CHAPTER II

OBJECTIVE OF THE WORK
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Synthesis of compounds to explore the potential biologically active agents still draws continued interest: molecular manipulation, combinations of biologically active moieties into one molecule and synthesis of totally newer moieties have been the methods of research.

The drug design by molecular manipulation is a productive source of new drugs. The biological study of natural products with medicinally useful property and their analogues furnish the early lead about the possible relation of chemical structure and overall biological behavior of the compounds. Further, it soon became evident that certain structural groups present in the natural products were also present in other compounds and exhibited same biological activity. This observation was a guiding thought in the present work in exploring the synthesis of some new compounds with a desire to obtain highly potent, more specific and less toxic drugs. The molecular manipulation of a promising lead compound is still a major line of approach for the discovery of drugs. Molecular manipulation involves the efforts to combine the separate groups having similar activity in one compound by eliminating, substituting or adding new moiety to a parent lead compound. Thus by making gradual changes in the structure of the compound may result in gradual change in the
physicochemical properties and hence the biological activity of the compound. The investigations that have been carried out during the present work have been divided into following parts.

**Part 1:**

**Azetidin-2-ones**

The β-lactam is an essential structural moiety for a number of medicinally important natural and synthetic products. Considerable efforts have been focused on strategies for the de novo construction of four membered systems. The potential of this reactive ring as a synthetic intermediate has also been well recognized and methods for selective opening have been developed. However general technologies for incorporation of intact β-lactam are rare. The chemistry of β-lactams has taken an important place in organic chemistry, since the discovery of penicillin by Sir Alexander Flaming in 1928 and shortly thereafter cephalosporin compounds which were both used as successful antibiotics. Even now the research in this area is still stimulated by the development of bacterial resistance to widely used antibiotics of this type. There is a continuous need for the functionlised β-lactams or for new active principle in the β-lactam series.

In recent years the way β-lactams are viewed has changed considerably. Presently their interest stems not only from being a structural feature of β-lactam antibiotics, but also from their
valuable utility as synthetic intermediates, mainly as masked α and β- amino acid derivatives. It is established fact that the azetidinone moiety is known to potentiate the biological activity. The role of β-lactams, which are endowed with unique structure and potent antibacterial activity, need not be over emphasized. The β-lactam drugs are still most prescribed antibiotics in medicine. The biological activities of β-lactam antibiotics are generally believed to be associated with chemical reactivity of the β-lactam ring.

β-lactam also possesses antibacterial, antifungal, anticancer, antiviral and cholesterol absorption inhibitory activities. Azetidin-2-ones substituted at the 3rd position with aryloxy group were synthesized as this group increases antimicrobial activity. During the present investigation azetidin-2-ones of the following type were prepared, characterized and screened for the biological activity associated with them.

\[ Z = \text{substituted phenyl.} \]
The synthesized compounds were screened for antibacterial, antifungal and anticancer activity using the literature method.

**Part 2:**

**1,2,4-Triazoles**

Heterocycles bearing symmetrical triazoles or 1,3,4-thiadiazoles are reported to show broad spectrum of antibiotic activity. Similarly substituted 1,2,4-triazoles and their N-bridged heterocycles have received considerable attention during last two decades as they are endowed with variety of biological activities and have a wide range of therapeutic properties, some of which were commercialised as agrochemical fungicides, insecticides, herbicides and plant growth regulatory activities. These compounds also possess antibacterial, antiinflammatory and analgesic activities. The 1,2,4-triazole nucleus has been incorporated into wide variety of the therapeutically interesting drugs including H₁ and H₂ histamine blockers, cholinesterase active agents, CNS stimulants, anti-anxiety agents and sedatives.

Since certain 1,2,4-triazoles and thiadiazoles have displayed diverse biological activities; it was planned during present work to generate a system, which combines these two components in a ring to give compact and planar structure. The abundant references from literature reveal that 4-thiazolidinones are active as potent antibacterial, antifungal, antiinflammatory, analgesic and
antitubercular agents. Mizzoni and Eisman have established that the presence of N-C-S linkage in thiazolidinones was the major factor for contributing the various biological activities of this class compounds. The biological importance of thiazole derivatives was emphasized when Franc C Pennington had isolated a new antibiotic from the culture growth of a strain of streptomyces and found to be showing high *invitro* activity against mycobacterium tuberculosis. The structure of antibiotic was found to be (-)2,5-carboxypentyl-1,4-thiazolidinones and had been named as actithiazic acid.

![Chemical Structure of Actithiazic Acid](attachment:structure.png)

Hence numbers of synthetic derivatives incorporating this structure were synthesized and the compounds thus obtained had low toxicity. The study of thiazolidinone derivatives was boosted up when it was found that antibiotic penicillin had also thiazolidin ring. Hence synthesis of triazole derivatives bearing thiazolidinone was designed expecting enhanced biological activities than the parent moieties. It was also planned to exploit amino group at 4*th* position of triazole ring so as to get certain Schiff bases of biological interest and also to condense certain keto/diketo compounds to study their biological activity. Modification of Schiff
bases bearing triazole moiety was also carried out by replacing mercapto group with certain biologically active amino functional compounds. The condensed N-bridge head triazoloderivatives like triazolothiadiazoles exhibited potent biological activity may be due to the fact that the condensation of two heterocyclic moieties into one generally enhances biological activity of the condensed heterocyclic system.

All the following types of compounds were characterized by elemental analysis and spectral studies in addition to their specific chemical tests.

**Triazoles:**

i. Mercapto triazoles:

![Mercapto triazole](image1)

ii. Triazolo Schiff bases:

![Triazolo Schiff base](image2)

R=H, -CH3, -Br, -Cl, -F, -NO2, -NH2, -OCH3

iii. Triazolothiazolidin-4-ones:

![Triazolothiazolidin-4-one](image3)

iv. Triazolo Schiff bases bearing Benzothiazole moiety:

![Triazolo Schiff base with Benzothiazole moiety](image4)

R=H, -OH, -CH3, -Br, -Cl, -F, -NO2, -NH2, -OCH3
v. Mercaptotriazoles:

\[
\begin{array}{c}
\text{H}_3\text{CN} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{C}_2\text{H}_5 \\
\text{N} \\
\text{F} \\
\text{N} \\
\text{O} \\
\text{N} \\
\text{N} \\
\text{C}_2\text{H}_5 \\
\text{N} \\
\text{SH} \\
\text{N} \\
\text{H}_2 \\
\text{R} = \text{-H, -CH}_3, \text{-Br, -Cl, -F, -NO}_2, \text{-NH}_2, \text{-OCH}_3
\end{array}
\]

vi. Triazolothiadiazoles:

\[
\begin{array}{c}
\text{H}_3\text{CN} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{C}_2\text{H}_5 \\
\text{N} \\
\text{F} \\
\text{N} \\
\text{O} \\
\text{N} \\
\text{N} \\
\text{C}_2\text{H}_5 \\
\text{N} \\
\text{S} \\
\text{N} \\
\text{N} \\
\text{R}
\end{array}
\]

Part 3:

Pyrazolines

Pyrazolines have played a crucial part in the development of theory in heterocyclic chemistry and also used extensively as a useful synthons in organic synthesis. Various substituted pyrazolines and their derivatives are important biological agents and a significant amount of research activity has been directed towards this class. Pyrazole nucleus and pyrazolines are associated with broad spectrum of biological activities. Pyrazolines constitute an important class of heterocycles, which display interesting biological properties such as antitumour, antibacterial, antifungal, antiviral, antiparasitic, insecticidal, pesticidal, antiinflammatory, antiarthritic and antidepressant activities.

A classical synthesis of these compounds involves base catalysed aldol condensation reaction of aromatic aldehydes and ketones to give α and β-unsaturated ketones called as chalcones. It is of interest to mention here that many chalcones are already known to
be associated with therapeutically important properties. As pyrazolines are derived from therapeutically important chalcones itself, the pyrazolines obtained are expected to display significant biological and medicinal activities. Chalcones undergo subsequent cyclisation reaction with hydrazines/hydrazides offering 2-pyrazolines. In this method hydrazones are formed as intermediates, which can be subsequently cyclised to 2-pyrazolines in the presence of suitable cyclising agents like acetic acid. It has been reported recently that fairly good antifungal activity is observed particularly with inclusion of pyrazoline moiety.

Therefore number of following type of pyrazolines was synthesised, characterised by systemic elemental analysis, spectral studies etc., and evaluated for their antibacterial and antifungal activities.
Part 4:

1,3,4-Oxadiazole

During the past few years the synthesis and biological activities of 1,3,4-oxadiazoles have been extensively investigated. 1,3,4-Oxadiazole derivatives are well known to have a wide range of biological activities like antiinflammatory, antifungal, antiparasitic, antimicrobial etc. It is known that the Ames test is a well established method to examine the mutagenicity of chemical compounds. This is due to its ability of prescreening a large number of chemicals for any mutagenic and thus for any suspected carcinogenic effects. It is worth to mention that various experimental results support the hypothesis that environmental factors are major cause of cancer. This prompted many researchers to investigate biological as well as the genotoxic activities of 1,3,4-oxadiazoles.

The bioactive moiety 1,3,4-oxadiazole is one of the prominent moiety presently studied in the field of medicinal chemistry. The design of such bioactive compounds involves the idea of bioisostearism as one of the successful technique. The substitution of sulphur for oxygen in the heterocyclic ring represents an example of an approach that is commonly known as bioisostearism which is one of the important physicochemical properties that is associated with biological activities of this class of compounds. The
1,3,4-Oxadiazole ring is bioisostearic analogue of 1,3,4-thiadiazole rings. Hence during present work it was planned to carry out the investigations towards the synthesis of following type of 1,3,4-oxadiazoles and exploit some of their biological activities.

The various types of compounds as discussed above were prepared and characterised by semi micro analytical methods for C, H, N, and Infrared, $^1$H NMR and Mass spectral data in addition to useful chemical tests. The characterisation of compounds is discussed in detail. The representative compounds in each class were screened for various biological activities and their results are discussed at length with possible structure activity relationship wherever it is possible.