Research programs for the discovery of new drugs and for improving the evolution criteria are under way in many laboratories. In addition knowledge of specific constituents of the mycobacterium cell and their biochemical roles has advanced considerably in the recent years and may permit a more rational approach to the design of new drug action on specific targets. Also, recent improvements in the knowledge of the mechanism of action of available drugs and the biochemical mechanism of resistance to them may be used as a basis for design new and better drugs to care the mycobacterial diseases.

The current environment for discovery and development of new pharmaceuticals agents could hardly be ware challenging. Public policies and attitudes are requiring reduction in health care expenditures and increase efficiencies, resulting in major health care reform in the United States. At the sometime, major diseases remain untreated and paradoxically, scientific progress continues with ever increasing acceleration.

The last few decades have witnessed massive advances in biochemistry, physiology, pharmacology and genetics. This has to a better understanding of working the body at the molecular level. This in turn has resulted a much better understanding of the structure and function of important drug targets e.g. enzymes and receptors and that how drugs can be designed for these targets.

Advances in genetics engineering have been used to produce human proteins and enzymes in fast growing microbial cells, allowing these molecules to be obtained in far greater yields than if they were extracted from human tissue. This makes it easier to study these micro molecules and to design drugs that will interact with them. Mapping of human DNA through human genome project has immense implications for medicinal chemistry.

Advances in chemistry have made possible the synthesis of complexes molecules. Enantiometry is an important process in medicinal chemistry since life is inherently chiral and the drug targets within the body are chiral. As such, they can distinguish between the enantiomers of a chiral drug, so the use of recemic drug is
inherently wasteful, since only one enantiomer is ideally designed to interact with its target. Moreover, the existences of the “wrong” enantiomer could create problems if it interacted with a different receptor, resulting inside effects.

The focus of drug design has switched from structure oriented to target oriented research, e.g. development of the antiulcer agent cimetidine. Histamine was the lead compound for the project and various strategies were used to find an analog that would prevent it fitting its receptor. Once an antagonist was developed, a theory was proposed on how it might interact with the histamine receptor at a molecular level. Further analogs were then synthesized to test theory and the theory was continuously modified as required.

In the nineteenth century, chemistry developed as a science, both in terms of experimental procedures and scientific theory. Scientist isolated and purified single compounds from natural extracts. Method of organic synthesis were developed that helped chemists altering structures in a predictable way.

The chemists started separating out the various components of ancient positions to discover whether a single compound was responsible for the medicinal effect known as the active principle.

Drugs are chemicals of low molecular weight (~100-500) which interact with macromolecular targets to produce a biological response. The biological response may be therapeutically useful in the case of medicines or harmful in the case of poisons. Most drugs used in medicine are potential poisons if taken in higher doses than recommended.

Drugs are classified by their chemical structures. Drugs classified in this way share a common structural feature and often share similar pharmacological activity. For example, all penicillin’s contain a β-lactum ring and kill bacteria by the same mechanism, as a result, this classification can sometimes be useful in medicinal chemistry. However, it is not foolproof. Sulfonamides have a similar structure and are mostly antibacterial. However some sulfonamides are useful in the treatment of diabetes. Similarly all steroids have a tetracyclic structure, but the pharmacological effect of different steroids can be quite different e.g. Testosterone is a sex hormone and Spironolactone is a diuretic.
Finally classifying drugs according to their molecular target is the most useful classification as far as medicinal chemist is concerned, since it allows a rational comparison of the structure involved.

Such compounds either in extract form or in pure form become a part of pharmacopoeia. For instance, though the Chinese drug, Mauhany was in use for over 5000 years for the treatment of various types of fever and respiratory ailments, its active principle ephedrine was isolated in 1887. In 1925 chemical investigations followed by pharmacological evaluation led this compound into the modern medicine. Similarly during this period, urea stibamine was introduced as the first drug in 1920 for the treatment of Kala azar, in 1930 De Raywolfia preparation were first employed for sedative and hypotensive properties.

A drug is a substances having abnormal effect on certain body functions. Estrichnine stimulates the action of heart and aspirin still it action since both of them effects abnormally the two substances are known as drugs. Chemical sciences contributed extensively new discoveries leading to useful drug after 1930.

The modern concept of drug discovery supported in 1933 by Gerhard Domayk with his finding of "Prontosil Red" a compound responsible for the antibacterial activity. The advent of sulphonamides draw attention to the different activity of various chemicals for bacterial and human cells, this important factor prompted the Florey and chain in 1939 to investigate penicillins which was discovered ten years earlier by Alexander Fleming.

A large number of important drugs have been introduced during the period of 1940 to 1960. This period is known as 'Golden Period' of new drug discovery. Thus starting from 1933-the first antibacterial drug prontosil leading various sulpha drugs; 1940-penicillin; 1945-chloroquine (antimalarial); 1950-methyldopa (antidiabetic); 1957-chlorothiaido (diuretic); 1958-adrenergic (beta blockers coronary vasodilatory); 1960-semi synthetic penicillin (antibiotics); 1965-trimethoprim (antimicrobial); 1967-disodium chromoglycate (antiallergic); 1972-cimetidine (H2-antagonist); 1975-verampril (calcium antagonist); 1981-captooril (antihypertensive) etc. There are some specific examples representing new therapeutics.

The spectacular chemotherapeutical properties of penicillin and its dramatic time was development for the treatment of wound made penicillin, a most commonly used inexpensive drug.
The word ‘drug’ is derived from the French word ‘drogue’ which means a dry herb. According to “WHO” a drug may be defined as “any substance or product which is used or intended to be used for modifying or exploring physiological system or pathological status for the benefit of recipient”.

The ultimate product of a successful drug design effort. Our goal for this is to begin to deconvolute this information in order to apply it to design of new drugs. Taking in view of the applicability of heterocyclic compounds, we have undertaken the preparation of piperazine derivatives nucleus. The placement of a wide variety of substituents of these nuclei has been designed in order to evaluate the synthesized products for their pharmacological profile against several strains of bacteria and fungi.

AIMS AND OBJECTIVES

In the pharmaceutical field, there is a need for new and novel chemical inhibitors of biological functions. Our efforts are focused on the introduction of chemical diversity in the molecular framework in order to synthesizing pharmacologically interesting piperazine derivatives of widely different composition. During the course of research work looking to the applications of piperazine derivatives, several entities have been designed, generated and characterized using spectral studies. The aims and objectives of the work carried out are as under.

1. To synthesize pharmacologically active entities like arylamide, sulphonamides, Mannich bases, Schiff’s bases, thiazolidinones, 2-azetidinones, 5-Oxo-imidazolines etc.
2. To characterise these products for structural elucidation using spectroscopic techniques like IR, $^1$H NMR and Mass spectral studies.
3. To check the purity of all compounds using thin layer chromatography.
4. To evaluate these new products for better drug potential against different strains of bacteria and fungi.
INTRODUCTION

Piperazine was used early in the 20\textsuperscript{th} century for the treatment of gout. Giround discovered the anthelmintic activity of piperazine, synthesized by Cloez in 1853, fortuitously in 1942; the same effect was observed by Biosmare in 1948 and conformed by Bayared in 1949. Structural modification of this molecule in the search for effective filaricidal resulted in diethyl carbamazine synthesized by Kishner et al in 1946 and studied pharmacologically by Hewitt et al in 1947. Clinical studies have shown that the drug is highly effective against both ascaris lumbricoides and enterobius (oxyuris) vermicularis.

CHEMISTRY

Piperazine is a six member cyclic secondary diamine with the nitrogen in the 1, 4 - position. It can also be called diethelenediamine for convenience its molecular formula can be written $C_4H_{10}N_2$, and structural formula shown as under (I).

![Structural formula of piperazine](image)

PHYSICAL PROPERTIES

Piperazine is soluble in water and ethanol, but insoluble in ether. An aqueous solution reacts strongly alkaline, the $P^{ka}$ being 9.8. It occurs in the form of hygroscopic plates M.P. 104\textdegree C and B.P. 140\textdegree C. It is available as the hexahydrate which contains about 44% of base and in addition, as various salt such as citrate $C_{24}H_{46}N_6O_{14}$, M.P. 182\textdegree-187\textdegree C, adipate $C_{10}H_{20}N_2O_4$, M.P. 256\textdegree-257\textdegree C, phosphate, calcium acetate and tartrate.

ECONOMIC ASPECTS

Total production of piperazine is about 3 million lb/yr. Most of this is converted to one of the salts since these are widely used as animal anthelmintics and are more easily administrated in this form.
STORAGE & HANDLING

Anhydrous piperazine should be stored in a dry, airconditioned building at a temperature below 60°F. On contacting oxygen, piperazine will darken in colour to a deep yellow after a long period of time. When anhydrous piperazine is exposed to the atmosphere, it will pick up moisture and will tend to cake and darken in warm weather.

HEALTH & SAFETY

Anhydrous piperazine itself has a low acute oral toxicity. However the investigation of large amounts should be avoided and in case where large amounts have been swallowed, vomiting should be induced and medical attention obtained promptly. Piperazine exhibits a sensitizing potential so that pronged exposure to small quantities or a short exposure to a single massive quantity should be avoided.

Because of its alkalinity, piperazine can cause serious eye damage. When piperazine has accidentally been introduced into the eye flushing for 15 minute with running water is recommended as the first-aid measure. Piperazine exhibits a high vapours pressure and should be handled in well-ventilated areas only.

PHARMACOLOGICAL EFFECT

The effects of piperazine on *ascaris* have been investigated intensively. The gross effect is a paralysis of muscle that results in expulsions of the worm by peristalsis. Affected worms recover if incubated in a saline medium at 37°C. Further studies have shown that piperazine blocks the response of *ascaris* muscle to acetylcholine, an action that is much weaker in skeletal muscle preparations. It has been proposed that piperazine acts on *ascaris* muscle by altering the permeability of the cell membrane to ions that are responsible for the maintenance of the resting potential. Piperazine also inhibits production of succinate by Ascaris at concentrations that resulting paralysis and bioclade of the stimulatory effects of acetylcholine.

Orally administrated piperazine is almost devoid of pharmacological activity. Intravenous administration results in a transient fall in blood pressure. Lethal doses cause convulsions and respiratory depression. A large number of substituted piperazine derivatives exhibit anthelmintic activities.

Various derivatives have found actual or potential use as antihistamines, hypertension, anesthetic, analgesic epilepsy, anticonvulsant, antispasmodic, burn shock and hemorrhagic shock. Other application of piperazine and its derivatives
except medicine was rubber antioxidants, corrosion inhibitors, additives, wetting emulsifying, cosmetic, dyeing industry, resin, polymers, synthetic fibers and analytical reagent.

**SYNTHETIC ASPECT**

Preparation of piperazine at atmospheric pressure; diethylene triamine was heated with Raney nickel under various experimental conditions. The results of these experiments are tabulated below. In all cases ammonia was evolved and piperazine formed according to the reaction. A temperature at about 150°C or somewhat higher was found to be most suitable for the reaction (II).

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{Ni} \\
\text{CH}_2\text{CH}_2\text{NH}_2 + \text{NH}_3 & \quad \text{H}_2\text{C} - \text{C} \quad \text{H}_2 \\
\text{H}_2\text{H}_2
\end{align*}
\]

(II)

Autoclave method of piperazine; The autoclave was charged with 150 gm of N-(2-hydroxy ethyl)-ethylene diamine in 200 ml of dioxane 5-30 gm of catalyst was added, and reaction was carried out for three hours at a temperature in the range 200-300°C. The reaction mixture filtered from catalyst was distilled; dioxane-water azeotrope distilled at 87°C, then dioxane at 100-103°C, and finally piperazine at 140-150°C. Raney nickel appeared the catalyst at choice; copper chromium oxide, activated alumina, silica gel, cupric oxide and iron, were intermediate in effectiveness.\textsuperscript{1-9}

**THERAPEUTIC IMPORTANCE**

R. Rastogi et al\textsuperscript{10} prepared N-(2-substituted-ethyl)-N′-aryl piperazine (III) as potential antihookworm agents.
N. Serradji et al. have synthesized a variety of analogues 1-[4-methoxy-3,5-dimethyl benzyl]-4-[3-(ethyl amino)-2-pyridyl]piperazine hydrochloride (IV) and evaluated for their anti HIV activity.

\[ \text{IV} \]

L-Romero et al. and S. Ali et al. have been synthesized various piperazines derivatives and evaluated its antiviral activity.

R. B. Petigara et al. synthesized various N\textsuperscript{1}-N\textsuperscript{4}-disubstituted piperazine derivatives in which the N\textsuperscript{1} substituents are 3,4,5-trimethoxy benzoyl alkyl (V) and screened for CNS activity, majority of the compounds produced CNS depressant effects as shown by gross observation of intact animals and confirmed by motor activity studies in some conditional avoidance behavior.

\[ \text{V} \]

S. K. Saxena et al. synthesized piperazine derivatives (VI) and B. M. Khadilkar et al. (VII) showed best CNS depressant, anti-inflammatory, diuretic activities.
R. C. Tripathi et al\textsuperscript{17} have been synthesized piperazine derivatives and evaluated its hypotensive and CNS depressant activities.

Pyrazole derivatives (VIII) and (IX) containing substituted piperazine nucleus possess antitumor activity evaluated by A. Ejima and S. Ohsuki.\textsuperscript{18}
The effect of (X) hydrochloride on blood pressure of cat was studied by B. M. Khadilkar et al\textsuperscript{19} for intracerebroventricular administration at the dose of 50-µg/kg weights. The fall in B.P. was so rapid that cat died within 15 minutes.

\[
\text{(X)}
\]

S. K. Agrawal et al\textsuperscript{20} prepared 1-(3-carboxyphenoxy)-3-(N\textsuperscript{1}-N\textsuperscript{4}-phenypiperazinyl) -propane (XI), some of these compounds show potent CNS depressant, hypotensive and \(\alpha\)-adrenoceptor blocking activities.

\[
\text{(XI)}
\]

U. V. Kargaonkar et al\textsuperscript{21} have prepared ethyl-8-[4-(3-chlorophenyl)-1-piperazinyl methyl]-2-oxocoumarin-4-acetate (XII) as most effective anti-inflammatory agents. Analgesic and anti-inflammatory activities of piperazines reported by several research workers\textsuperscript{22-27}.

\[
\text{(XII)}
\]

Preparation and activity against \textit{plasmodium berghei} of compound 1-(4-methoxycinnamoyl)- 4 - [5-(4-chloro/bromo)phenyl-4-oxo-2-oxazin-2-yl] - piperazine (XIII) were described by Herrin and his co-workers\textsuperscript{28}. Some nitrogen containing
heterocycles found to possess high antimalarial activity, which was described by F. S. Mikhalitsym et al.\textsuperscript{29}

L. C. Meurer and his coworkers\textsuperscript{30} synthesized alkyl & halo substituted 8-(1-piperazinyl)imidazol [1,2-\(\alpha\)]pyrazine and studied their hypoglycemic activity. In these derivatives some compounds showed potent hypoglycemic activity. Varieties of hypoglycemic agents contained with piperazine moiety were also assessed by several investigators.\textsuperscript{31,32}

Some piperazine derivatives are showed a useful activities like as brain protectant\textsuperscript{33}, diagnosis of schizophrenia\textsuperscript{34}, neurokinine\textsuperscript{35,36}, serration antagonist receptors\textsuperscript{37-39}, heart muscle receptor\textsuperscript{40}, and cholesterol reducing agents\textsuperscript{41}, HIV-I inhibitors\textsuperscript{42,43}, dopamine transporter\textsuperscript{44-46}, sorbitol dehydrogenase inhibitor\textsuperscript{47-49}, spermicidal agent\textsuperscript{50}. Besides the anathematic application of piperazine\textsuperscript{51-53}, anesthetic\textsuperscript{54}, antiparkinson\textsuperscript{55}, anticonvulsant\textsuperscript{56-58}, antidepressant agents\textsuperscript{59}, antipshycotic\textsuperscript{60-61}, antiallergic\textsuperscript{62-64}, antiulcer\textsuperscript{65}, insecticide\textsuperscript{66}, antiparasitics\textsuperscript{67}, and normalipemic hypoglycemic & hypotriglyceridemic activity.\textsuperscript{68}

5-\{[4- [4- (Fluorophenyl) -1- piperazinyl] - butyryl] amino\}-5\(H\)-dibenzo[a,d] cyclohepene] (XIV) selectively for cardiac tissue over vascular tissue, thereby conferring antianginal activity without an effect on blood pressure by M. Kurokawa et. al.\textsuperscript{69}
Introduction of piperazine derivatives

G. R. Brown\textsuperscript{70} synthesized 1 - (Arylsulfonyl) - 4 - \{[1-(4-pyridyl)piperazine-1-yl] carbonyl\}piperazines and analogs (XV) are useful as oxidosqualene cyclase inhibitors. 2-Piperazine-1-acetic acid derivatives are used as platelet aggregation inhibitors and antithrombotics\textsuperscript{71}, piperazinyl ethyl indazoles as calmodulin inhibitors\textsuperscript{72} and tryptase inhibiting alkynediol piperazine carboxylic esters\textsuperscript{73}.

S. Paris et.al.\textsuperscript{74} synthesized pyrrolo[3,2,1-i,j]quinoline (XVI) and documented as potential therapeutic application in asthma.

[(Piperazine)alkylthio]pyridine (XVII) was recommended for the control helicobacter pylori bacteria by G. Hanauer and his co-workers\textsuperscript{75}.
S. Seshadri et al. prepared dimeric products (XVIII) and (XIX) of dithioacetals with piperazine showed moderate to significant activity. These compounds also show better activity against gram negative bacteria as compared to gram positive bacteria.

\[
\begin{align*}
\text{(XVIII)} & \quad \text{H}_3\text{COHN-SO}_2\text{N} = \text{C-N} - \text{SCH}_3 & \quad \text{SCH}_3 \\
& \quad \text{N-C} = \text{N-SO}_2\text{NHCOCH}_3 \\
\end{align*}
\]

S. J. Brickner et al. prepared potent, synthetic oxazolidinones (XX) which is currently in clinical development for the gram positive bacterial infections caused by strains of *Staphylococci, Streptococci & Enterococci*. The *in vitro* and *in vivo* activities of above compound, against representative strains are similar to these of vancomycin. These compounds demonstrate potent *in vitro* activity against mycobacterium tuberculosis.

\[
\begin{align*}
\text{(XX)} & \quad \text{HO-CO} & \quad \text{F} & \quad \text{N} & \quad \text{O} & \quad \text{CH}_3 \\
& \quad \text{N} & \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{N} \\
\end{align*}
\]
Some quinazolinone derivatives containing substituted piperazines (XXI) found to possess strong antibacterial activity.\textsuperscript{78-84} Substituted piperazinyl-phenyl-oxazolidione derivatives used as antibacterial agents, which showed MIC of 0.5 µg/ml against \textit{S. auresas} by G. D. Cung et. al.\textsuperscript{85}

\[
\text{(XXI)}
\]

7-[(4- Substituted phenylpierazine-1-yl) - alkoxy]- 4 -methylchromene-2-ones (XXII) as potential atypical antipsychotics synthesized and evaluated by S. H. Bhosale and his co-workers.\textsuperscript{86}

\[
\text{(XXII)}
\]

\[
N^1 - (2- \text{Substituted-4-nitrophenyl}) - N^4-(2,3 - \text{disubstitutedpropyl}) - \text{piperazines (XXIII) as useful antifungal agent prepared and characterized by G. L. Talesara et. al.}\textsuperscript{87}
\]

\[
\text{(XXIII)}
\]
Preparation and biological evaluation of (5-methyl-1H-indol-2-yl)-4-methyl-piperazine-1-yl)-methanone (XXIV) as potent human histamine H₄ antagonists by J. D. Venable and his co-workers.  

\[
\text{NHM} \quad \text{CH}_3
\]

(XXIV)

N-{4-[4-(2,3-Dichlorophenyl)-piperazine-1-yl]trans-but-2-enyl}-4-pyridine-2-yl-benzamide (XXV) as selective probes with high affinity for the dopamine D3 receptor has been prepared by P. Grundt et al.  

\[
\text{Cl} \quad \text{Cl} \quad \text{NN} \quad \text{OC} \quad \text{N} \quad \text{Cl} \quad \text{Cl}
\]

(XXV)

N-(2-Chloro-6-methylphenyl)-2-(6-(4-(2-hydroxyethyl)-piperazine-1-yl-2-methyl pyrimidine-4-ylamino)thiazole-5-carboxamide (XXVI), a dual Src/Abl kinase inhibitors with potent antitumor activity in preclinical assays has been synthesized and discovered by L. J. Lombardo et al.
Several investigators synthesized varieties of new compounds with piperazine moiety and found their antimicrobial activities such as antifungal and antibacterial.\textsuperscript{91-101}

Flunarizine (brand name sibelium) \{1-cinnamyl-4-[(4',4''-difluorodiphenyl)-methyl]-piperazine\}(XXVII) was discovered at Janssen Pharmaceutical in 1967. Flunarizine is a drug classified as a calcium channel blocker. Flunarizine is a selective calcium entry blocker with calmodulin binding properties and histamine H1 blocking activity by W. K. Amery.\textsuperscript{102} It is effective in the prophylaxis of migraine, occlusive peripheral vascular disease, vertigo of central and peripheral origin, and as an adjuvant in the therapy of epilepsy. It may help to reduce the severity and duration of attacks of paralysis associated with the more serious form of alternating hemiplegia. Potent visodilator improve cerebral blood flow reduce duration and incidences of migraine attack by J. M. Van Nueten.\textsuperscript{103}
Lomerizine \{1-(2'''',3'''',4''''-trimethoxybenzyl)-4-[(4',4'''-difluorodiphenyl)-Methyl]-piperazine\} (XXVIII) is a calcium channel blocker with antimigraine properties.\textsuperscript{104-108}

Thus the important role displayed by piperazine derivatives for various therapeutic and biological activities prompted us to synthesize some arylamide, sulphonamides, Mannichbases, Schiff’s bases, 4-thiazolidinones, 2-azetidinones, 5-oxo-imidazolines etc. bearing piperazine moiety in order to active compounds having better biological activities as described in the following parts.

STUDIES ON PIPERAZINE DERIVATIVES

PART – I : STUDIES ON ARYLAMIDE
PART- II : STUDIES ON SULPHONAMIDES
PART - III : STUDIES ON MANNICH BASES
PART- IV : STUDIES ON SCHIFF’S BASES
PART- V : STUDIES ON 4-THIAZOLIDINONES
PART- VI : STUDIES ON 2-AZETIDINONES
PART- VII : STUDIES ON 5-OXO-IMIDAZOLINES