolyl formazans](image2.png)

N-aryl-1,4-dihydropyridines (92) were synthesized and screened for their antidyslipidemic and antioxidant activities.\(^{172}\)

![Chemical structure of N-aryl-1,4-dihydropyridines](image3.png)

Some new [5-(pyridin-2-yl)-1,3,4-thiadiazol-2-ylthio] acetic acid arylidene-hydrazide derivatives (93) were synthesized and tested in vitro for their antimycobacterial activity against a strain of *Mycobacterium tuberculosis* and *Mycobacterium avium*.\(^{173}\)

![Chemical structure of 5-(pyridin-2-yl)-1,3,4-thiadiazol-2-ylthio] acetic acid arylidene-hydrazide derivatives](image4.png)
A novel series of isonicotinyl hydrazide derivatives (94) have been synthesized and tested in vitro for their antimycobacterial activity against *Mycobacterium tuberculosis* H₃₇Rv using Alamar-Blue susceptibility test.\textsuperscript{174}

\[
\begin{align*}
&\text{(94): } R = \text{aryl/ het.}
\end{align*}
\]

Some (E)-N’-(monosubstituted-benzylidene) isonicotinohydrazide derivatives (95) were synthesized and tested in vitro for their antimycobacterial activity against *Mycobacterium tuberculosis* H₃₇Rv using Alamar-Blue susceptibility test.\textsuperscript{175}

\[
\begin{align*}
&\text{(95): } R = \text{halo/CN/NO}_2/\text{alkoxy/OH}
\end{align*}
\]

4-(Quinolin-4-yl)-N-(4-(trifluoromethyl) phenyl) pyrimidin-2-amine (96) was synthesized and evaluated for their cytotoxic activity.\textsuperscript{176}
Schiff bases of 5-mercapto-3-(3'-pyridyl)-4H-1,2,4-triazole-4-yl-thiosemicarbazide (97) were synthesized and screened for their antibacterial, antifungal and anticonvulsant activities.\textsuperscript{177}

\[\text{(97): } \text{Ar = aryl/substituted aryl groups}\]
SECTION-1.5: GENERAL REVIEW AND BIOLOGICAL SIGNIFICANCE OF 2- AZETIDINONE AND THEIR RELATED DERIVATIVES

The carbonyl derivatives of azetidine is designated as 2-azetidinones (98) or more commonly known as β-Lactam.

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{O} \\
\end{array}
\]

Natural and synthetic azetidinone derivatives occupy a central place among medicinally important compounds due to their diverse and interesting antibiotic activities. The utility of azetidinones as synthones for various biologically active compounds, as well as their recognition as cholesterol absorption inhibitors and enzyme inhibitors, has given impetus to these studies. In the late 1990s, several groups reported novel methodologies for the synthesis of azetidinones of potential biological activities by applying known methods. Since then a plethora of work has appeared in the literature. It would therefore be useful to review the work done in this area more frequently.

Until 1970 most of the β-Lactam antibiotic chemistry was revolving around either penicillin or cephalosporin. The isolation of 7α-methoxycephalosporins from Streptomyces in 1971 stimulated the search for novel β-Lactam antibiotics from microbes. This extensive quest for novel β-lactam skeleton has led to the isolation of active antibiotics not only from eukaryotic fungi, actinomycetes but also from bacteria. This has led to the expansion of β-Lactam antibiotic family to an ever-increasing number. Currently, following classes of β-Lactam antibiotics are known-carumonam, aztreonam, thienamycin and nocardicins and besides from penicillins and cephalosporins.

Carbacephems which are the carbon analogues of cephalosporins, are sensational new antibiotics. Superior stability of this antibiotic over cephalosporin and the ease with which it can be derivative at 3-position, is
synthetically attractive. With the approval of first carbacephem, loracarbef (lorabid) (99) is used clinically and the interest is continued further.

![Chemical structure of loracarbef (99)](image)

The tricyclic β-Lactam antibiotics, trienems (100) are also a new class of tricyclic carbapenems, a highly potent, broad-spectrum antibacterial agent, effective against gram-positive, gram-negative and anaerobic pathogenic bacteria has attracted the synthetic as well as biological community.

![Chemical structure of trienem (100)](image)

**SYNTHESIS**

Staudinger’s Ketene-imine reaction is the most common method for the synthesis of azetidinones and it has been reviewed recently by Palmo et al. The reaction is carried out thermally or photochemically using acid chlorides in the presence of triethylamine or α-diazoketones as ketene precursors. The previous decade has also seen the use of microwave radiation in synthesizing azetidinones.
Intramolecular cyclization of $\beta$-amino acids in the presence of certain reagents including such as acyl chloride, phosphorous trichloride and thionyl chloride provides $\beta$-Lactams.\(^{223}\)

The reaction of $\beta$-amino esters with Grignard reagents lead to the formation of azetidinones.\(^{224}\)

The reaction of acid chloride with imines in the presence of a base provides $\beta$-Lactam.\(^{225}\)

**BIOLOGICAL SIGNIFICANCE**

4-Aryl-1-(4'-\(\alpha\)-methoxy-imino-carbomethoxy-methyl-thiazole-2'-yl)-3-chloro-2-azetidinones (101) were prepared and evaluated for their *in vitro* anti-tubercular activity against Mycobacterium tuberculosis.\(^{226}\)
1-Substituted-2-oxo-3-chloro / 3-(2-Chlorophenoxy)-4-(2-aryl-indole-3-yl)-azetidinones (102) have been synthesized and were found to be CNS active and antiinflammatory activities.  

![Chemical Structure](image)

(102): $R = H/CH_3/OCH_3$; $X = F/Cl/Br$

3-Chloro-2-oxo-4-(substituted-phenyl)-azetidin-1-yl-thioureas (103) are found to exhibit antiparkinsonian activity.  

![Chemical Structure](image)

(103); $X = CH_3/OCH_3/Cl/Br/NO_2$

1,3,7,9-Tetrabromo-10-[a-{2-(2-hydroxy-phenyl)-3-chloro-4-oxo-1-azetidinyl amino}-acetyl]-phenothiazines (104) have been synthesized and shown tuberculstatic activity.  

![Chemical Structure](image)

(104): $X = CH_3/OCH_3/Cl/Br/NO_2$
A series of 3-chloro-4-(2",4"-dichlorophenyl)-4-methyl-1-(substituted-1',3'-benzothiazol-2'yl)-azetidin-2-ones (105) were synthesized and reported to be pharmacologically active against *S. aureus, B. subtilis, E.coli* and *S.typhi* bacterial strain and *C.albicans* fungal strain.\(^{230}\)

\[
(105): R = 4,6-NO_2/\text{SO}_3\text{H}/\text{CH}_3/\text{OCH}_3
\]

Some 2-[2'-{4"-substituted-aryl-3"-chloro-2"-oxo-azetidinone}-acetyl-amino]-4-phenyl-1,3-thiazole (106) have been synthesized and tested for their antifungal activity against *A. niger, A. flavus* and antibacterial activity *B. subtilis, E.coli, K. pneumoniae* and *S. aureus* respectively.\(^{231}\)

\[
(106): R = \text{H/2,3,4-Cl/Br/OCH}_3/\text{NO}_2/4,4'\text{-N(CH}_3)_2
\]

A novel series of 1'-[(benzimidazol-2-yl)thioacetamidyl]-3'-chloro-4'-aryl-azetidin-2'-one (107) have been synthesized and screened for their antibacterial activity against *E.coli, B.subtilis* and *S.aureus* and antifungal activity against *A.niger, C.albicans* and *C.krusei*.\(^{232}\)

\[
(107): R = \text{NO}_2/\text{OCH}_3/\text{OH/Cl}
\]
2-Azetidinone derivatives of carbazole (108) were synthesized and evaluated for their antibacterial activity against *E.coli*, *B.subtilis*, *K.pneumoniae* and *S.aureus* and antifungal activity against *A.niger*, *F.oxysporum*, *T.viride* and *A.flavus*.233

![Image of 2-Azetidinone derivatives of carbazole (108)]

(108) : Ar = aryl/substituted aryl groups

3"-Chloro-4"-(substituted phenyl)-1"-[4-(coumarin-3-yl)-thiazol-2-yl]-2"-azetidinones (109) have been found to possess antimicrobial activity.234

![Image of 3"-Chloro-4"-(substituted phenyl)-1"-[4-(coumarin-3-yl)-thiazol-2-yl]-2"-azetidinones (109)]

(109) : Ar = aryl/substituted aryl groups

Some new 2-azetidinone derivatives of phenothiazine (110) were synthesized and screened for their anti-inflammatory activity by rat paw oedema method.235

![Image of Some new 2-azetidinone derivatives of phenothiazine (110)]

(110) : X = H/6-Br; R = H/4-Cl/4-OH/4-OCH₃
A new series of 3-(3-chloro-2-oxo-4-substituted-aryl-azetidin-1-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-substituted-3H-quinazolin-4-ones (111) have been synthesized and screened for their anti-inflammatory activity by rat paw oedema method.\(^{236}\)

\[
\text{(111)} : R = \text{H/CH}_3/\text{C}_6\text{H}_5; \text{ R}_1 = \text{aryl/substituted aryl groups}
\]

Some new carbazolyl-thiadiazol-2-oxo-azetidines (112) have been found to possess antimicrobial, anticonvulsant and anti-inflammatory agents.\(^{237}\)

\[
\text{(112)} : \text{Ar = aryl/substituted aryl groups}
\]

Novel N-substituted-3-chloro-2-azetidinone (113) was synthesized and evaluated for their anticonvulsant activity by pentylene tetrazole induced method.\(^ {238}\)

\[
\text{(113)} : \text{R = Piperazine}
\]
A novel series of 3-chloro-4-[4-(2-oxo-2H-chromen-4-ylmethoxy)-phenyl]-1-phenyl-azetidin-2-one derivatives (114) have been synthesized and reported to possess antimicrobial and cytotoxic activities.  

![Chemical structure](image1.png)  

(114) : $R = \text{6-CH}_3/\text{7-CH}_3/\text{6-Cl}/\text{5,6-benzo}/\text{7,8-benzo}; R_1 = \text{Cl/Br}$

A new series of 2-[(4-azetidin-2-one)-3-chloro-4-phenyl]-1H-phenylbenzimidazoles (115) have been synthesized and screened for their antibacterial, antifungal, anti-inflammatory and analgesic activities.  

![Chemical structure](image2.png)  

(115) : $R = R_1 = R_2 = \text{H/Cl/OH/CH}_3/\text{N(CH}_3)_2/\text{OCH}_3$

Some benzothiazolyl azetidinones (116) have been synthesized and screened for their antimicrobial activity.  

![Chemical structure](image3.png)  

(116) : $\text{Ar} = \text{aryl/substituted aryl groups}$

2-Azetidinone derivatives of 2-methyl imidazoles (117) have been synthesized and screened for their antimicrobial activity.  

![Chemical structure](image4.png)  

(117) : $\text{Ar} = \text{aryl/substituted aryl groups}$
SECTION-1.6: GENERAL REVIEW AND BIOLOGICAL SIGNIFICANCE OF 4-THIAZOLIDINONE AND THEIR RELATED DERIVATIVES

Thiazolidinones (118) are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds. Thiazolidinones with a carbonyl group at position 2, 4, or 5 have been subject of extensive study in the recent past. Numerous reports have appeared in the literature which highlight their chemistry and use. 4-Thiazolidinones possess almost all types of biological activities. This diversity in the biological response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. The potential of 4-thiazolidinones as drugs is under consideration by the pharmaceutical industry since the beginning of the 20th century. A comprehensive review has been reported on 4-thiazolidinones in 1961. Later on a review article appeared which deals with the use of thiazolidinone derivatives as stabilizer for polymeric materials. Recently two reviews have been presented; one relates to the preparation of rhodanines (2-thiono-4-thiazolidinones) and the other describes their uses as intermediate in organic synthesis.

\[
\text{SN} \\
\begin{array}{c}
\text{O} \\
\text{2} \\
\text{3} \\
\text{4} \\
\text{5} \\
\text{1}
\end{array}
\]

SYNTHESIS

Several methods for syntheses are available in literature which involves conventional one pot, two pot synthesis and microwave as well as combinatorial syntheses methods.

The dithiocarbamates formed by the reaction of primary amine with CS\(_2\) in the presence of a base react with haloalkanoic acid in presence of NaHCO\(_3\) to give substituted 2-thiono-4-thiazolidinones.
Substituted 2-imino-4-thiazolidinones are obtained in good yields by the reaction of symmetrical and unsymmetrical thioureas with various substituted and unsubstituted $\alpha$-haloalkanoic acids, their esters, acid chlorides, amides or carbamates. The reaction proceeds via the intermediate isothiourea which cyclizes in refluxing acetic acid, ethanol, or benzene in the presence of sodium acetate or pyridine.

$\alpha$-Mercaptoalkanoic acids have been extensively used for the synthesis of 4-thiazolidinones. The substituted and unsubstituted $\alpha$-mercaptoalkanoic acids react conveniently with Schiff bases of aromatic aldehydes and aliphatic or aromatic amines in different solvents to give a variety of 2-substituted-4-thiazolidinones.
Schiff bases obtained by the condensation of ketones and amines also react with $\alpha$-Mercaptoacetic acid to give 2,2-disubstituted-4-thiazolidinones.  

\[
\begin{align*}
R-N=C-R_1 + HS-C-COOH & \rightarrow RNH-CHR_1 \\
& \quad HOOC-C=S \\
\end{align*}
\]

Where, $R = \text{Alkyl or aryl}; R_1 = \text{Aryl or heterocyclic}$  
$R_2 = R_3 = \text{H or alkyl}; R_2R_3 = \text{Arylidene}$

BIOLOGICAL SIGNIFICANCE

4-Thiazolidinones have been shown to have various important biological activities such as antibacterial, antifungal, antiviral, diuretic, antituberculostatic, anti-HIV, antihistaminic, anticonvulsant, anti-inflammatory and analgesic properties. The biological activity of 1, 3-thiazolidin-4-one is reported to be associated with their ability to assume butterfly like conformations. This imparts a binding mode similar to that provided by other non nucleoside reverse transcriptase inhibitors. Some novel styryl derivatives are found to possess anticancer activity as well as to revert the transform phenotype at human fibrosacoma cells.
Some novel 3-(5'-substituted 3'-phenylindole-2'-amino)-spiro-(indol-3''-2-thiazolidine)-2, 4-diones (119) have been synthesized and assayed for their antimicrobial, anthelmintic and anticonvulsant activities.\(^\text{294}\)

![Chemical structure of 119](image)

(119) : \(R = \text{CH}_3/\text{OCH}_3/\text{Br}/\text{Cl}\)

Some 5-arylidine derivatives (120 to 122) have been reported to possess antibacterial, coronary dilator, antihypertensive and muscle relaxant activities.\(^\text{295-298}\)

![Chemical structures of 120-122](image)

(120-122): \(\text{Ar}_1 = \text{Ar}_2 = \text{aryl/substituted aryl groups}\)

4-Thiazolidinone derivatives of 2-methyl-benzimidazole (123) have been synthesized and evaluated for their antimicrobial activity.\(^\text{299}\)

![Chemical structure of 123](image)

(123): \(\text{Ar}_1 = \text{Ar}_2 = \text{aryl/substituted aryl groups}\)
A novel series of succinimido (2-aryl-4-oxo-3-\{(quinolin-8-yloxy)acetyl\}amino\}-1,3-thiazolidin-5-yl)acetates (124) have been synthesized and evaluated for their antibacterial activity against *E.coli, S.albus, S.faecalis, K.pneumoniae, S.typhi, P.aeuroginosa, P.mirabilis* and *S.aureus* and antifungal activity against *A.fumigatus* and *C.albicans*. All the compounds have shown significant inhibition of bacterial and fungal growth.

![Chemical Structure](image)

(124) : \( R = H/Cl/OCH_3/CH_3/N(CH_3)_2 \)

Some new 5-arylidene-2-aryl-3-(benzotriazoloacetamidyl)-1,3-thiazolidin-4-ones (125) were synthesized and tested for their antibacterial, antifungal and analgesic activities.

![Chemical Structure](image)

(125) : \( Ar = \text{aryl/substituted aryl groups} \)
A novel series of 4-thiazolidinone derivatives (126) were synthesized and evaluated for their antimicrobial activity.\(^{302}\)

\[
\begin{align*}
\text{Ar} & \quad \text{Ar}_1
\end{align*}
\]

(126) : \(\text{Ar} = \text{Ar}_1 = \text{aryl} / \text{substituted aryl groups}\)

Some new 4-thiazolidinone derivatives of 2-mercaptobenzoxazole (127) have been synthesized and evaluated for their antimicrobial activity.\(^{303}\)

\[
\begin{align*}
\text{Ar} & \quad \text{Ar}_1
\end{align*}
\]

(127) : \(\text{Ar} = \text{Ar}_1 = \text{aryl} / \text{substituted aryl groups}\)

A novel series of thiazolidinone derivatives of pyrazine (128) were synthesized and evaluated for their antimicrobial activity.\(^{304}\)

\[
\begin{align*}
\text{R}
\end{align*}
\]

(128) : \(\text{R} = \text{alkyl/substituted aryl groups}\)

2-{5-Arylidine-2-phenyl-3-(acetylamino)-1,3-thiazolidin-4-ones}-2-mercaptobenzothiazole (129) have been synthesized and screened for their antimicrobial and anti-inflammatory activity.\(^{305}\)

\[
\begin{align*}
\text{R}, \text{R}_1, \text{R}_2, \text{R}_3
\end{align*}
\]

(129) : \(\text{R}, \text{R}_1, \text{R}_2, \text{R}_3 = \text{aryl/substituted aryl groups}\)
3-[(4’-(p-chlorophenyl)-thiazol-20-yl)-2-[(substituted thiazolidinone)-aminomethyl]-6-bromo quinazolin-4-ones (130) were reported as anti-inflammatory agents.\(^{306}\)

![Chemical Structure](image)

(130) : R = aryl/substituted aryl groups

Some [2-(6-substituted-benzothiazole-2-yl-imino)-4-oxo-3-phenyl-thiazolidin-5-yl]-acetic acids (131) have synthesized and evaluated for their anti-inflammatory activity.\(^{307}\)

![Chemical Structure](image)

(131) : R = H/Cl/CH\(_3\)

2-(Substituted aryl)-3-(N’-imidazolyl-acetamidyl)-5-arylidene-4-oxothiazolidines (132) have been synthesized and tested for their biological activities such as antibacterial, antifungal, anti-inflammatory and analgesic.\(^{308}\)

![Chemical Structure](image)

(132): R = R\(_1\) = aryl/substituted aryl groups
Some 2-aryl-4-oxo-thiazolidin-3-yl-amides (133) were synthesized and evaluated for their antiproliferative activity against five human prostate cancer cell lines using the sulforhodamine B assay.\(^{309}\)

\[
\text{(133)} : R = \text{ph/biphenyl}
\]

4-Thiazolidinones (134) have been synthesized and screened for their antiproliferative activity against five human colon cancer cell lines.\(^{310}\)

\[
\text{(134)}
\]

Some 4-thiazolidinones (135) have been reported to possess antimycobacterial activity against \textit{Mycobacterium tuberculosis H}_{37}Rv.\(^{311}\)

\[
\text{(135)} : R = \text{aryl/substituted aryl groups}
\]
4-thiazolidinones (136) have synthesized and evaluated for their antimycobacterial activity against *Mycobacterium tuberculosis H$_{37}$Rv*.$^{312}$

![Image of molecule 136]

(136) : $R = \text{CH}_3/\text{C}_2\text{H}_5/\text{CH}_2\text{CH} = \text{CH}_2$

A new series of 2-(2,6-dihalophenyl)-3-(pyrimidin-2-yl)-1,3-thiazolidin-4-ones (137) have been synthesized and evaluated for their anti-HIV activity.$^{313}$

![Image of molecule 137]

(137) : $R = \text{H/Me}; R_1 = \text{H/Cl/Me/MeO/OH}; R_2 = R_3 = \text{F/Cl}$

A new series of 2-aryl-3-heteroaryl-1,3-thiazolidin-4-ones (138) have been synthesized and found to possess anti-HIV activity.$^{314}$

![Image of molecule 138]

(138) : $R = \text{H/Me/ph} ; R_1 = \text{H/Me/Et}; R_2 = \text{Cl/F}; X = \text{C/N}$
Some quinazolinyl thiazolidines (139) were synthesized and screened for their antiperkinsonian activity against catatonia, hypokinesia, rigidity and tremor \textit{in vivo} in rats and mice. \textsuperscript{315}

![Chemical structure of quinazolinyl thiazolidines](image)

\begin{equation}
(139) : R = CH_3/C_2H_5 ; Ar = \text{aryl/heterocycles}
\end{equation}

4-Thiazolidinones (140) have been synthesized and evaluated for their antihistaminic activity. \textsuperscript{316}

![Chemical structure of 4-thiazolidinones](image)

\begin{equation}
(140) : R = H/\text{halo/CH}_3/\text{OCH}_3/\text{NO}_2/\text{NH}_2/iPr
\end{equation}

Some 2-(3,5-di-tert-butyl-4-hydroxy-phenyl)-3-(aminopropyl)-thiazolidinone (141) was synthesized and evaluated for their antioxidant activity. \textsuperscript{317}

![Chemical structure of 2-(3,5-di-tert-butyl-4-hydroxy-phenyl)-3-(aminopropyl)-thiazolidinone](image)

\begin{equation}
(141)
\end{equation}
A series of new 1,3-thiazolidine-4-ones (142) have been synthesized and evaluated for their antiviral activity against various types of viruses in HEL, HeLa and Vero cell cultures.\(^{318}\)

![Chemical Structure](image)

(142) : R = alkyl/ arylalkyl; Ar = aryl/ substituted aryl groups
**Table 1.2: Pharmacological activity of clinically used thiazolidinone derivative**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name of drug</th>
<th>Activity</th>
<th>Chemical structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Pioglitazone</td>
<td>Antidiabetic</td>
<td><img src="image1.png" alt="Chemical structure" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>drug</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Rivoglitazone</td>
<td>Antidiabetic</td>
<td><img src="image2.png" alt="Chemical structure" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>drug</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Rosiglitazone</td>
<td>Antidiabetic</td>
<td><img src="image3.png" alt="Chemical structure" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>drug</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Troglitazone</td>
<td>Antidiabetic</td>
<td><img src="image4.png" alt="Chemical structure" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>drug</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Englitateone</td>
<td>Antidiabetic</td>
<td><img src="image5.png" alt="Chemical structure" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>drug</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Ciglitazone</td>
<td>Antidiabetic</td>
<td><img src="image6.png" alt="Chemical structure" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>drug</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Ozolinone</td>
<td>Diuretic</td>
<td><img src="image7.png" alt="Chemical structure" /></td>
</tr>
<tr>
<td></td>
<td>Compound</td>
<td>Category</td>
<td>Chemical Structure</td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
<td>---------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>8.</td>
<td>Etozoline</td>
<td>Diuretic</td>
<td><img src="image" alt="Etozoline Diuretic" /></td>
</tr>
<tr>
<td>9.</td>
<td>Ralitoline</td>
<td>Anticonvulsant</td>
<td><img src="image" alt="Ralitoline Anticonvulsant" /></td>
</tr>
<tr>
<td>10.</td>
<td>Piprozolin</td>
<td>Choleretic</td>
<td><img src="image" alt="Piprozolin Choleretic" /></td>
</tr>
<tr>
<td>11.</td>
<td>Mezolidon</td>
<td>Antiulcer agent</td>
<td><img src="image" alt="Mezolidon Antiulcer" /></td>
</tr>
<tr>
<td>12.</td>
<td>Spiclamazine</td>
<td>Antipsychotic</td>
<td><img src="image" alt="Spiclamazine Antipsychotic" /></td>
</tr>
<tr>
<td>13.</td>
<td>Thiazidomycin</td>
<td>Antibiotics for several/streptomyces species</td>
<td><img src="image" alt="Thiazidomycin Antibiotics" /></td>
</tr>
<tr>
<td>14.</td>
<td>Epatrestat</td>
<td>Aldose reductase inhibitor</td>
<td><img src="image" alt="Epatrestat Aldose reductase inhibitor" /></td>
</tr>
</tbody>
</table>
SECTION-1.7: GENERAL REVIEW AND SIGNIFICANCE OF MICROWAVE ASSISTED SYNTHESIS

Microwave (MW) activation as a non-conventional energy source has become a very popular and useful technology in organic chemistry. The number of annual publications on microwave assisted organic chemistry is growing rapidly with almost more than thousand publications in print since the pioneering work of Gedye\textsuperscript{322} in 1986 (Fig. 1.7.1).

Most of these publications describe important accelerations for a wide range of organic reactions especially when carried out under solvent-free conditions. The combination of solvent-free reaction conditions and microwave irradiation leads to large reductions in reaction times, enhancements in conversions and sometimes\textsuperscript{323,324} in selectively with several advantages of the eco-friendly approach, termed as green chemistry.

In the electromagnetic spectrum, the microwave radiation region is located between infrared radiation and radiowaves. Microwaves have wavelengths of 1 mm-1 m, corresponding to frequencies between 0.3 and 300 GHz. Telecommunication and microwave radar equipment occupy many of the band frequencies in this region. In general, in order to avoid interference, the wavelength at which industrial and domestic microwave apparatus intended for heating operates is regulated to 12.2 cm,
corresponding to a frequency of 2.450 (0.050) GHz, but other frequency allocations do exist. It has been known for a long time that microwaves can be used to heat materials. In fact, the development of microwave ovens for the heating of food has more than a 50-year history. In the 1970s, the construction of the microwave generator, the magnetron, was both improved and simplified. Consequently, the prices of domestic microwave ovens fell considerably, leading to them becoming a mass product. The design of the oven chamber or cavity, however, which is crucial for the heating characteristics, was not significantly improved until the end of the 1980s.

In inorganic chemistry, microwave technology has been used since the late 1970s, while it has only been implemented in organic chemistry since the mid-1980s. The development of the technology for organic chemistry has been rather slow compared to combinatorial chemistry and computational chemistry. This slow uptake of the technology has been principally attributed to its lack of controllability and reproducibility, safety aspects and a generally low degree of understanding of the basics of microwave dielectric heating. Since the mid-1990s, however, the number of publications has increased significantly (Fig. 1.7.1). The main reasons for this increase include the availability of commercial microwave equipment intended for organic chemistry and the development of the solvent-free technique, which has improved the safety aspects, but are mostly due to an increased interest in shorter reaction times.

The short reaction times and expanded reaction range that is offered by microwave assisted organic synthesis are suited to the increased demands in industry. In particular, there is a requirement in the pharmaceutical industry for a higher number of novel chemical entities to be produced, which requires chemists to employ a number of resources to reduce the time for the production of compounds. Chemistry data- bases, software for diversity selection, on-line chemical ordering systems, open-access and high throughput systems for analysis and high-speed, parallel and combinatorial synthesis equipment have all contributed in increasing the throughput. The common factors for these technical resources are automation and computer-aided control. They do not, however, speed up the chemistry itself. Developments in the chemistry have generally been
concerned with novel highly reactive reagents in solution or on solid supports.

In general, most organic reactions have been heated using traditional heat transfer equipment such as oil baths, sand baths, water baths and heating jackets. These heating techniques are, however, rather slow and a temperature gradient can develop within the sample. In addition, local overheating can lead to product, substrate and reagent decomposition.

In contrast, in microwave dielectric heating, the microwave energy is introduced into the chemical reactor remotely and direct access by the energy source to the reaction vessel is obtained. The microwave radiation passes through the walls of the vessel and heats only the reactants and solvent, not the reaction vessel itself. If the apparatus is properly designed, the temperature increase will be uniform throughout the sample, which can lead to less by-products and or decomposition products. In pressurized systems, it is possible to rapidly increase the temperature far above the conventional boiling point of the solvent used.

**Fundamentals of microwave technology**

The fundamental mechanism of microwave heating involves agitation of polar molecules or ions that oscillate under the effect of an oscillating electric or magnetic field. In the presence of an oscillating field, particles try to orient themselves or be in phase with the field. However, the motion of these particles is restricted by resisting forces (inter-particle interaction and electric resistance), which restrict the motion of particles and generate random motion, producing heat. Since the response of various materials to microwave radiation is diverse, not all materials are amenable to microwave heating. Based on their response to microwaves, materials can be broadly classified as follows:

- Materials that are transparent to microwaves, e.g., sulphur
- Materials that reflect microwaves, e.g., copper
- Materials that absorb microwaves, e.g., water

Only materials that absorb microwave radiation are relevant to microwave chemistry. These materials can be categorised according to the three main mechanisms of heating (Figure 1.72), namely:
1. Dipolar polarization
2. Conduction mechanism and
3. Interfacial polarization.

**Figure 1.72: Methods of heating by microwave radiation**

**Dipolar polarization**

Dipolar polarization is a process by which heat is generated in polar molecules. On exposure to an oscillating electromagnetic field of appropriate frequency, polar molecules try to follow the field and align themselves in phase with the field. However, owing to inter-molecular forces, polar molecules experience inertia and are unable to follow the field. This results in the random motion of particles, and this random interaction generates heat. Dipolar polarisation can generate heat by either one or both the following mechanisms:

1. Interaction between polar solvent molecules such as water, methanol and ethanol and
2. Interaction between polar solute molecules such as ammonia and formic acid.
The key requirement for dipolar polarisation is that the frequency range of the oscillating field should be appropriate to enable adequate inter-particle interaction. If the frequency range is very high, inter-molecular forces will stop the motion of a polar molecule before it tries to follow the field, resulting in inadequate inter-particle interaction. On the other hand, if the frequency range is low, the polar molecule gets sufficient time to align itself in phase with the field. Hence, no random interaction takes place between the adjoining particles. Microwave radiation has the appropriate frequency (0.3-30 GHz) to oscillate polar particles and enable enough inter-particle interaction. This makes it an ideal choice for heating polar solutions.

In addition, the energy in a microwave photon (0.037 kcal/mol) is very low, relative to the typical energy required to break a molecular bond (80-120 kcal/mol). Therefore, microwave excitation of molecules does not affect the structure of an organic molecule, and the interaction is purely kinetic.

Conduction mechanism

The conduction mechanism generates heat through resistance to an electric current. The oscillating electromagnetic field generates an oscillation of electrons or ions in a conductor, resulting in an electric current. This current faces internal resistance, which heats the conductor. The main limitation of this method is that it is not applicable for materials that have high conductivity, since such materials reflect most of the energy that falls on them.

Interfacial polarization

The interfacial polarization method can be considered as a combination of the conduction and dipolar polarization mechanisms. It is important for heating systems that comprise a conducting material dispersed in a non-conducting material. For example, consider the dispersion of metal particles in sulfur. Sulfur does not respond to microwaves, and metals reflect most of the microwave energy they are exposed to, but combining the two makes them a good microwave-absorbing material. However, for this to take place, metals have to be used in powder form. This is because, unlike a metal surface, metal powder is a good absorber of microwave radiation. It
Apoorva Upadhyay                  Dr. H.S. Gour University (A Central University), Sagar

absorbs radiation and is heated by a mechanism that is similar to dipolar polarization. The environment of the metal powder acts as a solvent for polar molecules and restricts the motion of ions by forces that are equivalent to inter-particle interactions in polar solvents. These restricting forces, under the effect of an oscillating field, induce a phase lag in the motion of ions. The phase lag generates a random motion of ions and results in the heating of the system.

**Microwave heating and conventional heating a comparison**

In a typical reaction coordinate, the process begins with reactants, which have a certain potential energy level. In order to complete the transformation, these reactants must be activated to a transition state. Once there, they quickly react and return to a lower energy state, to give the product. Microwave energy provides the momentum to overcome the activation energy barrier and complete the reaction. One of the most important aspects of microwave energy is the rate at which it heats. Microwaves will transfer energy in $10^{-9}$ sec, with each cycle of the electromagnetic energy. The kinetic molecular relaxation from this energy is approximately $10^{-5}$ sec. The energy transfers faster than the molecules can relax, resulting in a non-equilibrium condition and high instantaneous temperatures that affect the kinetics of the system. This enhances the reaction rate, as well as the yields. Activated complexes do not normally exist long enough to have an opportunity to absorb microwave energy, although there are a number of stabilized intermediates, resistant stabilized intermediates and other intermediates that are much longer lived. Many of these have lifetimes longer than $10^{-9}$ sec, so the opportunity exists for them to couple directly with the microwave and be further enhanced. Most intermediates are highly polar species and many of them are even ionic in character, making them excellent candidates for microwave energy transfer. Microwave enhanced chemical reactions can be faster by as much as 1,000 fold. Microwave heating allows chemical reactions to be shifted from kinetic control to thermodynamic control because of the high energy available. This can change the product for a particular transformation.
Superiority of microwave method over conventional method

MORE chemistry offers a simple, non-conventional technique for the synthesis of a wide variety of compounds having medicinal, pharmaceutical and commercial importance.

- Highly accelerated reaction rate is the main advantage, which enables chemist to carry out a synthesis in much lesser time and in good yields.
- It provides a rapid inexpensive access to very high temperature and pressure in sealed container like Teflon bomb. In conventional method requires elaborate apparatus, longer heating times, large volume of organic solvents and heat allows virtually no control over energy input.
- Recent simplifications of MORE technique have increased safety and practical utility of microwave oven for their use in organic laboratories without any modification.
- Solvents used in organic synthesis are of major concern as environmental pollutants, many of which are proved carcinogenic, mutagenic and allergens.
- An Eco-friendly method is an important salient feature of MORE chemistry, since it requires no solvents (Dry media synthesis) or very little solvent as energy transfer medium. Very rapid synthesis also results in lesser evaporation of solvents preventing environmental pollution. Thus it is a step towards the Green Chemistry.
- The combination of supported reagents and microwave irradiation can be used to carry out a wide range of reactions in short times and with high conversions and selectivity without the need for solvents. This approach can prove beneficial since the recovery of solvents from conventional reaction systems always results in some losses. Recovery of both products and inorganic support/catalyst is generally possible, leading to an efficient and low waste route to a range of products.
Energy Transfer Medium

In MORE technique, organic solvents serve as an energy transfer medium. Any solvent having high dielectric constant and high boiling point is excellent transfer medium for a variety of microwave induced organic reactions. High boiling solvents like N,N-dimethyl formamide (DMF), o-dichlorobenzene and 1,2-dichloromethane are used commonly. Polar solvents with high dielectric constants absorb microwave energy better than non-polar solvents due to dipole rotation and are therefore, heated rapidly with higher energy transfer rates. Thus, DMF and dichloromethane are heated much faster than hexane or carbon tetrachloride in a microwave oven. Superheating of liquids is common under microwave irradiation. Water for example reaches 105°C (5°C above actual boiling point) and acetonitrile reaches 120°C an amazing 38°C higher than its boiling point. This superheating, which is not commonly seen in conventional heating, may help in increasing the rate of reaction. Rate of temperature increase is not only a function of dielectric properties but also the ionic strength, specific heat capacity, emissivity, geometry, sample volume and strength of the applied field. In practice, and as general route, almost all types of organic reaction that require heat can be performed using microwaves.

Fluid salts or ionic liquids, consisting entirely of ions, absorb microwave radiation in a highly efficient manner and are particularly attractive additives because they are relatively inert and stable at temperatures up to 200°C, have a negligible vapor pressure$^{327,328}$ and dissolve to an appreciable extent in a wide range of organic solvents. Energy transfer between the polar molecules that couple with the microwave radiation and the non-polar solvent bulk is rapid and often provides an efficient means of using non-polar solvents for synthesis using microwave irradiation. Boiling point and dielectric constant of commonly used solvents are listed in Table 1.7.1.
Table 1.7.1: Boiling point and dielectric constant of different solvents.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Solvents</th>
<th>Boiling point (°C)</th>
<th>Dielectric constant (ε) at 25°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetone</td>
<td>56.5</td>
<td>20.70</td>
</tr>
<tr>
<td>2</td>
<td>Acetonitrile</td>
<td>82.0</td>
<td>37.50</td>
</tr>
<tr>
<td>3</td>
<td>Benzene</td>
<td>80.1</td>
<td>2.27</td>
</tr>
<tr>
<td>4</td>
<td>1-Butanol</td>
<td>117.7</td>
<td>17.80</td>
</tr>
<tr>
<td>5</td>
<td>Chlorobenzene</td>
<td>132.1</td>
<td>5.62</td>
</tr>
<tr>
<td>6</td>
<td>Chloroform</td>
<td>61.7</td>
<td>4.81</td>
</tr>
<tr>
<td>7</td>
<td>Diethyl ether</td>
<td>34.6</td>
<td>4.34</td>
</tr>
<tr>
<td>8</td>
<td>Diethyl formamide</td>
<td>153.0</td>
<td>36.71</td>
</tr>
<tr>
<td>9</td>
<td>Methanol</td>
<td>64.7</td>
<td>32.70</td>
</tr>
<tr>
<td>10</td>
<td>Ethanol</td>
<td>78.4</td>
<td>32.40</td>
</tr>
<tr>
<td>11</td>
<td>n-Hexane</td>
<td>68.7</td>
<td>1.89</td>
</tr>
<tr>
<td>12</td>
<td>Dimethyl sulfoxide</td>
<td>189.0</td>
<td>46.60</td>
</tr>
<tr>
<td>13</td>
<td>Ethyl acetate</td>
<td>77.1</td>
<td>6.02</td>
</tr>
<tr>
<td>14</td>
<td>Pyridine</td>
<td>115.5</td>
<td>12.30</td>
</tr>
<tr>
<td>15</td>
<td>Water</td>
<td>100.0</td>
<td>78.50</td>
</tr>
</tbody>
</table>

Why does microwave irradiation speed up chemical reactions?

Since the introduction of microwave assisted organic synthesis in 1986, the main debate has dealt with the question of what actually alerts the outcome of the synthesis. Is it merely an effect of the thermally heat generated by the microwaves or is it an effect specific for microwave heating?

In order to able to make this distinction, the term specific microwave effect should be defined. Historically, specific microwave effects have been claimed, when the outcome of a synthesis performed using microwave heating differ from its thermally heated counterpart. Some of the earlier reports have, in later experiments not been reproduced329 while some are
definitely debatable and others are hard to explain.\textsuperscript{330} The main advantage of using microwave assisted organic synthesis is the shorter reaction times. The rate of the reaction can be described by the Arrhenius equation (1).

\[ K = A e^{-\Delta G/RT} \] (1)

Considering equation (1), there are basically two ways to increase the rate of a chemical reaction. First, the pre-exponential factor $A$, which describes the molecular mobility and depends on the frequency of vibrations of the molecules at the reaction interface. P. Lidstrom et al.\textsuperscript{331} have described how microwave induce an increase in molecular vibrations and it has been proposed that this factor, $A$ can be affected.\textsuperscript{332} Other authors, however, have proposed that microwave irradiation produces an alteration in the exponential factor by affecting the free energy of activation, $\Delta G$.\textsuperscript{332}

Microwave heating can be very rapid, producing heat profiles not easy accessible by other heating techniques. Experiments performed using microwave assisted organic synthesis may therefore result in a different outcome when compared to conventionally heating reaction, even if the final temperature is the same. It has been shown, for example, that the heating profile can alter the regioselectivity in the sulfonation of naphthalene.\textsuperscript{333} In poorly design single mode systems, hot spots may be encountered, which is frequently a problem in multi mode-systems. In these systems the problem can give rise to local temperature which higher than the temperature measured in the bulk. Similarly, this superheating effect can also results in temperature much higher than expected when performing the reflux reactions in microwave ovens. These effects can sometimes give rise to unexpected results. Additionally, the accuracy of the temperature measurements when performing microwave assisted organic synthesis can appear to be uncontrolled. These inaccuracies in temperature measurement often occur when performing the reactions in domestic ovens with microtitre plates or on solid supports, where there are inherent difficulties in measuring the temperature accurately.\textsuperscript{334,335}
Significance of microwave assisted synthesis

Synthesis of aziridines

Among the various protocols known for the synthesis of the title compounds, the focused microwave approach under ‘dry’ conditions is especially notable in view of the observation that elimination predominates over the Michael addition under MW irradiation when compared to the classical heating under the same conditions.\(^{336}\)

\[
\begin{align*}
&\text{X} = \text{electron withdrawing group} \\
&\text{Bentonite} \\
&\text{R'} = \text{electron donating group}
\end{align*}
\]

Synthesis of pyrroles

The classical Pall-Knorr Cyclization of 1,4-diketones to give pyrroles is dramatically speeded-up under microwave irradiation and high yields are obtained.\(^{337}\)

\[
\begin{align*}
\text{R} = \text{CH}_2\text{C}_6\text{H}_5/4-\text{MeOC}_6\text{H}_4
\end{align*}
\]

Synthesis of imidazoles

An important classical preparation of imidazoles is form an \(\alpha\)-diketone, an aldehyde and ammonia. Here again, excellent yields can be obtained in reaction times of a few minutes.\(^{338}\)
Synthesis of pyrazoles

Another recent application of microwaves in the synthesis of pyrazoles from hydrazones using the Vilsmeier cyclization method by treatment with POCl₃ and DMF.³³⁹

Where \( R = \text{H/OH}; R_1 = \text{H/CH}_3; R_2 = \text{H/NO}_2; R_3 = \text{NO}_2; R_4 = \text{CH}_3/C_2H_5 \)

Synthesis of benz-imidazoles, oxazoles and thiazoles

Ring closure reactions of appropriate o-substituted anilines to give benzimidazoles, benzoxazoles and benzothiazoles take place much faster and in significantly high yield under microwave conditions³⁴⁰ than conventionally.³⁴¹

Where \( Z = \text{NH}_2/\text{OH}/\text{SH}; Y = \text{NH/O/S} \)

Synthesis of pyridines

A rapid and high yielding protocol for the synthesis of 1,4-dihydropyridine in the presence of silica gel under microwave irradiation has been described.³⁴²
Synthesis of 2-aryl-1,2,3,4-tetrahydro-4-quinolones

Another solventless cyclization reaction using montmorillonite K 10 clay under microwave irradiation conditions was used to synthesize 2-aryl-1,2,3,4-tetrahydro-4-quinolones from 2-amino chalcones which are valuable precursors for the medicinally important quinolones.\textsuperscript{343}

\[
\begin{align*}
\text{R} & = \text{CN, CO}_2\text{Me, CO}_2\text{Et} \\
\text{R}_1, \text{R}_2 & = \text{alkyl} ; \quad \text{R} = \text{CN, CO}_2\text{Et}
\end{align*}
\]

Synthesis of bridgehead nitrogen heterocycles

Microwave energy has found application in the rapid synthesis of bridgehead nitrogen heterocycles under solvent free conditions. Rahmouni et al. have synthesized pyrimidino[1,6-a] benzimidazoles and 2,3-dihydroimidazo[1,2-c]pyrimidines under microwave irradiation in moderate yields from N-acylimidates and activated 2-benzimidazoles and imidazoline ketene aminals, respectively.\textsuperscript{344}
Synthesis of 2-oxazolines

Oxazolines are readily synthesized from carboxylic acids and a,a,a-tris(hydroxymethyl)methylamine under microwave irradiation conditions.\textsuperscript{345}

\[
\text{RCOOH} + \text{H}_2\text{NCH}_{2}\text{OH} \xrightarrow{\text{MW, 2-5 min}} \text{MW, 80-95}\% \\
\text{where } R = \text{2-furyl, phenyl, heptadecanyl}
\]

Synthesis of 2-aroylbenzofurans

Naturally occurring and pharmacologically important 2-aroylbenzofurans are easily obtainable in the solid state from o-tosyl-oxyketones and salicylaldehydes in the presence of a base such as potassium fluoride doped alumina using microwave irradiation.\textsuperscript{346}

\begin{center}
\includegraphics[width=0.5\textwidth]{synthesis.png}
\end{center}

Synthesis of $\beta$-Lactams

In a preliminary report, Bose et al.\textsuperscript{ref} had described an efficient and rapid synthesis of number of $\beta$-Lactams under microwave irradiation. Further in closed Teflon vessels using KF and phase transfer catalyst, $\beta$-lactams have been synthesized in few minutes from ketene silyl acetal and aldimines.\textsuperscript{347}

\[
\text{H}_3\text{C} \xrightarrow{\text{KF-18 Crown 6}} \text{MW 300W, 7 min} \\
\text{93\% (anti/syn=63/35)}
\]
The efficient and rapid synthesis of novel azetidin-2-ones has been established by both conventional and microwave irradiation.\(^{348}\)

![Chemical Structure](image1)

Where \(R = 2,3,4 - \text{OH}/2,3,4 - \text{Cl}/4-\text{NO}\_2/2,4 - \text{OCH}\_3/3,4,5 - (\text{OCH}\_3)\_3\)

Srivastava S. K. \textit{et al} have synthesized 2-azetidinones by both conventional and microwave irradiation method.\(^{349}\)

![Chemical Structure](image2)

Where \(\text{Ar} = \text{aryl/substituted aryl groups}\)

**Synthesis of thiazolidinone derivatives**

2-\{[2'-\text{chloro}-7'-\text{methoxyquinoline}-3'-yl]\}-3-\{3''-\text{hydroxy}-6''-\text{substituted phenyldiazenyl}\} phenyl]-5-methyl-1,3-thiazolidin-4-one have been synthesized by the reaction of 3-\{[(1 \text{E})-(2'-\text{chloro}-7'-\text{methoxyquinoline}-3'-yl) \text{methylene}]amino\}-4-(substituted phenyldiazenyl) phenol with thiolactic acid. The reaction was carried out by both conventional and microwave methods.\(^{350}\)
An efficient and extremely fast procedure for the synthesis of 4-thiazolidinones by the reaction of arylidene-[(2-benzothiazolylthio)-acetamidyl] with thioglycolic acid in DMF in the presence of a catalytic amount of anhydrous ZnCl$_2$ under microwave irradiation is described.  

Where R = H/ 2,3,4- Br/ 2,3,4- F/2,3,4–NO$_2$/ 2,3,4–CH$_3$

Where R = aryl/ substituted aryl groups
SECTION-1.8: AIM AND WORK PLAN OF THE RESEARCH

It has been observed from the literature that the evolution in the pharmaceutical industry has led to synthesis, identification, screening, development and interpretation of the mode of action of biologically active compounds. In the heterocyclic series, the most promising agents are the Phenothiazine, 5-Nitroindazole and Isonicotinamide as well as their azetidinones and thiazolidinones derivatives. These combinations gave various biologically active compounds of therapeutic important.

The work plan of the research has been divided into three parts.

Part I : Synthesis of new heterocyclic compounds.

Part II : Characterization of the compounds by chemical methods, microanalytical data and spectral techniques.

Part III : Evaluation of the biological activity of the synthesized products viz.

(a) Antibacterial activity and
(b) Antifungal activity.

Eleven series of the compounds have been synthesized by following the Schemes-1, 2 and 3 respectively.
SCHEME-1

\[ \text{Ar} = \text{Ar}_1 = \text{Various substituted aryl groups} \]

Series-1
(AU-01 to AU-05)

Series-2
(AU-06 to AU-10)

Series-3
(AU-11 to AU-15)
Series-1: 4-Arylideneamino-3-mercapto-5-[[phenothiazin-10-yl] methyl]-1,2,4-triazoles.

The compounds of the Series-1 (AU-01 to AU-05) have been synthesized through by following five steps of the Scheme-1 (Table 1.8.1).

Table 1.8.1: List of the synthesized compounds under series-1.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Chemical name</th>
<th>Ar</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU-01</td>
<td>4-Benzylideneamino-3-mercapto-5-[[phenothiazin-10-yl]methyl]-1,2,4-triazole</td>
<td>C$_6$H$_5$</td>
<td>C$<em>{22}$H$</em>{17}$N$_5$S$_2$</td>
</tr>
<tr>
<td>AU-02</td>
<td>4-(2-Chloro-benzylideneamino)-3-mercapto-5-[[phenothiazin-10-yl]methyl]-1,2,4-triazole</td>
<td>2-ClC$_6$H$_4$</td>
<td>C$<em>{22}$H$</em>{16}$N$_5$S$_2$Cl</td>
</tr>
<tr>
<td>AU-03</td>
<td>4-(2-Bromo-benzylideneamino)-3-mercapto-5-[[phenothiazin-10-yl]methyl]-1,2,4-triazole</td>
<td>2-BrC$_6$H$_4$</td>
<td>C$<em>{22}$H$</em>{16}$N$_5$S$_2$Br</td>
</tr>
<tr>
<td>AU-04</td>
<td>4-(2-Nitro-benzylideneamino)-3-mercapto-5-[[phenothiazin-10-yl]methyl]-1,2,4-triazole</td>
<td>2-NO$_2$C$_6$H$_4$</td>
<td>C$<em>{22}$H$</em>{16}$N$_6$O$_2$S$_2$</td>
</tr>
<tr>
<td>AU-05</td>
<td>4-(2-Methoxy-benzylideneamino)-3-mercapto-5-[[phenothiazin-10-yl]methyl]-1,2,4-triazole</td>
<td>2-OCH$_3$C$_6$H$_4$</td>
<td>C$<em>{23}$H$</em>{19}$N$_5$O$_2$S$_2$</td>
</tr>
</tbody>
</table>
Series-2: 2-Aryl-3-(3-mercapto-5-phenothiazin-10-ylmethyl-[1,2,4]-triazol-4-yl)-thiazolidine-4-ones.

The compounds of the Series-2 (AU-06 to AU-10) have been synthesized from compounds of Series-1 (AU-01 to AU-05) as precursors (Table 1.8.2).

Table 1.8.2: List of the synthesized compounds under series-2.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Chemical name</th>
<th>Ar</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU-06</td>
<td>2-Phenyl-3-(3-mercapto-5-phenothiazin-10-ylmethyl-[1,2,4]-triazol-4-yl)-thiazolidin-4-one</td>
<td>C₆H₅</td>
<td>C₂₄H₁₉N₅O₃S₃</td>
</tr>
<tr>
<td>AU-07</td>
<td>2-(2-Chloro-phenyl)-3-(3-mercapto-5-phenothiazin-10ylmethyl-[1,2,4]-triazol-4-yl)-thiazolidin-4-one</td>
<td>2-ClC₆H₄</td>
<td>C₂₄H₁₉N₅O₃Cl</td>
</tr>
<tr>
<td>AU-08</td>
<td>2-(2-Bromo-phenyl)-3-(3-mercapto-5-phenothiazin-10ylmethyl-[1,2,4]-triazol-4-yl)-thiazolidin-4-one</td>
<td>2-BrC₆H₄</td>
<td>C₂₄H₁₉N₅O₃Br</td>
</tr>
<tr>
<td>AU-09</td>
<td>2-(2-Nitro-phenyl)-3-(3-mercapto-5-phenothiazin-10ylmethyl-[1,2,4]-triazol-4-yl)-thiazolidin-4-one</td>
<td>2-NO₂C₆H₄</td>
<td>C₂₄H₁₉N₆O₃S₃</td>
</tr>
<tr>
<td>AU-10</td>
<td>2-(2-Methoxy-phenyl)-3-(3-mercapto-5-phenothiazin-10ylmethyl-[1,2,4]-triazol-4-yl)-thiazolidin-4-one</td>
<td>2-OCH₃C₆H₄</td>
<td>C₂₅H₂₁N₅O₂S₃</td>
</tr>
</tbody>
</table>
Series-3: 5-Arylidene-2-aryl-3-(3-mercapto-5-phenothiazin-10-ylmethyl-[1,2,4]-triazol-4-yl)-thiazolidine-4-ones.

The compounds of the Series-3 (AU-11 to AU-15) have been synthesized from compounds of Series-2 (AU-06 to AU-10) as precursors (Table 1.8.3).

Table 1.8.3: List of the synthesized compounds under series-3.

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Chemical name</th>
<th>Ar</th>
<th>Ar₁</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU-11</td>
<td>5-Benzylidene-2-phenyl-3-(3-mercapto-5-phenothiazin-10-ylmethyl-[1,2,4]-triazol-4-yl)-thiazolidin-4-one</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>C₃₁H₂₃N₅OS₃</td>
</tr>
<tr>
<td>AU-12</td>
<td>5-(2-Chloro-benzylidene)-2-(2-chloro-phenyl)-3-(3-mercapto-5-phenothiazin-10-ylmethyl-[1,2,4]-triazol-4-yl)-thiazolidin-4-one</td>
<td>2-ClC₆H₄</td>
<td>2-ClC₆H₄</td>
<td>C₃₁H₂₁N₅OS₃Cl₂</td>
</tr>
<tr>
<td>AU-13</td>
<td>5-(2-Bromo-benzylidene)-2-(2-bromo-phenyl)-3-(3-mercapto-5-phenothiazin-10-ylmethyl-[1,2,4]-triazol-4-yl)-thiazolidin-4-one</td>
<td>2-BrC₆H₄</td>
<td>2-BrC₆H₄</td>
<td>C₃₁H₂₁N₅OS₃Br₂</td>
</tr>
<tr>
<td>AU-14</td>
<td>5-(2-Nitro-benzylidene)-2-(2-nitro-phenyl)-3-(3-mercapto-5-phenothiazin-10-ylmethyl-[1,2,4]-triazol-4-yl)-thiazolidin-4-one</td>
<td>2-NO₂C₆H₄</td>
<td>2-NO₂C₆H₄</td>
<td>C₃₁H₂₁N₇O₅S₃</td>
</tr>
<tr>
<td>AU-15</td>
<td>5-(2-Methoxy-benzylidene)-2-(2-methoxy-phenyl)-3-(3-mercapto-5-phenothiazin-10-ylmethyl-[1,2,4]-triazol-4-yl)-thiazolidin-4-one</td>
<td>2-OCH₃C₆H₄</td>
<td>2-OCH₃C₆H₄</td>
<td>C₃₃H₂₇N₅O₅S₃</td>
</tr>
</tbody>
</table>
SCHEME – 2

1. \[ \text{O}_2\text{N-}[\text{NHNCOOC}_2\text{H}_5] \]
2. \[ \text{O}_2\text{N-}[\text{NHNCONHN}=\text{H}] \]
3. \[ \text{O}_2\text{N-}[\text{NHNCONHN}=\text{N}] \]
4. \[ \text{O}_2\text{N-}[\text{NHNCONHN}=\text{Cl}] \]
5. \[ \text{O}_2\text{N-}[\text{NHNCONHN}=\text{Ar}] \]
6. \[ \text{O}_2\text{N-}[\text{NHNCONHN}=\text{Ar}_1] \]

Series - 4 (AU-16 to AU-20)
Series - 5 (AU-21 to AU-25)
Series - 6 (AU-26 to AU-30)
Series - 7 (AU-31 to AU-35)

\[ \text{Ar} = \text{Ar}_1 = \text{Various substituted aryl groups} \]
**Series-4: N-(arylidene amino acetamidyl)-5-nitroindazoles.**

The compounds of the **Series-4 (AU-16 to AU-20)** have been synthesized by following three steps of the **Scheme-2 (Table 1.8.4).**

**Table 1.8.4: List of the synthesized compounds under series-4.**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Chemical name</th>
<th>Ar</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU-16</td>
<td>N-(benzylidene amino acetamidyl)-5-nitroindazole</td>
<td>C₆H₅</td>
<td>C₁₆H₁₃N₅O₃</td>
</tr>
<tr>
<td>AU-17</td>
<td>N-(4-chlorobenzylidene amino acetamidyl)-5-nitroindazole</td>
<td>4-ClC₆H₄</td>
<td>C₁₆H₁₂N₅O₃Cl</td>
</tr>
<tr>
<td>AU-18</td>
<td>N-(3-bromobenzylidene amino acetamidyl)-5-nitroindazole</td>
<td>3-BrC₆H₄</td>
<td>C₁₆H₁₂N₅O₃Br</td>
</tr>
<tr>
<td>AU-19</td>
<td>N-(3-nitrobenzylidene amino acetamidyl)-5-nitroindazole</td>
<td>3-NO₂C₆H₄</td>
<td>C₁₆H₁₂N₆O₅</td>
</tr>
<tr>
<td>AU-20</td>
<td>N-(4-methylbenzylidene amino acetamidyl)-5-nitroindazole</td>
<td>4-CH₃C₆H₄</td>
<td>C₁₇H₁₅N₅O₃</td>
</tr>
</tbody>
</table>
Series-5: N-[(4-aryl-3-chloro-2-oxo-azetidine) acetamidyl]-5-nitroindazoles.

The compounds of the Series-5 (AU-21 to AU-25) have been synthesized from compounds of Series-4 (AU-16 to AU-20) as precursors (Table 1.8.5).

Table 1.8.5: List of the synthesized compounds under series-5.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Chemical name</th>
<th>Ar</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU-21</td>
<td>N-[(4-phenyl-3-chloro-2-oxo-azetidine)-acetamidyl]-5-nitroindazole</td>
<td>C₆H₅</td>
<td>C₁₈H₁₄N₅O₄Cl</td>
</tr>
<tr>
<td>AU-22</td>
<td>N-[(4-(4-chlorophenyl)-3-chloro-2-oxo-azetidine)-acetamidyl]-5-nitroindazole</td>
<td>4-ClC₆H₄</td>
<td>C₁₈H₁₃N₅O₄Cl₂</td>
</tr>
<tr>
<td>AU-23</td>
<td>N-[(4-(3-bromophenyl)-3-chloro-2-oxo-azetidine)-acetamidyl]-5-nitroindazole</td>
<td>3-BrC₆H₄</td>
<td>C₁₈H₁₃N₅O₄ClBr</td>
</tr>
<tr>
<td>AU-24</td>
<td>N-[(4-(3-nitrophenyl)-3-chloro-2-oxo-azetidine)-acetamidyl]-5-nitroindazole</td>
<td>3-NO₂C₆H₄</td>
<td>C₁₈H₁₃N₆O₆Cl</td>
</tr>
<tr>
<td>AU-25</td>
<td>N-[(4-(4-methylphenyl)-3-chloro-2-oxo-azetidine)-acetamidyl]-5-nitroindazole</td>
<td>4-CH₃C₆H₄</td>
<td>C₁₉H₁₆N₅O₄Cl</td>
</tr>
</tbody>
</table>
Series-6: N-[(4-oxo-2-aryl-1,3-thiazolidine)-acetamidyl]-5-nitroindazoles.

The compounds of the Series-6 (AU-26 to AU-30) have been synthesized from compounds of Series-4 (AU-16 to AU-20) as precursors (Table 1.8.6).

Table 1.8.6: List of the synthesized compounds under series-6.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Chemical name</th>
<th>Ar</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU-26</td>
<td>N-[(4-oxo-2-phenyl-1,3-thiazolidine)-acetamidyl]-5-nitroindazole</td>
<td>C₆H₅</td>
<td>C₁₈H₁₅N₅O₄S</td>
</tr>
<tr>
<td>AU-27</td>
<td>N-[(4-oxo-2-(4-chlorophenyl)-1,3-thiazolidine)-acetamidyl]-5-nitroindazole</td>
<td>4-ClC₆H₄</td>
<td>C₁₈H₁₄N₅O₄SCl</td>
</tr>
<tr>
<td>AU-28</td>
<td>N-[(4-oxo-2-(3-bromophenyl)-1,3-thiazolidine)-acetamidyl]-5-nitroindazole</td>
<td>3-BrC₆H₄</td>
<td>C₁₈H₁₄N₅O₄SBr</td>
</tr>
<tr>
<td>AU-29</td>
<td>N-[(4-oxo-2-(3-nitrophenyl)-1,3-thiazolidine)-acetamidyl]-5-nitroindazole</td>
<td>3-NO₂C₆H₄</td>
<td>C₁₈H₁₄N₆O₆S</td>
</tr>
<tr>
<td>AU-30</td>
<td>N-[(4-oxo-2-(4-methylphenyl)-1,3-thiazolidine)-acetamidyl]-5-nitroindazole</td>
<td>4-CH₃C₆H₄</td>
<td>C₁₉H₁₇N₅O₄S</td>
</tr>
</tbody>
</table>
Series-7: \( N-[(4\text{-}oxo\text{-}5\text{-}arylidene}\text{-}2\text{-}phenyl\text{-}1\text{,}3\text{-}thiazolidine)\text{-}acetamidyl]\)-5\text{-}nitroindazole. \\

The compounds of the Series-7 (AU-31 to AU-35) have been synthesized from compounds of Series-6 (AU-26 to AU-30) as precursors (Table 1.8.7).

Table 1.8.7: List of the synthesized compounds under series-7.

<table>
<thead>
<tr>
<th>Compds</th>
<th>Chemical name</th>
<th>Ar</th>
<th>Ar₁</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU-31</td>
<td>( N-[(4\text{-}oxo\text{-}5\text{-}benzylidene}\text{-}2\text{-}phenyl\text{-}1\text{,}3\text{-}thiazolidine)\text{-}acetamidyl])-5\text{-}nitroindazole</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>C₂₅H₁₉N₅O₄S</td>
</tr>
<tr>
<td>AU-32</td>
<td>( N-[(4\text{-}oxo\text{-}5-(4\text{-}chlorobenzylidene)\text{-}2-(4\text{-}chlorophenyl)\text{-}1\text{,}3\text{-}thiazolidine)\text{-}acetamidyl])-5\text{-}nitroindazole</td>
<td>4-ClC₆H₄</td>
<td>4-ClC₆H₄</td>
<td>C₂₅H₁₇N₅O₄SCl₂</td>
</tr>
<tr>
<td>AU-33</td>
<td>( N-[(4\text{-}oxo\text{-}5-(3\text{-}bromobenzylidene)\text{-}2-(3\text{-}bromophenyl)\text{-}1\text{,}3\text{-}thiazolidine)\text{-}acetamidyl])-5\text{-}nitroindazole</td>
<td>3-BrC₆H₄</td>
<td>3-BrC₆H₄</td>
<td>C₂₃H₁₇N₅O₄SBr₂</td>
</tr>
<tr>
<td>AU-34</td>
<td>( N-[(4\text{-}oxo\text{-}5-(3\text{-}nitrobenzylidene)\text{-}2-(3\text{-}nitrophenyl)\text{-}1\text{,}3\text{-}thiazolidine)\text{-}acetamidyl])-5\text{-}nitroindazole</td>
<td>3-NO₂C₆H₄</td>
<td>3-NO₂C₆H₄</td>
<td>C₂₅H₁₇N₇O₆S</td>
</tr>
<tr>
<td>AU-35</td>
<td>( N-[(4\text{-}oxo\text{-}5-(4\text{-}methylbenzylidene)\text{-}2-(4\text{-}methylphenyl)\text{-}1\text{,}3\text{-}thiazolidine)\text{-}acetamidyl])-5\text{-}nitroindazole</td>
<td>4-CH₃C₆H₄</td>
<td>4-CH₃C₆H₄</td>
<td>C₂₇H₂₃N₅O₄S</td>
</tr>
</tbody>
</table>
SCHEME – 3

\[
\begin{align*}
\text{Series - 8} \\
&\text{(AU-36 to AU-40)} \\
\text{ArCHO} \\
\text{Series - 9} \\
&\text{(AU-41 to AU-45)} \\
\text{Ar} \\
\text{Series - 10} \\
&\text{(AU-46 to AU-50)} \\
\text{Ar}_{1} \text{CHO/EtONa} \\
\text{Series - 11} \\
&\text{(AU-51 to AU-55)} \\
\end{align*}
\]

\[\text{Ar} = \text{Ar}_{1} = \text{Various substituted aryl groups}\]
Series-8: 2-(Isonicotinamid-4-y1) acetylhydrazino arylidenes.

The compounds of Series-8 have been synthesized by following three steps of Scheme-3 (Table 1.8.8).

Table 1.8.8: List of the synthesized compounds under series-8.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Chemical name</th>
<th>Ar</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU-36</td>
<td>2-(Isonicotinamid-4-yl) acetylhydrazino</td>
<td>C₆H₅</td>
<td>C₁₅H₁₄N₄O₂</td>
</tr>
<tr>
<td></td>
<td>benzylidene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AU-37</td>
<td>2-(Isonicotinamid-4-yl) acetylhydrazino-4-</td>
<td>4-ClC₆H₄</td>
<td>C₁₅H₁₃N₄O₂Cl</td>
</tr>
<tr>
<td></td>
<td>chlorobenzylidene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AU-38</td>
<td>2-(Isonicotinamid-4-yl) acetylhydrazino-3-</td>
<td>3-BrC₆H₄</td>
<td>C₁₅H₁₃N₄O₂Br</td>
</tr>
<tr>
<td></td>
<td>bromobenzylidene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AU-39</td>
<td>2-(Isonicotinamid-4-yl) acetylhydrazino-3-</td>
<td>3-NO₂C₆H₄</td>
<td>C₁₅H₁₃N₅O₄</td>
</tr>
<tr>
<td></td>
<td>nitrobenzylidene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AU-40</td>
<td>2-(Isonicotinamid-4-yl) acetylhydrazino-4-</td>
<td>4-CH₃C₆H₄</td>
<td>C₁₆H₁₆N₄O₂</td>
</tr>
<tr>
<td></td>
<td>methylbenzylidene</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Series-9: 4-Aryl-3-chloro-1-[(isonicotinamid-4-yl) acetamido]-2-oxo-azetidines.

The compounds of the Series-9 (AU-41 to AU-45) have been synthesized from compounds of Series-8 (AU-36 to AU-40) as precursors (Table 1.8.9).

Table 1.8.9: List of the synthesized compounds under series-9.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Chemical name</th>
<th>Ar</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU- 41</td>
<td>4-Phenyl-3-chloro-1-[(isonicotinamid-4-yl) acetamido]-2-oxo-azetidine</td>
<td>C₆H₅</td>
<td>C₁₇H₁₅N₄O₃Cl</td>
</tr>
<tr>
<td>AU- 42</td>
<td>4-(4-Chlorophenyl)-3-chloro-1-[(isonicotinamid-4-yl) acetamido]-2-oxo-azetidine</td>
<td>4-ClC₆H₄</td>
<td>C₁₇H₁₄N₄O₃Cl₂</td>
</tr>
<tr>
<td>AU- 43</td>
<td>4-(3-Bromophenyl)-3-chloro-1-[(isonicotinamid-4-yl) acetamido]-2-oxo-azetidine</td>
<td>3-BrC₆H₄</td>
<td>C₁₇H₁₄N₄O₃ClBr</td>
</tr>
<tr>
<td>AU- 44</td>
<td>4-(3-Nitrophenyl)-3-chloro-1-[(isonicotinamid-4-yl) acetamido]-2-oxo-azetidine</td>
<td>3-NO₂C₆H₄</td>
<td>C₁₇H₁₄N₅O₅Cl</td>
</tr>
<tr>
<td>AU- 45</td>
<td>4-(4-Methylphenyl)-3-chloro-1-[(isonicotinamid-4-yl) acetamido]-2-oxo-azetidine</td>
<td>4-CH₃C₆H₄</td>
<td>C₁₈H₁₇N₄O₃Cl</td>
</tr>
</tbody>
</table>
Series-10: 2-Aryl-3-[(isonicotinamid-4-yl) acetamido]-4-oxo-1,3-thiazolidines.

The compounds of the Series-10 (AU-46 to AU-50) have been synthesized from compounds of Series-8 (AU-36 to AU-40) as precursors (Table 1.8.10).

Table 1.8.10: List of the synthesized compounds under series-10.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Chemical name</th>
<th>Ar</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU-46</td>
<td>2-Phenyl-3-[(isonicotinamid-4-yl) acetamido]-4-oxo-1,3-thiazolidine</td>
<td>C₆H₅</td>
<td>C₁₇H₁₆N₄O₃S</td>
</tr>
<tr>
<td>AU-47</td>
<td>2-(4-Chlorophenyl)-3-[(isonicotinamid-4-yl)acetamido]-4-oxo-1,3-thiazolidine</td>
<td>4-ClC₆H₄</td>
<td>C₁₇H₁₆N₄O₃SCI</td>
</tr>
<tr>
<td>AU-48</td>
<td>2-(3-Bromophenyl)-3-[(isonicotinamid-4-yl)acetamido]-4-oxo-1,3-thiazolidine</td>
<td>3-BrC₆H₄</td>
<td>C₁₇H₁₆N₄O₃SBr</td>
</tr>
<tr>
<td>AU-49</td>
<td>2-(3-Nitrophenyl)-3-[(isonicotinamid-4-yl)acetamido]-4-oxo-1,3-thiazolidine</td>
<td>3-NO₂C₆H₄</td>
<td>C₁₇H₁₆N₅O₅S</td>
</tr>
<tr>
<td>AU-50</td>
<td>2-(4-Methylphenyl)-3-[(isonicotinamid-4-yl)acetamido]-4-oxo-1,3-thiazolidine</td>
<td>4-CH₃C₆H₄</td>
<td>C₁₆H₁₈N₄O₃S</td>
</tr>
</tbody>
</table>
Series-11: 5-Arylidene-2-aryl-3-[(isonicotinamid-4-yl) acetamido]-4-oxo-1,3-thiazolidines.

The compounds of the Series-11 (AU-51 to AU-55) have been synthesized from compounds of Series-10 (AU-46 to AU-50) as precursors (Table 1.8.11).

**Table 1.8.11: List of the synthesized compounds under series-11.**

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Chemical name</th>
<th>Ar</th>
<th>Ar&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU-51</td>
<td>5-Benzylidene-2-phenyl-3-[(isonicotinamid-4-yl) acetamido]-4-oxo-1,3-thiazolidine</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>C&lt;sub&gt;24&lt;/sub&gt;H&lt;sub&gt;20&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;S</td>
</tr>
<tr>
<td>AU-52</td>
<td>5-(4-Chlorobenzylidene)-2-(4-chlorophenyl)-3-[(isonicotinamid-4-yl)acetamido]-4-oxo-1,3-thiazolidine</td>
<td>4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>C&lt;sub&gt;24&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;SCl&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>AU-53</td>
<td>5-(3-Bromobenzylidene)-2-(3-bromophenyl)-3-[(isonicotinamid-4-yl)acetamido]-4-oxo-1,3-thiazolidine.</td>
<td>3-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>C&lt;sub&gt;24&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;SBr&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>AU-54</td>
<td>5-(3-Nitrobenzylidene)-2-(3-nitrophenyl)-3-[(isonicotinamid-4-yl) acetamido]-4-oxo-1,3-thiazolidine</td>
<td>3-NO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3-NO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>C&lt;sub&gt;24&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;N&lt;sub&gt;6&lt;/sub&gt;O&lt;sub&gt;7&lt;/sub&gt;S</td>
</tr>
<tr>
<td>AU-55</td>
<td>5-(4-Methylbenzylidene)-2-(4-methylphenyl)-3-[(isonicotinamid-4-yl)acetamido]-4-oxo-1,3-thiazolidine</td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>C&lt;sub&gt;26&lt;/sub&gt;H&lt;sub&gt;24&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;S</td>
</tr>
</tbody>
</table>
Part II: Characterization of the synthesized compounds

All the melting points were taken in open capillary tubes. Formation of the compounds was routinely checked by TLC using silica gel ‘G’ and the spots were exposed to iodine vapours for visualization. IR spectra were recorded on Shimadzu 8201 PC spectrophotometer. The $^1$H NMR spectra were recorded at 300 and 400 MHz and $^{13}$C NMR spectra were recorded at 100 MHz on Bruker DRX-300 in CDCl$_3$ using TMS as an internal standard on δ scale. The FAB mass spectra were recorded on a Jeol SX 102 mass spectrometer. Microwave assisted reactions were carried out in Microwave oven (Bajaj 2100 ETC, 800W, 2450 MHz). Elemental analysis were performed on a Carlo Erba-1108 analyser. All the compounds gave satisfactory C, H and N percentage within the experimental limits. The chemical reagents used in the synthesis were purchased from Merck and Sigma - Aldrich and purified by either distillation or recrystallization before use.

Part III: Biological Activity of the synthesized compounds

All the synthesized compounds were screened for their antibacterial activity against *Escherichia coli*, *Bacillus subtilis* and *Salmonella typhi* at 50 and 100 µg/mL concentrations and antifungal activity against *Aspergillus flavus*, *Penicillium citrinum* and *Fusarium oxysporum* at 50 and 100 µg/mL concentrations by filter paper disk technique. Standard antibacterial Streptomycin and antifungal Griseofulvin were also tested under the similar conditions for comparison. Some of the compounds were found to display remarkable biological activity.