CHAPTER-I
GENERAL INTRODUCTION
Introduction

Sufficient work in modern chemistry and its various uses in various academic disciplines including industry involves molecular manipulation. In the field of science chemistry occupies an important position to tackle several problems. Chemistry of Heterocycles forms the fundamental principal of life and society. The present work is so designed to correlate reactivity of several classes of aromatic compounds containing heteroatoms taking into account their structure activity relationship. This helps one to design new classical chemical entities for better pharmacological activities.

Current trend in drug design for developing new clinically effective agents through the structural modification of the lead nucleus. The examples of drug discovery without a lead are quite few in number. The lead is a prototype compound that has desired biological activity but may have many undesirable characteristics like high toxicity, insolubility or metabolism problems. Inspite of the great success of the classical methods of drug design, their unpredictability and the tremendous amount of wasted effort expended have necessitated the development of more rational methods with a much higher predictive capability. The approach involving selection of lead nucleus remains unchanged. However ways to select substituent's for structural modification were changed. The knowledge of drug metabolism in vitro can be utilized to improve a wide variety of drug characteristics. Innovation of newer chemical entities for better health is continuous
process. Hence many chemists find this field quiet interesting so as to develop newer drugs associated with diverse biological activity.

Two major objectives that lie behind the optimization of the lead nucleus are a) to maximize the drugs desired activity and b) to minimize the intensity and frequency of side effects associated with the drugs. To obtain a lead compound generally molecular manipulation is followed as it is still important method for finding new drugs. Condensation of more than two moieties into a single compound is most general method of modification. The physicochemical properties such as solubility behavior has an important role to play in drug action. A suitable derivatization to increase lipophilicity would be important as certain organisms (like mycobacterium tuberculosis) have lipid layer around the cell wall. Therefore such a drug could be lipid soluble and enhances the anti-tubercular action.

The objective of present work is to get the compounds which show similar biological activities as that of lead moieties and development of new novel drug moieties like traizoles, Oxadiazoles and their derivatives, 2-azetidinones, pyrazolines and other related heterocyclic moieties.
The novel drug moieties were designed expecting their potent pharmacological activities belonging to the above class of drug moieties.

As a part of interesting heterocyclic the present work deals with development of important heterocyclic derivativies such as 3,4-di-substituted -5-mercapto-s-triazoles, Schiff bases, azetidinones chalcones, pyrazolines, triazolo-thiadiazoles, hydrazino triazole type of compounds which have marked importance in the field of chemistry. These moieties largely referred due to their simple preparation methods and large range of reactivity and pharmacological activity. All these facts are driving force to develop novel classes of above heterocyclic systems with wide structural variations. The above type of drug molecules play pivotal role in medicinal chemistry hence it was thought interesting to study such type of moieties. Considering therapeutic applications of 5-membered heterocyclic compounds, it is planned to synthesize certain symmetrical mercapto triazoles like 3-substituted-4-amino-5-mercapto triazole and several of its triazolo thiadiazole derivatives of medicinal interest.

It is well known fact that when two different heterocyclic nuclei are fused to obtain single compound may yield such compounds which exhibit increased pharmacological activity. So it is decided during the present work to prepare the fused derivatives using substituted 4-amino-5-mercapto triazole and 3-pyridyl substituted-4(carboxamido aryl/aryloxy)-5-mercepto traizoles.
Abundant references are available with regard to the study of azetidinones. Azetidinone derivatives are known to possess wide therapeutic activity as Anticonvulsant, Herbicidal and Anti-inflamatory. Azetidione was found in the structure of the Antibiotic Penicillin. The β-lactam ring of the penicillin molecule is thought to be responsible for biological activity of β-lactam antibiotics. The literature survey reveals that β-lactam antibiotics are the major class in antibiotics and is the biggest therapeutic segment in the pharmaceutical market. Some of them also been used as β-lactmase enzyme inhibitors and their other pharmacological properties are analgesic, anti-inflammatory and antimicrobial activities. Therefore it is planned in the present work to synthesize certain novel, more potent, less toxic and more selectively acting Azetidinones by following the pure synthetic route expecting better yield and quality drugs.

Pyrazolines belong to a 5 membered nitrogen heterocyclic group. For the synthesis of Pyrazolines several synthetic methods are reported by many reasearchers. Majority of Pyrazolines are known to posses potent pharmacological activities. This necessaited an active work for the discovery of better compounds belonging to this class. Because of this number of methods for their preparation have been explained in the pyrazoline chemistry. A general method of preparation is based on the reaction of chalcones with hydrazides.
Based on the above facts our work was to prepare a series of specially substituted pyrazolone derivatives and correlate the activity with their structures.

A) Triazoles

(a)

(b)

\[ Z = \]

\[ , \]

etc.
B) 3,4 disubstituted triazoles bearing INH and Pyrazinamide moieties

I)  

II)  

III)
C) Oxadiazoles and their triazolo derivatives

(I)

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{Z} \\
\text{NHCOCH}_3 & 
\end{align*}
\]

\( Z = \)

\[
\begin{align*}
\text{Cl} & \\
\text{N} & \\
\text{N} & \\
\text{N} & \\
\text{N} & \\
\text{H}_3 & \\
\text{CH} & \\
\text{CH} & \\
\text{CH} & \\
\text{CH} & \\
\text{Cl} & \\
\text{etc} & 
\end{align*}
\]

(II)

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{Z} \\
\text{NHCOCH}_3 & \\
\text{NH} & \quad \text{C} \\
\text{N} & \\
\text{N} & \\
\text{NHCOCH}_3 & \\
\text{O} & 
\end{align*}
\]

(III)

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{Z} \\
\text{NH}_2 & \\
\text{NHCOCH}_3 & \\
\text{Br} & \\
\text{Br} & 
\end{align*}
\]
D) Schiff base and Azetidinones

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{H}_2\text{C} \\
\text{H}_3\text{C} & \quad \text{H}_2\text{C} \\
\text{N} & \quad \text{N} \\
\text{C} & \quad \text{C} \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

II)

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CH}_2 \\
\text{N} & \quad \text{N} \\
\text{C} & \quad \text{C} \\
\text{H}_3\text{C} & \quad \text{CH}_2 \\
\text{Z} & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{Z} = \quad \text{C} & \quad \text{CH}_2 \quad \text{CH}_3 \\
\text{C} & \quad \text{CH}_3 \\
\end{align*}
\]

E) Pyrazolines

\[
\begin{align*}
\text{Ar}^{1} & \quad \text{N} \quad \text{N} \quad \text{Ar}^{2} \\
\text{Ar}^{1} & \quad \text{N} \quad \text{N} \quad \text{Ar}^{2} \\
\text{O} & \quad \text{C} \quad \text{H}(\text{CH}_2)_4 \quad \text{C} \quad \text{O} \\
\end{align*}
\]
Considering the facts discussed above the preparation of s-Triazoles and its derivatives, oxadiazoles, 2-Azetidinones and Pyrazolines was carried out. Their characterization was done by spectroscopic methods and their antimicrobial screening was also done.

It is planned for antifungal screening of above compounds against different fungi and comparative study of their activity. It is also intended to carry out the study on percentage inhibition as recorded using rat hind paw oedema method by comparing with the reference. Since the compounds exhibiting anti-inflammatory property do exhibit analgesic property, we have evaluated certain important derivaties of the above class for analgesic activity also.

The literature survey throws light on anticancer and anti-tubercular activities of above type of moieties. Selected few compounds were evaluated from each class for anti-cancer and anti-tubercular activity and establish the possible structure and activity among the prepared compounds.

The various references of the said heterocyclic compounds also prompted us to investigate the antihelmentic activity associated with the compounds in general and triazole derivatives in particular.

An attempt has been made to carryout in-vivo study of the synthesized heterocyclic compounds by conducting animal experiments to know their effect on normal healthy albino rats. Employing kindney function tests and liver function tests