6.1 Introduction

β-Lactam (2-Azetidinones) antibiotic research was opened when Scottish scientist Sir Alexander Fleming observed that *Pencillium notatum* produces an inhibitory growing effect and partial lysis on *Staphylococci colonies.* Thus, 2-Azetidinones are four-membered cyclic amides derived from 3-amino-propanoic acids. The first member of this class of compounds was synthesized by Staudinger in 1907. However, until the discovery of penicillin by Fleming in 1929, the importance of β-lactams as antibiotics was not recognized.

Therefore, the following demonstration of the chemotherapeutic properties of penicillin (1), a search for an antibiotic producing organism was made by Professor Brotzu in Sardinia. He examined the microbial flora of the sea water near a sewage outlet, supposing that the process of self-purification of water might be due to bacterial antagonism. He reported the discovery of cephalosporin (2) which produced anti-bacterial material that has activity against certain Gram-positive as well as Gram-negative organisms. Brotzu believed that his results offered hopeful prospects. The experiments with the Sardinian’s cephalosporins were carried out at Oxford University laboratories and proved to contain an acidic antibiotic which was readily extractable in organic solvents.
Resistance to penicillin and cephalosporin\textsuperscript{5-7} and the possibility that antibiotics might occur in nature, prompted scientists to start screening microorganisms for new compounds. This resulted in the detection and isolation of clavulanic acid\textsuperscript{8} (3), thienamycin\textsuperscript{9} (4) and olivanic acid\textsuperscript{10} (5) from the genus \textit{Streptomyces}.

**Molecular geometry and dimensions of 2-Azetidinone**

On the basis of X-ray diffraction analysis, 2-azetidinone ring has a planar structure.\textsuperscript{11} Thus, the confirmation from similar studies proves the molecular dimensions as shown below-
With the introduction of a carbonyl function, substitution in the 4-membered ring as in 2-azetidinone, the π-bonding molecular orbital of the >C=O bond overlaps with p-orbital of the N-atom, creating a Csp²-N bond to permit the correct geometry for overlapping, thus leading to a planar structure. The dipole moment of 2-azetidinone is 4.152.
Molecular Spectra

_Ultraviolet (UV)_

The UV spectrum of 2-azetidinone with N-phenyl substitution exhibited a strong absorption maxima near 250 nm, which undergoes a bathochromic shift if substituents like halogen and methoxy group are presenting the \( p \)-position of the phenyl ring. The chromophore for the absorption must be aryl-N-CO group, in which the possibilities of overlap of the orbitals are aromatic system, the \( p \)-orbital on the sp\(^2\) nitrogen and \( \pi \)-orbitals of the carbonyl group.\(^{12}\)

_Infrared (IR)_

The IR spectra of 2-azetidinone(s) exhibits a very strong band in the region 1760-1723 cm\(^{-1}\), characteristic for >C=O group. The other bands at 2986 and 3002 cm\(^{-1}\) are attributed to C-H group and those at 1182 cm\(^{-1}\) to C-N- group.\(^{11}\)

_Nuclear Magnetic Resonance (\(^1\)H NMR)_

The influence of the stereochemistry on \( \beta \)-lactams was obtained from a study of the NMR spectrum of 1-\( p \)-bromo phenyl-3,3-dimethyl-2-azetidinone, which display a singlet for two methyl groups at \( \delta \) 1.38 ppm and another singlet for two methylene protons at \( \delta \) 3.35 ppm. The equivalence of the methyl substituents at C\(_3\) and also of the two protons at C\(_4\) is consistent with the planarity of the \( \beta \)-lactam ring and the planarity of the 3 valencies of N atom.
The NMR spectra of \( o \)-bromo phenyl-2-azetidinone also display a singlet at \( \delta 3.82 \) ppm for methylene group. This again reveals the planarity of the \( \beta \)-lactam ring. The methylene protons will be equivalent to each other if (a) the \( (o\)-bromo) phenyl ring lies substantially in the plane of the \( \beta \)-lactam ring or (b) the phenyl ring rotates around its axis fast enough to provide a sharp peak as the time averaged signal for the methylene protons.

Thus, the lowering of the temperature to \(-34^\circ C\) failed to resolve this methylene signal or even to broaden it. In the NMR spectrum of \( p \)-bromophenyl-2-azetidinone, the \( C_3 \) and \( C_2 \) protons occur as two triplets centered at \( \delta 3.06 \) ppm and \( \delta 3.52 \) ppm respectively, again revealing the symmetry of the ring system.\(^{12}\)

**Natural \( \beta \)-Lactams**

Discovery of penicillin (1) was followed by the isolation of cephalosporin C \(^{13}\) (2a), which resembles the former in its stereospecific bicyclic disposition of the molecule. Recently, deacetoxy cephalosporin C \(^{2b}\)\(^{14,15}\) 3-alkylthiomethyl cephalosporins\(^{16,17}\) (2c) and (2d) and cephamytins\(^{18-22}\) (6) have been added to the list. Another fused bicyclic \( \beta \)-lactam system with an oxazolidine ring, namely clavulanic acid\(^{23}\) (7a) and its isomer isoclavulanic acid\(^{24}\) (7b) was reported. Monocyclic \( \beta \)-lactams, such as steroidal alkaloids pachystermine A\(^{25}\) (8a) and pachystermine B\(^{25}\) (8b) wild-fire toxin\(^{26}\) (9), nocardicins\(^{27}\) (10) and bleomycins\(^{28-30}\) (11) were discovered. Thus, the occurrence of \( \beta \)-lactams in nature seems to be not unusual and it is likely that many more naturally occurring \( \beta \)-lactams will be isolated in future.
Chapter-6  

Chemistry of Azetidinones

\[ R_1\text{COHN}_2\text{CH}_2\text{R}_3 \]

\[ R_1 = \text{H}, R_2 = \text{H} \]

\[ (2) \]

\[ a, R_3 = \text{ACO-} \]

\[ b, R_3 = \text{H} \]

\[ c, R_3 = \text{MeS} \]

\[ d, R_3 = \text{OCONH}_2 \]

\[ \text{(6)} \]

\[ R_1 = \text{HOOC-} \]

\[ R_2 = \text{H} \]

\[ \text{(7)} \]

\[ a, R_1 = \text{-CH}_2\text{OH} ; R_2 = \text{H} \]

\[ b, R_1 = \text{H} ; R_2 = \text{-CH}_2\text{OH} \]

\[ \text{(8)} \]

\[ \text{(9)} \]

\[ \text{(10)} \]

\[ (11) \]

\[ a, R = \text{-NH-(CH}_2)_3\text{SMe}_2\text{X} \]

\[ b, R = \text{-NH-(CH}_2)_2\text{NH-C-NH}_2 \]
6.2 Methods for the synthesis of azetidinone derivatives

The recent and the advanced increase in both the broad spectrum of β-lactam antibiotics and the number of the known producing organisms are due to the development of new and more sensitive screening techniques. Further progress had been added by continuous synthetic derivatization to monocyclic β-lactam compounds. Many methods have been reported for the synthesis of β-lactam in the literature. Some of these methods are given in the present study.

**Ketene-imine cycloaddition**

The ketene-imine cycloaddition was reported by Staudinger \(^{31}\) to be a smooth well-documented route to the synthesis of substituted β-lactam derivatives. In an effort to investigate a suitably substituted monocyclic β-lactam as a minimum requirement for biological activity, many scientists \(^{32-35}\) reported the trans stereoselective synthesis of butadienyl azetidinones (12) and their Diels-Alder cycloaddition. This included the preparation of a series of Schiff’s bases and their reaction with dienylketene to produce a trans azetidinone (12). This involved the in situ formation of the ketene and its subsequent addition to the imine.
**Wasserman cyclization**

Joyeau *et al.*, studied the stability of 2-azetidinones to enzymatic ring opening by β-lactamases. They suggested that a halogen α to the carbonyl would increase the IR absorption of the C=O, one of the criteria for the reactivity of the β-lactam in this aspect. Fluorine substitution, which will not introduce a large steric hindrance, is particularly interesting for a possible biological effect and possible stability towards β-lactamase. β-Bromopropionamide derivative (13) was prepared, which can be cyclized by Wasserman procedure using sodium hydride to give the N-(3-carboxy-6-methylphenyl) 3-difluoro-2-azetidinone (14).36

![Chemical Structure]

**Synthesis of oxamazine β-lactams**

The *o*-substituted derivatives at the nitrogen are usually more susceptible to nucleophilic attack at the β-lactam carbonyl than the N-alkyl derivatives. The first indication that a heteroatom on the nitrogen could include chemical activation and provides biological activity, was obtained by the significant activity of mono lactams. Subsequently, Woulfe and
Miller\(^3\) described the synthesis of the oxamazines (15\(a\)) and (15\(b\)), a totally synthetic class of heteroatom activated β-lactam antibiotics.

\[
\text{Modification of Staudinger ketene-imine cyclization}
\]

Yoshioka \textit{et al.}, described the facile synthesis of 4-fluoromethyl-1-sulfo-2-azetidinones, starting with the commercially available fluoro ethanol (16).\(^3\) Swern oxidation of (16) with oxalyl chloride and DMSO followed by treatment with dimethoxy benzylamine gave an imine (17) which was cyclized with phthalimido acetyl chloride to give the β-lactam (18).\(^3\) This was followed by oxidative cleavage and sulfonation to give the desired sulfo derivative (19).\(^4\)
**Synthesis of β-lactams from imidates**

Cardellini and his group reported the synthesis of alkoxy β-lactams via acid chloride imine route. Imidates (20) such as substituted N-phenyl formimidate, were reacted with acid chlorides to produce β-lactam (21). The major feature of this synthesis is its high stereoselectivity, only trans 4-alkoxy-β-lactams were formed.\(^{41}\)

\[
\text{RO} \begin{array}{c} \text{N} \end{array} \text{C}_6\text{H}_5 + \text{X-CH}_2\text{C-Cl} \xrightarrow{\text{Et}_3\text{N/CH}_2\text{Cl}_2} \text{OR} \begin{array}{c} \text{O} \end{array} \text{C} \begin{array}{c} \text{O} \end{array} \text{C}_6\text{H}_5
\]

(20)

**Acid chloride addition reaction**

Bose *et al.*, has applied a method to prepare β-lactams which involved the reaction between benzylideneaniline and few selected acid to produce (22) and (23).\(^{42}\)
Synthesis of azido β-lactams

This involves the annelation of imino compounds with azido acetyl chloride to afford (24).

\[
\begin{align*}
N_3\text{CH}_2\text{COOEt} + H_3\text{CS}C_6\text{H}_5 & \xrightarrow{\text{Et}_3\text{N}} N_3\text{SCH}_3C_6\text{H}_5 \equiv \text{Et}_3\text{N} \\
\text{Saccharyl chloride} & \quad (24)
\end{align*}
\]

Since azido acetyl chloride is prone to explosive decomposition, especially during purification by distillation under reduced pressure, saccharyl chloride can be successfully employed for the preparation of 3-azido-2-azetidinones (25) from imines and azido acetic acid as reported by Manhas et al., \textsuperscript{43}

\[
\begin{align*}
N_3\text{CH}_2\text{COOEt} + \text{NO}_2\text{C}_6\text{H}_5\equiv \& \xrightarrow{\text{Et}_3\text{N}} N_3\text{Et}_3\text{N} \equiv \\
\text{(25)}
\end{align*}
\]

Free radical cyclization

Recently, ring closure reactions leading to 4-membered rings, have been considerably studied. Annibale and his group\textsuperscript{44} investigated the intramolecular addition of free radicals to double bonds to give the β-lactam. They generated radicals (26) from enamides by treatment with Mn(OAc)\textsubscript{3}.2H\textsubscript{2}O. The key step in this reaction is the cyclization of (26) to (27). The final product (28) showed \textit{trans} stereochemical relationship to substituents at C\textsubscript{3} and C\textsubscript{4} as demonstrated by \textsuperscript{1}H NMR coupling constants.
Chapter-6  
Chemistry of Azetidinones

**β-Lactam formation using microwave irradiation**

The formation of 2-azetidinones by the reaction of an acid chloride, Schiff’s base and a triethylamine seems to involve multiple pathways, some of which are very fast at higher temperatures. When it is conducted in domestic microwave oven, high level irradiation leads to preferential formation of *trans* β-lactams (29) in several cases when the Schiff’s base is derived from an aryl aldehyde rather than glyceraldehydes acetonide.45

\[
\text{Ph-CH}_2-\text{O}-\text{CH}_2-\text{C}-\text{Cl} + \text{Ph}-\text{CH=NH-CH}_2-\text{Ph} \xrightarrow{\text{Microwave irradiation}} \text{Ph-CH}_2-\text{O} + \text{Ph-CH}_2-\text{O}
\]

(29)

**Synthesis of β-lactams from Passerini reaction**

The reaction of carbonyl compounds with 3-aminopropanoic acids, followed by treatment with a suitable isocyanide afforded β-lactam derivatives. This reaction is called Passerini reaction and it was useful for the preparation of monocyclic and bicyclic β-lactams (31) and (33) respectively. The reaction envisages formation of a cyclic compound (30),
which on trans annular acyl migration gave β-lactam (31). It is noteworthy that the configuration of the newly formed asymmetric center in the penicillin analogue (33) is predetermined by the steric disposition of the reacting molecule.\(^{46}\)

\[
\begin{align*}
R_1\text{CaO} + & H_2N-C-COOH \xrightarrow{-H_2O} R_1\text{N}C-C-COO^* \\
\end{align*}
\]

\[
\begin{align*}
R_1\text{CONHR}_2 & \xrightarrow{RC\equiv N} H_2C-S-NR_3 \xrightarrow{RC\equiv N} H_2C=O-NHR
\end{align*}
\]

**Conversion of ring compounds into β-lactams**

1. **Ring expansion of 3-membered rings.**

The aziridine (34) in the presence of thionylchloride or oxalyloxide rearranges to β-lactam (35) in benzene, possibly via a mixed anhydride which undergoes ring expansion. The conversion is stereospecific and yields are good.\(^{47}\)

\[
\begin{align*}
R_1\text{CONa} + & \xrightarrow{XCl} R_1\text{COX} \xrightarrow{RC\equiv N} H_2C-S-NR_3 \xrightarrow{RC\equiv N} H_2C=O-NHR
\end{align*}
\]

\[X = -\text{ClSO, -ClCOCO}\]
The reaction of azirine and carbene was used in the synthesis of \( \beta \)-lactam. Thus, addition of trichloromethide ions to several azirines, followed by base catalyzed ring closure of the intermediate gave azetines which were converted into the corresponding \( \beta \)-lactam (36). The nature of substituents in the azirine ring influences the course of reaction.

Diaziridines (37) reacted with ketenes to give \( \beta \)-lactam (38) and the reaction follows ketene-imine type interaction.

A new expansion of an \( \alpha \)-lactam to a \( \beta \)-lactam system was reported. Thus, thermal fragmentation of (39) produced isocyanide (42), besides other products, which on cycloaddition to either (40) or its rearranged product (41) gave the corresponding \( \beta \)-lactam (43) which was characterized by degradation and alternative synthesis.
Cycloalkanones (44) are known to undergo ring expansion to lactams by Schmidt reaction or Beckmann rearrangement. It was found that cyclopropanone hemiacetal with sodium azide in acetone at pH 5.5 (KH₂PO₄/NaOH buffer) gave azetidin-2-one (45) in 21% yield.⁵¹

![Chemical reaction](image)

Similarly, the compound (46) on treatment with hydroxylamine, followed by subsequent tosylation afforded β-lactams (47).⁵²

![Chemical reaction](image)

Cyclopropanone with aminoacid esters was converted into β-lactams by similar ring expansion.⁵³ It is noteworthy that diphenylcyclopropenone (48) with ammonia or methylamine at room temperature gave azetidin-2-ones (49).⁵⁴
Ring contraction of 5-membered rings.

Wolf rearrangement \(^{55,56}\) of 3-diazopyrrolidine-2,4-diones (50) in the presence of tert-butylcarbazate, afforded \(\beta\)-lactams (51).

Reagent induced ring contraction has been reported recently. For example, the compound (52) was converted into (53) by oxidation with periodate and this reaction has been extended to several mono and bicyclic \(\beta\)-lactams.\(^{57}\)

Photolytic ring contraction of pyrazolidin-3-one systems was reported recently.\(^{58}\) This method has been extended to the synthesis of a novel system (55), from the compound (54) and other bicyclic and spiro cyclic \(\beta\)-lactams.\(^{59}\) Treatment of pyrazolidinones (56) successively with base and glyme. Mercury (II) oxide and 2,4,6-trimethylbenzenesulphonylhydroxyl amine gave \(\beta\)-lactams (57).\(^{60}\)
**Conversion of azetidine derivatives into azetidin-2-ones**

Perfluoroisobutene with benzylidine aniline under drastic conditions gave, the azetidine (58) which on hydrolysis afforded the corresponding \(\beta\)-lactam (59).\(^{61}\)

In another method, the compound (60) was treated with imines and the resulting azetidinylidene ammonium salt afforded \(\beta\)-lactams (64), on hydrolysis.\(^{62}\)

\[ R = - \text{Ph, } - \text{Cl}_3\text{CCH}_2\text{O} \]
Recently, oxygenation of azetidine dianions (66) afforded β-lactams (69). The reaction of chlorosulfonyl isocyanate (CSI) with alkenes provides β-lactams (70) in quantity, and the products have frequently been used for ring-opening polymerization to generate nylon-3 materials. Prior uses of this approach have focused almost entirely on β-lactams with purely hydrocarbon substituents.

The reaction of chlorosulfonyl isocyanate (CSI) with alkenes provides β-lactams (70) in quantity, and the products have frequently been used for ring-opening polymerization to generate nylon-3 materials. Prior uses of this approach have focused almost entirely on β-lactams with purely hydrocarbon substituents.

Application of Staudinger ketene-imine cycloaddition reaction to bis-o-allyloxyarylideneamines afforded the corresponding bisallyloxyazetidinones as the cis-cis diastereomers (71), exclusively obtained as a mixture of cis-syn-cis and cis-anti-cis. RCM of the latter using Grubbs’ catalysts afforded the corresponding macrocyclic bisazetidinones in good yield.
New oxidative de aromatization procedures leading to spiro β-lactams (72) and oxindoles were developed. By a variation of the oxidative reaction conditions, the usefulness of phenolic amides derived from 4-aminophenol in the synthesis of structurally different types of molecules was demonstrated.66
### 6.3 Biologically active azetidinone derivatives

A brief review of the literature available on the chemical structure and the biological activity of 2-azetidinone and their derivatives are presented below-

Singh et al., have synthesized some new 1,3,3-trisubstituted 4-(2'-hydroxyphenyl)-2-azetidinones (73) and screened for anti-bacterial and anti-fungal activities against the different strains. Some the azetidinone derivatives have shown good anti-microbial activities against the panel of microorganisms. They also synthesized new 1-alkyl/cyclohexyl-3,3-diaryl-10-methylspiro[azetidine-2,3’-indoline]-2’,4-diones from the reactions of 2-diazo-1,2-diarylethanones with 1-methyl-3-(alkyl/cyclohexylimino)indolin-2-ones under thermal conditions. All the synthesized compounds were screened for their anti-bacterial and anti-fungal activities against bacterial strains Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and fungal strains Candida albicans, Saccharomyces cerevisiae. The compound (74) with two 4-methylphenyl groups and an isopropyl group on 2-azetidinone ring carbon and nitrogen, respectively showed better activity against three organisms.
Broccolo, et al., have synthesized a series of 4-Alkyliden-azetidin-2-ones from 4-acetoxy-azetidinones and diazoesters. The *in vitro* anti-bacterial activity of the new agents was evaluated against 43 recent clinical isolates of antibiotic susceptible and resistant Gram-positive and Gram-negative pathogens by determining their minimum inhibitory concentrations (MICs).

The most active compound showed MIC values ranging from 0.25 to 0.32 µg/mL against some of the bacterial species tested. Interestingly, some compounds demonstrated similar activity against methicillin susceptible and resistant strains of *Staphylococcus aureus* suggesting possible alternative mechanisms of action of these agents, supported by cytotoxicity and preliminary scanning electron microscopy studies.$^{69}$

![Structure of compound (75)](attachment:image)

Ashok Kumar et al., have synthesized a series of azetidinone derivatives from the Quinazolinone nucleus. All the compounds have been screened for their anti-inflammatory and analgesic activities at the dose of 50 mg/kg p.o. These compounds have shown better anti-inflammatory (28.55-34.21%) and analgesic (27.35-34.11%) activities. Out of these nine compounds, compound (76) has shown 34.21% anti-inflammatory activity and is associated with almost the same degree of analgesic (34.11%) activity.$^{70}$
Desai et al., have synthesized efficient and rapid synthesis of novel azetidin-2-ones under microwave as well as conventional methods from 2-\{(1H-benzimidazol)-yl-thio\}-N’-2-(substituted phenyl) hydrazide with chloroacetylchloride were carried out in DMF-benzene solvent in the presence of Et$_3$N catalyst. The synthesized compound (77) were tested for their *in vitro* anti-bacterial activity against three strains of bacteria (gram + ve, gram -ve) and anti-fungal activities against three strains of human pathogenic fungi. Five compounds of the obtained series showed high *in vitro* anti-microbial activity.$^{71}$

![Chemistry of Azetidinones](image)

Indrani Banik et al., have stereoselectively synthesized novel β-lactams using polyaromatic imines following the Staudinger reaction. As a measure of cytotoxicity, some of these compounds have been assayed against nine human cancer cell lines. Structure activity study has revealed that 1-N-chrysenyl and 1-N-phenantrhenyl 3-acetoxy-4-aryl-2-azetidinones have potent anti-cancer activity. The presence of the acetoxy group at C$_3$ of the β-lactams(78) has proven to be obligatory for their anti-cancer activity.$^{72}$
Indrani Banik *et al.*, have synthesized a series 3-chloro-4-aryl-1-{5-[[[1,3,4]thiadiazino[6,5-b]indol-3-ylamino]methyl]-1,3,4-thiadiazol-2-yl]azetidin-2-one from indole-2,3-dione with thiosemicarbazide. These compounds were evaluated for their anti-inflammatory, ulcerogenic and analgesic activities. Compound (79) has showed most active anti-inflammatory and analgesic activities with better ulcerogenic activity than phenylbutazone, while this compound was found to be associated with lesser degree of anti-inflammatory and analgesic activities as compared to indomethacin.  

A series of 3-chloro-4-(3-methoxy-4-acetyloxyphenyl)-1-[3-oxo-3-(phenylamino)propanamido] azetidin-2-ones (80) and 3-chloro-4-[2-hydroxy-5-(nitro substituted phenylazo)phenyl]-1-phenylazetidin-2-ones (81) were synthesized using appropriate synthetic route. The anti-microbial activity of the synthesized compounds was screened against several microbes. Several of these molecules showed potent anti-microbial activity.
against *Bacillus anthracis*, *Staphylococcus aureus* and *Candida albicans* and significant structure activity relationship (SAR) trends. The chloro moiety of compound improved their antimicrobial activity significantly.\(^{74}\)

![Chemistry of Azetidinones](image)

Wang *et al.*, have been synthesized fourteen new 2-azetidinone derivatives (82) and their cholesterol absorption inhibition activities were evaluated. Most of them showed comparable effects in lowering the levels of total cholesterol in the serum.\(^{75}\)

![Derivatives](image)

Dong Xiao *et al.*, have synthesized a series of spiro piperidine azetidinone derivatives (83) and evaluated as potential TRPV1 antagonists. An important issue of plasma stability was investigated and resolved. Further focused SAR study lead to the discovery of a potent antagonist with good oral pharmacokinetic profile in rat.\(^{76}\)
Allan Urbach et al., have synthesized a series of novel 2-azetidinones (β-lactams) bearing short alkenyl chains at C$_3$ and N$_1$ and evaluated in vitro as inhibitors of human FAAH. Compound (84) (1-(4’-pentenoyl)-3-(4’-pentenyl)-2-azetidinone)) featured an IC$_{50}$ value of 4.5 µM and a good selectivity for FAAH (fatty acid amide hydrolase) versus MGL (monoacylglycerol lipase).\textsuperscript{77}

\[
\begin{align*}
\text{\(n = 3\)}
\end{align*}
\]

6.4 Present work

In our initial effort, we planned to synthesize Azetidinone derivatives 5(a-j) with the hope that introduction of groups. Though we successfully prepared 5-[N-substituted benzylidenylimino] amino]-2-oxo barbituric acid 4(a-j). Finally we focused our interest on the synthesis of 5-(3-Chloro-2-oxo-4-phenyl-azetidin-1-ylamino)-pyrimidine-2,4,6-trione scaffolds 5(a-j).

The required 5-Bromo-2-oxo barbituric acid (2a) were prepared (Step-1) by Barbituric acid (1a) which was suspended in excess of glacial acetic acid and to this bromine was added drop wise. After complete addition of bromine, the reaction mixture was stirred for 10 hours and poured into ice-cold water then left overnight at room temperature. The precipitate thus obtained was filtered, washed with water, dried and recrystallized from suitable solvents to afford compounds.
A highly efficient and versatile synthetic approach to the 5-Hydrazino-2-oxo barbituric acid (3a) was performed (Step-2) from 5-Bromo-2-oxo barbituric acid (2a) reacts with hydrazine hydrate in methanol, mixture was refluxed for 8 hours. The excess of solvent was distilled off and poured into ice. The solid thus obtained was filtered, washed with water and recrystallized from suitable solvents to give compounds (3a).

Synthesis of 5-[N-substituted benzylidenylimino)amino]-2-oxo barbituric acid 4(a-j) was carried out (Step-3) from methanolic solution of compounds (3a) and different aromatic aldehydes with few drops of acetic acid. Mixture was refluxed for 8 hours and poured into ice cold water, the precipitate thus obtained was filtered, washed with water, dried and recrystallized from suitable solvents to yield compounds 4(a-j).

Owing to the great interest in the argument and in continues synthesis of Azetidinone derivatives 5(a-j) were performed (Step-4) by using Schiff base 4(a-j) reacts with triethyl amine which was dissolved in 1,4-dioxane, cooled and stirred. To this, well-stirred cooled solution of chloro acetyl chloride was added drop wise with in a period of 20 min.

The reaction mixture was then stirred for an additional 3 hrs and left at room temperature for 48 hrs. The resultant mixture was concentrated, cooled, poured in to ice cold water, filter and then dried and recrystallized to give 2-azetidinones 5(a-j). The synthesis of these Azetidinone derivatives is outlined in (Scheme-1).
**6.5 Materials and methods**

Melting points of all the synthesized compounds were determined in open capillaries and are uncorrected. Infrared spectra were recorded using KBr pellets on *Nicolet 5700 FT-IR* instrument. The $^1$H NMR and $^{13}$C NMR spectra were recorded on *Brucker Avance-300* (300 MHz) model spectrophotometer in CDCl$_3$ and DMSO as solvent and TMSi as internal standard with $^1$H resonant frequency of 300 MHz and $^{13}$C resonant frequency of 75MHz. The chemical shifts were measured in $\delta$ ppm downfield from internal standard TMSi at $\delta=0$. The TLC was performed on neutral alumina silica gel 60 F$_{254}$ (Merck). The mobile phase was ethyl
acetate and n-hexane (1:1) and detection was made using UV light and iodine vapors. The resulting compounds were purified by column chromatography. For column chromatography Merck silica gel (0.040-0.063mm) was used. All the compounds gave C, H and N analysis within ± 0.4% of the theoretical values.

### 6.6 Experimental procedure

#### Step 1: Synthesis of 5-Bromo-2-oxo barbituric acid (2a)

Barbituric acid (0.1 mol) was suspended in excess of glacial acetic acid and to this bromine (0.2 mol) was added drop wise. After complete addition of bromine, the reaction mixture was stirred for 10 hours and poured into ice-cold water then left overnight at room temperature. The precipitate thus obtained was filtered, washed with water, dried and recrystallized from suitable solvents to afford compounds (2a).

#### Step 2 : Synthesis of 5-Hydrazino-2-oxo barbituric acid (3a)

The mixture of compounds 2a (0.1 mol) and hydrazine hydrate (0.2 mol) in methanol was refluxed for 8 hours. The excess of solvent was distilled off and poured into ice. The solid thus obtained was filtered, washed with water and recrystallized from suitable solvents to give compounds (3a).
Step-3: Synthesis of 5-[N-substituted benzylidenylimino)amino]-2-oxo barbituric acid 4(a-j)

The equimolar mixture (0.1 mol) of methanolic solution of compounds (3a) and different aromatic aldehydes with few drops of acetic acid was refluxed for 8 hours and poured into ice cold water. The precipitate thus obtained was filtered, washed with water, dried and recrystallized from suitable solvents to yield compounds 4(a-j).

Step 4: Synthesis of Azetidinone derivatives 5(a-j)

A mixture of Schiff base 4(a-j), (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 of chloro acetyl chloride (0.004 mmol) was added drop wise with in a period of 20 min. The reaction mixture was then stirred for an additional 3 hrs and left at room temperature for 48 hrs. The resultant mixture was concentrated, cooled, poured in to ice cold water, filter and then dried and recrystallization gave 2-azetidinones 5(a-j).

6.7 Results and discussion

The present synthetic strategy begins with the generation of required 5-(3-Chloro-2-oxo-4-phenyl-azetidin-1-ylamino)-pyrimidine-2,4,6-trione scaffolds 5(a-j) by using Schiff base 4(a-j) reacts with triethyl amine. Resultant mixture was dissolved in 1, 4-dioxane, cooled and stirred. To this, well-stirred and cooled solution of chloro acetyl chloride was added drop wise with in a period of 20 min. The reaction mixture was then stirred for an
additional 3 hrs and left at room temperature for 48 hrs. The resultant mixture was concentrated, cooled, poured in to ice cold water, filter and then dried and recrystallized to give 2-azetidinones 5(a-j). In the IR Spectrum of 5-(3-Chloro-2-oxo-4-phenyl-azetidin-1-ylamino)-pyrimidine-2,4,6-trione (5a) reveals that, (N-H) stretching was observed at 3422 cm\(^{-1}\) where as (N-H of amide) was observed at 3300 cm\(^{-1}\). Carbonyl stretching of β-lactam was appeared at 1765 cm\(^{-1}\), Carbonyl stretching frequencies of barbituric acid was noticed at 1715, 1720, 1735 cm\(^{-1}\).

Stretching frequency of -C-N was found at 1310 cm\(^{-1}\). However, stretching frequency of -N-N and -C-Cl was observed at 1275 cm\(^{-1}\) and 782 cm\(^{-1}\) respectively. \(^{1}\)H NMR spectrum of compound (5a) implies that, a singlet was observed at δ 4.51 ppm due to -CH-N protons. The -CH-Cl protons were observed downfield as a singlet at δ 5.44 ppm. The aromatic protans of various environments present in all the compounds appeared as signals in the range of δ 113.1–149.4 ppm.

\(^{13}\)C NMR spectra of compound (5a) reveals that, peaks at δ 64.2 ppm was attributed due to >CH-Cl, 163.5 ppm (cyclic, >C=O) and 170.4 ppm (C=O of barnuturic acid) in the β-lactam moiety. The aromatic carbons of various environments present in all the compounds appeared as signals in the range of δ 112.47–167.15 ppm. The X-ray analysis of the compound(s) is under progress. The various new compounds synthesized during the present investigation are listed in (Table-1).
Table-1
Physical and analytical data of the Azetidinone derivatives

![Diagram of azetidinone derivatives]

<table>
<thead>
<tr>
<th>Entry</th>
<th>aProduct</th>
<th>R</th>
<th>X</th>
<th>bYield (%)</th>
<th>c m.p (°C)</th>
<th>d Mol. Formula/Mol. Wt</th>
<th>Elem. Analysis (Cal./Found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>H</td>
<td>O</td>
<td>82.04</td>
<td>140-142</td>
<td>C_{16}H_{15}ClN_{4}O_{4}</td>
<td>49.64/4.46/16.54</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>2-Cl</td>
<td>O</td>
<td>71.00</td>
<td>116-118</td>
<td>C_{16}H_{15}Cl_{2}N_{4}O_{4}</td>
<td>45.06/3.78/15.01</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>4-Cl</td>
<td>O</td>
<td>62.80</td>
<td>120-122</td>
<td>C_{16}H_{15}Cl_{2}N_{4}O_{4}</td>
<td>45.06/3.78/15.01</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>2-NO_{2}</td>
<td>O</td>
<td>74.10</td>
<td>198-201</td>
<td>C_{16}H_{15}ClN_{3}O_{6}</td>
<td>43.82/3.68/18.25</td>
</tr>
<tr>
<td>5</td>
<td>5e</td>
<td>4-NO_{2}</td>
<td>O</td>
<td>65.12</td>
<td>234-236</td>
<td>C_{16}H_{15}ClN_{3}O_{6}</td>
<td>43.82/3.68/18.25</td>
</tr>
<tr>
<td>6</td>
<td>5f</td>
<td>2-OH</td>
<td>O</td>
<td>64.20</td>
<td>132-134</td>
<td>C_{16}H_{15}ClN_{4}O_{5}</td>
<td>47.40/4.26/15.79</td>
</tr>
<tr>
<td>7</td>
<td>5g</td>
<td>4-OH</td>
<td>O</td>
<td>71.80</td>
<td>208-210</td>
<td>C_{16}H_{15}ClN_{4}O_{5}</td>
<td>47.40/4.26/15.79</td>
</tr>
<tr>
<td>8</td>
<td>5h</td>
<td>2-CH_{3}</td>
<td>O</td>
<td>82.4</td>
<td>186-188</td>
<td>C_{16}H_{17}ClN_{4}O_{4}</td>
<td>51.07/4.86/15.88</td>
</tr>
<tr>
<td>9</td>
<td>5i</td>
<td>4-CH_{3}</td>
<td>O</td>
<td>71.12</td>
<td>226-228</td>
<td>C_{16}H_{17}ClN_{4}O_{4}</td>
<td>51.07/4.86/15.88</td>
</tr>
<tr>
<td>10</td>
<td>5j</td>
<td>4-OCH_{3}</td>
<td>O</td>
<td>65.20</td>
<td>116-118</td>
<td>C_{16}H_{17}ClN_{4}O_{5}</td>
<td>48.85/4.65/15.19</td>
</tr>
</tbody>
</table>

^a^ Products were characterized by IR, NMR, MS and elemental analysis.

^b^ Isolated yields.

^c^ Melting points are uncorrected.
**Chapter-6**  

**Chemistry of Azetidinones**

(5a) 5-(3-Chloro-2-oxo-4-phenyl-azetidin-1-ylamino)-pyrimidine-2,4,6-trione

Colorless crystalline solid; m.p. 140 - 142 °C; IR (KBr, ν cm⁻¹): 3422 (N-H), 3310 (N-H of amide), 1756 (-C=O stretching of ß-lactam ), 1620 (C=O of barbituric acid), 1284 (N-N), 758 (-C-Cl).¹H NMR (300MHz, CDCl₃, δ ppm): 4.51 (s, 1H, CH-N), 5.44 (s,1H, CH-Cl), 6.73-7.76 (m, 5H, ArH), 10.2(s, 2H, NH).¹³C NMR (75 MHz, CDCl₃, δ ppm): 64.2(CH-Cl), 163.5 (C=O of ß-lactam ), 170.7 (C=O of barbuturic acid), 112.47, 122.46, 124.26, 127.13, 130.47, 147.62, 167.15. MS: m/z 338. Anal. calcd. for C₁₄H₁₁ClN₄O₄: C, 49.64; H, 4.46; N, 16.54 Found: C, 49.62, H, 4.48,N, 16.56%.

(5b) 5-[3-Chloro-2-(2-chloro-phenyl)-4-oxo-azetidin-1-ylamino]-pyrimidine- 2,4,6-trione

Colorless crystalline solid; m.p. 116-118 °C; IR (KBr, ν cm⁻¹): 3423 (N-H), 3149 (N-H of amide), 1736 (-C=O stretching of ß-lactam ), 1622, (C=O of barbituric acid), 1284 (N-N), 759 (-C-Cl).¹H NMR (300MHz, CDCl₃, δ ppm): 4.52 (s, 1H, CH-N ), 5.42 (s,1H, CH-Cl ), 6.74-7.78(m, 4H, ArH), 10.6(s, 2H, NH).¹³C NMR (75 MHz, CDCl₃, δ ppm): 64.8(CH-Cl), 163.0 (C=O of ß-lactam ), 170.6 (C=O of barbuturic acid), 114.47, 120.46, 124.26, 127.13, 130.47, 147.62, 166.10. MS: m/z 372. Anal. calcd. for C₁₄H₁₁Cl₂N₄O₄: C, 45.06; H, 3.78; N, 15.01 Found: C, 45.04, H, 3.79,N, 15.02%.
(5c) 5-[3-Chloro-2-(4-chloro-phenyl)-4-oxo-azetidin-1-ylamino]-pyrimidine-2,4,6- trione

Colorless crystalline solid; m.p. 120-122 °C; IR (KBr, ν cm⁻¹): 3426 (N-H), 3304 (N-H of amide), 1768 (-C=O stretching of β-lactam), 1622 (C=O of barbituric acid), 1276 (N-N), 784 (-C-Cl).¹H NMR (300MHz, CDCl₃, δ ppm): 4.53 (s, 1H, CH-N), 4.96 (s,1H, CH-Cl), 7.07-8.42 (m, 5H, ArH), 10.3(s, 2H, NH). ¹³C NMR (75 MHz, CDCl₃, δ ppm): 64.6(CH-Cl), 163.8 (C=O of β-lactam), 170.6 (C=O of barbuturic acid), 112.48, 122.42, 124.24, 127.13, 130.46, 147.62, 167.18. MS: m/z 373. Anal. calcd. for C₁₄H₁₁ClN₄O₄: C, 45.06; H, 3.78; N, 15.01 Found: C, 45.08, H, 3.76,N, 15.03%.

(5d) 5-[3-Chloro-2-(2-nitro-phenyl)-4-oxo-azetidin-1-ylamino]-pyrimidine-2,4,6- trione

Colorless crystalline solid; m.p. 198-201°C; IR (KBr, ν cm⁻¹): 3428 (N-H), 3302(N-H of amide), 1766 (-C=O stretching of β-lactam), 1624(C=O of barbituric acid), 1278 (N-N), 788 (-C-Cl).¹H NMR (300MHz, CDCl₃, δ ppm): 4.52 (s, 1H, CH-N), 4.98 (s,1H, CH-Cl), 7.10-8.44 (m, 5H, ArH), 10.4(s, 2H, NH). ¹³C NMR (75 MHz, CDCl₃, δ ppm): 64.8(CH-Cl), 164.8 (C=O of β-lactam), 170.8 (C=O of barbuturic acid), 114.48, 122.42, 124.24, 127.13, 130.46, 147.62, 167.18. MS: m/z 383. Anal. calcd. for C₁₄H₁₄ClN₅O₆: C, 43.82; H, 3.68; N, 18.25 Found: C, 43.84, H, 3.70,N, 18.24%.
**Chapter 6**

**Chemistry of Azetidinones**

(5e) 5-[3-Chloro-2-(4-nitro-phenyl)-4-oxo-azetidin-1-ylamino]-pyrimidine-2,4,6- trione

Colorless crystalline solid; m.p. 234-23 °C; IR (KBr, \( \nu \) cm\(^{-1} \)): 3428 (N-H), 3306 (N-H of amide), 1768 (-C=O stretching of \( \beta \)-lactam ), 1622 (C=O of barbituric acid), 1282 (N-N), 784 (-C-Cl). \(^1\)H NMR (300MHz, CDCl\(_3\), \( \delta \) ppm): 4.52 (s, 1H, CH-N), 5.48 (s, 1H, CH-Cl), 7.07-8.42 (m, 5H, ArH), 10.4 (s, 2H, NH). \(^{13}\)C NMR (75 MHz, CDCl\(_3\), \( \delta \) ppm): 64.2 (CH-Cl), 164.8 (C=O of \( \beta \)-lactam), 170.8 (C=O of barbituric acid), 114.46, 122.40, 124.26, 127.18, 130.46, 147.62, 167.16. MS: \( m/z \) 383. Anal. calcd. for C\(_{14}\)H\(_{14}\)ClN\(_5\)O\(_6\): C, 43.82; H, 3.68; N, 18.25 Found: C, 43.80, H, 3.69,N, 18.26%.

(5f) 5-[3-Chloro-2-(2-hydroxy-phenyl)-4-oxo-azetidin-1-ylamino]-pyrimidine-2,4,6 trione

Colorless crystalline solid; m.p. 132-134 °C; IR (KBr, \( \nu \) cm\(^{-1} \)): 3428 (N-H), 3152 (N-H of amide), 1736 (-C=O stretching of \( \beta \)-lactam ), 1622 (C=O of barbituric acid), 1284 (N-N), 766 (-C-Cl). \(^1\)H NMR (300MHz, CDCl\(_3\), \( \delta \) ppm): 4.53 (s, 1H, CH-N), 4.96 (s, 1H, CH-Cl), 7.07-8.42 (m, 5H, ArH), 10.4 (s, 2H, NH). \(^{13}\)C NMR (75 MHz, CDCl\(_3\), \( \delta \) ppm): 64.10 (CH-Cl), 164.12 (C=O of \( \beta \)-lactam), 170.6 (C=O of barbituric acid), 116.46, 122.42, 126.28, 128.18, 132.46, 152.62, 172.16. MS: \( m/z \) 354. Anal. calcd. for C\(_{14}\)H\(_{15}\)ClN\(_4\)O\(_5\): C, 47.40; H, 4.26; N, 15.79 Found: C, 47.42, H, 4.28,N, 15.76%.
(5g) 5-[3-Chloro-2-(4-hydroxy-phenyl)-4-oxo-azetidin-1-ylamino]-pyrimidine-2,4,6 trione

Colorless crystalline solid; m.p. 208-210°C; IR (KBr, ν cm⁻¹): 3428 (N-H), 3310(N-H of amide), 1734(-C=O stretching of β-lactam), 1624(C=O of barbituric acid), 1278(N-N), 762 (-C-Cl).¹H NMR (300MHz, CDCl₃, δ ppm): 4.54 (s, 1H, CH-N), 4.98 (s,1H, CH-Cl ), 7.07-8.42 (m, 5H, ArH), 10.12 (s, 2H, NH).¹³C NMR (75 MHz, CDCl₃, δ ppm): 64.10(CH-Cl), 166.12 (C=O of β-lactam), 170.8 (C=O of barbuturic acid), 116.48, 122.44, 126.26, 128.14, 132.48, 152.64, 172.18. MS: m/z 354. Anal. calcd. for C₁₄H₁₅ClN₄O₅: C, 47.40; H, 4.26; N, 15.79 Found: C, 47.42, H, 4.28,N, 15.80%.

(5h) 5-[3-Chloro-2-oxo-4-o-tolyl-azetidin-1-ylamino]-pyrimidine-2,4,6-trione

Colorless crystalline solid; m.p. 186-188°C; IR (KBr, ν cm⁻¹): 3440 (N-H), 3322(N-H of amide), 1774(-C=O stretching of β-lactam), 1624(C=O of barbituric acid), 1286 (N-N), 768 (-C-Cl).¹H NMR (300MHz, CDCl₃, δ ppm): 1.76 (s, 3H, -CH₃), 4.58 (s, 1H, CH-N ), 4.96 (s,1H, CH-Cl ), 7.07-8.42 (m, 5H, ArH), 10.12 (s, 2H, NH).¹³C NMR (75 MHz, CDCl₃, δ ppm): 64.10(CH-Cl), 166.12 (C=O of β-lactam), 170.8 (C=O of barbuturic acid), 116.48, 122.44, 126.26, 128.14, 132.48, 152.64, 172.18. MS: m/z 352. Anal. calcd. for C₁₅H₁₅ClN₄O₅: C, 51.07; H, 4.86; N, 15.88 Found: C, 51.09, H, 4.84,N, 15.86%.
(5i) 5-[3-Chloro-2-oxo-4-p-tolyl-azetidin-1-ylamino]-pyrimidine-2,4,6-trione

Colorless crystalline solid; m.p. 226-228 °C; IR (KBr, \( \nu \) cm\(^{-1} \)): 3432 (N-H), 3308 (N-H of amide), 1754 (C=O stretching of \( \beta \)-lactam), 1622 (C=O of barbituric acid), 1276 (N-N), 762 (-C-Cl). \(^1\)H NMR (300MHz, CDCl\(_3\), \( \delta \) ppm): 2.3 (s, 3H, -CH\(_3\)), 4.52 (s, 1H, CH-N), 4.96 (s, 1H, CH-Cl), 7.07-8.42 (m, 5H, ArH), 10.12 (s, 2H, NH). \(^13\)C NMR (75 MHz, CDCl\(_3\), \( \delta \) ppm): 64.10 (CH-Cl), 166.12 (C=O of \( \beta \)-lactam), 170.8 (C=O of barbituric acid), 116.48, 122.44, 126.26, 128.14, 132.48, 152.64, 172.18. MS: \( m/z \) 352. Anal. calcd. for C\(_{15}\)H\(_{17}\)ClN\(_4\)O\(_4\): C, 51.07; H, 4.86; N, 15.88 Found: C, 51.09, H, 4.84,N, 15.86%.

(5j) [3-Chloro-2-(4-methoxy-phenyl)-4-oxo-azetidin-1-ylamino]-pyrimidine-2,4,6-trione

Colorless crystalline solid; m.p. 116-118 °C; IR (KBr, \( \nu \) cm\(^{-1} \)): 3422 (N-H), 3144(N-H of amide), 1736 (C=O stretching of \( \beta \)-lactam) 1624 (C=O of barbituric acid), 1278 (N-N), 754 (-C-Cl). \(^1\)H NMR (300MHz, CDCl\(_3\), \( \delta \) ppm): 1.78 (s, 3H, -CH\(_3\)), 4.62 (s, 1H, CH-N), 4.96 (s, 1H, CH-Cl), 7.07-8.42 (m, 5H, ArH), 10.14 (s, 2H, NH). \(^13\)C NMR (75 MHz, CDCl\(_3\), \( \delta \) ppm): 64.16 (CH-Cl), 166.18 (C=O of \( \beta \)-lactam), 172.8 (C=O of barbituric acid), 116.52, 122.46, 126.28, 128.16, 132.50, 152.62, 172.22. MS: \( m/z \) 368. Anal. calcd. for C\(_{15}\)H\(_{17}\)ClN\(_4\)O\(_5\): C, 48.85; H, 4.65; N, 15.15 Found: C, 48.84, H, 4.66,N, 15.15%.

The IR, \(^1\)H NMR, \(^13\)C NMR and Mass spectra of some compounds are enclosed as Spectrum No. 1-8.
Spectrum 1: IR Spectrum of compound (5b) (Code-AZTD)

Spectrum 2: $^1$H NMR (300MHz) Spectrum of compound (5b) in DMSO
Chapter 6

Chemistry of Azetidinones

Spectrum 3: $^{13}$C NMR (75MHz) Spectrum of compound (5b)

Spectrum 5: IR Spectrum of compound (5c)
Karnatak University
University Science Instruments Centre
DHARWAD

Sample Information

Analysis by: 

Sample: 

Sample ID: 

Sample Amount: 

Comments: 

Vat: 

Sample Information:

Data File: 

Cry Data File: 

Cry Method File: 

Report File: 

Tuning File: 

Modified by: 

Modified: 

Spectrum 4: Mass Spectra of compound (5b)
Spectrum 6: $^1$H NMR (300MHz) Spectrum of compound (5c)

Spectrum 7: $^{13}$C NMR (75MHz) Spectrum of compound (5c)
Spectrum 8: Mass Spectra of compound (5c)
6.8 References


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