Chapter II
Preparation of starting materials
Chapter II

Contents at a Glance

2.1 Introduction

2.2 Chemistry of intermediates used in synthesis of present work:
   2.2.1 Amidine derivatives
   2.2.2 Imidate ester derivatives
   2.2.3 Thiosemicarbazone derivatives
   2.2.4 Dimethylaminomethylene ketone derivatives
   2.2.5 Chalcone derivatives

2.3 Present work

2.4 Schematic presentation of the synthesis of starting materials \textit{viz}
   i) Amidines
   ii) Imidate esters
   iii) Thiosemicarbazones
   iv) Dimethylaminomethylene ketones
   v) Chalcones

2.5 Interpretation of spectral data for the elucidation of structure of compounds

2.6 Mechanism of formation of compounds

2.7 Experimental section

2.8 References
Abstract

This chapter describes the synthesis of amidines and imidate esters from 2-oxy/amino-4’-benzonitrile, thiosemicarbazone from 2-oxy-4’-benzaldehyde, dimethylaminomethylene ketone and chalcone from 2-oxy-4’-acetylphenyl derivatives of 1,4-benzodiazepine (2.094-2.100). [Compound 2.094-2.100 have been used as precursors in the synthesis of a variety of fused heterocyclic systems in Chapter III, IV and V]. The structures of all compounds have been established by elemental analysis, IR, $^1$H NMR, and MS spectral data.
2.1 Introduction

1,4-Benzodiazepines have been recognized in the literature as ‘privileged heterocyclic medicinal scaffolds’ by virtue of their ability to provide ligands to a number of functionally and structurally discrete biological receptors. This feature of 1,4-benzodiazepines has evoked considerable attention of chemists in recent years, exploration of which has led this nucleus to emerge with a wide array of pharmacodynamic applications.

Ubiquity of 1,4-benzodiazepines in chemical literature\(^1\)\(^-\)\(^2\) is undoubtedly a consequence of multifarious biological response which they elicit in combating a variety of body ailments. Impressive medicinal properties endowed in this nucleus, has stimulated intense research efforts to be directed toward the synthesis of their structural analogues, on the premise that different constitution and biological activities in the new materials could allow them to be used as novel chemotherapeutic agents.

The literature\(^3\)\(^-\)\(^4\) is replete with examples showing that sometimes the coupling of biologically active molecules with bioactive pharmacophores such as isoxazole, pyrazole, oxadiazole, imidazole, benzimidazole, thiadiazole, triazole, tetrazole, pyrrole, pyridine, piperidine, piperazine, quinoline, and pyrimidine heterocyclic scaffolds produce interesting series of compounds with enhanced biological activities. Based on this trend, it was expected that the incorporation of some of the above biologically active pharmacophores into 1,4-benzodiazepine nucleus could produce compounds with enhanced biological properties.

The chemical modification of heterocyclic systems, by incorporating the molecular entities having the proven record of bioactive potential offers a continuous challenge to medicinal chemists in search of compounds with promising bio-pharmacological profiles.

Recently, pyrimidine and pyrimidine based drugs have been widely studied as this nucleus has also been recognized to belong to the class of privileged ligands for a number of functionally and structurally discrete biological receptors. The
impressive biological activity of 1,4-benzodiazepines and pyrimidine has evoked considerable attention of chemists to explore the possibility of utilizing their inherent potentialities in the synthesis of novel scaffolds of biological interest. It is with this idea in mind that the present study was framed and was proposed to be undertaken. It was hoped that synthesis and biological evaluations of the 1,4-benzodiazepines incorporated with bioactive pharmacophores would form a rational approach towards the study of their structure activity relationships.\textsuperscript{5-10}

### 2.2 Chemistry of intermediates used in synthesis of present work

2.2.1 Amidine derivatives

2.2.2 Imidate ester derivatives

2.2.3 Thiosemicarbazone derivatives

2.2.4 Dimethylaminomethylene ketone derivatives

2.2.5 Chalcone derivatives

#### 2.2.1 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, and antiviral activity.

#### 2.2.1.1 Synthesis of amidine derivatives

Methods used for the synthesis of amidine derivatives:

Benzaldehyde oxime (2.001) has been converted into corresponding benzhydroxymoyl chloride (2.002) with NCS. Treatment of the mixture of 2.002 and imine with triethylamine at 0 °C affords 4,5-dihydro-1,2,4-oxadiazole 2.003 in good yield. Oxadiazole on hydrogenolysis with Raney nickel in methanol at room temperature gives substituted amidine 2.004 in 74-91% yield (Scheme-2.1).\textsuperscript{11}
The ability of amidinates \([\text{RC(NR’)}_2]^{-}\) to act as four electron, bidentate ligands for main group elements, transition metals, and the lanthanides is well established. 1,2-Amidinates have proven to be versatile ligands due to the ease with which the steric and electronic properties of the resultant metal complexes can be tuned by means of substitution at the nitrogen atoms. Conversion of \(p\)-R-benzoyl chloride (2.005) with 2-aminoethylpyridine in the presence of triethylamine to a suitable amide 2.006 which generates imine chloride 2.006 via reaction with PCl₅. Imine chloride 2.006 on reaction with substituted aniline in the presence of triethylamine yields (2-pyridine)-ethyl-functionalized benzamidinate (2.007)° (Scheme-2.2).

**Scheme-2.1**

**Scheme-2.2**
Microwave reactions of primary and secondary amines (2.009) with imidoylenzotriazoles (2.008) give various polysubstituted amidines (2.010) in good yields (Scheme-2.3).

Scheme-2.3

A generalized synthesis of amidines 2.012 from thioimidate 2.011, using a buffered protonic catalysis in non-aqueous medium (Scheme-2.4) is as follows:

Scheme-2.4

Amidine derivatives 2.014 have also been synthesized from nitrile compounds 2.013 by two different methods (Scheme-2.5).

Scheme-2.5

2-cyanopyrazine is activated with sodium methoxide at room temperature and then compound 1,4-(2-imino-4-(4-methoxyphenyl-thiazol-3-(2H)-yl)phenyl)ethanone (2.015) is added to the reaction content and refluxed in absolute methanol for 12 h to give amidine derivative 2.016 (Scheme-2.6).
Chapter-II: Preparation of starting materials

Condensation of 4-(trifluoromethoxy)aniline (2.018) with ammonium thiocyanate (2.017) and benzytrimethylammonium tribromide in methyl cyanide gives 2-amino-6-(trifluoromethoxy)benzothiazole (2.019), which on further reaction with appropriate acetamide in presence of POCI₃ in dry toluene led to the formation of the desired aceticamides 2.020 (Scheme-2.7).

2.2.2 Imidate ester derivatives

Imidates, also known as imidoates, imidic acid esters, or imido esters, are esters of the hypothetical imidic acids or iso-amides (Fig.-2.1). Cyclic imidates can be divided in three groups: (1) the imidate function lies completely within the ring, e.g. oxazolines and dihydro-oxazines; (2) the oxygen function has an exocyclic position; (3) the imino-nitrogen has an exocyclic position (Fig.-2.2).
Chapter-II: Preparation of starting materials

The nitrogen analogue of imidates is the amidine group. In comparison to amidines, imidates have a smaller dipole moment. This shows that conjugation in the imidate group is less pronounced than in the case of amidines. However, the conjugation favours a planar arrangement of the imidate group fig.-2.3.

The conformation of imidates is presented in fig.-2.4. For ring imidates with an exocyclic oxygen function where n=2-8, the conformation is syn because of steric requirements. However, when the ring size increases (n=9-13), the imidates tend to exist in the anti form. High barriers for inter-conversion of the syn and anti forms of o-imidates were observed.

2.2.2.1 Synthesis of imidate ester derivatives:

The classical method to synthesize imidates 2.023 is the Pinner reaction.20 Hereby, a nitrile 2.021 is condensed with an alcohol 2.022 under anhydrous conditions in the presence of hydrogen chloride or hydrogen bromide at 0 °C (Scheme-2.8).
Chapter-II: Preparation of starting materials

Scheme-2.8: Pinner Reaction

Imidate esters \(2.025\) are easily produced from the amide \(2.024\) by treatment with 'Meerwein's reagent' (Scheme-2.9).\(^{21}\)

Scheme-2.9

Synthesis of imidates via imino chlorides:

a. The Hoesch reaction

The Hoesch reaction\(^{22}\) for the preparation of hydroxyaryl ketones is very similar in procedure to the Pinner reaction. Essentially, the method consists in condensing a nitrile \(2.026\) with a phenol \(2.027\) or phenolic ether in the presence of zinc chloride and anhydrous hydrogen chloride in a suitable solvent, the reaction proceeds via the imino chloride and then the ketimine hydrochloride to the ketone (Scheme-2.10).

Scheme-2.10
b. Reaction with alkoxides and phenoxides

The reaction of imino chlorides 2.029 with alkoxides or phenoxides 2.030 may be regarded as a modification of the Pinner synthesis, resulting again in the formation of imidates 2.031 (Scheme-2.11).²²

\[
\text{H}_{5}\text{C} = \text{C} \text{H}_{5}\text{C} \text{Cl} + \text{C}_{6}\text{H}_{5}\text{ONa} \rightarrow \text{H}_{5}\text{C} = \text{C} \text{H}_{5}\text{OC}_{6}\text{H}_{5} + \text{NaCl}
\]

Scheme-2.11

Synthesis of imidates from amides:

a. Direct alkylation

Wallach and Bleibtreu found that thioacetanilide (2.033) with ethyl iodide (2.034) in the presence of sodium ethoxide formed ethyl N-phenylthioacetimidate (2.035) (Scheme-2.12).²²

\[
\text{H}_{5}\text{CC} \text{S} + \text{C}_{2}\text{H}_{5}\text{I} \rightarrow \text{H}_{5}\text{CC} \text{SC}_{2}\text{H}_{5}
\]

Scheme-2.12

b. Alkylation of silver salts

Tafel and Enoch prepared the silver derivatives of amides 2.037 and found that they yielded imidates 2.038 on treatment with ethyl iodide, the product being obtained finally by lixiviating the mass with ether and saturating with hydrogen chloride (Scheme-2.13).²²

\[
\text{C}_{6}\text{H}_{5}\text{CONH}_{2} \rightarrow \text{C}_{6}\text{H}_{5}(=\text{NH})\text{Ag} \stackrel{\text{C}_{2}\text{H}_{5}\text{I}}{\longrightarrow} \text{C}_{6}\text{H}_{5}(=\text{NH})\text{OC}_{2}\text{H}_{5}
\]

Scheme-2.13

Synthesis of imidates from ortho esters:

Claisen suggested a two-stage mechanism for the interaction of ethyl orthoformate and aniline, with the intermediate formation of \(N,N'-\)diphenylformamidine (Scheme-2.14 and 2.15).²²
A) \[2\text{C}_6\text{H}_5\text{NH}_2 + \text{CH(OHC}_2\text{H}_3)_3 \rightarrow \text{CH(=NC}_6\text{H}_5)\text{NH}_2\text{H}_5 + 3\text{C}_2\text{H}_5\text{OH}\]

\[2.039 \quad 2.040 \quad 2.041 \quad 2.042\]

Scheme-2.14

B) \[\text{CH(=NC}_6\text{H}_5)\text{NH}_2\text{H}_5 + \text{CH(OHC}_2\text{H}_3)_3 \rightarrow 2\text{CH(=NC}_6\text{H}_5)\text{OC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{OH}\]

\[2.041 \quad 2.043 \quad 2.044 \quad 2.045\]

Scheme-2.15

He postulated step A to be rapid and step B slow, on the grounds that the imidate was isolated only after prolonged heating, whereas the amidine formed readily.

Synthesis of imidates by transesterification:

Imidates may be transesterified by refluxing with an alcohol 2.047 of higher boiling point than that used in their formation (Scheme-2.16)\(^{23}\).

\[\begin{array}{c}
\text{HC} \\
\text{OC}_2\text{H}_5 \\
\text{NC}_6\text{H}_5 \\
\end{array} + (\text{CH}_3)_2\text{COH} \rightarrow \begin{array}{c}
\text{HC} \\
\text{O(\text{CH}_3)_3} \\
\text{NC}_6\text{H}_5 \\
\end{array} + \text{C}_2\text{H}_5\text{OH} \]

\[2.046 \quad 2.047 \quad 2.048 \quad 2.049\]

Scheme-2.16

Synthesis of imidates from aldehydes and ketones:

Ketone 2.050 in the presence of alcohol 2.053, hydrogen chloride (2.051) and hydrazoic acid (2.052) yield imidates 2.054 (Scheme-2.17)\(^{23}\).

\[\begin{array}{c}
\text{CH}_3\text{COCH}_3 \\
\end{array} + \text{HCl} + \text{N}_2\text{H} + \text{C}_2\text{H}_5\text{OH} \rightarrow \begin{array}{c}
\text{H}_3\text{CC} \\
\text{OC}_2\text{H}_5 \\
\text{NCH}_3\text{HCl} \\
\end{array} \]

\[2.050 \quad 2.051 \quad 2.052 \quad 2.053 \quad 2.054\]

Scheme-2.17

Synthesis of imidates from unsaturated systems:

The addition of primary amines 2.055 to ethoxyacetylene (2.056) in refluxing ethanol gives rise to imidates 2.057, but amidines 2.058 may also be formed by the further interaction of the amine (Scheme-2.18)\(^{23}\).
\[
\text{RNH}_2 + \text{C}_2\text{H}_5\text{OC}≡\text{CH} \rightarrow \text{CH}_3\text{C}(=\text{NR})\text{OC}_2\text{H}_5 + \text{CH}_3\text{C}(=\text{NR})\text{NHR}
\]

\[
\begin{array}{ccc}
2.055 & 2.056 & 2.057 & 2.058 \\
\end{array}
\]

Scheme-2.18

Likewise, ethoxyethylene (2.059) reacts with compounds of the type AcNH\(_2\) (2.060) under the influence of acid catalysts in acetone to yield diimidates 2.061 (Scheme-2.19).\(^{23}\)

\[
\text{C}_2\text{H}_5\text{OCH}≡\text{CH}_2 + \text{AcNH}_2 \rightarrow \text{CH}_3\text{CH}[\text{OC}(=\text{NH})\text{CH}_3]
\]

\[
\begin{array}{ccc}
2.059 & 2.060 & 2.061 \\
\end{array}
\]

Scheme-2.19

Miscellaneous syntheses of imidates:

Methyl N-phenylcarbomethoxyformimidate (2.064) has been prepared by the action of methyl methoxydichloroacetate (2.063) on aniline (2.062) in boiling xylene (Scheme-2.20).\(^{24}\)

\[
\text{C}_6\text{H}_5\text{NH}_2 + \text{COOCH}_3 \rightarrow \text{H}_2\text{COOCC}≡\text{C}(\text{OCH}_3)_2\text{OCH}_3
\]

\[
\begin{array}{ccc}
2.062 & 2.063 & 2.064 \\
\end{array}
\]

Scheme-2.20

Ethanolamine (2.065) in dilute potassium cyanide solution reacts with cyanogen (2.066) giving an oxalldiimide 2.067 (Scheme-2.21).\(^{24}\)

\[
2\text{NH}_2\text{CH}_2\text{CH}_2\text{OH} + (\text{CN})_2 \rightarrow \left(\text{NH} \right)\text{H}_2\text{NH}_2\text{CH}_2\text{C}≡\text{C}\text{OCH}_3\text{OCH}_3
\]

\[
\begin{array}{ccc}
2.065 & 2.066 & 2.067 \\
\end{array}
\]

Scheme-2.21

Chlorothioformimidates (2.070) are reported to be formed from the interaction of isocyanides 2.068 and sulphenyl chlorides 2.069 (Scheme-2.22).\(^{24}\)

\[
\text{RNC} + \text{RSCl} \rightarrow \text{CIC}(=\text{NR})\text{SR}′
\]

\[
\begin{array}{ccc}
2.068 & 2.069 & 2.070 \\
\end{array}
\]

Scheme-2.22
Imidate hydrochlorides are used in the preparation of certain polymerisable acrylates.\textsuperscript{24} When hydrogen chloride (2.073) is passed through a mixture of alcohol 2.072 and an αβ-unsaturated nitrile 2.071, αβ-chloroimidate hydrochlorides 2.074 are obtained (Scheme-2.23).

\begin{equation*}
\begin{array}{c}
\text{H}_2\text{C} \equiv \text{CCN} \quad \text{2.071} \\
\text{OCOCH}_3 \\
\text{C}_2\text{H}_5 \quad \text{2.072} \\
\text{+ 2HCl} \quad \text{2.073} \\
\rightarrow \text{CH}_3\text{ClCH} \equiv \text{NH.HCl} \\
\text{OCOCH}_3 \\
\text{C}_3\text{H}_5 \quad \text{2.074}
\end{array}
\end{equation*}

\textbf{Scheme-2.23}

Imidate hydrochlorides derived from dibasic aliphatic acids can be used as additives, \textit{e.g.} for food products and synthetic polymers, to prevent the catalytic action of metals on the organic materials; they inhibit, for example, their autoxidation.

\subsection*{2.2.3 Thiosemicarbazone derivatives}

In organic chemistry, a semicarbazone is a derivative of an aldehyde or ketone formed by a condensation reaction between a ketone or aldehyde and semicarbazide. A thiosemicarbazone is an analogue of a semicarbazone which contains a sulfur atom in place of the oxygen atom.

\begin{equation*}
\begin{array}{c}
\text{R}_1 \\
\text{N} \\
\text{N} \\
\text{S} \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4
\end{array}
\end{equation*}

\textbf{General formula for thiosemicarbazones }R_1, R_2, R_3, R_4 = \text{H, or any organic substituent}

Thiosemicarbazones are thiourea derivatives and the studies on their chemical and structural properties have received much attention due to the widespread application in the chemotherapeutic field.\textsuperscript{25} Thiosemicarbazones are compounds that have been studied for a considerable period of time for their biological properties. These are a class of small molecules that have been evaluated over the last 50 years as antiviral and as anticancer therapeutics, as well as for their parasiticidal action against \textit{Plasmodium falciparum} and \textit{Trypanosoma cruzi} which
are the causative agents of malaria and Chagas’s disease, respectively. These compounds have aroused interest as versatile intermediates for preparing various (e.g. heterocyclic) derivatives as well. Thiosemicarbazones can be used for making electrodes or complexes formation of metallic ions. Thiosemicarbazones exhibit various biological activities such as antitubercular, antimicrobial, anti-inflammatory, antiviral, anticonvulsant, antihypertensive, anesthetic, anticancer, hypoglycemic, and cytotoxic activities among others.

2.2.3.1 Synthesis of thiosemicarbazone derivatives:

Refluxing aldehyde or ketone 2.075 with a thiosemicarbazide 2.076 generates thiosemicarbazones 2.077. For aldehydes, the reaction is usually complete in less than 3 h and no acetic acid is required. For ketones, the reaction is usually run overnight with 1% acetic acid. Yields are generally greater than 90% except with a few specific ketones such as the 2-substituted aryl ketones (Scheme-2.24).

Thiosemicarbazones 2.080 were prepared by condensation of substituted arylisothiocyanate with menthone hydrazone 2.079 (Scheme-2.25).
Preparation of 4-acylthiosemicarbazone-3-methyl-1-(4’-methylphenyl)-2-pyrazolin-5-one: 4-Acyl-3-methyl-1-(4’-methylphenyl)-2-pyrazolin-5-one react (2.082) with thiosemicarbazide 2.083 in ethanol or methanol at reflux temperature in water bath to give 2.084,\textsuperscript{30} the synthesized compound 2.084 is crystallized in aqueous ethanol as a yellow prismatic crystal (Scheme-2.26).

\[ \begin{align*}
\text{H}_3\text{C} & \quad \text{R} \\
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{N} \\
\text{CH}_3 & \\
\text{2.082} & \\
\end{align*} \quad + \quad \begin{align*}
\text{H}_3\text{N} & \quad \text{N} \quad \text{R}_1 \\
\text{S} & \quad \text{N} \quad \text{R}_2 \\
\text{2.083} & \\
\end{align*} \quad \xrightarrow{\text{2.084}} \\
\begin{align*}
\text{H}_3\text{C} & \quad \text{N} \\
\text{N} & \quad \text{S} \\
\text{R}_1 & \quad \text{H} \\
\text{R}_2 & = \text{CH}_3\text{CH}_2 \\
\text{CH}_3 & \\
\text{2.084} & \\
\end{align*}

Scheme-2.26

2.2.4 Dimethylaminomethylene ketone derivatives: Already discussed in chapter I in section 1.4.1.

2.2.5 Chalcone derivatives: Already discussed in chapter I in section 1.4.2.

2.3 Present work:

It was mentioned in Chapter I and II that the active synthons such as amidines, imidate esters, thiosemicarbazones, dimethylaminomethylene ketones, and chalcones etc, undergo nucleophilic displacements with bidentate nucleophiles\textsuperscript{31-38} to furnish a wide variety of ring structures and thus provide an unprecedented opportunity to a chemist for a one step synthesis of difficultly accessible fused heterocyclic systems containing oxadizole, imidazole, benzimidazole, thiadiazole, isoxazole, pyrazole, pyrimidine, benzodiazepine, benzothiazepine, and benzoazepine etc. The installation of these pharmacophores on to the 1,4-benzodiazepine nucleus from the corresponding amidines, imidate esters, thiosemicarbazones, dimethylaminomethylene ketones, and chalcones etc will be described in detail in the subsequent Chapters III, IV and V.
This chapter presents a stepwise procedure for the synthesis of various starting materials 2.094-2.100 required in the synthesis in the subsequent chapters from 2-phenoxyl and 2-phenylamino substituted derivatives of 1,4-benzodiazepines (Flow chart-2.1). These were obtained from isatin based on the strategy shown in (Scheme-2.27). The strategy shown in (Flow chart-2.1) has been formulated so as to incorporate amidines, imidate esters, thiosemicarbazones, dimethylaminomethylene ketones, and chalcones on 1,4-benzodiazepine nucleus. The importance of these active synthons in the synthesis of hetero ring annulated novel 1,4-benzodiazepine derivatives of medicinal interest has been discussed previously in the proposed plan of research work given in Chapter I.

Isatin has attracted the attention of chemists owing to its broad spectrum of pharmacological properties. This has precisely been the reason for selecting isatin for the preparation of difficultly accessible novel heterocyclic scaffolds of medicinal importance from this nucleus.

In view of the impressive biological properties exhibited by (a) isatin (b) 1,4-benzodiazepine and (c) heterocyclic scaffolds containing oxadiazole, imidazole, benzimidazole, thiadiazole, isoxazole, pyrazole, pyrimidine, benzodiazepine, benzothiazepine, and benzoazepine nucleus, it was considered of interest in the present work to prepare the molecules in which these bioactive pharmacophores were brought together to become the part of the same molecular framework. A perusal of the literature revealed that active synthons such as the amidine, imidate esters, thiosemicarbazones, dimethylaminomethylene ketones, and chalcones offered very facile synthetic entry to the synthesis of five, six, and seven membered heterocyclic rings on their reaction with bidentate nucleophiles such as the acetyl chloride, ethylenediamine, o-phenylenediamine, ammonium iron sulfate, hydrazine hydrate, and hydroxylamine hydrochloride (to give five membered rings), urea, thiourea, acetamidine, and guanidine (to give six membered rings), o-phenylenediamine, o-aminothiophenol, and o-aminophenol (to give seven membered rings). The above synthons are readily available from the reaction of appropriate reagents (discussed in the later part in this chapter) on the compounds containing COCH$_2$ group in the molecule. This chapter is devoted to the preparation of the 1,4-benzodiazepine nucleus bearing these active synthons in its molecule. The flow chart 2.1 shows how these
Chapter-II: Preparation of starting materials

were prepared from 2.089. The key intermediate 2.089 was obtained through the strategy shown in scheme-2.27. The aim of this chapter is to show how 2.089 was synthesized following the scheme-2.27 and how it was converted to active synthons 2.094-2.100 by employing the strategy shown in flow chart 2.1.

In view of the reported procedure for the preparation of 1,4-benzodiazepine nucleus from isatin it was envisaged that the most appropriate starting material for the preparation of 2.089 could be the commercially available isatin (2.085). Consideration of factors of reactivity of the starting material, easy accessibility, synthetic economy, and simplicity in the operational procedure led us to favour the use of a reported synthetic procedure for its preparation from 1-chloroacetylisatin (2.086). The potential of isatin in the synthesis of heterocyclic compounds through the expansion of its ring has been well established in the literature.\(^{39-41}\) The highly labile nature of the lactam function of the isatin ring allows the cleavage of its ring on reaction with nucleophilic reagents to give the ring opened product which undergoes concurrent cyclocondensation leading to ring enlargement to give the six or seven membered heterocyclic rings. This feature of isatin has been very elegantly exploited by Ogata and Motsumoto\(^{42-44}\) to develop a highly innovative technique for the synthesis of 5-methylcarboxylate substituted derivatives of 1,4-benzodiazeatin-2-one from the reaction of 1-chloroacetylisatin (2.086) with methanolic solution of hexamine. An attractive feature of this reaction was that it provided a very convenient one-pot synthetic entry to the 1,4-benzodiazepine nucleus. This methodology was applied by us to obtain the 5-carboxehoxy substituted analogue of 1,4-benzodiazepin-2-one (2.087) in an acceptable yield. Treatment of the carbomethoxy function of 2.087 with N-methylpiperazine\(^{45}\) formed the corresponding 5-carboxamide derivative (2.088). The amide (NH-C=O) function present in the seven membered heterocyclic ring of 1,4-benzodiazepine nucleus 2.088 had the potential to provide an easy access to the corresponding 2-Cl (or 2-SMe group) from its reaction with POCl\(_3\)\(^{45}\) (or with ‘Lawesson’ reagent\(^{46}\) followed by treatment with MeI). The 2-Cl atom (an imino chloride or imidoyl chloride species) or 2-SMe group (an imino thiomethyl ether group) were highly reactive species activated for nucleophilic attack. In order to curtail an extra step which the formation of 2-SMe group required, we preferred to employ the 2-Cl atom in 2.089 for its subsequent
replacement with the amine and hydroxyl bearing pharmacophores indicated in flow chart-2.1, to generate the corresponding 2-substituted analogues 2.090 and 2.091 respectively. The key intermediates (2.094, 2.095) and (2.096, 2.097) were formed from the reaction of 2.090 and 2.091 with H₂N-OH.HCl + KOH (in MeOH)\(^\text{17}\) and with ROH (CH₃OH) + HCl\(^\text{48}\) (the amidine derivatives 2.094, 2.095 and imidate ester derivatives 2.096, 2.097 respectively) as shown in the flow chart-2.1.

2-Chloro derivative 2.089 on its reaction with \(p\)-hydroxybenzaldehyde yielded 2.092. It reacted with thiosemicarbazide to provide a very convenient synthetic entry to intermediate thiosemicarbazone 2.098 (flow chart-2.1)\(^\text{49}\).

In another reaction, 2.089 on treatment with \(p\)-hydroxyacetophenone\(^\text{50}\) afforded its incorporation on 2-position of 1,4-benzodiazepine nucleus to give 2.093, which reacted smoothly with commercial dimethylformamide dimethylacetal to yield the corresponding dimethylaminomethylene ketone\(^\text{51}\) intermediate 2.099. On the other hand base catalyzed condensation of 2.093 with benzaldehyde yielded intermediate chalcone 2.100 in good yield (flow chart-2.1)\(^\text{52}\).

### 2.4 Schematic presentation of the synthesis of starting material from isatin:

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{C} & \quad \text{ClCOCH₂Cl} \\
2.085 & \\
\text{N} & \quad \text{ClCOCH₂Cl} \\
2.086 & \\
\text{N} & \quad \text{COOMe} \\
2.087 & \\
\text{H} & \quad \text{NCH₃} \\
\text{N} & \quad \text{Cl} \\
\text{O} & \quad \text{R₁} \\
2.089 & \\
\text{POCl₃} \text{or PCl₅} & \text{Dimethylaniline} \text{DMA(Base)} \\
2.088 & \\
\end{align*}
\]

`Scheme-2.27`
Chapter II: Preparation of starting materials

Flow chart-2.1
Structure of compounds (2.094-2.100) whose synthesis is described in the experimental section in this chapter:

Fig.-2.6
Table-2.01: Physical and analytical data of the compounds 2.094-2.100:

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compound</th>
<th>Molecular formula</th>
<th>M.W.</th>
<th>M.P. (°C)</th>
<th>Yield (%)</th>
<th>Elemental analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VII</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(cald/ exp) C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(cald/ exp) H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(cald/ exp) N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(cald/ exp) S</td>
</tr>
<tr>
<td>1</td>
<td>2.094</td>
<td>C$<em>{22}$H$</em>{25}$N$<em>{7}$O$</em>{2}$</td>
<td>419</td>
<td>170-72</td>
<td>86</td>
<td>62.99/62.77</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.01/5.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23.37/23.28</td>
</tr>
<tr>
<td>2</td>
<td>2.095</td>
<td>C$<em>{22}$H$</em>{24}$N$<em>{6}$O$</em>{3}$</td>
<td>420</td>
<td>181-83</td>
<td>85</td>
<td>62.84/62.61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.75/5.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19.99/20.07</td>
</tr>
<tr>
<td>3</td>
<td>2.096</td>
<td>C$<em>{23}$H$</em>{26}$N$<em>{6}$O$</em>{2}$</td>
<td>418</td>
<td>72-74</td>
<td>69</td>
<td>66.01/66.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.26/6.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20.08/19.99</td>
</tr>
<tr>
<td>4</td>
<td>2.097</td>
<td>C$<em>{23}$H$</em>{25}$N$<em>{5}$O$</em>{3}$</td>
<td>419</td>
<td>81-83</td>
<td>64</td>
<td>65.85/65.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.01/5.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.70/16.78</td>
</tr>
<tr>
<td>5</td>
<td>2.098</td>
<td>C$<em>{23}$H$</em>{25}$N$<em>{5}$O$</em>{2}$S</td>
<td>463</td>
<td>255-57</td>
<td>90</td>
<td>59.59/59.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.44/5.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21.15/21.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.92/6.90</td>
</tr>
<tr>
<td>6</td>
<td>2.099</td>
<td>C$<em>{26}$H$</em>{29}$N$<em>{5}$O$</em>{3}$</td>
<td>459</td>
<td>280-82</td>
<td>65</td>
<td>67.95/67.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.36/6.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.24/15.31</td>
</tr>
<tr>
<td>7</td>
<td>2.100</td>
<td>C$<em>{30}$H$</em>{28}$N$<em>{4}$O$</em>{3}$</td>
<td>492</td>
<td>320-22</td>
<td>72</td>
<td>73.15/72.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.73/5.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.37/11.32</td>
</tr>
</tbody>
</table>

Table-2.02: Spectral data of compound 2.094-2.100:

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compound</th>
<th>IR(KBr)cm$^{-1}$</th>
<th>$^1$H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>1</td>
<td>2.094</td>
<td>2620-3540 [broad OH str.]</td>
<td>7.88 [2H, s, NH$_2$]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3320-60 [NH str.]</td>
<td>7.33-7.77 [4H, m, ArH]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2940 [C-H str. ArH]</td>
<td>6.50-7.32 [4H, m, (phenylamino)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1690 [C=O str.]</td>
<td>4.01 [1H, s, NH]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1645 [NH bending]</td>
<td>3.63 [2H, s, CH$_2$ (azepine ring)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1600 [C=C str.]</td>
<td>3.20 [4H, t, CH$_2$ (piperazine ring)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1570-1600 [C=N str.]</td>
<td>2.27 [4H, t, CH$_2$ (piperazine ring)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1535 [C=C str. ArH]</td>
<td>2.26 [3H, s, CH$_3$]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1430 [C-H bending CH$_3$]</td>
<td>2.23 [1H, s, OH]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1180 [C-N str.]</td>
<td>[M$^+$]: 419 (8%), 225 (98%), 115 (11%), 379 (33%), 157 (36%), 285 (27%)</td>
</tr>
</tbody>
</table>
Chapter II: Preparation of starting materials

| 2 | 2.095 | 2600-3510 [broad OH str.]  
3310 [NH str. (NH₂ group)]  
2855 [C-H str. ArH]  
1690 [C=O str.]  
1635 [NH bending]  
1615 [C=C str.]  
1580 [C=N str.]  
1530 [C=C str. ArH]  
1480 [C-H bending CH₃]  
1170 [C-N str.]  
1080 [C-O str.] | 7.89 [2H, s, NH₂]  
7.33-7.78 [4H, m, ArH]  
7.09-7.32 [4H, m, (phenoxyl)]  
3.61 [2H, s, CH₂ (azepine ring)]  
3.20 [4H, t, CH₂ (piperazine ring)]  
2.28 [4H, t, CH₂ (piperazine ring)]  
2.25 [3H, s, CH₃]  
2.33 [1H, s, OH] |
| 3 | 2.096 | 3330-3360 [NH str.]  
2960 [C-H str. ArH]  
1680 [C=O str.]  
1625-35 [C=N str.]  
1580 [NH bending]  
1530 [C=C str. ArH]  
1470 [C-H bending CH₃]  
1170-90 [C-N str.]  
1090 [C-O str.] | 7.33-7.75 [4H, m, ArH]  
6.49-7.09 [4H, m, (phenylamino)]  
4.21 [1H, s, NH]  
3.91 [1H, s, C=NH]  
3.61 [2H, s, CH₂ (azepine ring)]  
3.47 [3H, s, OCH₃]  
3.20 [4H, t, CH₂ (piperazine ring)]  
2.27 [4H, t, CH₂ (piperazine ring)]  
2.24 [3H, s, CH₃]  
[M⁺]: 418 (12%), 255 (98%), 130 (48%), 210 (23%), 361 (17%), 182 (13%) |
| 4 | 2.097 | 3350 [NH str.]  
2950 [C-H str. ArH]  
1670 [free C=O str.]  
1590 [NH bending]  
1595-1610 [C=N str.]  
1555 [C=C str. ArH]  
1440 [C-H bending CH₃]  
1160 [C-N str.]  
1140 [C-O str.] | 7.33-7.83 [4H, m, ArH]  
6.35-7.20 [4H, m, (phenoxyl)]  
3.7 [1H, s, C=NH]  
3.6 [2H, s, CH₂ (azepine ring)]  
3.40 [3H, s, OCH₃]  
3.21 [4H, t, CH₂ (piperazine ring)]  
2.27 [4H, t, CH₂ (piperazine ring)]  
2.23 [3H, s, CH₃] |
| 5 | 2.098 | 3360-95 [NH str.]  
2990 [C-H str. ArH]  
1685 [free C=O str.]  
1620-1630 [C=N str.]  
1570 [C=C str. ArH]  
1590 [NH₂ bending]  
1480 [C-H bending CH₃]  
1170 [C-N str.]  
1120 [C-O str.]  
1040 [C=S str.]  
690 [C-S str.] | 8.53 [2H, s, NH₂]  
8.34 [1H, s, =CH]  
7.04-7.28 [4H, m, ArH]  
6.56-6.97 [4H, m, (phenoxyl)]  
3.60 [2H, s, CH₂ (azepine ring)]  
3.20 [4H, t, CH₂ (piperazine ring)]  
2.27 [4H, t, CH₂ (piperazine ring)]  
2.26 [3H, s, CH₃]  
2.20 [1H, s, NH]  
[M⁺]: 463 (11%), [M⁺+2]: 465 (4%), 255 (99%), 182 (30%), 320 (13%) |
### 2.5 Interpretation of spectral data for the elucidation of structure of compounds 2.094-2.100:

#### 2.5.1 Interpretation of spectral data of compounds

Structures of all the compounds (2.094-2.100) were established on the basis of elemental analysis, IR, $^1$H NMR, and MS data. Physical data of all the compounds were found to be consistent to the structures assigned to these molecules.

The physical microanalysis, IR, $^1$H NMR, and MS spectral data of all the compounds are given in table: 2.01 and 2.02 and the spectral graphs are presented in charts-2.1-2.15.

<table>
<thead>
<tr>
<th>No.</th>
<th>Compounds</th>
<th>IR Data</th>
<th>NMR Data</th>
<th>MS Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>2.099</td>
<td>2950 [C-H str. ArH]</td>
<td>7.13-7.85 [4H, m, ArH]</td>
<td>[M$^+$]: 459 (14%), 255 (100%), 360 (42%), 182 (19%), 113 (16%), 155 (14%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1690 [C=O str. α,β unsaturated]</td>
<td>6.96-7.10 [4H, m, (phenoxy)]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1660 [free C=O str.]</td>
<td>6.3 [1H, d, =HC-C=O]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1600 [C=C str. ArH]</td>
<td>4.9 [1H, d, =HC-N]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1570 [C=C unsaturated str.]</td>
<td>3.67 [2H, s, CH$_2$(azepine ring)]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1505 [C=N str.]</td>
<td>3.21 [4H, t, CH$_2$(piperazine ring)]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1440 [C-H bending CH$_3$]</td>
<td>2.90 [6H, s, 2CH$_3$]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1150 [C-N str.]</td>
<td>2.27 [4H, t, CH$_2$(piperazine ring)]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1040 [C-O str.]</td>
<td>2.23 [3H, s, CH$_3$]</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2.100</td>
<td>2950 [C-H str. ArH]</td>
<td>7.50-7.86 [4H, m, ArH]</td>
<td>[M$^+$]: 492 (12%), 255 (99%), 182 (36%), 178 (16%), 465 (18%), 400 (10%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1680 [C=O str. α,β unsaturated]</td>
<td>7.10-7.50 [4H, m, (phenoxy)]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1660 [free C=O str.]</td>
<td>6.70 [1H, d, =HC-C=O]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1620 [C=C unsaturated str.]</td>
<td>5.80 [1H, d, =HC-N]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1590 [C=C str. ArH]</td>
<td>3.67 [2H, s, CH$_2$(azepine ring)]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1550 [C=N str.]</td>
<td>3.20 [4H, t, CH$_2$(piperazine ring)]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1410 [C-H bending CH$_3$]</td>
<td>2.27 [4H, t, CH$_2$(piperazine ring)]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1150 [C-N str.]</td>
<td>2.25 [3H, s, CH$_3$]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1140 [C-O str.]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter-II: Preparation of starting materials

**Infrared spectra**

Infrared spectrum of compound 2.094 exhibited a twin peak at 3320 cm\(^{-1}\) and 3330 cm\(^{-1}\) which broadens to 3360 cm\(^{-1}\) for NH stretching and at 1645 cm\(^{-1}\) for NH bending of NH group. Appearance of broad peak ranging at 2620-3540 cm\(^{-1}\) was a characteristic feature of OH of amidine and disappearance of peak at 2220 cm\(^{-1}\) (CN str. of benzonitrile ring) provided a strong evidence for the formation of 2.094 from 2.090. The IR spectrum of 2.094 also exhibited bands at 2940 cm\(^{-1}\) (C-H str. ArH) and 1690 cm\(^{-1}\) (C=O str.), 1535 cm\(^{-1}\) (C=C str. ArH), 1570-1600 cm\(^{-1}\) (C=N str.), 1430 cm\(^{-1}\) (CH\(_3\) bending), and 1180 cm\(^{-1}\) (C-N str.). Similarly, the compound 2.095 showed absorptions in approximately same frequency regions with an additional peak at 1080 cm\(^{-1}\) (C-O str.).

The formation of compound 2.096 and 2.097 from 2.090 and 2.091 were ascertained by the appearance of peaks at 3330-60 cm\(^{-1}\) and 3350 cm\(^{-1}\) (NH str. of imidate) respectively, and C-O str. at 1090 and 1140 cm\(^{-1}\), other peaks which appeared in the IR spectrum of compound 2.096 and 2.097 were found to be present in the same region as of 2.094.

The formation of compound 2.098 from 2.092 was evident by the presence of peaks at 3360-95 cm\(^{-1}\) (NH str. twin peak), 1590 cm\(^{-1}\) (NH\(_2\) bending), 1040 cm\(^{-1}\) (C=S str.), 690 cm\(^{-1}\) (C-S str.) and 1620-1630 cm\(^{-1}\) (C=N str.) in IR spectrum. Appearance of additional peaks 2990 cm\(^{-1}\) (C-H str. ArH), 1570 cm\(^{-1}\) (C=C str. ArH), 1480 cm\(^{-1}\) (CH\(_3\) bending), 1170 cm\(^{-1}\) (C-N str.), 1120 cm\(^{-1}\) (C-O str.) clearly suggested the formation of compound 2.098 from compound 2.092.

The formation of compound 2.099 from 2.093 was ascertained by the presence of peaks at 1690 cm\(^{-1}\) (C=O str. of \(\alpha,\beta\)-unsaturated ketone) and 1570 cm\(^{-1}\) (C=C str. of \(\alpha,\beta\)-unsaturated ketone) in IR spectrum. Appearance of additional peaks 1660 cm\(^{-1}\) (C=O str.), 2950 cm\(^{-1}\) (C-H str. ArH), 1600 cm\(^{-1}\) (C=C str. ArH), 1505 cm\(^{-1}\) (C=N str.), 1440 cm\(^{-1}\) (CH\(_3\) bending) and 1150 cm\(^{-1}\) (C-N str.) clearly suggested the formation of compound 2.099 from compound 2.093. Appearance of peaks at 1680 cm\(^{-1}\) (C=O str. of \(\alpha,\beta\)-unsaturated ketone) and 1620 cm\(^{-1}\) (C=C str. of \(\alpha,\beta\)-unsaturated ketone) provided a strong evidence for the formation of 2.100 from 2.093.
\textbf{Chapter-II: Preparation of starting materials}

\textbf{\textit{H} NMR Spectra}

\textit{H} NMR spectrum of compound 2.094 at 400 MHz in CDCl$_3$ displayed characteristic signals for the presence of twenty five protons in the molecules, the appearance of an upfield singlet at $\delta$ 2.23 was attributed to the proton of OH group, another upfield singlet at $\delta$ 4.01 for one proton was due to NH of phenylamino group, and the downfield singlet at $\delta$ 7.88 was due to NH$_2$ group and a broad multiplet at $\delta$ 6.50-7.32 was due to aromatic protons of benzene ring and phenylamino group. The two triplets which appeared at $\delta$ 2.27, 3.20 were for four protons of two methylene groups and a singlet which appeared at $\delta$ 2.26 was for CH$_3$ group of methylpiperazine moiety and a singlet which was found to be present at $\delta$ 3.63 for CH$_2$ group of azepine ring. Similar peaks were observed in \textit{H} NMR spectrum of 2.095 except that an upfield singlet for one NH group at $\delta$ 4.01 was absent.

The formation of compound 2.096 was confirmed by the appearance of two singlets for two NH groups one at $\delta$ 4.21 (for phenylamino group) and second at $\delta$ 3.91 for =NH group, which also showed a singlet at $\delta$ 3.47 for 3 protons of OCH$_3$ group. Similarly, 2.097 with the exception of one NH singlet of phenylamino group which was absent showed the same peaks of \textit{H} NMR of 2.096.

Formation of thiosemicarbazone 2.098 from 2.092 was confirmed from its \textit{H} NMR spectrum which showed the downfield singlet for NH$_2$ group at $\delta$ 8.53, an upfield singlet at $\delta$ 2.20 for =NH group, and singlet at $\delta$ 8.34 for =CH group.

Formation of 2.099 from 2.093 were confirmed by their \textit{H} NMR spectra which showed the two doublets at $\delta$ 4.9 (=HC-N) and $\delta$ 6.3 (=HC-C=O) for two protons attached to carbon of $\alpha,\beta$-unsaturated ketone structure and a sharp singlet at 2.90 for six protons of two CH$_3$ groups attached to nitrogen atom.

Formation of chalcone 2.100 from 2.093 was confirmed by their \textit{H} NMR spectra which showed two doublets at $\delta$ 6.70 (=HC-C=O) and $\delta$ 5.80 (=HC-) for two proton attached to carbon of $\alpha,\beta$-unsaturated ketone and a multiplet for five protons of phenyl ring at $\delta$ 7.10-7.86.
2.6 Mechanism of formation of compound 2.087 and 2.094-2.100:

2.6.1 Mechanism of formation of compound 2.087 from 2.086:

A tentative mechanism for the formation of 2.087 from 2.086 is outlined in the scheme-2.28. The formation of 1,4-benzodiazepin-2-one-5-carboxylate derivatives from the corresponding N-chloroacetyl isatins 2.086 (a-i) from the reaction of the later with methanolic hexamine is believed to take place in two steps. The first step proceeds via the cleavage of the lactam function of isatin ring to give in succession the postulated intermediates A, B, C, D and E (Scheme-2.28). In the subsequent step the hexaminium salt E undergoes solvolysis with MeOH to generate the imine species 2.087. Delepine reaction has been known in the literature to afford the formation of an amine from activated alkyl halide from its reaction with hexamine. This reaction has been shown to proceed via the initial formation of hexaminium salt from alkyl halide and hexamine followed by hydrolysis to give the amine. The mechanism suggested in scheme-2.28 is based on the earlier precedence which exists in the literature in the formation of an amine from alkyl halide from Delepine reaction. We believe that irradiation of the reaction mixture with microwave facilitates the formation of 2.087 from 2.086 to take place instantaneously in less time.
2.6.2 Mechanism of formation of chloro derivative 2.089 from 2.088:

\[
\begin{align*}
\text{2.088} & \quad \text{Cl}^- \quad \text{P} & \quad \text{Cl} \quad \text{Cl} \\
\end{align*}
\]

\[
\begin{align*}
\text{2.089} & \quad \text{N} & \quad \text{O} \\
\end{align*}
\]

Scheme-2.29

2.6.3 Mechanism of formation of phenylamino derivative 2.090 from 2.089:

\[
\begin{align*}
\text{2.089} & \quad \text{H}_2N & \quad \text{C} & \quad \text{N} & \quad \text{Cl}^- \quad \text{HCl} \\
\end{align*}
\]

\[
\begin{align*}
\text{2.090} & \quad \text{N} & \quad \text{H} & \quad \text{O} \\
\end{align*}
\]

Scheme-2.30

2.6.4 Mechanism of formation of phenoxy derivative 2.091 from 2.089:

\[
\begin{align*}
\text{2.089} & \quad \text{HO} & \quad \text{C} & \quad \text{N} & \quad \text{Cl}^- \quad \text{HCl} \\
\end{align*}
\]

\[
\begin{align*}
\text{2.091} & \quad \text{O} & \quad \text{N} & \quad \text{C} \\
\end{align*}
\]

Scheme-2.31
2.6.5 Mechanism of formation of compound 2.094 and 2.095 from 2.090 and 2.091:

\[
\begin{align*}
\text{2.090, } X &= \text{ NH} \\
\text{2.091, } X &= \text{ O}
\end{align*}
\]

\[
\begin{align*}
\text{2.094, } X &= \text{ NH} \\
\text{2.095, } X &= \text{ O}
\end{align*}
\]

Scheme-2.32

2.6.6 Mechanism of formation of compound 2.096 and 2.097 from 2.090 and 2.091:

\[
\begin{align*}
\text{2.090, } X &= \text{ NH} \\
\text{2.091, } X &= \text{ O}
\end{align*}
\]

\[
\begin{align*}
\text{2.096, } X &= \text{ NH} \\
\text{2.097, } X &= \text{ O}
\end{align*}
\]

Scheme-2.33
2.6.7  Mechanism of formation of compound 2.098 from 2.092:

![Chemical reaction diagram showing the formation of compound 2.098 from 2.092.]

2.6.8  Mechanism of formation of compound 2.099 from 2.093:

![Chemical reaction diagram showing the formation of compound 2.099 from 2.093.]

Scheme-2.34

Scheme-2.35
Chapter-II: Preparation of starting materials

2.6.9 Mechanism of formation of compound 2.100 from 2.093:

![Mechanism Diagram]

2.7 Experimental section

1. Melting points were determined in open glass capillaries and are uncorrected.

2. The purity of the compounds checked by TLC on silica gel (G) plates. Iodine was used as visualizing agent.

3. IR spectra were recorded on FTIR-8400S CE (SHIMADZU).

4. $^1$H NMR spectra were recorded on model Brucker Avance II 400 NMR Spectrometer using CDCl$_3$ as solvent. Chemical shift are expressed in $\delta$ ppm.

5. Before analysis all samples were dried for one hour under reduced pressure.

6. Physical and spectral data for all the compounds are given in table 2.01 and 2.02.
Chapter-II: Preparation of starting materials

Synthetic procedure:

Experimental procedure for the preparation of 2.086-2.100:

Preparation of \(N\)-chloroacetyl isatin (2.086) from isatin (2.085):

Isatin (2.085) (10 g, 0.068 mol) was vigorously refluxed with chloroacetyl chloride (70 ml, 0.090 mol) for 10 h and the mixture was cooled for 2 h in an ice-bath. The precipitate was filtered, washed with 20 ml portion of ether, then air-dried and recrystallized with ethyl acetate to give 2.086, 10.00 g (yield 66%); m.p. 210-211 °C.

Preparation of methyl-1,3-dihydro-2\(H\)-[1,4]-benzodiazepin-2-one-5-carboxylate (2.087):

\(N\)-Chloroacetyl isatin (2.086), (2.23 g, 0.01 mol) and hexamethylenetetramine (hexamine) (1.40 g, 0.01 mol) was taken in dry methanol (20 ml) and the reaction mixture was refluxed for 14 h. Progress of reaction was checked by TLC. After completion of reaction, solvent was removed under reduced pressure and the solid was chromatographed over alumina (neutral) in C\(_6\)H\(_6\): MeOH (9.5:0.5) as an eluant. The product obtained was recrystallized from benzene to give 2.087, 1.25 g (yield 55%); m.p. 173-175 °C.

Preparation of 1,3-dihydro-2\(H\)-[1,4]-benzodiazepin-2-one-5-(4’-\(N\)-methylpiperazinyl)-carboxamide (2.088):

Methyl-1,3-dihydro-2\(H\)-[1,4]-benzodiazepin-2-one-5-carboxylate (2.087) (10.9 g, 0.05 mol) and \(N\)-methylpiperazine (5.0 g, 0.05 mol) were taken in ethanol (100 ml). The reaction mixture was refluxed for 12 h on the water bath. The completion of the reaction was checked by TLC. The reaction mixture was cooled and poured on ice, the resulting solid was filtered washed with dilute ethanol dried and recrystallized from ethanol-chloroform mixture (1:9), to give 2.088, 12.37 g (yield 74.6%); m.p. 257-258 °C.

Preparation of 2-chloro-[1,4]-benzodiazepine-5-(4’-methylpiperazinyl)-carboxamide (2.089):

A solution of 2.088 (10 g, 0.06 mol), \(N,N\)-dimethylaniline (14 ml, 0.1 mol), POCl\(_3\) (5 ml, 0.07 mol) and benzene (100 ml) were refluxed for 7 h and then allowed
to cool overnight. The reaction mixture was washed with ether (to remove \(N,N\)-dimethylaniline which is soluble in ether) and then with petroleum ether (to remove POCl\(_3\) which is soluble in petroleum ether). Cold water was then added to the reaction mixture and brought to the neutral point by addition of NaHCO\(_3\) solution. It was then extracted three times with dichloromethane to give 2.089, 8.0 g, (yield 75%); m.p. 120-122 \(^\circ\)C.

**Preparation of 2-[4’-cyanophenylamino]-[1,4]-benzodiazepine-5-[4’’-methylpiperazinyl]-carboxamide (2.090):**

To a solution of compound 2.089 (1.50 g, 0.01 mol) and 4-aminobenzonitrile (0.60 g, 0.01 mol) in \(N\)-methylpyrrolidone (7.5 ml) at 0-5 \(^\circ\)C was added potassium tert-butoxide (1.14 g, 0.01 mol) over a period of 7 h. The reaction was allowed to reach to room temperature and then cold water (300 ml) was added. The reaction mixture was filtered; the residue was suspended in water (150 ml) and acidified to pH 6-7 using conc. HCl. The product was filtered and washed with 15 ml of water. It was extracted by ethyl acetate (2×50 ml). The product obtained on evaporation of solvent was washed with 5.0 ml of chilled ethyl acetate. It was finally dried at 55-60 \(^\circ\)C under vacuum to give 2.090, 1.22 g (yield 64%); m.p. 298-299 \(^\circ\)C.

**Preparation of 2-[4’-cyanophenoxy]-[1,4]-benzodiazepine-5-[4’’-methylpiperazinyl]-carboxamide (2.091):**

To a solution of compound 2.089 (1.50 g, 0.01 mol) and 4-hydroxybenzonitrile (0.60 g, 0.01 mol) in \(N\)-methylpyrrolidone (7.5 ml) at 0-5 \(^\circ\)C was added potassium tert-butoxide (1.14 g, 0.01 mol) over a period of 6 h. The procedure described for the preparation of 2.090 from 2.089 was applied in the isolation and purification of 2.091, 1.26 g (yield 66%); m.p. 297-298.5 \(^\circ\)C.

**Preparation of 2-[4’-formylphenoxy]-[1,4]-benzodiazepine-5-[4’’-methylpiperazinyl]-carboxamide (2.092):**

To a solution of 2.089 (1.0 g, 0.003 mol) and \(p\)-hydroxybenzaldehyde (0.38 g, 0.0035 mol) in DMF (5 ml) was slowly added potassium-tert-butoxide (0.67 g, 0.006 mol) kept in an ice-water bath, then stirred at room temperature for 5 h until reaction was completed. Then mixture was poured into ice water and pH was
adjusted to 6 with 5% aqueous HCl and the mixture extracted with EtOAc three times. After removal of organic solvent in vacuo, crude product was purified by a silica column (eluent:petroleum ether/EtOAc) to give 2.092, 0.83 g (65% yield); m.p. 172-173 °C.

Preparation of 2-[4’-acetylphenoxyl]-[1,4]-benzodiazepine-5-[4’’-methylpiperazinyl]-carboxamide (2.093):

To a solution of 2.089 (1.0 g, 0.003 mol) and \( p \)-hydroxyacetophenone (0.476 g, 0.0035 mol) in DMF (3 ml) was slowly added potassium-tert-butoxide (0.67 g, 0.006 mol) at ice-water bath, then stirred at room temperature for 7 h until reaction was completed. Then mixture was poured into ice water and \( p \)H was adjusted to 6 with 5% aqueous HCl and the mixture extracted with EtOAc three times. After removal of organic solvent in vacuo, the crude product was purified by a silica column (eluent:petroleum ether/EtOAc) to give 2.093, 0.90 g (68% yield); m.p. 165-167 °C.

Preparation of 5-oxo-{(benzo-[1,4]-diazepin-2-ylamino)-carboximidamide-5-(4’’-methylpiperazinyl)}-carboxamide (2.094):

Hydroxylamine hydrochloride (1.0 g, 0.01 mol) in methanol (10 ml) was added to an equimolar stirred solution of potassium hydroxide in methanol (10 ml). The mixture was stirred for 15 min and the precipitated potassium chloride was removed by filtration. The filtrate was added to an equimolar amount of the above nitrile (3.86 g, 0.01 mol) 2.090, and the solution was stirred overnight at 40 °C, then cooled to room temperature and concentrated. The resulting residue was triturated with water giving, after drying under vacuum, a white solid consisting mainly of the title product which was purified on a silica column as above to give 2.094, 3.54 g (86% yield); m.p. 170-172 °C.

Preparation of 5-oxo-{(benzo-[1,4]-diazepin-2-ylamino)-carboximidamide-5-(4’’-methylenepiperazinyl)}-carboxamide (2.095):

Hydroxylamine hydrochloride (1.0 g, 0.01 mol) in methanol (10 ml) was added to an equimolar stirred solution of potassium hydroxide in methanol (10 ml). The mixture as stirred for 15 min and the precipitated potassium chloride was
Chapter-II: Preparation of starting materials

removed by filtration. The filtrate was added to an equimolar amount of the above nitrile (3.87 g, 0.01 mol) 2.091, and the solution was stirred overnight at 40 °C, then cooled to room temperature and concentrated. The resulting residue was triturated with water giving, after drying under vacuum, a white solid consisting mainly of the title product which was purified as above to give 2.095, 3.56 g (85% yield); m.p. 181-183 °C.

Preparation of 5-oxo-{(benzo-[1,4]-diazepin-2-ylamino)-ethylimidate-5-(4”'-methylpiperazinyl)-carboxamide (2.096):

The compound 2.090 (3.86 g, 0.01 mol) was dissolved in absolute ethanol (10 ml) and stirred for 15 min with ice-bath cooling. Then the imidate hydrochloride 2.096 was prepared by passing HCl gas through the above solution. HCl gas was passed for 8 h with constant stirring at room temperature. The completion of the reaction was checked by TLC, after completion, the precipitation of reaction mixture was done by adding diethyl ether to it, filtered, dried to yield 2.096, 2.88 g (69% yield); m.p. 72-74 °C.

Preparation of 5-oxo-{(benzo-[1,4]-diazepin-2-yloxy)-ethylimidate-5-(4”'-methylpiperazinyl)-carboxamide (2.097):

The compound 2.091 (3.87 g, 0.01 mol) was dissolved in absolute ethanol (10 ml) and stirred for 15 min with ice-bath cooling. Then the imidate hydrochloride 2.097 was prepared by passing HCl gas through the above solution. HCl gas was passed for 8 h with constant stirring at room temperature. The completion of the reaction was checked by TLC, after completion, the precipitation of reaction mixture was done by adding diethyl ether to it, filtered, dried to yield 2.097, 2.68 g (64% yield); m.p. 81-83 °C.

Preparation of 2-{4’-(benzylidenethiosemicarbazone)phenoxyl-[1,4]-benzdiazepine-5-(4”'-methylpiperazinyl)}-carboxamide (2.098):

A solution of 2.092 (1.17 g, 0.003 mol) and thiosemicarbazide (0.78 g, 0.0033 mol) in ethanol (6 ml) was heated to reflux for 3 h and monitored by TLC (CHCl₃/CH₃OH/AcOH 3:1:0.05). After reaction mixture was cooled, the solid was filtered out, washed with ethanol, and dried to give yellow solid of 2.098, 1.25 g (90% yield); m.p. 255-257 °C.
Chapter-II: Preparation of starting materials

Preparation of 2-{4'-(dimethylaminomethylene-oxo)phenoxy-[1,4]-benzodiazepine-5-(4''-methylpiperazinyl)}-carboxamide (2.099):

2.093 (2.82 g, 0.007 mol) was dissolved in N,N-dimethylformamide dimethylacetal (15 ml), and the solution was heated under reflux for 5 h and concentrated. The residue was triturated with hexane, filtered, and washed with hexane to give 2.099 as a brown powder, 2.08 g (yield 65%); m.p. 280-282 °C.

Preparation of 2-{4'-(1''-phenyl-prop-2-en-3-one)phenoxy-[1,4]-benzodiazepine-5-(4''-methylpiperazinyl)}-carboxamide (2.100):

A mixture of 2.093 (4.0 g, 0.01 mol), benzaldehyde (0.01 mol) and fused sodium acetate (0.015 mol) in glacial acetic acid was refluxed for 10 h. The reaction mixture was cooled and poured in to water. The resulting solid was filtered, washed with water and recrystallized from aq. ethanol to furnish pure 2.100, 3.50 g (yield 72%); m.p. 320-322 °C.

Chart-2.1 IR spectrum of 5-oxo-{(benzo-[1,4]-diazepin-2-ylamino)-carboximidamide-5-(4''-methylpiperazinyl)}-carboxamide (2.094)
Chapter II: Preparation of starting materials

Chart-2.2 IR spectrum of 5-oxo-[(benzo-[1,4]-diazepin-2-ylamino)-
  ethylimidate-5-(4''-methylpiperazinyl)]-carboxamide (2.096)

Chart-2.3 IR spectrum of 2-{4'-(benzylidenethiosemicarbzone)phenoxyl-[1,4]-
  benzodiazepine-5-(4''-methylpiperazinyl)}-carboxamide (2.098)
Chart-2.4 IR spectrum of \(\text{2-\{4'-\text{[(dimethylaminomethylene-oxo)phenoxy]-[1,4]-benzodiazepine-5-(4''-methylpiperazinyl]}}\)-carboxamide (2.099)

Chart-2.5 IR spectrum of \(\text{2-\{4'-\text{[(1''-phenyl-prop-2-en-3-one)phenoxy]-[1,4]-benzodiazepine-5-(4''-methylpiperazinyl]}}\)-carboxamide (2.100)
Chapter-II: Preparation of starting materials

Chart-2.6 $^1$H NMR spectrum of 5-oxo-{(benzo-[1,4]-diazepin-2-ylamino)-carboximidamide-5-(4”'-methylpiperazinyl)}-carboxamide (2.094)

Chart-2.7 $^1$H NMR spectrum of 5-oxo-{(benzo-[1,4]-diazepin-2-ylamino)-ethylimidate-5-(4”'-methylpiperazinyl)}-carboxamide (2.096)
Chapter-II: Preparation of starting materials

Chart-2.8 $^1$H NMR spectrum of 2-\(\text{4'}-(\text{benzylidenethiosemicarbazone})\)phenoxyl-\([1,4]\)-benzodiazepine-5-\(\text{4''-methylpiperazinyl}\})\)-carboxamide (2.098)

Chart-2.9 $^1$H NMR spectrum of 2-\(\text{4'}-(\text{dimethylaminomethylene-oxo})\)phenoxyl-\([1,4]\)-benzodiazepine-5-\(\text{4''-methylpiperazinyl}\})\)-carboxamide (2.099)
Chart-2.10 $^1$H NMR spectrum of 2-{4’-(1”'-phenyl-prop-2-en-3-one)phenoxy}-[1,4]-benzodiazepine-5-(4’'-methylpiperazinyl)}-carboxamide (2.100)

Chart-2.11 Mass spectrum of 5-oxo-{(benzo-[1,4]-diazepin-2-ylamino)-carboximidamide-5-(4’'-methylpiperazinyl)}-carboxamide (2.094)
Chapter-II: Preparation of starting materials

Chart-2.12 Mass spectrum of 5-oxo-\{(benzo-[1,4]-diazepin-2-ylamino)-
ethylimidate-5-(4''-methyipiperazinyl)}-carboxamide (2.096)

Chart-2.13 Mass spectrum of 2-\{4'-(benzylidenethiosemicarbazonephenoxyl-
[1,4]-benzodiazepine-5-(4''-methyipiperazinyl)}-carboxamide (2.098)
Chart-2.14 Mass spectrum of 2-{4’-(dimethylaminomethylene-oxo)phenoxy-[1,4]-benzodiazepine-5-(4’’-methylpiperazinyl)}-carboxamide (2.099)

Chart-2.15 Mass spectrum of 2-{4’-(1’’-phenyl-prop-2-en-3-one)phenoxy-[1,4]-benzodiazepine-5-(4’’-methylpiperazinyl)}-carboxamide (2.100)
2.8 References


Chapter-II: Preparation of starting materials


107


Chapter-II: Preparation of starting materials


