Chapter-I

Introduction
CHAPTER-I
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1.1 GENERAL INTRODUCTION

An enormous number of biologically active heterocyclic compounds have been known and this number has been continuously increasing rapidly, accordingly the literature on this subject has been very vast. Heterocyclic compounds occur widely in nature and also in a variety of non naturally occurring compounds. A large number of heterocyclic compounds are essential to life. Various compounds such as alkaloids, antibiotics, essential amino acids, the vitamins, haemoglobin, the hormones and a large number of synthetic drugs and dyes contain heterocyclic ring systems. Knowledge of heterocyclic chemistry is useful in biosynthesis and in drug metabolism as well. Nucleic acids are important in biological processes of heredity and evolution. There are a large number of synthetic heterocyclic compounds with important applications and many are valuable intermediates in synthesis.

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.

Benzodiazepines and its derivatives constitute an important class of heterocyclic compounds which possess a wide range of therapeutic and pharmacological properties. Derivatives of benzodiazepines are widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, and hypnotic agents. In the last decade, the area of biological interest of 1, 5-benzodiazepines has been extended to several diseases such as cancer, viral infection and cardiovascular disorders. In addition, 1, 5-benzodiazepines are key intermediates for the synthesis of various fused ring systems such as triazolo-, oxadiazolo-, oxazino- or furanobenzodiazepines. Besides, benzodiazepine derivatives are also of commercial importance as dyes for acrylic fibers in photography.

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

1.2 1, 5-BENZODIAZEPINES

The broad spectrum of biological properties exhibited by 1, 5-benzodiazepines have triggered the development of these materials in heterocyclic chemistry. The pace of research and development in this area has been accelerating fast and there seem to be virtually no limit to the number of interesting ring system that can be created in the laboratory today by a combination of ingenuity and perseverance. The heterocyclic system with seven atoms, once considered chemical oddities are today just as easily obtained as their five- and six- membered counter parts. A rapid development in this area represents an intriguing blend of pure and applied heterocyclic chemistry. The practical importance of azepines are not limited to their application as psychopharmacological or anti-neoplastic agents alone but their additional novel applications are continuously emerging. Recent demonstrations that some of these compounds can be used as anti-HIV agents have stimulated further research in this area with yet another perspective.

1.2.1 Biological aspects of 1, 5-benzodiazepines

1,5-Benzodiazepines and their polycyclic derivatives have attracted attention of chemist in the field of drugs and pharmaceuticals.\(^\text{10-11}\) These compounds are widely used as anti-convulsant,\(^\text{12}\) anti-anxiety, analgesic,\(^\text{13}\) sedative,\(^\text{14}\) anti-depressive, hypnotic and anti-inflammatory agents.\(^\text{15}\) Other than their biological importance, benzodiazepine derivatives are commercially used as dyes for acrylic fibers.\(^\text{16}\) Moreover, 1,5-benzodiazepine derivatives are valuable synthetic equivalents that can be used in the preparation of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino- or furano-benzodiazepines.\(^\text{17}\) Research in this area is very active and is directed towards the synthesis of compounds with enhanced pharmacological profiles. Table-I gives the list of pharmacological properties of the 1, 5-benzodiazepines whose antineoplastic and anti-HIV activity has appeared in the literature\(^\text{18}\).
### Table-I
Pharmacological properties of 1, 5-benzodiazepines

<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>1.</td>
<td><img src="image1" alt="Pirenzepine Structure" /></td>
<td>Pirenzepine</td>
<td>Act selectively as muscarinic receptor (M1) antagonist</td>
<td>19</td>
</tr>
<tr>
<td>2.</td>
<td><img src="image2" alt="Tibenonium Iodide Structure" /></td>
<td>Tibenonium iodide</td>
<td>Act as antibacterial agent Act as the platelet activating factor (PAF)</td>
<td>20</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image3" alt="Apofant Structure" /></td>
<td>Apofant</td>
<td>Act as the platelet activating factor (PAF)</td>
<td>21</td>
</tr>
<tr>
<td>S.No</td>
<td>Structure of the Compounds</td>
<td>Name of the Compounds</td>
<td>Pharmacological properties</td>
<td>References</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------</td>
<td>-----------------------</td>
<td>-----------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image" alt="TIBO Structure" /></td>
<td>TIBO</td>
<td>Shows Anti-HIV activity</td>
<td>22</td>
</tr>
<tr>
<td>5.</td>
<td><img src="image" alt="Nevirapine Structure" /></td>
<td>Nevirapine</td>
<td>Act as Anti-HIV agent</td>
<td>23</td>
</tr>
<tr>
<td>6.</td>
<td><img src="image" alt="Clobazam Structure" /></td>
<td>Clobazam</td>
<td>Act as Antiepileptic agent</td>
<td>24</td>
</tr>
</tbody>
</table>
Some benzodiazepine derivatives shown in Fig: 5.1 are highly pharmacologically active molecules. Pirezepine\textsuperscript{25} (1.001) acts selectively as muscarinic receptor (M1) antagonist. Tibenzonium iodide (1.002) acts as antibacterial agent and apafant\textsuperscript{26} (1.003) act as platelet activating factor (PAF). TIBO\textsuperscript{27} (1.004) as well as nevirapine\textsuperscript{28} (1.005) act as anti-HIV agents, clobazam\textsuperscript{29} (1.006) act as anti-epileptic agent and clazapine\textsuperscript{30} (1.007) is effective as anti-psychotic agent. Benzothienobenzodiazepine (1.008) and thienobenzodiazepine or olanzapine (1.009) also act as effective anti-psychotics. Flurazepam\textsuperscript{31} (1.010) and halazepam\textsuperscript{32} (1.011) possess anxiolytic, anti-convulsant, sedative and skeletal / muscle relaxant properties.
1.010

1.011

Fig. 1.1

1.2.2 Synthetic aspect of 1, 5-benzodiazepines

The interesting physiological properties associated with these molecules required the flexibility in the method of their synthesis, and this could be the reason for literature to be replete with wide variety of methods for their synthesis. Some of the reported methods for the synthesis of 1, 5-benzodiazepines are described below:

1. The reaction of chalcones (1.013) with o-phenylenediamine (1.012) in presence of 1-2 drop of piperidine in alcoholic solution gives 1,5-benzodiazepines (1.014) (Scheme-5.11).\(^{33}\)

\[
\begin{align*}
\text{NH}_2 & \quad + \quad \text{NH}_2 \\
\text{Ar} & \quad \xrightarrow{\text{Het}} \\
\text{1.012} & \quad \text{1.013} & \quad \text{1.014}
\end{align*}
\]

Scheme-1.01

2. 1,5-Benzodiazepine (1.017) were synthesized from the reaction between 1.016 and aromatic aldehyde 1.015 in the presence of catalytic amounts of trifluoroacetic acid in ethanol under reflux conditions (Scheme-1.02).\(^{34}\)

\[
\begin{align*}
\text{1.015} & \quad \xrightarrow{\text{H}_2N\text{NH}_2 \quad \text{E�OH}} \\
\text{1.016} & \quad \xrightarrow{\text{HO} \quad \text{E�OH/H} \quad \text{CF}_3\text{COOH}} \\
\text{1.017}
\end{align*}
\]

Scheme-1.02
3. Condensation of alkenes \(1.018\) and acetone \(1.019\) in the presence of \(\text{Fe(NO}_3\text{)}_3\) yielded the respective 3-acetyl-5-alkylisoxazolines \(1.020\). The \(1.020\) upon Claisen-Schmidt condensation with aldehydes gives 3-cinnamoyl-5-alkylisoxazoline \(1.021\). The \(1.021\) upon condensation with \(\alpha\)-phenylenediamine in presence of \(\text{KHSO}_4/\text{SiO}_2\) generates 4-(5-acetyl-2-isoxazolin-3-yl)-2-aryl-2,3-dihydro-1H-1,5-benzodiazepines \(1.022\) (Scheme-1.03).\(^{35}\)

![Scheme-1.03](image1)

4. Reaction between 1,2-diamino-3,4-dimethylbenzene \(1.023\) and \(1.024\) was carried out in the dark and the compounds 2-nitrophenyl-2,3-dihydro-1H-benzodiazepines \(1.025\) were the only products isolated in moderate to good yields (Scheme-1.04).\(^{36}\)

![Scheme-1.04](image2)
5. To produce the fused diazepines 1.028, the hydrochloride of the required Mannich base 1.027 and the diamine 1.026 were refluxed in ethanol in the presence of anhydrous sodium acetate (Scheme-1.05).  

\[
\begin{align*}
R & \quad NH_2 \\
R & \quad NH_2 \\
\text{1.026} & \quad O \\
\text{1.027} & \quad N(CH_3)_2\text{HCl} \\
\text{AcONa anh.} & \quad \text{-HN(CH}_3\text{)}_2\text{-HCl} \\
\text{-H}_2\text{O} & \quad \text{1.028}
\end{align*}
\]

Scheme-1.05

6. o-Nitroaniline (1.029) and chalcones 1.030 were treated with low-valent titanium prepared from titanium tetrachloride and samarium powder in anhydrous tetrahydrofuran to produce 2, 3-dihydro-1H-1, 5-benzodiazepines (1.031) (Scheme-1.06).  

\[
\begin{align*}
\text{1.029} & \quad \text{O} \\
\text{1.030} & \quad \text{TiCl}_4/\text{Sm} \\
\text{THF, 5min r.f.} & \quad \text{1.031}
\end{align*}
\]

Scheme-1.06

1.3 ETRAVIRINE

1.3.1 Biological aspects of etravirine

For the past several years, multidisciplinary group of organic chemists, crystallographers, molecular modelers, virologists, and biologists has been striving to develop effective anti-HIV drugs. The non-nucleoside reverse transcriptase
inhibitors (NNRTI) play a pivotal role as key components of “highly active antiretroviral therapy” [HAART].\textsuperscript{40-44} NNRTIs have an ability to target an allosteric binding pocket on the reverse transcriptase (RT) enzyme. This property allows them to be useful as broadspectrum agents against human immunodeficiency virus (HIV) RT mutations. These efforts have resulted in the discovery of the diarylpyrimidine (DAPY) family of NNRTIs. By combining chemical synthesis with broad antiviral screening, bioavailability and safety assessments in animals, and analysis of three-dimensional structure activity relationships, has led the identification of the DAPY analogues TMC 120 (R 147681) and TMC 125 (R 165335) as promising drug candidates.\textsuperscript{40} In phase II studies TMC 125 was also found to significantly reduce viral load after 7 days of treatment in anti-retroviral experienced patients whose HIV viruses carried RT mutations.\textsuperscript{44}

The diarylpyrimidine-based NNRTIs constitute the second –generation drugs and are useful for treatment of HIV infected patients with NNRTI-resistant viruses. Etravirine (TMC 125 (1.074)41,C20H15BrN6O11)45,2,4-[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 other antiretroviral agents in adult patients with multidrug-resistant HIV infections.\textsuperscript{46} Tibotec pharmaceuticals, Ltd. developed etravirine (TMC 125), and it is now marketed by Tibotec Therapeutics, a division of Ortho Biotech Products, L.P. under the brand name Intelectence.\textsuperscript{45} Etravirine has a flexible molecular structure, allowing it to bind to 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{47,48} TMC 125 and TMC 278 are diarylpyrimidine (DAPY) NNRTIs with high activity against wild –type and mutant virus strains including K103N. A distinct feature of these compounds is the innate flexibility between aromatics rings, allowing the compound to adopt multiple conformations, and this is one explanation for the potent activity against many resistance virus strains.\textsuperscript{47,48,49,50} Etravirine is extraordinary by virtue of its potency against the single mutants K103N and Y181C and the double mutants K103N + Y181C and L100I+ K103N\textsuperscript{47}. The exceptional spectrum of activity of etravirine might be attributed to its ability to bind the RT enzyme in more than one conformationally distinct mode.\textsuperscript{51-53}
1.3.2 Synthetic aspects of etravirine

1. Reaction of 2,4,6-trichloropyrimidine (1.033), and 3,5,-dimethyl-4-hydroxybenzonitrile (1.034), in presence of N,N-diisopropylethylamine (DIEA) 1,4-dioxan at 70°C yields 4-[2,6-dichloro-4-pyrimidinyloxy]3,5-dimethylbenzonitrile (1.035). To a solution of compound (1.035) and 4-aminobenzonitrile in N-methylpyrroldione at 0-5°C, potassium tert-butoxide is added and this forms 4-[[6-chloro-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile (1.037). Etravirine (1.038) is obtained by the reaction of 1.037 in DCM and bromine solution at 0-5°C (scheme-1.07)
2. Reaction of 5-bromo-2, 4, 6-trichloropyrimidine (1.039), 4-amino benzonitrile (1.040) in the presence of diisopropylethylamin in refluxing 1, 4-dioxan to gave diarylamine derivative 1.041 whose reaction with 4-hydroxy-3, 5-dimethylbenzonitrile (1.042), in presence of NaH in N-methyl pyrrolidone solvent to gave the compound 1.043. Etravirine (1.044) is obtained on the reaction of 1.043 with ammonia in 1,4-dioxane \(^{54}\) (Scheme-1.08)
1.4 CHEMISTRY OF THE INTERMEDIATES USED IN SYNTHESIS IN THE PRESENT WORK

1.4.1 Amidine derivatives

N-Aryl amidines are important synthons for the synthesis of several heterocyclic compounds. These compounds show a wide spectrum of biological activity like antibacterial, antimicrobial, anticancer and antiviral activity.

Methods used for the synthesis of amidine derivatives:

1. Benzaldehyde oxime (1.044) is converted into corresponding benzohydroximoyl chloride (1.045) with NCS. Treatment of the mixture of 1.046 and imine 1.046 1.0 with triethylamine at 0°C affords 4, 5-dihydro-1, 2, 4-oxadiazole 1.047 in good yield. Oxadiazole on hydrogenolysis with Raney nickel in methanol at room temperature gives substituted amidine 1.048 in 74-91% (scheme-1.09).

2. Microwave reaction of primary and secondary amines (1.050) with imidoylbenzotriazoles (1.049) gives various polysubstituted amidines 1.051 in good yields (scheme-1.10).
3. A generalized synthesis of amidines \textbf{1.053} from thioimidate \textbf{1.052}, using a buffered protonic catalysis in nonaqueous medium \textsuperscript{57} (scheme-1.11) is as follows:

\[
\text{HN} = \text{S} \text{CH}_2 \text{CH}_3 + \text{RNH}_2 \xrightarrow{\text{HOAc (NaOAc)}} \text{HN} = \text{NR} \text{N(C}_{16}\text{H}_{33})_2 \cdot 2\text{HCl}
\]

\textbf{1.052}

\textbf{Scheme-1.11}

4. Amidine derivatives \textbf{1.055} have also been synthesized from nitrile compounds \textbf{1.054} by two different methods \textsuperscript{58}: A) Pinner reaction \textsuperscript{59}, B) Thioimidate route \textsuperscript{60} (scheme-1.12)

\[
\begin{align*}
\text{R} \quad \text{CN} & \xrightarrow{\text{NH}_4\text{Cl}/\text{MeOH}} \text{NH}_2 \\
\text{R} \quad \text{CN} & \xrightarrow{\text{1. H}_2\text{S (g)}} \text{C} = \text{NH} \\
\end{align*}
\]

\textbf{1.054}

\textbf{Scheme-1.12}
5. Condensation of 4-(trifluoromethoxy) aniline 1.056 with ammonium thiocyanate and benzyltrimethylammonium tribromide (1.056) in methyl cyanide gives 2-amino-6-(trifluoromethoxy) benzothiazole (1.057), which on further reaction with appropriate acetamide in the presence of POCl₃ in dry toluene led to the formation of the desired acetamidines 1.058 (scheme-1.13)

![Scheme-1.13]

1.4.2 Imidate ester derivatives

Methods used for the synthesis of imidate ester derivatives;

1. The classical method to synthesize imidates 1.062 is the pinner reaction62. Hereby a nitrile 1.059 is condensed with an alcohol 1.060 under anhydrous conditions in the presence of hydrogen chloride or hydrogen bromide at 0°C (Scheme-1.14a)

![Scheme-1.14a: Pinner reaction]
2. Imidate ester 1.065 are easily produced from the amide 1.063 by treatment with ‘Meerwein's reagent’ (Scheme-1.14b)

\[ R'C(\text{OEt})_3 + OR' \rightarrow R'C(\text{OEt})_3 \]  

\[ R'C(\text{OEt})_3 \rightarrow R'C(\text{OEt})_3 \]  

Scheme-1.14b

3. Reaction of methylanthranilate (1.066) with triethyl orthoformate (excess) gives N-(2-carbomethoxyphenyl) imidate ester (1.067) and quinazolinones (in a small amount but significant yield) (1.068) (Scheme-1.14c)

\[ \text{RC}(\text{OEt})_3 \rightarrow \text{RC}(\text{OEt})_3 \]  

\[ \text{R'(OEt)}_3 \rightarrow \text{R'(OEt)}_3 \]  

Scheme-1.14c

4. Miscellaneous synthesis

Methyl N-phenyl carbomethoxyformimidate (1.071) has been prepared by the action of methyl methoxydichloroacetate (1.070) on aniline (1.069) in boiling xylene (Scheme-1.15a)

\[ \text{C}_6\text{H}_5\text{NH}_2 + \text{C}(\text{OCH}_3)\text{Cl}_2 \rightarrow \text{CH}_3\text{OOC} \]  

\[ \text{C}(\text{OCH}_3)\text{Cl}_2 \rightarrow \text{CH}_3\text{OOC} \]  

Scheme-1.15a

Chlorothioformimidates 1.074 are prepared from the interaction of isocyanides 1.072 and sulphenylchlorides (Scheme-1.14b)

\[ \text{RNC} + \text{R'SCl} \rightarrow \text{CIC(=NR)SR} \]  

\[ \text{R'SCl} \rightarrow \text{CIC(=NR)SR} \]  

Scheme-1.15b
5. **Imidate synthesis from unsaturated system**

The addition of primary amines $1.075$ to ethoxyacetylene ($1.076$) in refluxing ethanol gives rise to imidates, $1.077$ but amidines may also be formed by the further interaction of the amine$^67$ *(Scheme-1.16a)*

$$\text{RNH}_2 + \text{C}_2\text{H}_5\text{OC}≡\text{CH} \rightarrow \text{CH}_3\text{C}≡\text{NR} \text{OC}_2\text{H}_5 + \text{CH}_3\text{C}≡\text{NR} \text{NHR}$$

*Scheme-1.16a*

Secondary amines $1.078$ on the other hand, do not give imidate formation, as the intermediate $1.079$ is incapable of undergoing the required tautomeric shift $^68$ *(Scheme-1.16b)*

$$\text{R}_2\text{NH} + \text{C}_6\text{H}_5\text{OC}≡\text{CH} \rightarrow \text{H}_2\text{C}≡\text{C(OC}_6\text{H}_5)\text{NR}_2$$

*Scheme-1.16b*

### 1.4.3 Chalcone derivatives

Chalcones are $\alpha$, $\beta$-unsaturated ketones containing the reactive ketoethylenic group $\text{CO-CH=CH}$. The chemistry of chalcones has generated intensive scientific studies throughout the world. Special interest has been focused on the synthesis and biodynamic activities of chalcones. The name “Chalcones” was given by Kostanecki and Tambor.$^69$ These compounds are also known as benzalacetophenone or benzylidene acetophenone. In chalcones, two aromatic rings are linked by an aliphatic three carbon chain. Chalcones bear very good synthan framework so that a variety of novel heterocycles with good pharmaceutical profile can be designed.

**Synthetic aspects of chalcones:**

Different methods are reported in the literature for the preparation of chalcones. The chalcones are versatile reactive intermediates which are used to synthesize several heterocyclic ring systems like five-membered *(e.g. pyroles, pyrazoles, imidazoles, isoxazoles, oxazoles, thiazoles, etc.)*, six-membered *(e.g. pyridines, pyrimidines, triazines, etc.)*, seven-membered *(e.g. benzodiazepines,*
benzoxazepines, benzothiazepines, etc.) having different heterocycles and carbocycles as substituents in these rings.

Conventional methods:

**Synthesis of E-chalcones**

(a) **Claisen-Schmidt condensation:** The Claisen-Schmidt condensation between acetophenone (1.081) and benzaldehydes (1.082) is a valuable C-C bond forming reaction which allows α,β-unsaturated ketones called chalcones (1.083) to be obtained. Traditionally, the Claisen-Schmidt condensation\(^7\) is carried out at 50°C using 10-60% of alkali hydroxide or sodium ethoxide over a period of 12-15 hr. (Scheme-1.17).

![Scheme-1.17](image)

Since aldol condensation is reversible, Claisen-Schmidt condensation\(^7\) approach using enol ether has emerged as an alternative pathway for this reaction. 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. Therefore, several modifications have been made to overcome these problems. There is still a need for the development of selective and better strategies for the one-step generation of α, β-unsaturated carbonyl compounds. It is widely accepted that there is a need to develop clean and economic process, where the use of non-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 but also for many bimolecular reactions heterogeneous catalysts give better selectivity than homogeneous catalysts.
(b) Compound 1.087 was prepared by treating compound 1.086 with pinacol (bromomethyl) boronate in the presence of sodium hydride in DMSO and further deprotection in alkaline condition. Compound 1.086 was obtained from 1.084 and 1.085 as shown in the (Scheme-1.18)

\[
\begin{align*}
\text{CHO} & \overset{\text{(a)}}{\longrightarrow} \overset{\text{reflux}}{\longrightarrow} \overset{\text{(b)}}{\longrightarrow} \overset{\text{(c)}}{\longrightarrow} \\
1.084 & \quad 1.085 & \quad 1.086 & \quad 1.087 \\
\text{Reaction conditions: (a) KOH, MeOH (b) NaH, Pinacol (bromoethyl)boronate, THF (c) NaOH, H}_2\text{O}
\end{align*}
\]

Scheme-1.18

(c) **Suzuki reaction:** A general method for the synthesis of chalcones based on Suzuki reaction between phenyl boronic acid (1.088) and cinnamyl chloride (1.089) or between benzoyl chloride (1.091) and phenyl vinyl boronic acid (1.092) is described in the Scheme-1.19.

\[
\begin{align*}
\text{Ph} & \text{BOH} \quad \overset{\text{Cl}}{\longrightarrow} \overset{\text{Ph}}{\longrightarrow} \overset{\text{KOH, MeOH}}{\longrightarrow} \overset{\text{Pd} \cdot \text{CuI}}{\longrightarrow} \\
1.088 & \quad 1.089 & \quad 1.090 & \quad 1.091 & \quad 1.092 \\
\end{align*}
\]

Scheme-1.19

(d) **Heck reaction:** Coupling of an aryl vinyl ketone (1.093) with an aryl iodide (1.094) in Heck reaction condition also resulted chalcones 1.095 and other flavonoids (Scheme-1.20).

\[
\begin{align*}
\text{MeO} & \overset{\text{(1)Pd (OAc)}_2\text{Ph}_3\text{P, CH}_3\text{CN, Et}_3\text{N}}{\longrightarrow} \overset{\text{MeO}}{\longrightarrow} \overset{\text{MeO}}{\longrightarrow} \\
1.093 & \quad 1.094 & \quad 1.095 \\
\end{align*}
\]

Scheme-1.20
Introduction

(e) **From Cinnamic acid and its derivatives:** Cinnamic acid and phenol, cinnamic anhydride, cinnamoyl chloride and benzene, cinnamoyl chloride and phenol have been used for the synthesis of chalcones and their analogues.

(f) **From o-Iodophenyl acetate and palladium:** A convenient palladium catalyzed procedure for the synthesis of o-hydroxychalcones, flavanone, and benzo[b]furanes has been described where o-iodophenyl acetates were used as a common precursor.

(g) **From Schiff bases:** In presence of acid, arylaminoketones derived from Schiff bases undergo hydramine cleavage to yield primary aromatic amine and chalcones.

(h) **From Enamines:** The synthesis of chalcones has also been affected by the interaction of benzaldehyde with N-α-styryl morpholine.

(i) **From Organometallic compounds:** Chalcones have also been synthesized by acetylinic Grignard reagents, cadmium derivatives and cinnamyl chloride in ether, phenyl magnesium bromide and cinnamonitrile in presence of ammonium chloride and methylmagnesium iodide with benzaldehyde.

(j) **From critical water:** Recently, Zhu et al. has carried out Claisen-Schmidt condensation reaction of aromatic aldehyde and ketone in critical water.

**Synthesis of Z-chalcones**

Generally, Z-chalcones have great synthetic applications and are synthesized more easily than their E-isomers. There have been a few reports 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. Recently, various Z-chalcone derivatives were easily synthesized in a stereoselective manner from 1,3-diaryl-2-propynyl silyl ether (1.097) which were obtained by the reaction
of silyl acetylenes (1.096) with aldehyde catalyzed by a chiral ammonium fluoride. Compound 1.097 on catalytic isomerization by potassium t-butoxide resulted to the corresponding siloxy allene 1.098. Acid treatment of 1.098 produced in one-pot reaction of the Z-chalcones derivatives 1.099 (Scheme-1.21).

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, rate of reactions, and yield in synthesis of chalcones has been achieved by means of microwave and ultrasound 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-Toluenesulphonic acid
- KF-Al₂O₃
- Zirconium tetrachloride
- Piperidine
- Aqueous alkali
Ultrasound irradiated synthesis of chalcones

Recently, following heterogenous catalysts have been successfully used for the synthesis of chalcones and their analogues under ultrasound irradiation:

- Potassium carbonate
- Basic Al₂O₃
- Amino grafted Zeolite
- Ba(OH)₂
- Pulverized KOH
- KF-Al₂O₃

1.4.4 Synthetic aspects of dimethylamino methylene ketones

Synthetic aspects

The enaminones were first synthesized via condensation of methyl aryl or heteroaryl ketones 1.100(a-g) with DMFDMA in refluxing xylene. The desired compounds were obtained in low yield, consequently this synthetic approach was modified by condensing the methyl ketones with slightly excess of DMFDMA in the absence of solvent [Scheme1.22]. Under these condition the reaction products 1.101(b-g) were obtained in almost quantitative yields on cooling in a much more economical way.

\[
\begin{align*}
\text{1.100 (a-g)} & \quad \text{Δ} & \quad \text{MW} & \quad \text{1.101 (a-g)} \\
\end{align*}
\]

![Scheme 1.22](image)

It has been found that phenylacetone 1.102 condensed with N, N dimethylformamide-dimethylacetal (DMF-DMA) in refluxing xylene to yield 1.103 Compound. Compound 1.103 readily reacted with cyanothioacetamide in refluxing ethanolic piperidine to yield 6-methyl-5-phenyl-2-thioxo-1, 2-dihydropyridine-3-carbonitrile 1.104a and with cyanoacetamide to give pyridone 1.104b [Scheme 1.23].
The enolizable ketones 1.105 are first converted to corresponding α-tosyloxy ketones 1.106 using HTIB or PSHTIB.\textsuperscript{100} [Hydroxy (tosyloxy) iodo benzene], [Polymer-supported HTIB]. The reaction of 1.106 with (R=H, DMF and R=CH\textsubscript{3}, DMA) as solvent generated iminium salt intermediate 1.107, which on subsequent treatment with water cleanly afforded α-formyloxy ketones and α-acetoxy ketones 1.108, respectively, within 15–45 min. [Scheme 1.24]

Anelli \textit{et al} work was of particular interest, as these researchers reported that the primary carboxamides 1.109 could be treated in methanol at 45°C to furnish methyl esters 1.111, via an N-acyl formamidine intermediate 1.110 [scheme-1.25]
Meso-1, 2-diphenyl- 1, 2-ethanediol 1.112 gives trans-stilbene epoxide 1.113 stereospecifically. [Scheme 1.26]

Cycloalkanones 1.114 were heated with two equivalents of DMFDMA for 16 h to prepare α-enaminoketones 103 1.115 the crude intermediate 1.115 reacted with 1.116 to give 1.117, 1.118 and 1.119 [Scheme-1.27]

A general indole synthesis involves reaction of an o- nitrotoluene derivative 1.120 with DMF-DMA in refluxing DMF forming a nitro N, N-dimethyl
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enaminone 1.121. Reduction of nitro group is accompanied by spontaneous cyclization to an indole 1.122 [Scheme-1.28]

\[ \text{HC(O)(OMe)₂NMe₂} \xrightarrow{\text{DMF, reflux}} \text{MeO} \quad \text{MeO} \quad \text{MeO} \]
\[ \text{NO₂} \quad \text{NO₂} \quad \text{H₂} \quad \text{Pd/C, 83\%} \quad \text{MeO} \]

Scheme-1.28

A non-acidic and regioselective route\textsuperscript{104} to Mannich’s bases from ketones 1.123 and esters involves reaction with DMF acetals at a high temperature to form enamine ketones 1.124 which are readily reduced by lithium aluminium hydride to the Mannich bases 1.125 [Scheme 1.29].

\[ \text{O} \quad \text{C} \quad \text{H} \quad \text{N} \quad \text{M} \quad \text{e} \quad \text{2} \]
\[ \text{LiAlH₄} \quad \text{diethyl ether} \quad 81\% \]

Scheme-1.29

The reaction of trans-cyclohexane-1, 2-diol 1.126 with DMF dimethyl acetal leads to the formation of cyclohexane epoxide 1.127 with inversion of configuration. [Scheme-1.30]

\[ \text{OH} \quad \text{OH} \quad \text{HC(O)(OMe)₂NMe₂} \xrightarrow{\text{75-130°C, 84 h}} \]

Scheme-1.30

Ethyl 2-amino-4-(2-ethoxy-2-oxoethyl)thiazole-5-carboxylate 1.130, prepared from diethylacetone-1,3-dicarboxylate 1.128, sulfuryl chloride and thiourea according to the procedure described in the literature, was transformed with \textit{N},\textit{N}-dimethylformamide dimethyl acetal (DMFDMA) into ethyl 4-[(1-(dimethylamino)-3-ethoxy-3-oxoprop-1-en-2-yl]-2-
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[(dimethylamino)methyleneamino]thiazole-5-carboxylate\textsuperscript{105} \textbf{1.131} through \textbf{1.130} in 77 % yield. [Scheme 1.31]

Scheme-1.31

### 1.5 PRESENT WORK

Human immunodeficiency virus (HIV) belongs to the retroviruse family and causes the acquired immunodeficiency syndrome (AIDS). However, resistance to anti-HIV compounds develops rapidly, sometimes within a few days of initiating the treatment\textsuperscript{106-107}. Errors made by the viral enzyme RT and cellular RNA polymerase II result in about one mutation per viral replication cycle (1 base change in 10,000 RNA nucleotides), which, together with the rapid replication of the virus, is responsible for rapid emergence of drug resistant mutants\textsuperscript{108}. The “quasispecies” nature of HIV infection complicates development of drugs, as the successful therapy must anticipate the potential genetic flexibility of this moving target. This concept is the part of highly active antiretroviral therapy (HAART)\textsuperscript{109-110} in which potent combinations of inhibitors are used to maximally suppress viral replication, thereby reducing the number of viral variants generated and the opportunity to select for resistant mutants. The most common combinations used in HAART generally include two or three RT inhibitors and one or two protease inhibitors. This combination of three to four drugs can significantly reduce the morbidity and mortality of HIV-1 infected patients.

However, as a result of emerging drug-resistant HIV mutants, increasing numbers of HIV-infected patients fail to respond to HAART. To overcome this limitation of the drugs the development of new anti-HIV drugs is urgently required. To fulfill this requirement a number of RT inhibitors were discovered and introduced in the clinical practice. Reverse transcriptase (RT) is one of the most important enzymes in the HIV-1 life cycle. It has two known drug-target sites, the substrate binding site and an allosteric site, which is distinct from, but closely located to, the substrate binding site\textsuperscript{111-112}. Non-nucleoside reverse transcriptase
inhibitors (NNRTIs) interact with the allosteric binding site, a highly hydrophobic cavity, in a noncompetitive manner to cause distortion of the three-dimensional structure of the enzyme and thus inhibit RT catalytic function. NNRTIs currently approved for AIDS therapy include nevirapine, delavirdine, efavirenz, and etravirine (TMC125).

The diarylpyrimidine-based NNRTIs such as etravirine (TMC-125, 1.032, fig-1.2) 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-pyridinyl]oxy]-3,5-dimethylbenzonitrile, was approved in 2008 by the U.S. Federal Drug Administration for its use in combination therapy along with 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 literature on the potency of benzo (or pyrido) diazepinone class of compounds reveals that the activity of these molecules enhanced and inhibition extended by substitution of this ring system with halogen, pyrrolyl, pyrazolyl, aryl and pyridyl groups. The presence of these has been demonstrated to confer activity against mutant RT enzymes resistant to other classes of non-nucleoside RT inhibitors. In view of the previous precedence in literature on benzo (or pyrido) diazepine rings showing that proper modifications in the substitution pattern of the molecule have resulted in the development of new broad spectrum HIV-1 RT, the aim of the present work was to focus research on this family of compounds by exploring the feasibility of the development of next generation NNRTI agents from this class.

Literature is replete with wide variety of examples showing that one of important tools for medicinal chemists in defining the potential activity of novel chemical entities is to synthesize a large number of related compounds with
diverse structures and then to study the role played by each part of the molecule in imparting the specific activity displayed by the molecule. These studies sometimes allow quite interesting revelations to emerge concerning to the structural requirements of the drugs and help one to adopt a rational approach for the design of new drugs. Inspite of the massive efforts so assiduously undertaken, ever since the pharmacological activity of 1,5-benzodiazepine have been known, it has not been possible yet to generalize, the structural requirements which a potential anti-HIV agent belonging to 1,5-benzodiazepine class must fulfill. Nonetheless, a rational approach in design of the drugs from 1, 5-benzodiazepine class possessing the specificity in its anti-HIV activity continues to be the most sought after goal.

A perusal of the structure of etravirine (1.032, Fig.-1.2) reveals that its molecule essentially contains three bioactive fragments viz.

(i) 6-amino pyrimidine part.
(ii) p-cyano phenylamino part (present at 2-position of pyrimidine ring).
(iii) p-cyano phenoxyl 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 these molecules 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 (1.032) has so far not been functionalized to produce the oxadiazole and imidazole (and other) five membered rings) in its molecule. The present study intended to incorporate these rings in their molecules, the structures of which have been shown in Fig-1.3 (Structures 1.132-1.162).

To our knowledge no attempt has been made in the literature to incorporate the indicated pharmacophores depicted in fig-1.3 in structures, (1.132-1.162) on the 2-position of 1, 5-benzodiazepine nucleus.
Condensed heterocyclic systems 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 undertake investigation on the synthesis of condensed nitrogen-sulfur heterocyclic systems containing above nuclei fused to the 1,5-benzodiazepine framework. It was hoped that synthesis of these condensed heterocyclic systems 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 ring
- 1,5 Benzoxazepine ring
- 1,5 Benzothiazepine ring

1,5-Benzodiazepine 2-one required in this study were prepared from ethylacetoacetate and o-phenylenediamine. Inspired by the bioactive profiles of the 1,5-benzodiazepine-2-ones nucleus, it was planned to convert the C=O group of 1,5-benzodiazepine-2-ones nucleus, to the corresponding chloro derivative by treatment of 1,5-benzodiazepine-2-ones nucleus, with POCl₃ (in presence of dimethylaniline). The amide function of the seven membered heterocyclic ring of 1,5-benzodiazepine nucleus has the potential to provide an easy access to the corresponding 2-Cl and 2-SMe group from its reaction with POCl₃ and with P₂S₅ (or Lowesson’s reagent, followed by treatment with CH₃I). The 2-Cl atom (an iminochloride (imidoyl chloride) derivative and 2-
SMe group (an iminothiomethyl ether group) are highly reactive species known to be activated for nucleophilic attack. We have preferred to employ the 2-Cl atom appended on 1.166 for its reaction and subsequent replacement with hydroxyl and amine bearing pharmacophores (shown in 1.167-1.172) to yield the corresponding 2- substituted derivatives 1.132, 1.133, 1.134, 1.135 and 1.136 respectively [Scheme-1.32].

The strategy outlined in scheme 1.33 shows the preparation of compounds 1.138-1.145 from the key intermediates 1.173, 1.174 and 1.175, 1.176 which will be readily available from 1.132 and 1.133 on their reaction with H2N-OH.HCl + KOH (in MeOH)\textsuperscript{120} and with ROH (CH3OH) + HCl\textsuperscript{121} respectively, following the procedure reported in the literature for such reactions on other substrates containing the nitrile group.

Thiosemicarbazones derived from aldehydes provide a very convenient synthetic entry to amino thiadiazole derivatives on their reaction with NH4Fe(SO4)\textsubscript{2}\textsuperscript{122}. This strategy was applied on 1.166 (Scheme-1.34) to generate the aminothiadiazole derivative 1.146.

An innovative procedure for the formation of isoxazole and pyrazole rings has been developed recently, utilizing the potential of the corresponding dimethyl amino methylene ketone derivatives, obtained from the reaction of compounds containing a COCH\textsubscript{2} group with commercial dimethyl formamide dimethyl acetal (DMF DMA)\textsuperscript{123-124}. The dimethylamino methylene ketone derivative 1.179, was obtained from the reaction of 1.177 with DMF DMA\textsuperscript{121-126}. Compound 1.177 was readily available from the reaction of 1.166 with p-hydroxy acetophenone (scheme-1.34).

The most recorded method for the preparation of chalcones\textsuperscript{127} makes use of Claisen Schmidt reaction\textsuperscript{128-129} which involves the base catalyzed condensation of a ketone (for example acetophenone)\textsuperscript{130} and an aldehyde (for example benzaldehyde)\textsuperscript{131} to form an α, β- unsaturated ketone substituted with aryl residues (to give the chalcones). This strategy was applied on 1.177 and benzaldehyde to yield the chalcone 1.178 (scheme-1.34). 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{132-133} with urea, thiourea, acetamidine, guanidine etc. (to form the pyrimidine ring)\textsuperscript{134-137} with o-phenylenediamine, o-aminophenol and o-aminothiophenol (to form the benzodiazepine, benzoxazepine and benzothiazepine rings)\textsuperscript{138-139}. In scheme 1.35 the products 1.147 and 1.148 which resulted from the reaction of chalcone derivative 1.178 with hydroxylamine hydrochloride (1.182) and hydrazine hydrate (1.183) have been shown. Compounds 1.147 and 1.148 were obtained from 1.147a and 1.148a respectively, on their oxidation with o-iodoxybenzoic acid (IBX)\textsuperscript{140-141} following the protocol reported for this process in the literature.

The scheme 1.35 depict explorations of further examples of the reaction of chalcone derivative 1.178 with urea (1.184) and thiourea (1.185) to form the corresponding pyrimidine ring incorporated products 1.149 and 1.150 respectively and with o-phenylenediamine (1.186), o-aminophenol (1.187) and aminothiophenol (1.188) to form the corresponding 1,5 benzodiazepine , 1,5-benzoxazepine and 1,5-benzothiazepine ring incorporated products 1.151, 1.152,1.153 respectively (scheme 1.35).

The dimethylaminomethylene ketone derivative 1.179 behaved in the same way as do the chalcone in their reaction with hydroxylamine hydrochloride (3.04), hydrazine hydrate (1.183), urea (1.184), thiourea (1.185), guanidine (1.189), acetamidine (1.190), o-phenylenediamine (1.186), o-aminophenol (1.187), and o-aminothiophenol (1.188) etc.\textsuperscript{142} to form 1.154, 1.155, 1.156, 1.157, 1.158, 1.159, 1.160, 1.161 and 1.162 respectively (scheme-1.36).

The purity of all compounds was routinely checked by TLC and wherever found necessary the compounds were purified by column chromatography and preparative TLC. The structure of all the compounds was 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 biological properties.

Structures of the compounds whose synthesis has been described in the thesis in chapters II,III,IV, and V, using the schemes 1.32,1.33,1.34,1.35 and 1.36.
Fig-1.3 Contd.
Fig 1.6 Contd.
Fig-1.6
Scheme 1.33
Scheme 1.34
Scheme 1.35
Scheme 1.36
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