Introduction
Chapter at a Glance

CHAPTER –I: INTRODUCTION

1.1 Introduction

1.2 1,5-Benzodiazepine
  1.2.1 Biological aspects of 1,5-Benzodiazepine
  1.2.2 Biological aspects of annulated 1,5-Benzodiazepine
  1.2.3 Synthetic aspects of annulated 1,5-Benzodiazepine

1.3 Etravirine
  1.3.1 Biological aspects of Etravirine
  1.3.2 Synthetic aspects of Etravirine

1.4 Chemistry of the intermediates used in the synthesis in the present work
  1.4.1 Oxoketene dithioacetals
  1.4.2 Chalcones
  1.4.3 Dimethyl aminomethylene ketones

1.5 Brief outline of present work

1.6 References
Chapter-I: Introduction

1.1 Introduction

Heterocyclic compounds are of immense significance due to their wide spectrum of pharmacodynamic applications. These compounds have attracted the attention of chemists and biologist due to their varied nature of physicochemical and pharmacological activities. The literature on heterocyclic compounds is replete with examples of a large number of synthetic methods of naturally occurring physiologically active systems. The range of known compounds is virtually limitless, encompassing their impressive spectrum of physical, chemical and biological properties.

Heterocyclic compounds containing nitrogen atoms constitute the core structure of a number of important physiologically active molecules and play a vital role in the metabolism of living cells. A survey of literature on the nitrogen heterocycles reveals that pyrazole, isoxazole, carbazole, pyrimidine, diazepines and oxazepines etc, form an important constituents of a wide variety of materials products with pharmacodynamic applications.

The most widely studied application of heterocycles is in the preparation of biologically active and medicinally important molecules. Modern drug discovery focuses on the synthesis of specific biomolecular targets, which invariably contain a heterocyclic component. A key challenge in the synthesis of such targets continues to be the development of new pathways and improvement of existing pathways.

As the main study in the thesis centers around on the synthesis of condensed nitrogen heterocyclic systems containing benzodiazepine nucleus, in this context it seems necessary to present a brief review of biological and synthetic aspects of benzodiazepine and condensed benzodiazepine system.

1.2 Benzodiazepines

Benzodiazepine (sometimes colloquially, “benzo”; often abbreviated “BZD”) is a psychoactive nucleus whose core chemical structure has the fusion of a benzene ring and a diazepine ring. The first benzodiazepine, chlordiazepoxide (Librium) 1.01, was discovered accidentally by Leo Sternbach in 1955. Oxezepam
(1.02) was synthesized in 1961, nitrazepam 1.03 in 1962, and nimetazepam 1.04 in 1964² [Fig -1.1].

![Chemical structures of Librium, Oxezepam, Nitrazepam, and Nimetazepam]

Fig -1.1

1.2.1 Biological aspects of 1,5-Benzodiazepine:

1,5-Benzodiazepine and their polycyclic derivatives have attracted attention of chemist in the field of drugs and pharmaceuticals.³⁴ These compounds are widely used as anti-convulsant,⁵ anti-anxiety,⁷ analgesic, sedative,⁸ anti-depressive, hypnotic and anti-inflammatory agents.⁶ Other than their biological importance, benzodiazepine derivatives are commercially used as dyes for acrylic fibers.⁹ Moreover, 1,5-benzodiazepine derivatives are valuable synthetic equivalent that can be used in the preparation of other fused ring compounds such as- oxadiazolo-, triazolo-, or furano-benzodiazepine.¹⁰ Research in this area is very active and is directed towards the synthesis of compounds with enhanced pharmacological profiles. Table-1 gives the list of pharmacological properties of the 1, 5-benzodiazepine.
Table 1: Pharmacological properties of substituted and tricyclic derivative of 1, 5-benzodiazepine

<table>
<thead>
<tr>
<th>S.No</th>
<th>Structure of the compounds</th>
<th>Name of the compounds</th>
<th>Pharmacological properties</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
<td>V</td>
</tr>
<tr>
<td>1</td>
<td><img src="image" alt="Tibenzonium iodide" /></td>
<td>Tibenzonium iodide</td>
<td>Act as antibacterial agents</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Nevirapine" /></td>
<td>Nevirapine</td>
<td>Act as anti-HIV agent</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Clobazam" /></td>
<td>Clobazam</td>
<td>Act as antiepileptic agent</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Clozapine" /></td>
<td>Clozapine</td>
<td>Act as antipsychotics agent</td>
<td>13</td>
</tr>
</tbody>
</table>

Benzodiazepine and their polycyclic derivatives are known to exhibit a wide spectrum of biological activities and have found applications in the pharmaceutical industry. Some benzodiazepines and allied derivative are known to exhibit muscle relaxant, anticoagulant, antiobesity, antibacterial, calcium channel blockers, cholecystokinin antagonist, thrombopoietin receptor agonist, endothelin antagonist, vasopressin receptor antagonist activity.
1.2.2 Biological aspects of face ‘c’ annulated 1, 5-benzodiazepine:

Face ‘c’ annulated 1, 5-benzodiazepine show various pharmacological activities. Aptazepine\(^\text{26}\) (1.05) show antagonistic activity, methylazaaptazepine\(^\text{27}\) 1.06, olanazapine\(^\text{13}\) 1.07 and substituted) 9H, 10H, 3[N-4-methyl-2-benzamidothiophen3-yl-carbonyl amino [2-(2’pheny-11’-ethylenyl)-]-10-(aryl) thiazolidin-o[4,5b]1,5-benzodiazepines\(^\text{28}\) 1.08 are antidepressive, potential anticonvulsant and antipsychotics agents (Fig-1.2).

1.05       1.06         1.07

1.2.3 Synthetic aspects face ‘c’ annulated 1, 5-benzodiazepine:

1,5-Benzodiazepine are easily prepared by reacting the corresponding β-diketones and o-phenylenediamine in the presence of solvent or catalyst in a one pot reaction. Some of the reported method for the synthesis of 1, 5-benzodiazepine are described below.
By using Boron sulfonic acid:

Synthesis of annulated 1,5-benzodiazepine 1.11 has been reported by condensation of o-phenylenediamine 1.09 with ketone 1.10 which is catalysed by boron sulfonic acid at room temperature\(^2^9\) (Scheme-1.1).

![Scheme-1.1](image)

Using H\(_2\)O/EtOH solvent:

By using the solvent H\(_2\)O/EtOH, synthesis of annulated 1,5-benzodiazepine 1.13 from o-phenylenediamine 1.09 and ketone 1.12 at room temperature catalyzed by boron sulfonic acid\(^2^9\) (Scheme-1.2).

![Scheme-1.2](image)

Catalyzed by silica-supported dodecatungstophosphoric acid:

Silica supported 12-tungstophosphoric acid (HPW/SiO\(_2\)) as solid acid catalyst has been used for the synthesis of annulated 1,5-benzodiazepine 1.16 by reaction of o-phenylenediamine 1.14 with ketones 1.15\(^3^0\) (Scheme-1.3).

![Scheme-1.3](image)
1.3 Etravirine

1.3.1 Biological aspects of Etravirine:

![Etravirine](image)

Fig-1.3

Etravirine (TMC 125 \textsuperscript{1.17}, C_{20}H_{15}BrN_{6}O_{11} \textsuperscript{31}, 2,4-[[6-amino-5-bromo-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile, was approved in 2008 by the U.S. Federal Drug administration for use in combination therapy along with antiretroviral agents in adult patients with multi-drug-resistant HIV infections \textsuperscript{33}. Etravirine has a flexible molecular structure, allowing it to bind multiple conformations in a hydrophobic binding pocket adjacent to the catalytic site of reverse transcriptase and retain its activity in the presence of mutations that confer resistance to first-generation NNRTIs \textsuperscript{34,35}. Etravirine is a diarylpyrimidine (DAPY), a type of organic molecule having some conformational isomerism that can bind the reverse transcriptase enzyme in multiple conformations, allowing for a more robust interaction between etravirine and the enzyme, even in the presence of mutations. Etravirine can be used by patients infected with HIV that is resistant to other NNRTIs \textsuperscript{36}. Etravirine is extraordinary by virtue of its potency against the single mutants K 103 N and Y 181 C and the double mutants K 103N + Y 181 C and L1001 +K103N \textsuperscript{34}. The exceptional spectrum of activity might be attributed to its ability to bind the RT enzyme in more than one conformationally distinct modes \textsuperscript{37-39}. Some other etravirine derivatives \textsuperscript{1.18} 4-(6-chloro-2-(4-cyanophenylamino) pyrimidin-4-yl oxy)-3,5-dimethylbenzonitrile, \textsuperscript{1.19} 4-(4-amino-5-bromo-6-(4-bromo-2,6-4-yloxy)-3,5-dimethylbenzonitrile \textsuperscript{1.20}, 4-(6-amino-5-bromo-2-(4-cyanophenylamino) pyrimidin-4-
1.21 4-(4-amino-5-bromo-6-(4-bromo-2,6-dimethylphenoxy)pyrimidin-2-ylamino) benzonitrile (Fig 1.4).

1.3.2 Synthetic aspects of etravirine:

Reaction of 5-bromo-2,4,6-trichloropyrimidine 1.22 and 4-amino benzonitrile 1.23 in the presence of diisopropylethylamine in refluxing 1,4-dioxane gives diarylamine derivative 1.24 whose reaction with 4-hydroxy-3,5-dimethylbenzonitrile 1.25 in presence of NAH in N-methylpyrrolidone solvent affords 1.26. Etravirine 1.27 is obtained on the reaction of 1.26 with ammonia in 1,4-dioxane (Scheme-1.4).
Reaction of 2,4,6-trichloropyrimidine 1.28 and 3,5-dimethyl-4-hydroxybenzonitrile 1.29, N,N-diisopropylethylamine and 1,4-dioxane at 70°C yields 4-(((2,6-dichloro)-4-pyrimidinyl)oxy)-3,5,-dimethylbenzonitrile 1.30. To a solution of compound 1.30 and 4-aminobenzonitrile in N-methylpyrrolidone at 0-5°C, potassium tert-butoxide is added which forms 4-[[6-Chloro-2-(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile 1.31 this on heating with aq. Ammonia and 1,4-dioxane in an autoclave at 120°C gives 4-[[6-amino-2-(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-5-dimethylbenzonitrile 1.32. Etravirine 1.33 is obtained by the reaction of 1.32 in DCM and bromine solution at 0-5°C33 (Scheme-1.5).
1.4 Chemistry of the intermediates used in synthesis in the present work

Following intermediates have been used in the present synthetic work.

14.1 Oxoketene dithioacetals

14.2 Chalcone

14.3 Dimethylaminomethylene ketone

In view of the importance which the above intermediates portray in synthesis, it seems necessary to highlight their chemistry in the account to followed that prompted us to use these in synthesis, in the present work:

14.1 Oxoketene dithioacetals

Introduction:

Heterocyclic ketene S,S-acetals 1.34, cyanoketene S,S-acetals 1.35 are important synthons for the synthesis of a wide variety of new heterocycles and fused heterocycles40 (Fig 1.5).
α-Oxoketene dithioacetals containing active functional groups have been exploited in a variety of synthetic applications. Conjugated olefin ketene dithioacetals have served as carbonyl umpolung reagent and Diels-Alder dienes. Conjugated olefin ketene dithioacetals 1.36 have been extensively utilized for the synthesis of heterocyclic compounds, Diels-Alders dienes, and the synthesis of β-oxothiolcarboxylates (Fig: 1.6).

α-Oxoketene dithioacetals, especially the dimethyl thioacetals have recently received considerable attention due to their synthetic importance for the construction of a variety of alicyclic, aromatic and heterocyclic nucleus. The direct displacement of the methylthio group of ketene dithioacetals by an addition-elimination mechanism has proved to be a convenient method for preparing the useful heterocyclic compounds.
(a) Synthetic aspects of oxo-ketenedithioacetals:

The first synthesis of α-oxoketene dithioacetals 1.39 was reported in 1910 by Kebler\textsuperscript{50} and co-workers. The product was obtained by alkylation of β-oxo dithioic acids 1.38 with alkyl halides under basic conditions. The β-oxo dithioic acids, however, were obtained in poor yield by reaction of an aryl ketone 1.37 with CS\textsubscript{2} and KOH at 110\textdegree{}C followed by neutralization with sulphuric acid (Scheme 1.6).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textbf{1.37}};
\node (b) at (2,0) {\textbf{1.38}};
\node (c) at (4,0) {\textbf{1.39}};
\draw[->, thick] (a) -- (b) node[midway, above] {KOH, H\textsubscript{2}O, \textit{CS\textsubscript{2}}, 110\textdegree{}C};
\draw[->, thick] (b) -- (c) node[midway, above] {CH\textsubscript{3}J};
\end{tikzpicture}
\end{center}

\textbf{Scheme-1.6}

The reaction of ketones and methylene compounds with carbon disulphide in the presence of hydroxide and alkoxide bases has been known since 1891 when Meyer\textsuperscript{51} and Wege reported the preparation of the desaurins \textbf{1.41} by treatment of ketones \textbf{1.40} with carbon disulphide and powdered NaOH\textsuperscript{52} (Scheme 1.7).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textbf{1.40}};
\node (b) at (4,0) {\textbf{1.41}};
\draw[->, thick] (a) -- (b) node[midway, above] {4 eq NaOH, \textit{CS\textsubscript{2}}, heat, 8h (40\%)};
\end{tikzpicture}
\end{center}

\textbf{Scheme-1.7}

Apitzsch, reported in a series of papers\textsuperscript{53} to illustrate that treatment of a ketone \textbf{1.42} containing two adjacent methylene group with potassium hydroxide and carbon disulphide afforded salts having the 1,4-thiopyrone structure \textbf{1.43} (Scheme 1.8).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textbf{1.42}};
\node (b) at (4,0) {\textbf{1.43}};
\draw[->, thick] (a) -- (b) node[midway, above] {4 eq KOH, 2eq CS\textsubscript{2}};
\end{tikzpicture}
\end{center}

\textbf{Scheme-1.8}
In 1960 Thuiller and Vialle investigated the chemistry of \( \alpha \)-oxoketene dithioacetals 1.45 and found that these could be prepared directly from ketones 1.44 and \( \text{CS}_2 \) in good yields by using sodium tert-amylate as the base and two equivalent of an alkyl halides\textsuperscript{54} (Scheme: 1.9).

\[
\begin{align*}
\text{O} & \quad \text{R} \\
1.44 & \quad \text{Sodium tert-amylate, \text{CS}_2} \\
\text{ii CH}_3\text{X} & \quad \text{R} \\
1.45 \\
\end{align*}
\]

Scheme- 1.9

1.4.2 Synthetic aspects of chalcones:

(a): Conventional methods:

Synthesis of (E) chalcones

Claisen-Schmidt condensation

The Claisen-Schmidt condensation between acetophenone 1.46 and benzaldehyde derivatives 1.47 is a valuable C-C bond forming reaction which allows \( \alpha, \beta \)-unsaturated ketones called chalcones 1.48 to be obtained. Traditionally, the Claisen-Schmidt condensation\textsuperscript{55} is carried out at 50°C using 10-60% of alkali hydroxide or sodium ethoxide over a period of 12-15 hr. The preparation of \( \alpha, \beta \)-unsaturated ketones requires at least two steps, aldol formation and dehydration (Scheme-1.10).

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 \\
1.46 & \quad \text{CHO} \\
1.47 & \quad \text{Base} \\
1.48 \\
\end{align*}
\]

Scheme-1.10

Since aldol condensation is reversible, Claisen-Schmidt condensation\textsuperscript{56} approach of using enol ether has emerged as an alternative pathway for this reaction.
Moreover, Claisen-Schmidt condensation of cycloalkanones is not straightforward as these reactions proceed beyond monocondensation. In addition, many of these methods require harsh reaction conditions, expensive and toxic reagents, poor yield and low selectivity. Although several modifications have been made to counter these problems, there is still a need for the development of selective and better strategies for the one-step generation of $\alpha, \beta$-unsaturated carbonyl compounds.

It is widely accepted that there is a need to develop clean and economic process, where the use of toxic substances and the generation of waste can be avoided. The replacement of liquid by solid base catalysts for the production of fine chemicals not only allows easy separation and recycling of the catalysts from the reaction mixture. This provides an additional advantage in reactions using these reagents. Also for many bimolecular reactions heterogeneous catalysts have been found to give better selectivity than homogeneous catalysts.

The following basic solids have received much attention over the years as potential catalysts for Claisen-Schmidt condensation.

(a) Basic catalysts
- Sodium hydroxide$^{57}$
- Potassium hydroxide$^{58}$
- Potassium carbonate$^{59}$
- Barium hydroxide$^{60}$

(b) Acid catalysts
- Dry HCl$^{61}$
- AlCl$_3$$^{62}$
- BF$_3$ or BF$_3$-Et$_2$O$^{63}$
- Zn(Bpy)(OAc)$_2$$^{64}$
- Titanium (IV) Chloride$^{65}$
- Silica-sulphuric acid$^{66}$
- FeCl$_3$$^{66}$
Recently an improved procedure for the Claisen-Schmidt condensation using molecular iodine for the synthesis of $\alpha,\alpha'$-bis (arylmethylidene) cycloalkanones 1.51 has been reported. The yield is high and reactions complete in 10-15 min. under mild condition in the absence of solvent from 1.49 and 1.50 (Scheme-1.11).

**Scheme-1.11**

**Suzuki reaction:**

A general method for the synthesis of chalcones 1.54 based on Suzuki reaction between cinnamyl chloride 1.53 and phenyl boronic acids 1.52 or between benzyol chloride 1.55 and phenyl vinyl boronic acids 1.56 is described (Scheme-1.12).

**Scheme-1.12**

**Heck reaction:**

Coupling of an aryl vinyl ketone 1.57 with an aryliodide 1.58 in Heck reaction also resulted chalcones 1.59 and other flavonoids (Scheme- 1.13).

**Scheme-1.13**
Schiff bases:

In presence of acid, arylaminoketone derived from Schiff bases\(^6^9\) undergo hydramine cleavage to yield primary aromatic amine and chalcones.

Organometallic compounds:

Chalcones are also synthesized by acetylinic Grignard reagents\(^7^0\) cadmium derivatives and cinnamyl chloride in ether, phenyl magnesium bromide and cinnamonitrile in presence of ammonium chloride and methylmagnesium iodide with benzaldehyde.

Other methods:
The following methods of chalcone synthesis are also reported in the literature.

- Oxidative decarboxylation of \(\gamma\)-oxo acids in presence of lead oxide\(^7^1\).
- Heating a mixture of benzal chloride and acetophenone at 120-130°C in presence of copper powder\(^7^2\).
- Reduction of \(\alpha\)-epoxy chalcones by chromus chloride in acetone media\(^7^3\).
- Condensing substituted \(\beta\)-chlorovinyl ketone with phenolic ethers in presence of stannic chloride\(^7^4\).
- Thermal decomposition of \(\alpha\)-diazoacetophenone\(^7^5\).

Synthesis of (Z)-chalcones:

Generally, (E)-chalcones derivatives are of current interest and are synthesized far more easily than the (Z)-isomer. There have been a few reports\(^7^6\) concerning to the synthesis of (Z)-isomer of chalcones. Moreover, the general synthetic methods for the (Z)-chalcone is only the photoisomerization of the corresponding (E)-isomer and it takes time to produce the (Z)-chalcones\(^7^7\).

Recently, various (Z)-chalcone derivatives were easily synthesized in a stereoselective manner from 1, 3-diaryl-2-propynyl silyl ether 1.61, which were obtained by the reaction of silylacetylenes with aldehyde catalyzed by a chiral ammonium fluoride. Compound on catalytic isomerization by potassium-t-butoxide results the corresponding siloxy allene 1.62. Acid treatment of 1.62 produces in one-pot reaction of the (Z)-chalcones derivatives\(^7^8\) 1.63 (Scheme-1.14).
(b): Non-conventional methods

During the last few decades, chemical application of microwave and ultrasound irradiation has received a lot of attention and widespread research is going on in these areas. Significant enhancement of selectivity, rates and yield in synthesis of chalcones has been achieved by means of MW and US irradiation.

Microwave irradiated synthesis of chalcones

The following heterogenous catalysts have been used for the synthesis of chalcones and their analogous under microwave irradiation.

- Potassium carbonate
- Barium hydroxide
- \( p \)-Toluene sulphonic acid
- KF-Al\( _2\)O\( _3 \)
- Zirconium tetrachloride
- Piperidine
- Aqueous alkali

Ultrasound irradiated synthesis of chalcones

Recently following heterogenous catalyst have been successfully used for the synthesis of chalcones and their analogues under ultrasound irradiation.

- Potassium carbonate
- Basic Al\( _2\)O\( _3 \)
- Amino grafted Zeolite
- Ba(OH)\( _2 \)
- Pulverized KOH
- KF-Al\( _2\)O\( _3 \)
1.4.3 Dimethyl aminomethylene ketones:

Enaminones has been recently extensively utilized as precursors for the synthesis of heteroaromatics. It has been reported that methylalkyl ketones and methylaryl ketones condense readily with dimethylformamide dimethylacetal (DMF-DMA) to yield enaminones, whose chemistry has recently attracted considerable interest.\(^91\)

(a) Synthetic aspects of dimethylamino methylene ketones:

Anelli \textit{et al} work was of particular interest, as these researchers reported that the primary carboxamides \textbf{1.64} could be treated in methanol at 45°C to furnish methyl esters \textbf{1.66}, via an N-acyl formamidine intermediate\(^92,93\) \textbf{1.65} (Scheme-1.15).

![Scheme-1.15](image)

A facile and efficient method to prepare compound \textbf{1.68}, (which had been previously obtained by a Vilsmeier reaction using DMF/POCl\(_3\)\(^94\)), involved the reaction of dimethylformamide-dimethylacetal (DMF-DMA) with \textbf{1.67} to afford the title compound in better purity and higher yield (Scheme-1.16).

![Scheme-1.16](image)
Cycloalkanones 1.69 were heated with two equivalents of DMF-DMA for 16 h to prepare α-enaminoketones\(^95\) 1.70. The crude intermediate 1.70 reacted with 1.71 to give 1.72 (Scheme-1.17).

\[
\begin{array}{cccc}
1.69 & \xrightarrow{\text{DMF-DMA}} & 1.70 & \xrightarrow{\text{DMF-DMA}} 1.71 & \xrightarrow{\text{Ac}_2\text{O}} 1.72 \\
\end{array}
\]

Scheme-1.17

In presence of \(N, N\)-dimethylformamide dimethyl acetal (DMF-DMA), the addition reaction of vinylarenes 1.73 with electron deficient alkynes 1.74 proceed smoothly to give the adducts of 1,2-disubstituted 3,4-dihyronapthalenes\(^96\) 1.75 as shown in the following (Scheme-1.18).

\[
\begin{array}{cccc}
1.73 & + \text{R''OOC=COOR'} & \xrightarrow{\text{DMF-DMA}} & 1.75 \\
\end{array}
\]

Scheme-1.18

Cyclization of two amino groups by DMF-DMA:

Hydrazides 1.76 were converted to 3amino pyrimido[5,4-c]cinnolines 1.77 by refluxing with DMF-DMA in diethylene glycol dimethyl ether\(^97,98\) (Scheme-1.19).
1.5 Out come of our present research work

Non- nucleoside inhibitors of reverse transcriptase (NNRTIs) are part of certain multidrug regimens used in the treatment of HIV infection. Three virus specific proteins, reverse transcriptase (RT), protease, and gp41 are important targets for currently approved anti-HIV drugs. Additionally, a CCR5 virus coreceptor antagonist and an HIV integrase inhibitor have recently been approved for treatment of HIV infection.

As of February 2008, 32 anti-HIV drugs have been licensed by the U.S. Food and drug administration (FDA). These compounds include 11 HIV Protease inhibitors, 17 nucleoside and non-nucleoside reverse transcriptase (RT) inhibitors, 1 fusion inhibitor, 1 entry inhibitor (CCR5 co-receptor antagonist), 1 integrase inhibitor and 1 multiclass combination product. Clinical combinations of these drugs, known as highly active antiretroviral therapy (HAART), has significantly reduced the morbidity and mortality of AIDS. However, increasing number of HIV/AIDS patients on HAART regimens fail to respond to current antiretroviral drug combinations because of the emergence of drug-resistant HIV mutants.

The diarylpyrimidine-based NNRTIs such as etravirine (TMC-125, Fig-1.3) constitute the second-generation drugs and are useful for treatment of HIV infected patients with NNRTI-resistant viruses. Etravirine (TMC125) 2,4-[[6-amino-5-bromo-2-[4-cyanophenyl]amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile, was approved in 2008 by the U.S. Federal Drug Administration for its use in combination therapy alongwith other antiretroviral agents in adult patients with multidrug-resistant HIV infections. In order to avoid the appearance of the drug resistance observed in Etravirine monotherapy resulting from the enzyme mutation, recently proper modifications in the substitution pattern of etravirine have been sought which have resulted in the development of new broad spectrum of RT inhibitors.

A perusal of the structure of etravirine (1.17) reveals that its molecule essentially contains three bioactive fragments viz.
(i) 4-amino pyrimidine part.
(ii) p-cyano phenylamino part (present at 2-position of pyrimidine ring).
(iii) p-cyano phenoxy part (present at 4-position of the pyrimidine ring).

In addition to etravirine there are other compounds possessing a pyrimidine ring in their molecules viz. raltegravir etc which have recently emerged as the most powerful HIV-integrase inhibitors for the treatment of HIV-1 infection. One of these contains an oxadiazole ring, apart from the presence of the pyrimidine nucleus in its molecule. The presence of a cyano group in etravirine can offer an unprecedented opportunity to a chemist for its elaboration to the oxadiazole and imidazole rings following the reported procedures available for these in the literature. The cyano group contained in etravirine 1.17 has so far not been functionalized to produce the oxadiazole and imidazole (and other five membered rings) in its molecule. The present study intends to incorporate these rings in their molecules, the structures of which have been shown in (Fig-1.7) 1.89, 1.90 and 1.91.

To our knowledge no attempt has been made in the literature to incorporate the indicated pharmacophores depicted in Fig-1.7 Structures 1.83-1.22 on the 2-position of 1,5-benzodiazepine nucleus.

Condensed heterocyclic system containing imidazole, benzimidazole, oxadiazole, thiazole, pyrazole, isoxazole, pyrimidine, diazepine, oxazepine, thiazepine nuclei have attracted the attention of chemists, on account of the significant medicinal properties associated with them. In view of the prodigious range of activities of these compounds, it was considered worthwhile in the present work to undertaken investigation on the synthesis of condensed nitrogen-sulfur heterocyclic system containing above nuclei fused to the 1, 5-benzodiazepine frame work. It was hoped that synthesis of these condensed heterocyclic system and evaluation of their biological properties would provide a rational approach to the study of structure activity relationship of these molecules.
With this idea in mind it was proposed in the present work to condense 1,5-benzodiazepines with following biologically active pharmacophores:

- Imidazole
- Benzimidazole
- Oxadiazole
- Thiadiazole
- Pyrazole ring
- Isoxazole ring
- Pyrimidine ring
- 1,5-Benzodiazepine
- 1,5-Benzoazepine
- 1,5-Benzothiazepine

In order for our synthetic plan depicted in Schemes 1.20-1.29 could succeed, to give the desired products we required a good synthesis of compound 1.83 (Scheme-1.20) which contained an SMe group at face ‘a’ of its molecule. Carbonyl compounds with an adjacent CH2 group have been known to undergo reaction with CS2 and CH3I in the presence of a base to form the corresponding oxoketenedithioacetal derivatives.110-114 Oxoketene dithioacetals are useful 3-carbon-1,3-dipolarophiles which have been extensively employed in the literature in the preparation of five, six, and seven membered rings, from the reaction of bidentate nucleophiles.115,116 It has been reported earlier that oxoketenedithioacetal derivatives reacted smoothly with o-phenylenediamine to form the 1,5-benzodiazepine nucleus containing a thiomethyl ether function at its 2-position. The same methodology was employed in the present work to obtain 1.83 from the reaction of o-phenylenediamine with 1.79 in (Scheme-1.20). Compounds 1.79 in turn was obtained from the reaction of commercial N-benzyl piperidone with CS2+MeI in presence of the base (NaOEt). The iminothiomethyl ether function is a highly reactive species known to be highly activated for nucleophilic attack. This property of iminothiomethyl ether function was utilized in the present work to replace this, with hydroxyl and amine group bearing pharmacophores indicated in (Scheme-1.20) to yield the corresponding 2-aryl and heteryl amine substituted
derivatives of cyclohexano annulated of 1,5-benzodiazepine 1.84-1.88 respectively. The synthetic pathways that would lead to the formation of other related compounds 1.89-1.91 have been shown in Schemes-1.21 respectively.

The strategy outlined in schemes 1.20 and 1.21 envisaged the preparation of compounds 1.84, 1.85, 1.86, 1.87, 1.88, 1.89, 1.90 and 1.91 from the key intermediates 1.80 and 1.81 which were readily available from 1.84 on their reaction with H$_2$N-OH.HCl + KOH (in MeOH) and with ROH (CH$_3$OH) + HCl (g.) respectively, following the procedure reported for such reactions in the literature on other substrates containing the nitrile group. Established protocols on the amidine derivatives 1.80 and imidate ester derivatives 1.81 were used, employing the reagents indicated in schemes 1.21 to afford the compounds 1.89, 1.90, and 1.91 respectively.

Thiosemicarbazones derived from aldehydes provide a very convenient synthetic entry to amino thiadiazole derivatives on their reaction with NH$_4$Fe(SO$_4$)$_2$. This strategy was applied on 1.95 (Scheme-1.22) to generate the corresponding aminothiadiazole derivative 1.96 via 1.82.

An innovative procedure for the formation of isoxazole and pyrazole rings has been developed recently, utilizing the potential of the corresponding dimethylaminomethylene ketone derivatives, obtained from the reaction of compounds containing a COCH$_2$ group with commercial dimethyl formamide dimethyl acetal (DMF-DMA). The dimethylaminomethylene ketone derivatives 1.94 was obtained from the reaction of 1.92 with DMF-DMA. Compound 1.92 was readily available from the reaction of 1.83 with p-hydroxy acetophenone (Scheme-1.22).

The most recorded method for the preparation of chalcones makes use of Claisen Schmidt reaction which involves the base catalyzed condensation of a ketone (for example acetophenone) and an aldehyde (for example benzaldehyde) to form an $\alpha$, $\beta$-unsaturated ketones substituted with aryl residues (chalcones). This strategy was applied on benzaldehyde to form the chalcone 1.93
Chalcones are useful enone derivatives which have been extensively employed in the literature in the preparation of five, six and seven membered heterocyclic rings from their reaction with bidentate nucleophiles such as hydroxylamine hydrochloride and hydrazine hydrate (to form the isoxazole and pyrazole rings)\textsuperscript{129-131} with urea, thiourea, acetalidine, guanidine etc. (to form the pyrimidine ring)\textsuperscript{132-136} with o-phenylenediamine, o-aminophenol and o-aminothiophenol (to form the benzodiazepine, benzoxazepine and benzothiazepine rings).\textsuperscript{137,138} In Scheme 1.23, the products 1.97 and 1.98 that resulted from the reaction of chalcone derivative 1.93 with hydroxylamine hydrochloride and hydrazine hydrate have been shown. Compounds 1.97 and 1.98 were obtained from 1.97a and 1.98a respectively, on their oxidation with o-iodoxybenzoic acid (IBX)\textsuperscript{139,140} following the protocol reported for this process in the literature on other substrates.

The schemes 1.27 and 1.29 have been drawn to show explorations of further examples of the reaction of chalcone derivative 1.93 with urea and thiourea (Scheme-1.27) to form the corresponding pyrimidine ring incorporated products 1.15 and 1.16 respectively and with o-phenylenediamine, o-aminophenol and o-aminothiophenol to form the corresponding 1,5-benzodiazepine, 1,5 benzoxazepine and 1,5 benzothiazepine ring incorporated products 1.20, 1.21 and 1.22 respectively (Scheme-1.29).

The dimethylaminomethylene ketone derivatives 1.94 behaved in the same way as do the chalcones in their reactions with hydroxylamine hydrochloride, hydrazine hydrate, urea, thiourea, guanidine, acetalidine o-phenylenediamine, o-aminophenol and o-aminothiophenol etc.\textsuperscript{141} The strategy depicted earlier in (Scheme-1.24) which explored the preparation of the corresponding isoxazole and pyrazole derivatives 1.99 and 1.10 (Scheme-1.24) from the reaction of 1.94 with NH\textsubscript{2}OH.HCl and NH\textsubscript{2}NH\textsubscript{2}.H\textsubscript{2}O respectively. The treatment of the intermediate 1.94 with urea thiourea, guanidine and acetamidine gave the pyrimidine derivatives 1.11, 1.12, 1.13 and 1.14 respectively (Scheme-1.26) and corresponding benzodiazepine, benzoxazepine and benzothiazepine derivatives 1.17, 1.18 and 1.19 were obtained.
on its reaction with o-phenylenediamine, o-aminophenol and o-aminothiophenol respectively (Scheme-1.28).

The purity of all compounds was routinely checked by TLC and the compounds were purified by column chromatography and preparative TLC. The structure of all the compounds were established on the basis of microanalysis, IR, \textsuperscript{1}HNMR and mass spectral data. The formation of products was rationalized by giving plausible mechanisms. The compounds were screened for their antimicrobial activities.
Structure of the compounds whose synthesis is proposed to be undertaken in the present work
Fig-1.7
Scheme-1.20
Scheme-1.21
Scheme-1.22
Scheme 1.23

Scheme 1.24
Scheme-1.25

Scheme-1.26
Scheme 1.27