Overview

The Chapter-2 covers with the synthesis and characterization of Schiff bases of 3-(isoindol-1,3-dione methyl)-6-hydroxy benzoic acid hydrazide (IHBH). The arylidene group present in the structure is of importance by considering the fact that it can be transformed into various heterocyclic ring compounds. The availability of the presence and significant biological properties of the members known so far prompted the authors to extend moieties like 2-azetidinones.

In this context, the present chapter emphasizes on the synthesis and characterization of 2-azetidinones. The whole chapter is divided into two sections. The brief reviews on the 2-azetidinones is summarized in Section-A and the experimental work is included in Section-B.
Brief Review on 2-Azetidinones

Azetidin-2-ones (β-lactams) represent a very important class of compounds because of their well-known biological activity [1] and their usefulness as intermediates in organic synthesis [2]. Many synthetic methods were developed for the formation of the β-lactam ring including [2+2]-cycloadditions, cyclization reaction, carbene insertion reactions, and rearrangement of heterocyclic compounds [3]. In this review, the recent methods of synthesis of the azetidin-2-one ring, besides some of the most remarkable advances in the more classical approaches are reported.

4.1 IMINE PLUS KETENES: THE STAUDINGER REACTION

The Staudinger reaction, reactions of ketenes with imines, is probably the most important synthetic tool to access β-lactams. Since its discovery by Staudinger, [4] this reaction has long been studied experimentally and theoretically to understand its mechanism(s) and the rationale for the stereoselectivity, and it has been applied to the synthesis of a wide variety of β-lactam structures (Scheme 1.1). This reaction is still nowadays one of the best means for the synthesis of lactams.

\[
\begin{align*}
\text{R}_3\text{H} & \quad + \quad \text{N}^{\text{R}_1}\text{N}^{\text{R}_2} \\
\text{C} & \quad + \\
\text{Cis-isomer} & \quad \text{Trans-isomer}
\end{align*}
\]

Scheme 1.1

Very few examples of the synthesis of 4-amino-β-lactams are known because of their instability. These compounds undergo ring cleavage mainly by the fission of C3-C4 bond. Another possible mechanism of ring cleavage was observed when a hydrogen atom was present on C3 and was ascribed to the mesomeric effect of the \textit{exo}-cyclic nitrogen atom, as presented in Scheme 1.2.
Scheme 1.2

4-Unsubstituted 2-azetidinones is not viable, since it would require the use of formaldehyde-derived imines that are prone to oligomerize under the reaction conditions. An efficient alternative is offered by the use of formaldehyde N,N-dialkylhydrazones [5]. These reagents are more stable and also offer the possibility to use the extra nitrogen atom as a tool for inserting a chiral auxiliary to be used in diastereoselective reactions. The high efficiency of this approach is demonstrated by the synthesis of 2-azetidinones (Scheme 1.3).

Scheme 1.3

Several examples are known of the application of the Staudinger reaction in solid-phase syntheses, or polymersupported liquid-phase syntheses, of β-lactams [6]. The Mata group has developed a solid-phase synthesis of di- and trisubstituted β-lactams using a Wang resin functionalized with the imine reagent. The ketene was produced in situ starting from the carboxylic acid and the Mukaiyama’s reagent (Scheme 1.4).
4.2 ENOLATE-IMEINE CONDENSATION

The first example of this synthetic approach to $\beta$-lactams was described by Gilman and Speeter (after whom the reaction is named) in 1943. They described the condensation of the Reformatsky reagent derived from ethyl-R-bromoacetate with N-phenylbenzaldehyde [7]. Actually, under the name of Gilman-Speeter reaction, several kinds of conditions are described using zinc, lithium, aluminum, tin boron, zirconium, and titanium enolates, although most of these approaches end up producing the $\beta$-aminoesters.

Although the use of zinc enolates was the first to be described, still several recent examples of this reaction are known. Often the reaction gave origin to mixtures of $\beta$-lactams and $\beta$-aminoesters (Scheme 1.5) [8]. The use of high-intensity ultrasounds afforded in good yield mixtures of these two products, with their ratio depending on the structural characteristics of the imine and the R-bromoester [9].
4.3 KINUGASA CONDENSATION

The reaction of nitrones with terminal alkynes catalyzed by Cu(I), known as the Kinugasa reaction, is a relatively new and unexplored approach to β-lactams. Usually, the kinetic favored cis-3,4-disubstituted β-lactam cis-isomer is mainly obtained, but depending on the reaction conditions and the substitution pattern, epimerization to the thermodynamically more stable trans-isomer can occur (Scheme 1.6) [10].

Two mechanisms have been proposed for this highly versatile and efficient methodology, both considering an initial [3+2]-cycloaddition between the nitrone (1) and the in situ formed copper acetylide complex (2). Then, the intermediate isoxazoline (3) rearranges to the final azetidinone, passing through the bicyclic oxaziridine (4) or the ketene (Scheme 1.7) [11].
4.4 \textbf{ISOCYANATE CYCLOADDITION}

The [2+2]-cycloaddition of isocyanates to alkenes provides an easy route to \(\beta\)-lactams. The most used isocyanates chlorosulfonylisocyanate because of its exceptionally high reactivity. Furthermore, the resulting \(\beta\)-lactams can easily be converted into the \(N\)-unsubstituted derivatives by reducing treatment under basic conditions [12].

This reaction is mechanistically related to the addition of ketenes. Formally thermally not allowed, the low-energy orthogonal \(\pi\)-bond of the cumulene renders concerted thermal [2+2]-addition energetically feasible. \textit{Ab initio} calculations predict that the [2+2]-reaction takes place through a concerted suprafacial mechanism [13].

4.5 \textbf{[3+1]-ANNULATION}

Free-radical mediated stannylcarbonylation of azaenynes with tributyltin hydride and carbon monoxide appears to be a useful method for the synthesis of 3-(stannylmethylene)-2-azetidinones. For example, imine (5) was converted to azetidinone (6) in 84\% yield (\textbf{Scheme 1.8}) [14] Analogously, 3-silylmethylene derivatives such as (7) and 3-thiomethylene lactams were obtained using tris(trimethylsilyl)silane and hexanethiol, respectively, as radical mediators.
4.6 CYCLIZATIONS

A common approach to the azetidinone ring is based on the cyclization of $\beta$-amino acids and esters. In situ activation of the carboxylic acid group can be achieved using conventional amide coupling reagents such as carbodiimides, 2-chloro-1-methylpyridinium iodide (Mukaiyama’s reagent), and the redox couple di-(2-pyridinyl) disulfide/triphenylphosphine.

Recently, Sharma and co-workers have investigated the efficiency of some coupling reagents in promoting the cyclization of $\beta$-amino acids. Disulfide reagents such as di-(1,3-benzothiazol-2-yl) disulfide and 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (Lawesson’s reagent), (chloromethylene) dimethylammonium chloride, and phosphoryl chloride promoted the cyclodehydration of $\beta$-amino acids under mild conditions, affording the corresponding monolactams in good yields [15].

Tris(2-oxo-3-benoxazoliny1)phosphine oxide was also one of the best coupling reagents in the cyclization of amino acids (8) to carbapenam-3-carboxylates (9) (Scheme 1.8). The discrepancies in the yield values reported by different authors for
the synthesis of (9) under similar conditions can probably be ascribed to its instability [16].

\[\text{HOOC} \xrightarrow{\text{N}} \text{CO}_2\text{R} \rightarrow \text{H} \xrightarrow{\text{N}} \text{CO}_2\text{R}\]

4.7 SYNTHETIC 2-AZETIDINONES DERIVATIVES

The four membered 2-azetidinone rings (10) appears to be smallest cyclic system that is of accommodating the amide function as a consistent which is also known as \(\beta\)-lactam ring. Over the years it has been of great practical significance because of their good pharmacological and biological activities.

\[\text{Shanker et al. [17] indicated in their work that 2-acetyl-10-(hydrazine acetyl)phenothiazine on condensation with substituted aldehydes yields arylidene-2-acetyl-10-(hydrazine acetyl)phenothiazine which on cyclocondensation reactions with chloroacetyl chloride affords substituted 2-azetidinones (11). All the compounds were screened for their cardiovascular activity.}\]
Where, R= 2-Cl, 4-N(CH$_3$)$_2$, 4-OH, etc.

Kidwai and co-workers [18] have indicated on reaction of hydrazone derivatives with chloroacetyl chloride affording 2-azetidinones (12).

Where, R and R’= MTD,H; TZA,H; MTD,4-Cl, etc.

Jaish and Srivastava [19] have synthesized a series of 2-arylidene imino-5-(N$^{\prime}$-methyl - N$^{\prime}$ - piperazinyl methyl)-1, 3, 4-thiadiazole by condensation reaction of 2-amino-5-(N$^{\prime}$-methyl-N$^{\prime}$-piperazinylmethyl)-1,3,4-thiadiazole with various carbonyl compounds, which on cyclocondensation reaction with chloroacetyl chloride gave 1-[5-(N$^{\prime}$-methyl-N$^{\prime}$-piperazinylmethyl)-1’,3’,4’-thiadiazole-2’-yl]-4-substituted-3-chloro-2-azetidinones (13), which were screened for their antimicrobial activities.

where, R’ and R” = H, C$_6$H$_5$; H, N(CH$_3$)$_2$; etc.
Reddy [20] and coworkers have synthesized novel bisquinazolinoyl $\beta$-lactam derivatives (14) having following structure.

Where, $Z = 1,4$-$C_6H_4; 4,4'$-$C_6H_4-C_6H_4$ etc.

Thaker, Kachhadia, and Joshi, [21] have prepared 2-azetidinones bearing benzo[b] thiophene nucleus as potential antitubercular and antimicrobial agents.
Synthesis and Characterization of 2-Azetidinone derivatives

4.8 EXPERIMENTAL

Various Schiff bases based of 3-(isoindol-1,3-dione methyl)-6-hydroxy benzoic acid hydrazide (IHBH) (3a-3h) mentioned in chapter-2 on heterocyclization reaction with chloroacetyl chloride yield the biologically active 2-azetidinones (β-lactams) (7a-7h). These β-lactam derivatives were characterized by elemental analysis, infrared spectral data and $^1$H and $^{13}$C magnetic resonance spectral data. The research work is scanned in Scheme 4.1. Experimental procedures for the synthesis of this series of compounds have been adopted according to reported methods [18, 22-24].

4.8.1 Materials

The Schiff bases (3a-3h) have been selected for the synthesis of above said compounds. Their synthesis has already been described in Chapter-2. Other chemicals used were of LR grade.

4.8.2 Synthesis of 3-chloro-1-[3-(isoindol-1,3-dione methyl)-6-hydroxybenzoyl amino]-4-aryl-azetidin-2-ones (7a-7h)

A mixture of Schiff base (3a-3h) (0.002 mol) and triethyl amine (TEA) (0.004 mol) was dissolved in 1,4-dioxane (50 ml), cooled and stirred. To this well-stirred cooled solution chloroacetyl chloride (0.004 mol) was added drop wise within a period of 30 minutes. The reaction mixture was then stirred for an additional 3 h and left at room temperature for 48 h. The resultant mixture was concentrated, cooled, poured into ice-cold water, and then air-dried. The product thus obtained was purified by column chromatography over silica gel using 80% hexane: 20% ethyl acetate as an eluent. Recrystallization from ether/n-hexane gave 2-azetidinone (7a-7h), which were
obtained in 70-82% yield. The analytical and spectral studies of compounds (7a-7h) are described as follow.

\[ \text{schiff base} \]

\[ \text{Dioxane} \]
chloro acetyl chloride
Tri ethyl amine

\[ \text{(7a-h)} \]

2- Azetidiones

Ar =
- a - phenyl
- b - 4 - hydroxy phenyl
- c - 2 - hydroxy phenyl
- d - 4 -methoxy phenyl
- e - 4 - hydroxy-3-methoxy phenyl
- f - 4 - chlorophenyl
- g - 2 - nitro phenyl
- h - 5 -bromo-2-hydroxy-phenyl

Scheme 4.1
Compound-7a

3-Chloro-1-[3-(isoindol-1,3-dione methyl)-6- hydroxy- benzoyl amino]-4-phenyl- azetidin-2-one

<table>
<thead>
<tr>
<th>Molecular Formula: C_{25}H_{18}N_{3}O_{5}Cl</th>
<th>Elemental Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Weight: 475.5 g/mol</td>
<td>%C   %H   %N</td>
</tr>
<tr>
<td>Melting Point: 178-80°C (uncorrected)</td>
<td>Calculated 63.09 3.78 8.83</td>
</tr>
<tr>
<td>Yield: 70%</td>
<td>Found 63.0 3.7 8.7</td>
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</table>

**Infrared spectral features (KBr, cm\(^{-1}\))**

- 3377 N-H stretching
- 1591, 1161 Aromatic C-H
- 1697 C=O of β-lactam
- 3500(b) OH phenolic

Other bands as mentioned in parent Schiff base.

**\(^1\)H NMR spectral features (DMSO-d\(_6\), ppm)**

- 6.66-7.88 (Multiplet, Aromatic H + C\(_4\)H + NH of CONH + Isoindole-1,3-dione)
- 10.8 (1H of C\(_3\)H of β-lactam)
- 2.37 (2H of CH\(_2\))

**\(^{13}\)C NMR spectral features (DMSO-d\(_6\), ppm)**

- 114-130 Aromatic C
- 144, 153 C of β-lactam
- 169 C=O
- 136-145 C\(_3\)H
- 85 CH\(_2\)
Compound-7b

3-Chloro-[3-(isoindol-1,3-dione methyl)-6- hydroxy- benzoyl amino]-4-hydroxy phenyl-azetidin-2-one

Molecular Formula: C$_{25}$H$_{18}$N$_3$O$_6$Cl

Molecular Weight: 491.5 g/mol

Melting Point: 168-70°C (uncorrected)

Yield: 72%

**Elemental Analysis**

<table>
<thead>
<tr>
<th></th>
<th>%C</th>
<th>%H</th>
<th>%N</th>
</tr>
</thead>
<tbody>
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<td>Found</td>
<td>61.0</td>
<td>3.6</td>
<td>8.5</td>
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</table>

**Infrared spectral features (KBr, cm$^{-1}$)**

- 3377 N-H stretching
- 1591, 1161 Aromatic C-H
- 1697 C=O of $\beta$-lactam
- 3500(b) OH phenolic

Other bands as mentioned in parent Schiff base.

**$^1$H NMR spectral features (DMSO-d$_6$, ppm)**

- 6.65-7.85 (Multiplet, Aromatic H + C$_4$H + NH of CONH + Isoindole-1,3-dione)
- 10.4 (1H C$_3$H of $\beta$-lactam)
- 2.30 (2H of CH$_2$)

**$^{13}$C NMR spectral features (DMSO-d$_6$, ppm)**

- 114-130 Aromatic C
- 144, 153 $\beta$-lactam
- 169 C=O
- 119 C-O-H
- 85 CH$_2$
Compound-7c

3-Chloro-[3-(isoindol-1,3-dione methyl)-6- hydroxy- benzoyl amino]-2-hydroxy phenyl-azetidin-2-one

Molecular Formula: C_{25}H_{18}N_{3}O_{6}Cl  
Molecular Weight: 491.5 g/mol  
Melting Point: 184-85°C (uncorrected)  
Yield: 74%

Elemental Analysis

<table>
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<th>%N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculated</td>
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<td>3.66</td>
<td>8.54</td>
</tr>
<tr>
<td>Found</td>
<td>61.1</td>
<td>3.5</td>
<td>8.5</td>
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Infrared spectral features (KBr, cm\(^{-1}\))

<table>
<thead>
<tr>
<th>Wavenumber</th>
<th>Description</th>
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<tbody>
<tr>
<td>3377</td>
<td>N-H stretching</td>
</tr>
<tr>
<td>1591, 1161</td>
<td>Aromatic stretching</td>
</tr>
<tr>
<td>1697</td>
<td>C=O of (\beta)-lactam</td>
</tr>
<tr>
<td>3500(b)</td>
<td>OH phenolic</td>
</tr>
<tr>
<td></td>
<td>Other bands as mentioned in parent Schiff base.</td>
</tr>
</tbody>
</table>

\(^1\)H NMR spectral features (DMSO-\text{d}_6, ppm)

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>6.6-7.9</td>
<td>(Multiplet, Aromatic H + C(_4)H + NH of CONH + Isoindole-1,3-dione)</td>
</tr>
<tr>
<td>10.8</td>
<td>(1H of C(_3)H of (\beta)-lactam)</td>
</tr>
<tr>
<td>5.37</td>
<td>(H of OH)</td>
</tr>
<tr>
<td>2.35</td>
<td>(2H of CH(_2))</td>
</tr>
</tbody>
</table>

\(^13\)C NMR spectral features (DMSO-\text{d}_6, ppm)

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>119-130</td>
<td>Aromatic C</td>
</tr>
<tr>
<td>144, 153</td>
<td>(\beta)-lactam</td>
</tr>
<tr>
<td>119</td>
<td>C-O-H</td>
</tr>
<tr>
<td>166</td>
<td>C of CO</td>
</tr>
<tr>
<td>85</td>
<td>CH(_2)</td>
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</table>
**Compound-7d**

![Chemical Structure](image)

3-Chloro-[3-(isoindol-1,3-dione methyl)-6- hydroxy- benzoyl amino]-4-methoxy phenyl-azetidin-2-one

<table>
<thead>
<tr>
<th>Molecular Formula: C_{26}H_{20}N_{3}O_{6}Cl</th>
<th>Elemental Analysis</th>
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<tbody>
<tr>
<td>Molecular Weight: 505.5 g/mol</td>
<td>%C  %H  %N</td>
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<tr>
<td>Melting Point: 170-72°C (Uncorrected)</td>
<td>Calculated</td>
</tr>
<tr>
<td>Yield: 72%</td>
<td>Found</td>
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</tbody>
</table>

**Infrared spectral features (KBr, cm\(^{-1}\))**

- 3377  N-H stretching
- 1591, 1161 Aromatic stretching
- 1697  C=O of β-lactam
- 3500(b) OH phenolic
- 1239  Aryl alkyl ether

Other bands as mentioned in parent Schiff base.

**\(^1\)H NMR spectral features (DMSO-d\(_6\), ppm)**

- 6.66-7.9 (Multiplet, Aromatic H + C\(_4\)H + NH of CONH + Isoindole-1,3-dione)
- 10.4 (1H of C\(_3\)H of β-lactam)
- 4.37 (3H of OCH\(_3\))
- 2.35 (2H of CH\(_2\))

**\(^13\)C NMR spectral features (DMSO-d\(_6\), ppm)**

- 114-130 Aromatic C
- 144, 153 β-lactam
- 55 OCH\(_3\)
- 165 C of CO
- 85 CH\(_2\)
Compound-7e

3-Chloro-[3-(isoindol-1,3-dione methyl)-6- hydroxy- benzoyl amino]-4-hydroxy-3- methoxy phenyl-azetidin-2-one

Molecular Formula: C$_{26}$H$_{20}$N$_3$O$_7$Cl  
Molecular Weight: 521.5 g/mol  
Melting Point: 170-72°C (uncorrected)  
Yield: 75%

**Infrared spectral features (KBr, cm$^{-1}$)**

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<td>3377</td>
<td>N-H stretching</td>
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<td>1591, 1161</td>
<td>Aromatic stretching</td>
</tr>
<tr>
<td>1697</td>
<td>C=O of $\beta$-lactam</td>
</tr>
<tr>
<td>3500(b)</td>
<td>OH phenolic</td>
</tr>
<tr>
<td>1239</td>
<td>Aryl alkyl ether</td>
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<tr>
<td>Other bands</td>
<td></td>
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</table>

**Elemental Analysis**

<table>
<thead>
<tr>
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<th>% H</th>
<th>% N</th>
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<tr>
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<td>Found</td>
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**$^1$H NMR spectral features (DMSO-d$_6$, ppm)**

<table>
<thead>
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<tbody>
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<td>6.6-7.9</td>
<td>(Multiplet, Aromatic H + C$_4$H$_4$H + NH of CONH + Isoindole-1,3-dione)</td>
</tr>
<tr>
<td>10.4</td>
<td>(1H of C$_3$H of $\beta$-lactam)</td>
</tr>
<tr>
<td>4.34</td>
<td>(3H of OCH$_3$)</td>
</tr>
<tr>
<td>3.36</td>
<td>(1H of OH)</td>
</tr>
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<td>2.35</td>
<td>(2H of CH$_2$)</td>
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**$^{13}$C NMR spectral features (DMSO-d$_6$, ppm)**

<table>
<thead>
<tr>
<th>ppm</th>
<th>Description</th>
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<tbody>
<tr>
<td>114-130</td>
<td>Aromatic C</td>
</tr>
<tr>
<td>153,144</td>
<td>$\beta$-lactam</td>
</tr>
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<td>55</td>
<td>OCH$_3$</td>
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<td>C of CO</td>
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<td>85</td>
<td>CH$_2$</td>
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</table>
Compound-7f

3-Chloro-[3-(isoindol-1,3-dione methyl)-6- hydroxy- benzoyl amino]-4-chloro phenyl-azetidin-2-one

Molecular Formula: C_{25}H_{17}N_{3}O_{5}Cl_{2}

Molecular Weight: 510 g/mol

Melting Point: 200-02°C (uncorrected)

Yield: 74%

Elemental Analysis

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<td>Found</td>
<td>58.8</td>
<td>3.3</td>
<td>8.2</td>
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</table>

Infrared spectral features (KBr, cm⁻¹)

- 3377 N-H stretching
- 1591, 1161 Aromatic stretching
- 1697 C=O of β-lactam
- 3500(b) OH phenolic
- Other bands as mentioned in parent Schiff base.

¹H NMR spectral features (DMSO-d₆, ppm)

- 6.2-7.9 (Multiplet, Aromatic H + C₆H + NH of CONH + Isoindole-1,3-dione)
- 10.4 (1H of C₆H of β-lactam)
- 3.36 (1H of OH)
- 2.35 (2H of CH₂)

¹³C NMR spectral features (DMSO-d₆, ppm)

- 114-130 Aromatic C
- 144, 153 β-lactam
- 165 C of CO
- 85 CH₂
Compound-7g

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

3-Chloro-[3-(isoindol-1,3-dione methyl)-6-hydroxy- benzoyl amino]-2-nitro phenylazetidin-2-one

---

**Molecular Formula:** C\textsubscript{25}H\textsubscript{17}N\textsubscript{4}O\textsubscript{7}Cl

**Molecular Weight:** 520.5 g/mol

**Melting Point:** 182-83°C (uncorrected)

**Yield:** 78%

**Elemental Analysis**

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<td><strong>Found</strong></td>
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<td>3.2</td>
<td>10.7</td>
</tr>
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</table>

**Infrared spectral features (KBr, cm\textsuperscript{-1})**

- 3377 N-H stretching
- 1591, 1161 Aromatic stretching
- 1697 C=O of β-lactam
- 3500(b) OH phenolic
- Other bands as mentioned in parent Schiff base.

**\textsuperscript{1}H NMR spectral features (DMSO-\textsubscript{d\textsubscript{6}}, ppm)**

- 6.6-7.9 (Multiplet, Aromatic H + C\textsubscript{4}H + NH of CONH + Isoindole-1,3-dione)
- 10.4 (1H of C\textsubscript{3}H of β-lactam)
- 3.36 (1H of OH)
- 2.35 (2H of CH\textsubscript{2})

**\textsuperscript{13}C NMR spectral features (DMSO-\textsubscript{d\textsubscript{6}}, ppm)**

- 114-130 Aromatic C
- 144, 153 β-lactam
- 165 C of CO
- 86 CH\textsubscript{2}
Compound-7h

\[
\begin{align*}
\text{3-Chloro-}[3-(\text{isoindol-1,3-dione methyl})-6-\text{hydroxy-benzoyl amino}]\,-5\text{-bromo-2-hydroxy phenyl-azetidin-2-one}
\end{align*}
\]

Molecular Formula: \( \text{C}_{25}\text{H}_{17}\text{N}_{3}\text{O}_{6}\text{ClBr} \)

Molecular Weight: \( 571.5 \text{ g/mol} \)

Melting Point: \( 195-97^\circ\text{C} \) (uncorrected)

Yield: \( 82\% \)

**Infrared spectral features (KBr, cm\(^{-1}\))**

- 3377 \( \text{N-H stretching} \)
- 1591, 1161 \( \text{Aromatic stretching} \)
- 1697 \( \text{C=O of } \beta\text{-lactam} \)
- 3500(b) \( \text{OH phenolic} \)

Other bands as mentioned in parent Schiff base.

**Elemental Analysis**

\[
\begin{align*}
\%\text{C} & & \%\text{H} & & \%\text{N} \\
\text{Calculated} & 52.49 & 2.97 & 7.36 \\
\text{Found} & 52.4 & 2.9 & 7.3 \\
\end{align*}
\]

**\(^1\)H NMR spectral features (DMSO-\(d_6\), ppm)**

- 6.6-7.9 \( \text{Multiplet, Aromatic H + C}_4\text{H + NH of CONH+ Isoindole-1,3-dione} \)
- 10.4 \( 1\text{H of } \text{C}_3\text{H of } \beta\text{-lactam} \)
- 3.36 \( 1\text{H of OH} \)

**\(^13\)C NMR spectral features (DMSO-\(d_6\), ppm)**

- 114-130 \( \text{Aromatic C} \)
- 144, 153 \( \beta\text{-lactam} \)
- 165 \( \text{C of CO} \)
- 85 \( \text{CH}_2 \)
- 119 \( \text{C-O-H} \)
Figure 4.1 IR spectrum of Compound 7a

Figure 4.2 IR spectrum of Compound 7d
Figure 4.3 IR spectrum of Compound 7e
Figure 4.4 $^1$H NMR Spectrum of Compound 7a
Figure 4.5 $^1$H NMR Spectrum of Compound 7d
Figure 4.6 $^1$H NMR Spectrum of Compound 7e
Figure 4.7 $^{13}$C NMR Spectrum of Compound 7a
Figure 4.8 $^{13}$C NMR Spectrum of Compound 7c
Figure 4.9 $^{13}$C NMR Spectrum of Compound 7e
Figure 4.10 Mass Spectrum of Compound 7a
4.9 RESULTS AND DISCUSSION

Structures of Schiff bases, (3a-3h) have been already confirmed in the Chapter-2 of the thesis. It is known that azomethines are the important materials for the preparation of heterocyclic compounds like 2-azetidinones. These azomethines (3a-3h) on cyclocondensation reaction with chloroacetyl chloride in the presence of triethylamine (TEA) affords the bioactive 2-azetidinone (β-lactam) derivatives (7a-7h).

Their structures were confirmed by analytical and spectral data. The C, H and N contents of the prepared compounds were consistent with their predicted structures as presented in Scheme-4.1. The infrared spectra show the band in the region 1680-1710 cm$^{-1}$ for carbonyl (>C=O) group, which is the characteristic band for the cyclic β-lactam ring.

The proton magnetic resonance spectra of the prepared compounds (7a-7h) show two doublets. One around 10.4 ppm for CH proton at position-3 in the 2-azetidinone ring and other at 7.9 ppm for CH proton at position-4 in the azetidinone ring. All other signals are at their respective positions in the $^1$H NMR spectrum.

The $^{13}$C NMR spectra of all the compounds (7a-7h) show the signal for unsubstituted carbons of phenyl rings. The β-lactam carbons are appeared at 153 and 144 ppm.

The Mass spectrum (Figure 4.10) of the compound 7a shows the molecular ion peak at 476.6 m/z which is consistent with the molecular weight of 7a. All these data altogether confirm the structures of the compounds (7a-7h).

The analytical and spectral data for all the compounds (7a-7h) are presented. The IR, PMR and $^{13}$C NMR spectra are scanned in Figures 4.1-4.9 for selective compounds.
References:

1. For a selection of recent reviews on the biological activity of β-lactams, see:

2. For selected reviews on the “β-lactam synthon method”, see:


