CHAPTER 1

2-Dimethylaminomethylene-3-Oxobutanenitrile: A Convenient Precursor to The Unnatural Cytosine Derivatives And Study Of Antimicrobial Activity

1.1 INTRODUCTION

The development of an efficient methods for the synthesis of biologically active heterocyclic compounds are prime important in synthetic organic chemistry [1,2]. Structures containing such a moiety often play an important role due to their biological activities, particularly in cancer and virus research [3-6]. Among these heterocycles, pyrimidine derivatives are important class of heterocycles in pharmaceutical discovery [7, 8], Which showed analgesics [9], antihypertensive [10], antipyretics [11] and anti-inflammatory drugs [12]. Pyrimidines occur in pesticides [13], herbicides and plant growth regulators [14]. Fluorophoric pyrimidines are exceedingly important in nucleic acid chemistry [15]. Consequently, synthetic methodologies for synthesis of novel pyrimidines or pyrimidine-fused heterocycles are of special interests in the field of medicine and agriculture [16, 17]. Pyrimidines, in particular cytosine derivatives are of special interest because of their potential use as therapeutic agents. Cytosines exhibit promising antiviral [18], antitumour [19] and anti-AIDS [20] activities. The 1-alkylcytosines have proved to be useful model compounds in the studies of physicochemical properties and chemical reactions of the corresponding cytosine nucleosides [21-25]. Substituted cytosines have attracted considerable interest due to their various biological effects, specially, antiviral and anticancer properties of some nucleosides [26-29]. For
example 2', 3'-dideoxycytidine (DDC) was approved as a drug for treatment of AIDS [30]. Some other cytosine nucleosides were prepared and tested as potential anti-HIV agents [31-35]. Biological properties of alkylated cytosines are also interesting, and some of them are for instance *in vitro* inhibitors of Ra-nikhet disease virus (RDV) [36] or possess peptidyl transferase activity [37]. From literature it was also noted that, compounds containing an alkyl or sugar moiety on the pyrimidine nitrogen display anticancer activity [38].

**Literature update for cytosine synthesis:**

In literature numbers of methods have been reported for the synthesis of cytosine derivatives [39, 40]. Perhaps the most common methods for the preparation of these compounds involves the reactions of 3,3'-diethoxypropen- nitriles with urea, in presence of tBuONa in butanol under reflux condition [41-43]. 4-Amino-5-phenyl-2(1H)-pyrimidine was prepared by the reaction of 3-methoxy-2-phenylacrylonitriles with urea in ethanolic sodium ethoxide [44]. These two methods for the synthesis of cytosine derivatives involved the use of 3,3'-diethoxypropenitriles and 3-methoxy-2-phenylacrylonitriles. The preparation of these intermediates however is a multi-step process that requires special chemicals which are expensive and hazardous.

1. *C.W. Whitehead* and co-workers [45, 46] reported a simple and ingenious method for the synthesis of cytosine derivatives. The synthesis is popularly known as Whitehead synthesis of cytosine and leads to cytosine bearing 3-alkyl or aryl and 5-cyano / carboxy / ethoxy / carbonyl / nitro groups. The reactions of substituted nitriles and triethyl orthoformate gave the ethoxyacrylonitriles 1, which on reaction with substituted ureas 2 afforded corresponding β-ureidopropenenitrile derivatives 3. The ureidopropenenitriles
3 were cyclised in ethanolic sodium ethoxide to afford corresponding substituted cytosines 4 in 50-90 % yields.

\[
\begin{align*}
\text{R} = \text{CN, COOH, COOEt, CONH}_2, \text{CONHalkyl, CONdialkyl,} \\
\text{R}^1 = \text{alkyl, aryl group} \\
\text{X} = \text{O, S}
\end{align*}
\]

2. B.R. Baker and co-workers described the reactions of 3-methoxy-2-phenylacrylonitriles 5 with thiourea in ethanol and sodium ethoxide [47] or 3-anilino-2-phenyl acrylonitrile 6 with thiourea in ethanol/sodium ethoxide [48] to form 5-phenylthiocytosine 7 in good yield.

Similarly, 3-ethoxy-2-phenyl crotononitriles 8 or 3-anilino-2-phenyl crotononitriles 9 reacted with thiourea to give 4-amino-6-methyl-5-phenyl-2(1H) pyrimidinethione 10 in 75 % yield [48].
3. *S.G. Cottis et al.* reported the synthesis of 12 from α-ethoxymethylenemalononitriles 11 and thiourea in cold ethanolic ethoxide or in aqueous acetonic alkali in 12% yield [49].

It was also observed that, thiourea reacts with 2-cyano-2-ethoxycrotononitriles 13 in hot ethanolic ethoxide solution to give 4-amino-6-methyl-2-thioxo-1,2-dihydro-5-pyrimidine carbonitrile 14 in 80% yield [50].

The analogous use of substituted thiourea for the synthesis of thiocytosine was also noted in literature. Thus, 2-cyano-2-ethoxy crotononitrile 13 reacted with N-butyl thiourea in cold
methanolic methoxide furnished 4-amino-3-butyl-6-methyl-2-thioxo-2,3-dihydro-5-pyrimidinonecarbonitrile 15 in 54% yield [51].

\[
\begin{align*}
\text{H}_3\text{C} & \text{OC}_2\text{H}_5 \\
\text{NC} & \text{CN} \\
+ & \\
\text{H}_2\text{N} & \text{NHBu}
\end{align*}
\xrightarrow{\text{MeOH/NaOMe}}
\begin{align*}
\text{H}_3\text{C} & \\
\text{NC} & \text{Bu} \\
\text{S} & \\
\text{N} & \text{NH}_2
\end{align*}
\]

4. *M. Polonovsk* and co-workers [52], described the condensation of urea with \(\text{H}_3\text{C} (\text{OR})=\text{CHCN}\) 16 in the presence of 30% sodium methoxide in methanol furnished cytosine derivatives 17.

\[
\begin{align*}
\text{H}_3\text{C} & \text{OR} \\
\text{H}_2\text{CN} & \text{CN} \\
+ & \\
\text{H}_2\text{N} & \text{NH}_2
\end{align*}
\xrightarrow{\text{MeOH/NaOMe}}
\begin{align*}
\text{H}_3\text{C} & \\
\text{N} & \text{O} \\
\text{H} & \\
\text{NH}_2
\end{align*}
\]

\(R = \text{CH}_3\)

5. *H. Junek* and *M. Jachak et al.* [53] demonstrated the synthesis of 5-formylcytosine derivatives, in their method the condensation of freshly prepared cyanoacetaldehyde 18 with DMF-acetal was required to obtain 3-dimethylamino-2-formyl propenenitrile 19. Thus, compound 19 on reaction with urea and N-substituted ureas under acidic conditions to yield ureidopropenenitrile 20, which was cyclized by using triethylamine in acetonitrile gave corresponding 5-formyl cytosine derivatives 21 in 60-70% yields.
6. K. Golanikiewcz et al. [54] reported the synthesis of 1-substituted cytosine derivatives using uracil derivatives 22a-c. Thus, the reaction of 1-substituted uracils 22 with NaN₃ and POCl₃ in acetonitrile gave 6-substituted tetrazolo [1,5-c]pyrimidin-5-(6H)-one 23 in good yields. The tetrazolo pyrimidine 23 was then hydrogenated over 10 % Pd/C in methanol afforded 1-substituted cytosines 24a-c, in high yields. This is a novel synthetic route for the synthesis of cytosine nucleosides.
Previously, in our laboratory the syntheses of 5-benzoyl cytosines were reported in two steps [55,56]. In the first step the urediopropenitirile 29 were prepared by one pot condensation of aroylacetonitriles 25, triethylorthoformate 26 and substituted urea 27 in toluene at 100 °C for about 1 hr. The compound 29 was also prepared through an intermediate compound 28 which was obtained by stirring the mixture of aroylacetonitrile and DMF-acetal at room temperature. The compound 28 was further refluxed with substituted urea 27 in presence of catalytic amount of hydrochloric acid in ethanol to obtain the required urediopropenitrile 29. In both the reactions the yield was only up to 60 %. Further, this urediopropenitirile 29 was cyclized to corresponding cytosine derivatives 30 by refluxing compound 29 in CH$_3$ONa/CH$_3$OH or in (C$_2$H$_5$)$_3$N/acetonitrile for 2 hours.
These results encourage us to develop a new synthetic route towards cytosine derivatives with acetyl and nitrile substituents at 5-positions in pyrimidine nucleus.

These applications increase the demand for the synthetic derivatives of pyrimidine and stimulate organic chemists to explore the important biologically active nucleus as well as manipulation of its substituents. Further efforts to introduce efficient and practical methods towards rapid and quantitative N-alkylation of the pyrimidine base under mild conditions are being the most needed destination in this area.
1.2 PRESENT WORK

The methodology that we have planned towards cytosine synthesis and its alkylation is depicted in scheme-1. The alkylation of 5-acetyl cytosine 36 could be done with 2-bromo-N-phenyacetamides 39 in DMF using K₂CO₃ as base to obtain derivatives 40. The 5-acetyl cytosine 36 can be obtained by cyclisation of ureidopropenenitrile 35 in alkaline medium. However, the cyclisation under acidic condition would lead to 5-cyanopyrimidine derivatives 38. The ureidopropenenitiles 35 in turn could be obtained by the replacement of dimethylamino group of 2-dimethylaminomethylene-3-oxobutanenitrile 33 by ureas 34 under acidic condition.

Scheme-1
The Knoevenagel condensation of acetoacetonitrile 32 (which could be accessed from β-aminocrotononitrile 31 by acidic hydrolysis of the imino functionality) with dimethyl formamide dimethyl acetal would lead to 2-dimethylaminomethylene-3-oxobutanenitrile 33.

1.3 RESULTS AND DISCUSSION

Knoevenagel Condensation of 3-Oxobutanenitrile 32 with DMF-acetal: Synthesis of 2-dimethylaminomethylene-3-oxobutanenitrile 33

The literature method [58] involves the displacement of alkoxy group by dimethylamine from the 2-ethoxymethylene-3-oxobutanenitrile [EMME] furnished crystalline solid with the Trans (E) geometry. Our method involves the Knoevenagel Condensation of 3-oxobutanenitrile 32 obtained by acid hydrolysis of β-aminocrotononitrile [57] with dimethylformamide dimethyl acetal (DMF-DMA) at reflux temperature (120 minutes) furnished the brown coloured compound which was purified by column chromatography eluting with dichloromethane. After removal of the solvent and recrystallisation from isopropyl alcohol a light yellow solid in 84% yield was obtained. The yellow solid was characterized by spectral and analytical methods.

![Scheme-2](image-url)
The IR spectrum of this solid showed peak at 2241, 1667 cm$^{-1}$ for CN and C=O respectively. In the $^1$H NMR spectrum two signals at 3.20, 3.40 $\delta$ which were assigned to N-CH$_3$ of the dimethylamino group and the olefinic proton appeared at 7.78 $\delta$ ppm. The singlet at 2.42 $\delta$ ppm was assigned to the CH$_3$ moiety of the acetyl group (Spectrum No.1). The mass spectral analysis showed the molecular ion peak at [M]$^+$ 138 and the elemental analysis was in agreement with the molecular formula C$_7$H$_{10}$N$_2$O. Based on the spectral and analytical data structure 33 was assigned to this compound i.e. 2-dimethylaminomethylene-2-oxobutanenitrile, which exactly matched with the reported data in the literature.

![Structure 33](image)

**Spectrum No. 1: $^1$H NMR Spectrum of 2-dimethylaminomethylene-3-oxobutanenitrile, 33 in DMSO-d$_6$**
The confirmed compound 33 which is a versatile synthon having three electrophilic centers, could be utilized for the introduction of bidentate nucleophiles to construct various heterocyclic compounds such as cytosine derivatives, 5-cyano pyrimidines and pyrazole derivatives. Targeting toward the cytosine derivatives, the compound 33 was first converted to ureidopropenenitrile.

**Synthesis of β- ureidopropenenitrile:**

$\text{SN}^2$ displacement of protonated dimethylamino group in compound 33 can be performed by bidentate nucleophiles such as urea/substituted urea in ethanol under acidic condition. Thus condensation of acrylonitrile 32 with phenylethyl urea 34a yielded colourless needles after purification and crystallisation from chloroform-methanol in 67 % yield.

![Scheme-3](image)

<table>
<thead>
<tr>
<th>34,35</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>$\text{CH}_2\text{CH}_2\text{Ph}$</td>
</tr>
<tr>
<td>b</td>
<td>$\text{CH}_2\text{Ph}$</td>
</tr>
<tr>
<td>c</td>
<td>$\text{Ph}$</td>
</tr>
<tr>
<td>d</td>
<td>$\text{CH}_2\text{CH}_3$</td>
</tr>
<tr>
<td>e</td>
<td>$\text{CH}_3$</td>
</tr>
<tr>
<td>f</td>
<td>H</td>
</tr>
</tbody>
</table>
The IR spectrum of this colourless needles showed two bands at 3312 and 3278 cm\(^{-1}\), which were assigned to NH stretching frequency and the peak at 2219 cm\(^{-1}\) corresponded to CN group. In the \(^1\)H and \(^{13}\)C NMR spectrum, it was interesting to note that the protons attached to nitrogen and olefinic carbon in \(35a\) showed doubling of signals in \(^1\)H NMR. This was attributed to the restricted rotation around C=N as shown below, which is known for amide compounds in the literature [58].

The elemental analysis of these colourless needles was in agreement with the corresponding molecular formula C\(_{14}\)H\(_{15}\)N\(_3\)O\(_2\). The mass spectral analysis showed the molecular ion peak at \([M]^+\) 257. Based on the spectral and analytical data the structure \(35a\) was assigned to this compound i.e. 2-acetyl-3-phenylethyl ureidopropenenitrile. Having achieved the synthesis of ureidopropenenitrile \(35a\) the reaction sequence was elaborated using substituted ureas \(34b-f\) to get ureidopropenenitrile \(35b-f\). Accounts of these results are given in experimental section (Expt. No. 2, page No. 37). The \(^1\)H NMR (Spectrum No.2 of \(35a\)) and \(^{13}\)C NMR (Spectrum No.3 of \(35a\)) are shown below.
Spectrum No. 2: $^1$H NMR Spectrum of 2-Acetyl-3-phenylethyl ureidopropenitrile, 35a in DMSO-$d_6$

Spectrum No. 3: $^{13}$C NMR Spectrum of 2-Acetyl-3-phenylethyl ureidopropenitrile, 35a in DMSO-$d_6$
Synthesis of cytosine derivatives: 36a-f and 37a-b

1. Cyclization of ureidopropenenitrile using triethylamine in acetonitrile

Cyclisation of 35 involves the abstraction of replaceable proton from the secondary amide nitrogen followed by proton transfer from N-1 position to the amino group formed at C4 position. The abstraction of proton depends on its acidity as well as strength of base utilized during cyclisation. The substituent on the amide nitrogen decides the acidity of the proton hence it becomes important to select the base of suitable strength. In earlier report on the synthesis of 5-formyl [53] and 5-aroyl cytosine derivatives [55-56], ureidopropenenitrile were cyclised using triethylamine as a base by refluxing in acetonitrile. We thought of employing these reaction conditions to ureidopropenenitrile 35 obtained earlier. We started first with 35a and 35b because the substituent at amide nitrogen contains the aromatic ring which possess the electron withdrawing nature that would facilitate the proton abstraction in contrast to alkyl substituent with electron donating nature in case of 35d-e. The comparatively weaker base like triethylamine may produce the expected results.

![Scheme 4](image_url)
Thus, cyclization of 35a using triethylamine in acetonitrile at reflux temperature for 30 hrs furnished the crystalline compound on cooling to room temperature in low (43%) yields (Scheme 4). The obtained crystalline compound was characterized by spectral and analytical methods. For instance the IR spectrum of the compound showed band for the presence of NH stretching frequency at 3403, 3144 cm⁻¹ and the disappearance of sharp band at 2219 cm⁻¹ indicating the absence of nitrile functionality. In addition carbonyl stretching frequency for one ketone carbonyl and one amide carbonyl was observed at 1725, 1669 cm⁻¹. The ¹H NMR(Spectrum No-5) show multiplet in the downfield region in between 7.26-7.29 δ ppm corresponded to aromatic protons of the phenyl ring. The presence of two broad singlets at 10.05δ and 8.57δ ppm for NH protons clearly indicate that the compound exist in tautomeric form. The C₆-H proton appeared downfield as singlet at 8.72δ ppm. Two triplet for the methylene protons with J = 6.0 Hz at 4.1δ and 2.8δ ppm indicates the vicinal coupling of the two protons. The singlet in the upfield region at 2.40δ ppm was assigned to CH₃ group of the acetyl moiety present at C₅-position. The structure was also supported by ¹³C NMR (Spectrum No-6) which showed signal at 195.20 δ corresponds to acetylcarbonyl and signal at 157.70 δ ppm was attributed to amide carbonyl. The three signals in the upfield region at 45.0δ, 36.2δ and 26.1δ ppm were corresponded to two methylene carbons and one methyl carbon from the acetyl group. The six carbons of the aromatic ring and three carbons from C₄, C₅ and C₆-position were clearly appeared in between 154.2δ – 119.2δ ppm. The mass spectral analysis showed molecular ion peak at [M]⁺257. The elemental analysis was in well agreement with molecular formula C₁₄H₁₅N₃O₂. Based on the spectral and the analytical data, structure 36a was assigned to the product i.e. 4-amino-3-phenylethyl-5-acetyl-2[H]-pyrimidone.
Spectrum No. 4: $^1$H NMR Spectrum of 4-amino-5-Acetyl-3-phenylethyl-(1H)-pyrimidone, 36a in DMSO-d$_6$
Analogously compound 35b-f were subjected to cyclisation under similar reaction conditions. Thus, compound 35b suspended in acetonitrile containing triethylamine and refluxed for 30 hrs. A crystalline solid was obtained on cooling to room temperature in 47 % yield. The crystalline solid was characterised as 36b by spectral and analytical methods, accounts of which are given in the experimental section (Experiment No. 3, page No. 40). However, compounds 35c-f could not cyclise under these conditions. Though the products 36a and 36b directly crystallized from the reaction mixture and separated simply by filtration, the low yield and failure to cyclise the other ureidopropenenitriles created the need to employ the base having better strength than triethyl amine in order to cyclise the
ureidopropenenitriles 35c-f and 35a-b which were in our hand with better efficiency. Hence we planned the next attempt to carry out the cyclisations using potassium tert-butoxide in ethanol.

2. Cyclization of ureidopropenenitriles using potassium tert-butoxide/ ethanol

In this protocol we subjected the ureidopropenenitriles 35c for cyclisation using potassium tert-butoxide in ethanol at reflux condition. Thus, compound 35c was dissolved in ethanol and treated with potassium tert-butoxide at reflux temperature for 6 hrs. The wine red coloured solution was cooled to room temperature and the solvent was removed under reduced pressure to obtain the residue as the potassium salt (highly soluble in water). Upon acidification by adjusting the pH of the residue to 6.5 to 7 with aqueous acetic acid the yellow precipitate was obtained. The obtained compound was purified by crystallization from ethanol in 85% yield (Scheme 5) as pale yellow needles.

\[
\text{NH}_3
\]
\[
\text{H}_2\text{C}
\]
\[
\text{CN}
\]
\[
\text{O}
\]
\[
\text{R}
\]
\[
\text{H}_2\text{C}
\]
\[
\text{CH}_2\text{CH}_2\text{Ph}
\]
\[
\text{CH}_3\text{Ph}
\]
\[
\text{Ph}
\]
\[
\text{CH}_2\text{CH}_3
\]
\[
\text{CH}_3
\]
\[
\text{H}
\]

Scheme 5

<table>
<thead>
<tr>
<th>35,36</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH₂CH₂Ph</td>
</tr>
<tr>
<td>b</td>
<td>CH₃Ph</td>
</tr>
<tr>
<td>c</td>
<td>Ph</td>
</tr>
<tr>
<td>d</td>
<td>CH₂CH₃</td>
</tr>
<tr>
<td>e</td>
<td>CH₃</td>
</tr>
<tr>
<td>f</td>
<td>H</td>
</tr>
</tbody>
</table>

19
The IR spectrum of pale yellow needles showed band for the presence of NH stretching frequency at 3527, 3469 cm⁻¹ and the disappearance of sharp band at 2218 cm⁻¹ indicating the absence of nitrile functionality. In addition carbonyl stretching frequency for one ketone carbonyl and one amide carbonyl was observed at 1711, 1667 cm⁻¹. The ¹H NMR showed multiplet in the downfield region in between 7.42-7.32 δ ppm corresponded to aromatic protons of the phenyl ring. The presence of two broad singlets at 8.42δ and 9.8δ ppm for NH protons clearly indicate that the compound exist in tautomeric form. The C₆-H proton appeared downfield as singlet at 7.82δ ppm. The singlet in the upfield region at 2.40δ ppm was assigned to CH₃ group of the acetyl moiety present at C₅-position. The structure was also supported by ¹³C NMR which showed signal at 198.4 δ corresponds to acetylcarbonyl and signal at 165.2 δ ppm was attributed to amide carbonyl. The one singnals in the upfield region at 26.1δ ppm was corresponded to methyl carbon from the acetyl group. The six carbons of the aromatic ring and three carbons from C₄, C₅ and C₆-position were clearly appeared in between 150.1δ – 119.4δ ppm. The mass spectral analysis showed molecular ion peak at [M]⁺229. The elemental analysis was in well agreement with molecular formula C₁₂H₁₁N₃O₂. Based on the spectral and the analytical data, structure 36c was assigned to the product i.e. 4-amino-3-phenyl-5-acetyl-2[H]-pyrimidone. After confirmation of compound 36c, cyclisation of compounds 36d-f was performed analogously in 75-85% yields (Scheme 5). The compounds isolated after cyclisation of 35a-b from this method were exactly similar to 36a-b obtained earlier from triethylamine cyclisation. The spectral and analytical data of the compounds 36d-f and 36a-b are given in the experimental section (Experiment No. 4, Page No. 41). The formation of 5- acetylcytosine derivatives could be explained by following mechanism.
The cyclisation using potassium tert-butoxide produced cytosine derivatives 36a-f in 75-88% yield. The compounds were isolated by adjusting the pH to 6.5-7 using aqueous acetic acid. However, there were losses of 13-25% product when such a strong base was employed. The another factor was the pH which could insufficiently precipitate the cyclised compound. Hence we thought of employing the base like sodium methoxide for cyclisation and acidifying the compound to more acidic side to mitigate such difficulties.

3. Cyclization of ureidopropenenitrile using sodium methoxide/ methanol:

We again subjected the ureidopropenenitriles 35a for cyclisation using another stronger base i.e. sodium methoxide in methanol. Thus compound 35a dissolved in a solution of sodium methoxide in methanol at room temperature. After a short while the solid was separated with elevation of temperature of the reaction mass by 10°C indicated the formation of sodium salt at nitrogen of 35a. At reflux temperature the solid slowly went to the solution having orange red colour. The reaction time was comparatively more (8 hrs instead of 6 hrs) than that of
potassium tert-butoxide method. Workup procedure involved distillation and acidification to the higher pH (~2-3) of the obtained residue. The obtained solid was purified by crystallization from ethanol to furnish pale yellow needles in 77.4% yield (Scheme 6).

![Chemical structure](image)

<table>
<thead>
<tr>
<th>35,37</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH₂Ph</td>
</tr>
<tr>
<td>b</td>
<td>CH₃CH₂Ph</td>
</tr>
</tbody>
</table>

**Scheme 6**

The obtained crystalline needles were characterized by spectral and analytical methods. The IR spectrum showed band for the presence of OH stretching frequency at 3403 cm⁻¹, and NH stretching frequency at 3144 cm⁻¹ and the disappearance of sharp band at 2219 cm⁻¹ indicating the absence of nitrile functionality. In addition carbonyl stretching frequency for one ketone carbonyl was observed at 1735 cm⁻¹ however the carbonyl frequency for amides was absent. The ¹H NMR showed multiplet in the downfield region in between 7.20-7.34  δ ppm corresponded to aromatic protons of the phenyl ring. The presence of two broad singlets at 11.60δ for phenolic OH proton and 10.42δ ppm for NH protons clearly indicate that the compound exist in another tautomeric form. The C₆-H proton appeared downfield as singlet at 8.82δ ppm. Two triplet for the methylene protons with J = 6.0 Hz at 4.20δ and
2.80δ ppm indicates the vicinal coupling of the two protons. The singlet in the upfield region at 2.49δ ppm was assigned to CH₃ group of the acetyl moiety present at C₅-position. The structure was also supported by ¹³C NMR which showed signal at 198.2δ corresponds to acetyl carbonyl and signal for amide carbonyl was absent. The three singnals in the upfield region at 40.1δ, 31.2δ and 27.1δ ppm were corresponded to two methylene carbons and one methyl carbon from the acetyl group. The six carbons of the aromatic ring and three carbons from C₄, C₅ and C₆-position were clearly appeared in between 153.2δ – 126.8δ ppm. The mass spectral analysis showed molecular ion peak at [M]+257. The elemental analysis was in well agreement with molecular formula C₁₄H₁₅N₃O₂. Based on the spectral and the analytical data, structure 37a was assigned to the product i.e. 4-Imino-3-phenylethyl-5-acetyl-2-hydroxy-pyrimidine. Analogously treatment to the 35b produced similar tautomer 37b in 78.4% yield with the hydroxyl group at C₂-position. The hydroxy group in 37 was detected by blue coloration produced by FeCl₃ color test for phenol. The accounts of spectral and analytical data of compound 37b are given in the experimental section (Experiment No. 5, Page No. 43).

Experiencing the above shortcomings i.e. low yield in case of triethylamine method and formation of hydroxyimino tautomer 37 in case of sodium methoxide method, the attempt to cyclise ureidopropenenitriles 35 in potassium tert-butoxide was found to be superior to triethylamine and sodium methoxide method. Careful neutralization of residue obtained after cyclisation reaction to eliminate the possibility of tautomeric compounds 37 contamination and utilization of base having suitable strength are the important contributing factors towards the efficiency of the produced compounds 36a-f.
Synthesis of 5-cyano pyrimidine derivative, 38a-b.

In the previous section the ureidopropenenitrile 35, were cyclised to cytosines 36 in basic condition. The cyclisation took place between amide nitrogen and cyano group producing 4-amino pyrimidine derivatives. The first possible reason of not cyclising on the acetyl group may be the formation of anion on the amide nitrogen as well as the formation of enolate of the acetyl group under basic condition. Secondly the E / Z geometry of the ureidopropenenitriles 35 which should favor the cyclisation either at cyano group or at acetyl carbonyl. In order to solve this crisis we planned the cyclisation reactions in acidic media which will protonate the carbonyl oxygen to facilitate the nitrogen-carbon bond formation. Thus, compound 35a was dissolved in acetic acid and refluxed for 30 hrs. Only small amount of new product was formed as revealed by thin layer chromatography. The newly formed product was separated from the starting compound 35 by column chromatography eluting with dichloromethane. The desired fractions were collected and evaporated to furnish yellow compound which was crystallized as yellow needles from ethanol in 30.5% yield (Scheme 7). These crystalline needles were characterized by spectral and analytical methods.

![Scheme-7](https://example.com/scheme7.png)

<table>
<thead>
<tr>
<th>35,38</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH₂CH₂Ph</td>
</tr>
<tr>
<td>b</td>
<td>CH₂Ph</td>
</tr>
</tbody>
</table>

Scheme-7
The IR spectrum showed strong absorption band at 2240 cm\(^{-1}\) for CN and 1670 cm\(^{-1}\) for amide carbonyl. The carbonyl frequency corresponding to acetyl carbonyl similar to compounds 36 was clearly absent. In the \(^1\)H NMR of these crystalline needles in DMSO-d\(_6\) we observed a singlets at 1.7 \(\delta\) ppm for three protons corresponded to methyl group of C\(_4\)-CH\(_3\) protons. The multiplet between 7.1 \(\delta\) and 7.6 \(\delta\) ppm represented five aromatic protons. The C\(_6\)-H proton showed sharp singlet at 8.6 \(\delta\) ppm. Two triplets in the upfield region for two methylene protons at 4.15\(\delta\) and 2.82\(\delta\) ppm with \(J = 6.0\) Hz were clearly present. \(^{13}\)C NMR analysis showed presence of three signals at 50.05, 33.76 and 20.16 \(\delta\) ppm which were assigned to one methyl group attached to aromatic nucleus and remaining two corresponded to methylene carbons. The signal corresponding to ketone carbonyl was clearly absent and signal at 117.8\(\delta\) ppm corresponded to the nitrile group was appeared in the downfield region whereas the amide carbonyl signal appeared at 154.2\(\delta\) ppm. The six aromatic carbons and three carbons of the C\(_4\), C\(_5\) and C\(_6\) position appeared in between 145.5\(\delta\) and 127.1\(\delta\) ppm. The elemental analysis corresponds to molecular formula C\(_{14}\)H\(_{13}\)N\(_3\)O and mass spectral analysis showed molecular ion peak at [M]\(^+\)239. On the basis of above data, the structure 38a was assigned to this product i.e. 4-methyl-3-phenylethyl-5-cyano-2-[1H]-pyrimidone. After confirmation of 38a the attempt to cyclise 35b in acidic condition produced somewhat similar results. The compound 38b was also characterized by spectral and analytical methods and the data is given in the experimental section (Experiment No. 6, Page No. 44). However, this cyclization was unsuccessful on ureidopropenitriles 35c-f. Mechanism of formation of 5-cyano pyrimidine derivatives could be given as follows.
Herein we performed the cyclisation of 35 under mild acidic media. It is interesting to note that cyclisation of 35a-b in AcOH yielded 5-cyano-pyrimidine 38a-b in 30-35% yields. The low yield of 5-cyanopyrimidine derivatives indicated unfavorable geometry of the double bond of ureidopropenenitrile 35 to involve the acetyl group for cyclisation. The ureidopropenenitriles may have another isomer (cis to acetyl group) but with lesser amount which have attributed to the formation of 5-cyanopyrimidine derivatives. And the major isomer (trans to acetyl group) remained unreacted under acidic condition.

**Study of the N-alkylation of cytosine, 36b: Introduction of carbamoyl functionality:**

**Synthesis of 2-[3-Benzyl-5-acetyl- 4-imino-2-oxo-3,4-dihydropyrimidin-1(2H)-yl]-N-(4-aryl)acetamide, 40a-g.**

Many methods are reported in the literature for the indoduction of various substituents at N-1 positon of pyrimidine nucleus especially cytosine derivatives. These methods involve the protection of 4-amino nitrogen (either N-acyl or N-silylated) before being alkylated. As discussed in the introduction part the need to obtain the biologically important nucleus, many efforts are made towards cytosine derivatives having carbamoyl functionality at N-1 position. The carbamoyl moieties containing hydrophobic like phenyl groups fascilitate the receptor bindings. We chosed compound 36b for alkylation because it carries benzyl substituent at N-3 position using mild base without protecting the 4-amino group. The substituents utilized for N-alkylation were 2-bromo-N-aryl acetamides which would serve the purpose of introducing cabamoyl functionality. Thus, compound 36b was dissolved in
dimethyl formamide and treated with compound 39f in presence of potassium carbonate under stirring at room temperature for 12 hrs. The white solid was precipitated out on quenching in ice cold water which was purified by crystallization from dichloromethane: heptanes (2:8) as colorless solid in 91% yield (Scheme 8).

The structure of colorless solid was deduced from its IR, $^1$H, $^{13}$C NMR, mass spectroscopy and elemental analysis data. The IR spectrum showed the bands at 1713, 1656 and 1640 cm$^{-1}$ for acetyl and two amide carbonyl stretching frequencies. The two bands at 3288 and 3485 cm$^{-1}$ corresponded to amide NH and $\equiv$NH (imino) stretching. The $^1$H NMR spectrum (DMSO-d$_6$) showed two broad singlet at 8.51 $\delta$ and 10.05 $\delta$ for imino (=NH) and amide
(NH) protons respectively. The $^1$H NMR spectrum clearly indicates the N-alkylation at N-1 position and not at C$_4$-amino position. The aromatic protons appeared at their respective chemical shift positions and splitting pattern (Spectrum No. 6, Page No. 28). The $^{13}$C NMR (DMSO-d$_6$) spectrum of this solid showed the peaks at 26.9d, 43.5δ and 51.3 δ ppm for one methyl carbon and two methylene carbons whereas the peaks at 198.1, 168.8 and 153.5δ corresponded to one acetyl carbonyl carbon and two amide carbonyl carbons. (Spectrum No. 8, Page No.29). The aromatic carbons appeared in between 151.9δ and 116.9δ ppm. The mass spectrum of 40f showed the molecular ion peak at [M-1]$^+$443 which exactly matches with its molecular weight. The elemental analysis was in agreement with molecular formula C$_{21}$H$_{18}$Cl$_2$N$_4$O$_3$. On the basis these spectral and analytical data structure 40f was assigned to this compound i.e. 2-[3-benzyl-5-acetyl-4-imino-2-oxo-3,4-dihydropyrimidin-1(2H)-yl]-N-(2,4-dichlorophenyl)acetamide.

![Chemical Structure](image.png)

**Spectrum No. 6 :** $^1$H NMR Spectrum of 2-[3-Benzyl-5-Acetyl-4-imino-2-oxo-3,4-dihydropyrimidin-1(2H)-yl]-N-(2,4-dichlorophenyl)acetamide, 40f in DMSO-d$_6$
Analogously, compounds 40a-e and 40g were synthesized and characterized by IR, $^1$H, $^{13}$C NMR and elemental analysis and the results are given in the experimental section (Experiment No.7, Page No.46).

The N-alkylation proceeded with nucleophilic displacement of bromine at methylene carbon bearing it under mild basic condition in polar aprotic solvent. As N-3 position of 36b was already substituted and spectral analysis revealed the presence of imino group indicates that substitution was occurred at N-position and not at 4-amino group. Thus, presence of imine
nitrogen in tautomeric 36b was established by N-alkylation with 2-bromo-N-arylacetamides 39 to give 40 in 60-95% yields (Scheme 8). Our approach proposes obtaining the final product 40 after simple N-alkylation of 36 in presence of potassium carbonate, because this procedure provides what are likely to be functional organic molecules in a single step, it fulfils many (but not all) of the criteria of an ideal synthesis. Some of the pyrimidine derivatives 36 and 40 were tested for antimicrobial activity.

1.4 ANTIMICROBIAL ACTIVITY

Introduction to Bacteria

Infection is a major category of human disease and skilled management of antimicrobial drugs is of the first importance. The term chemotherapy is used for the drug treatment of parasitic infections in which the parasites (viruses, bacteria, protozoa, fungi and worms) are destroyed or removed without injuring the host.

Many substances that we now know to possess therapeutic efficacy were first used in the distant past. The Ancient Greeks used male fern, and the Aztecs chenopodium, as intestinal anthelminitics. The Ancient Hindus treated leprosy with chaulmoogra. For hundreds of years moulds have been applied to wounds, but, despite the introduction of mercury as a treatment for syphilis (16th century), and the use of Cinchona bark against malaria (17th century), the history of modern rational chemotherapy did not begin until Paul Ehrlich developed the idea from his observation that aniline dyes selectively stained bacteria in tissue microscopic preparations and could selectively kill them. He invented the word 'chemotherapy' and in 1906 he wrote:
“In order to use chemotherapy successfully, we must search for substances which have an
affinity for the cells of the parasites and a power of killing them greater than the damage
such substances cause to the organism itself ...This means ...we must learn to aim with
chemical substances.’’

The antimalerials pamaquin and mepacrine were developed form dyes and in 1935 the first
sulphonamides, linked with a dye (Prontosil), was introduced as a result of systematic
studies by Domagk. The results obtained with sulphonamides in puerperal in1928, Fleming
accidentally rediscovered the long –known ability of Penicillium fungi to suppress the
growth of bacterial cultures but the finding aside as a curiosity.

In 1939, principally as an academic exercise, Florey and Chain undertook an investigation
of antibiotics, i.e. substances produced by micro organisms that are antagonistic to the
growth or life of other micro organisms. They prepared penicillin and confirmed its
remarkable lack of toxicity.

**Introduction to Fungi**

Fungi are plant-like organisms that lack chlorophyll. Fungi are one of the five kingdoms of
life. Many fungi are beneficial and useful (edible mushrooms would be an example of these)
while some are harmful (some fungi can infect plants and people). There are over 100,000
species of fungi. Since they do not have chlorophyll, fungi absorb food from others. Since
they don’t use light to make food, fungi can live in damp and dark places. Fungi are
saprophytic organism, as they grow on dead organic matter. Most commonly, fungi grow as
pathogen on the skin if animals or people. This is sometimes called Ringworm symptom.

Fungus cause irritation to the nose and causes allergies. Over 37 million people have
allergies and many of them are caused by fungus. Buildings can get some fungi known as
Penicillium and Stachybotrys. They float in the air and can cause watery eyes and breathing problems.

Fungi also cause a number of plant and animal diseases: in humans, ringworm, athlete’s foot, and several more serious diseases are caused by fungi. Because fungi are more chemically and genetically similar to animals than other organisms, this makes fungal diseases very difficult to treat. Plant diseases caused by fungi include rusts, smuts, and leaf, root, and stem rots, and may cause severe damage to crops.

Classification of antimicrobial drugs
Antimicrobial agents may be classified to the type of organism against which they are active.

- Antibacterial drugs
- Antiviral drugs
- Antifungal drugs
- Antiprotozoal drugs
- Anthelmintic drugs

Experimental
A] Cultures used:

<table>
<thead>
<tr>
<th>Culture code</th>
<th>Culture name</th>
<th>Name of Culture Collection Centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli 2109</td>
<td>NICM, Pune</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa 2036</td>
<td>NICM, Pune</td>
<td></td>
</tr>
<tr>
<td>Bacillus subtilis 2250</td>
<td>NICM, Pune</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus 2079</td>
<td>NICM, Pune</td>
<td></td>
</tr>
<tr>
<td>Fungi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida albicans 3471</td>
<td>NICM, Pune</td>
<td></td>
</tr>
<tr>
<td>Aspergillus niger 545</td>
<td>NICM, Pune</td>
<td></td>
</tr>
</tbody>
</table>
**B) Media Used:**
For Bacteria: Muller Hinton agar (Hi-media)
For Fungi: Potato Dextrose agar (Hi-media)

**C) Inoculum Size:**
- Bacteria: $1 \times 10^8$ bacteria per ml
- Fungi: $1 \times 10^6$ spore per ml

**D) Concentration of Compound:** 100µg/ml. (Prepared in DMSO)

**E) Method used:** Agar diffusion assay (disc method, disc size 6mm)

**F) Dilution of Drug:** Stock prepared 1000µg/ml prepared in DMSO [100µg per disc]

### Antimicrobial activity of compounds 36 and 40

<table>
<thead>
<tr>
<th>Compound</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>S. aureus</em></td>
<td><em>E. Coli</em></td>
<td><em>B. subtilis</em></td>
<td><em>P. aeruginosa</em></td>
<td><em>A. niger</em></td>
<td><em>C. albicans</em></td>
</tr>
<tr>
<td>36a</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>36b</td>
<td>8.12</td>
<td>-</td>
<td>9.34</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>36c</td>
<td>-</td>
<td>9.23</td>
<td>-</td>
<td>8.23</td>
<td>8.12</td>
<td>8.45</td>
</tr>
<tr>
<td>36d</td>
<td>7.89</td>
<td>9.11</td>
<td>8.23</td>
<td>9.34</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>36e</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40a</td>
<td>12.11</td>
<td>-</td>
<td>14.54</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40b</td>
<td>9.12</td>
<td>8.34</td>
<td>8.11</td>
<td>7.12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40c</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40d</td>
<td>11.12</td>
<td>-</td>
<td>8.97</td>
<td>-</td>
<td>8.23</td>
<td>10.11</td>
</tr>
<tr>
<td>40f</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7.18</td>
<td>7.22</td>
</tr>
</tbody>
</table>
Results of antimicrobial activity
All the synthesized compounds 36a-e and 40a-d, f-g were tested against microorganism species at 1000 ppm concentration.

The observed results of antibacterial screening reported in above table indicate that compounds 30d and 40b are active against all bacterial species. Compound 40a showed good activity against *B. substilis* and *S. aureus* species. However compounds 36a, 36e and 40c are totally inactive against bacterial as well as fungal species.

From the antifungal assay it has been also observed that compound 36c, 40d and 40f are found to be active against *C. albicans and A. niger species*. Compound 36b, 36d, 40a, 40b and 40g are totally inactive against the fungal species.

From the above observation it is clear that the cytosine containing aryl acetamide functionality bearing chloro and trifluoromethyl substituent 40a showed significant antibacterial activity.

### 1.5 CONCLUSION

In this section we have reported simple methods for the synthesis of cytosine derivatives having acetyl or nitrile group at 5-position and studied their alkylation under mild condition. Although the work up procedure after cyclisation of ureidopropenenitrile using triethylamine was smooth. The poor yields obtained and failure to cyclise 35c-f in these reactions restrict the use of triethylamine for cyclization. The use of sodium methoxide is
also acceptable though it is producing the 2-hydroxy tautomomer, they can be converted to 36e-f with the adjustment of pH during the workup procedure. Potassium tert-butoxide worked superior to cyc

35a-f to corresponding cytosine derivatives 36a-f in good yield. The ureidopropenenitrile, 35a-f and cytosine derivatives 36a-f were characterized by IR, 1H and 13C NMR and elemental analysis. These are the new compounds added in the literature. The ureidopropenenitriles, 35a-f, can be cyclized into pyrimidine derivatives in two different methods. The cyclization in basic medium takes place at nitrile function while in acidic condition the carbonyl group is attacked by the nitrogen nucleophile of urea moiety. These cytosine derivatives are screened for biological activity, which is given in the activity section.

1.6 EXPERIMENTAL

EXPERIMENT No.1: Preparation of 2-Dimethylaminomethylene-oxobutanenitrile (33):

\[
\begin{align*}
&\text{NH}_2 \\
&\text{H}_3\text{C} \underset{\text{31}}{\text{C}} \text{NH} \underset{\text{32}}{\text{O}} \underset{\text{33}}{\text{C}} \text{CN} \\
&\text{DMF:DMA} \text{CN} \underset{\text{6N HCl}}{\text{90\%}} \text{CN} \underset{\text{84\%}}{\text{CN}} \underset{\text{Me}_2\text{N}}{\text{35a-f}} \\
\end{align*}
\]

Synthesis of 3-Oxobutanenitrile 32

B-Aminocrotononitrile (10.0gm, 0.12 mole) was slurried in water (12.5 mL) and conc. hydrochloric acid (12.5 mL) was added dropwise below 15°C within 1 hr. The reaction mixture was then heated to 80°C for 2 hrs. After completion of reaction (TLC check, chloroform:methanol 9:1), the reaction mixture was cooled to room temperature and diluted with ethyl acetate (100 mL). The insoluble materials were filtered through hyflo supercel
and the biphasic clear filtrate was separated, the aqueous layer was extracted twice with ethyl acetate (100 mL x 2). The combined ethyl acetate extracts were washed with saturated sodium chloride solution and the organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure to afford crude 3-oxobutanenitrile as light brown oil (9.0 gm, 90%) [lit bp. 80°C at 0.5mm/Hg]

**Synthesis of 2-Dimethylaminomethylen-3-oxobutanenitrile (33)**

The crude 3-oxobutanenitrile 32 (9.0 gm, 0.11 mole) obtained above, was dissolved in dimethylformamide dimethyl acetal (20 mL) at 25°C and stirred for 30 min. The reaction mixture was then heated to 70-80°C and maintained for 1 hr. After completion of reaction (TLC check, chloroform:methanol, 9:1), the reaction mixture was cooled to room temperature and the excess dimethylformamide dimethyl acetal was distilled under reduced pressure to give dark brown oil. The crude oil was purified by column chromatography on silica gel, eluting with dichloromethane to afford a pale yellow oil which was triturated with hexane to yield a yellow solid. (12.6 gm, 84%). Recrystallized from isopropyl alcohol; Yellow prisms, m.p. 65-68°C; (lit m.p 68°C); IR (KBr): 2241, 1711, 1537 cm⁻¹; ¹H NMR (DMSO-d₆) δ 7.78(s, 1H, CH), 3.4(s, 3H, -NCH₃), 3.20(s, 3H, -NCH₃), 2.42(s, 3H, -CH₃); ¹³C NMR (DMSO-d₆): δ 154.0, 114.86, 108.37, 24.67, 20.11; MS: 138[M]⁺, 123, 95, 81, 42. Anal. Calcd. for C₇H₁₀N₂O: C, 60.85; H, 7.30; N, 20.28

Found: C, 60.85; H, 7.25; N, 20.25
EXPERIMENT No. 2: Synthesis of 2-Acetyl-3-uredopropenenitriles (35a-f):

33

\[
\begin{align*}
\text{H}_2\text{NCONHR} & \quad (34a-f) \\
\text{H}_2\text{NCONHR} & \quad (34a-f)
\end{align*}
\]

**General Procedure**

To a suspension of 33 (10.0 gm, 0.074 mole) and urea/substituted ureas 34 (0.079 moles) in ethanol (250 mL), was added conc. hydrochloric acid (7.5 mL) and reaction mixture was heated to 60-65°C for 3 hrs. After completion of the reaction (TLC check, chloroform: methanol, 9:1), the solvent was evaporated to dryness under reduced pressure. The resulting solid obtained was stirred in cold ethanol (25 mL), collected, dried and recrystallized from methanol: chloroform (6:4) as colorless needles in 50-80% yield.

**2-Acetyl-3-phenylethylureidopropenenitrile (35a)**

m.p. 164-167 °C; Yield 14.8 g. (79.6 %); IR (KBr): 3312,3278,2219,1725, 1669, 1561 cm⁻¹; 

\(^1\text{H} \text{NMR (DMSO-d_6)}: \delta \ 11.32 \& 10.21(\text{d, 1H, NH, } J= 12.6 \text{ Hz} \& 12.9 \text{ Hz}), 8.40 \& 8.00(\text{d, 1H, olefinic CH, } J= 12.6 \& 12.9 \text{ Hz}), 7.23 (\text{m, 5H, Ar-H}), 3.45(\text{t, 2H, CH_2, } J=6.0 \text{ Hz, } & J = 4.8 \text{ Hz}), 2.78(\text{t, 2H, CH_2, } J = 4.8 \text{ Hz}), 2.32(\text{s, 3H, CH_3}); \ ^{13}\text{C} \text{NMR (DMSO-d_6): } \delta \ 195.5, 151.3, 150.2, 140.4, 128.6, 128.3, 126.5, 126.3, 125.4, 115.6, 89.5, 42.9, 38.1, 26.3; \text{ MS: 257[M]^+}, 144, 110, 95, 68, 43.

Anal. Calcd. for C_{14}H_{15}N_3O_2: C, 65.35; H, 5.88; N,16.33.

Found: C, 65.30; H, 6.02; N,16.54.
2-Acetyl-3-benzylureidopropenenitrile (35b)
m.p. 145-148 °C; Yield 13.2 g, (76.1%); IR (KBr): 3334, 3308, 2222, 1726, 1667, 1544 cm⁻¹;
¹H NMR (DMSO-d₆) δ 11.42 & 10.31 (d, 1H, NH, J= 12.3 Hz & 9.9Hz), 8.78 & 7.68 (t, 1H, NH, J = 5.3 Hz & 9.3 Hz), 8.40 & 8.00 (d, 1H, olefinic CH, J = 12.3 & 9.9 Hz), 7.30 (m, 5H, Ar-H), 4.45 (t, 2H, CH₂), 2.32 (s, 3H, CH₃); ¹³C NMR (DMSO-d₆): δ 195.2, 151.7, 150.2, 141.7, 128.8, 128.2, 127.8, 127.1, 126.2, 119.3, 89.4, 48.9, 26.4; MS: 243[M⁺], 144, 110, 95, 68, 43.
Anal. Calcd. for C₁₃H₁₃N₃O₂: C, 64.19; H, 5.39; N, 17.27.
Found: C, 64.02; H, 5.42; N, 17.46.

2-Acetyl-3-phenylureidopropenenitrile (35c)
m.p. 224-226 °C; Yield 11.2 g, (67.4%); IR (KBr): 3296, 3224, 2218, 1721, 1671, 1544 cm⁻¹;
¹H NMR (DMSO-d₆) δ 11.5 & 10.25 (d, 1H, NH, J=12.3 Hz and 12.9 Hz), 9.57 (s, 1H, NH), 8.40 & 8.10 (d, 1H, olefinic CH, J = 2.9Hz & 12.3 Hz), 7.50-7.47 (m, 5H, Ar-H), 2.32 (s, 3H, CH₃) ppm; ¹³C NMR (DMSO-d₆): δ 195.3, 152.2, 151.2, 137.4, 127.6, 127.1, 125.1, 125.1, 124.6, 118.2, 89.2, 35.5 ppm; MS: 229[M⁺], 137, 119, 110, 95, 77, 68, 43.
Anal. Calcd. for C₁₂H₁₁N₃O₂: C, 62.87; H, 4.84; N, 18.33.

2-Acetyl-3-ethylureidopropenenitrile (35d)
m.p. 199-202 °C; Yield 6.6 g, (50.1%); IR (KBr): 3325, 3198, 2219, 1723, 1666, 1554 cm⁻¹;
¹H NMR (DMSO-d₆) δ 11.37 & 10.23 (d, 1H, NH, J= 12.6 Hz), 8.32 (q, 1H, NH), 8.10 (d, 1H, olefinic CH, J = 12.3 Hz, & 13.2 Hz), 3.17 (q, 2H, CH₂), 2.30 (s, 3H, CH₃), 1.07 (t, 3H, CH₃) ppm; ¹³C NMR (DMSO-d₆): δ 195.3, 151.6, 150.1, 119.4, 88.7, 40.6, 26.3 ppm; MS: 181[M⁺], 144, 115, 106, 91, 44.

Found: C, 52.79; H, 6.03; N, 22.94.

2-Acetyl-3-methylureidopropenenitrile (35e)
m.p. 200-203 °C; Yield 7.6g, (63 %); IR (KBr): 3317,3276, 2218,1711,1661,1573 cm⁻¹; ¹H NMR (DMSO-d₆) δ 11.4 and 10.3 (d, 1H, NH, J = 10.5 Hz), 8.4 and 8.0 (d, 1H, olefinic CH, J = 11.1 and 12.6 Hz), 8.20 and 7.11 (bd, 1H, NH, J = 4.5 and 4.2 Hz), 2.7(s, 3H, CH₃), 2.3 (s, 3H, CH₃) ppm; ¹³C NMR (DMSO-d₆): δ 195.5, 152.1, 151.2, 115.6, 88.9, 28.2, 26.2 ppm; MS: 167[M⁺], 110, 95, 58, 43.

Anal. Calcd. for C₇H₉N₃O₂: C, 50.29; H, 5.43; N,25.14

Found: C, 50.35; H, 5.60; N, 25.30

2-Acetyl-3-ureidopropenenitrile (35f)
m.p. 196-199 °C; Yield 8.4g, (76 %); IR (KBr): 3371,3212,2219,1739, 1670,1552 cm⁻¹; ¹H NMR (DMSO-d₆) δ 10.20 & 11.30(d, 1H, NH, J =12.9Hz), 8.02 & 8.40(d, 1H, olefinic CH, J = 12.9 Hz), 7.70(bs, 1H, NH), 7.40 (bd, 1H, NH), 6.70 (bs,1H, NH), 2.30(s, 3H, CH₃) ppm;
¹³C NMR (DMSO-d₆): δ 194.5, 164.7, 155.2, 115.0, 98.2, 25.6 ppm; MS: 153[M⁺], 144, 110, 95, 68, 43.

Anal. Calcd. for C₆H₇N₃O₂: C,47.06; H, 4.61; N, 27.44

Found: C,47.23; H, 4.60; N, 27.37
EXPERIMENT No. 3: Synthesis of 5-Acetyl-3,4-dihydro-4-aminopyrimidin-2(1H)-one Derivatives (36a-b):

To a solution of 35 (0.004 mole) in acetonitrile (20 mL), was added triethylamine (1.2 mL), and the mixture was refluxed for 30 hrs. After completion of reaction (TLC check, chloroform: methanol, 9:1), the solvent was evaporated to dryness under reduced pressure. The resulting solid was stirred in cold ethanol (10 mL), collected, dried and recrystallized from methanol: chloroform (6:4). Compounds 36 obtained as pale yellow needles in 43-47% yield.

4-Amino-3-phenylethyl-5-Acetyl-2[1H]-pyrimidone (36a)
m.p. 220-222 °C; Yield 0.48 g, (43.0 %); IR (KBr): 3403, 3144, 1670, 1570, 1376 cm⁻¹; ¹H NMR (DMSO-d₆) δ 10.05(bs, 1H, NH), 8.72(s, 1H, olefinic CH), 8.57 (bs, 1H, NH), 7.26-7.29(m, 5H, Ar -H), 4.10 (q, 2H, N-CH₂, J=6.0 Hz), 2.80(t, 2H, CH₂, J=5.4Hz), 2.40(s, 3H, CH₃) ppm; ¹³C NMR (DMSO-d₆): δ 195.2, 157.7, 154.2, 140.5, 130.2, 128.5, 128.3, 126.8, 125.4, 119.2, 45.0, 36.2, 26.1 ppm; MS: 257[M⁺], 166, 137, 104, 95, 77.
Found: C, 65.30; H, 6.02; N, 16.56.

4-Amino-3-benzyl-5-Acetyl-2[1H]-pyrimidone (36b)
m.p. 215-217 °C; Yield 0.43 g, (47 %); IR (KBr): 3405, 3134, 1671, 1575, 1370 cm⁻¹; ¹H NMR (DMSO-d₆) δ 10.0(bs, 1H, NH), 8.50(bs, 1H, NH), 8.79 (s, 1 H, olefinic CH), 7.36-
7.15 (m, 5H, Ar-H), 5.18(s, 2H, N-CH₂), 2.42(s, 3H, CH₃) ppm; $^{13}$C NMR (DMSO-d₆): $\delta$
197.2, 152.4, 150.1, 143.4, 138.4, 129.3, 128.2, 127.8, 127.2, 126.8, 101.5, 44.5, 26.6 ppm;
Anal. Calcd. for C$_{13}$H$_{13}$N$_3$O$_2$: C, 64.19; H, 5.39; N, 17.27.
Found: C, 63.99; H, 5.15; N, 17.48.

EXPERIMENT No. 4: Synthesis of 5-Acetyl-3,4-dihydro-4-iminopyrimidin-2(1H)-one Derivatives (36a-f):

![Diagram of reaction](image)

General Procedure

A solution of 35 (0.0021 mole) and sodium tert-butoxide (0.28gm, 0.0025 mole) in ethanol (10 mL) was refluxed for 6 hrs. After completion of reaction (TLC check, chloroform: methanol, 9:1). The solvent was removed under reduced pressure and the oily residue obtained was treated with acetic acid to adjust pH up to 6.5-7.0. The solids obtained were collected, washed with ethanol, dried and recrystallized from ethanol to obtain pale yellow needles in 75-88% yield.

The spectral and analytical data of 36a and 36b is given in experiment No.3. The yield of 36a was 87% and that of 36b was 84.3%.
4-Amino-3-phenyl-5-Acetyl-2[1H]-pyrimidone (36c)

m.p. 113-115 °C; Yield 0.41 g, (85 %); IR (KBr): 3527,3469, 3282,3131, 1711,1667 cm⁻¹; 
¹H NMR (DMSO-d₆) δ 9.8(bs, 1H, NH), 8.42 (bs, 1H, NH), 7.82 (s, 1H, olefinic CH), 7.42-
7.32 (m, 5H, Ar-H), 2.42(s, 3H, CH₃) ppm; ¹³C NMR (DMSO-d₆): δ 198.4, 165.2, 150.1,
140.1, 134.2, 131.2, 130.2, 125.1, 120.1, 119.4, 115.2, 26.3 ppm; MS: 229[M]⁺, 186, 171,
143, 77, 44.

Anal. Calcd. for C₁₂H₁₂N₃O₂: C, 62.87; H, 4.84; N, 18.33.

Found: C, 65.82; H, 4.83; N, 18.26.

4-Amino-3-ethyl-5-Acetyl-2[1H]-pyrimidone (36d)

m.p. 164-167 °C; Yield 0.29 g, (76 %); IR (KBr): 3225,3198, 2219,1723, 1666 cm⁻¹; 
¹H NMR (DMSO-d₆) δ 10.05(bs, 2H, NH₂), 8.69(s, 1H, olefinic CH), 3.93(q, 2H, CH₂), 2.40(s,
3H, CH₃), 1.10(t, 3H, CH₃) ppm; ¹³C NMR (DMSO-d₆): δ 195.3, 157.1, 154.6, 140.1,


Found: C, 53.23; H, 6.34; N, 23.42.

4-Amino-3-methyl-5-Acetyl-2[1H]-pyrimidone (36e)

m.p. 225-226 °C; Yield 0.31 g, (88 %); IR (KBr): 3527,3469, 3282,3131, 1711, 1667 cm⁻¹; 
¹H NMR (DMSO-d₆) δ 9.80(bs, 1H, NH), 8.42(bs, 1H, NH), 8.69(s,1H, olefinic CH),
3.22(s, 3H, N-CH₃), 2.40(s, 3H,-CH₃) ppm; ¹³C NMR (DMSO-d₆): δ 195.3, 164.2, 159.3,
157.1, 154.6, 99.2, 29.4, 26.1 ppm; MS: 167 [M]⁺, 152, 139, 124, 110, 95, 57, 44.


Found: C, 50.46; H, 5.26; N, 24.86.
4-Amino-5-Acetyl-2[1H]-pyrimidone (36f)
m.p. 218-220°C; Yield 0.24 g. (75%); IR (KBr): 3527,3469, 3282,3131, 1711 cm⁻¹; \(^1\)H NMR (DMSO-d₆) δ 9.90 (bs, 2H, NH₂), 8.72(s, 1H, olefinic CH), 2.37(s, 3H, CH₃) ppm; \(^{13}\)C NMR (DMSO-d₆): δ 195.3, 164.2, 157.1, 154.6, 99.2, 29.4; MS: 153[M]⁺, 139, 124, 110, 95, 57, 44.
Anal. Calcd. for C₆H₇N₃O₂: C, 47.06; H, 4.61; N, 27.44
Found: C, 47.26; H, 4.71; N, 27.66.

EXPERIMENT No. 5: Synthesis of 1-(3-Benzyl-1, 4-dihydro-2-hydroxy-4-iminopyrimidin-5-yl)ethanone(37a-b):

To a solution of 35 (0.0102 mole) in methanol (50 mL), sodium methoxide (0.66gm, 0.0124 mole) was added and refluxed for 8 hrs. After completion of reaction (TLC check, chloroform: methanol, 9:1), the solvent was removed under reduced pressure and the residue obtained was dissolved in cold water and acidified with acetic acid to obtain the precipitate. Compound 37 were crystallized from ethanol to yield pale yellow needles in 77-78% yield.
4-Imino-3-phenylethyl-5-Acetyl-2-hydroxy-pyrimidine (37a)
m.p. 197-200 °C; Yield 0.41 g, (77.4 %); IR (KBr): 3405,3143, 1671,1575, 1366,1287 cm⁻¹; ¹H NMR (DMSO-d₆) δ 11.60(1H, OH), 10.42(bs, 1H, NH), 8.82(s, 1H, olefinic CH), 7.20-7.34 (m, 5H, Ar-H), 4.20(t, 2H, N-CH₂, J= 7.8 Hz), 2.80(t, 2H, CH₂, J= 7.5 Hz), 2.49(s, 3H, CH₃) ppm; ¹³C NMR (DMSO-d₆): δ 198.2, 167.7, 153.2, 148.3, 139.5, 128.6, 128.4, 128.1, 127.8, 127.4, 126.8, 40.1, 31.2, 27.1 ppm; MS: 257[M⁺], 166, 137, 104, 95, 77.
Found: C, 65.47; H, 5.95; N, 16.51.

4-Imino-3-benzyl-5-Acetyl-2-hydroxy-pyrimidine (37b)
m.p. 195-198 °C; Yield 0.40 g, (78.4 %); IR (KBr): 3148,1682,1564,1288 cm⁻¹; ¹H NMR (DMSO-d₆) δ 11.2(s,1H,OH), 9.92(s, 1H, NH), 8.72(s, 1H, olefinic CH), 7.31-7.34 (m, 5H, Ar-H), 5.10(s, 2H, N-CH₂), 2.42(s, 3H, CH₃) ppm; ¹³C NMR (DMSO-d₆): δ 198.2, 164.4, 154.2, 149.4, 145.3, 128.6, 128.2, 127.4, 127.2, 126.8, 125.0, 40.2, 26.6 ppm; MS: 243[M⁺], 242, 226, 183, 159, 138, 106, 91.
Anal. Calcd. for C₁₃H₁₃N₃O₂: C, 64.19; H, 5.39; N, 17.27.
Found: C, 64.44; H, 5.13; N, 17.06.

EXPERIMENT No. 6: Synthesis of 1-Benzyl-1,2-dihydro-6-methyl-2-oxopyrimidine-5-carbonitrile (38a-b):

![Chemical structure of 38a-b](image)

Acetic acid Reflux
30 hrs, 30-35%

35a-b

38a-b

44
A solution of 35 (0.004 mole) in acetic acid (10 mL) was refluxed for 30 hrs. After completion of reaction (TLC check, chloroform: methanol, 9:1), acetic acid was removed under reduced pressure and the residue obtained was dissolved in ethyl acetate (10 mL) and washed with a saturated sodium chloride solution. The organic layer was dried over sodium sulfate and evaporated under reduced pressure to give 38 as pale yellow solids which were recrystallized from ethanol as pale yellow needles in 30-35% yield.

4-methyl-3-phenylethyl-5-cyano[1H]-pyrimidone (38a)

m.p. 220-223 °C; Yield 0.29 g, (30.5 %); IR (KBr): 3453,3150, 2242,1670,1570, 1376 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.60(s, 1H, olefinic CH), 7.10-7.60(m, 5H, Ar-H), 4.15 (t, 2H, N-CH₂, J=6.0 Hz), 2.82 (t, 2H, CH₂, J=5.4Hz), 1.42(s, 3H, CH₃) ppm; ¹³C NMR (DMSO-d₆): δ 154.2, 145.2, 140.5, 130.2, 128.8, 128.4, 128.0, 127.1, 117.8, 95.4, 58.4, 50.02, 33.7, 20.1 ppm; MS: 239[M]⁺, 166, 137, 104, 95, 77.

Anal. Calcd. for C₁₄H₁₃N₃O: C, 70.28; H, 5.48; N, 17.56.

Found: C, 70.08; H, 5.24; N, 17.84.

4-methyl-3-benzyl-5-cyano-2[1H]-pyrimidone (38b)

m.p. 211-213 °C; Yield 0.32 g, (34.3 %); IR (KBr): 3415,3134,2240 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.79(s, 1H, olefinic CH), 7.06-7.50 (m, 5H, Ar-H), 5.18 (s, 2H, N-CH₂), 1.71(s, 3H, CH₃) ppm; ¹³C NMR (DMSO-d₆): δ 164.7, 160.0, 155.0, 141.5, 129.3, 128.2, 127.0, 126.8, 120.9, 97.6, 54.5, 48.5, 16.6 ppm; MS: 225[M]⁺, 183, 159, 138, 106, 91.


Found: C, 69.53; H, 4.77; N, 18.43.

45
EXPERIMENT No.7: Synthesis-(5-Acetyl-3-benzyl-3,4-dihydro-4-imino-2-oxopyrimidin-1(2H)-yl)-N-phenylacetamide (40a-g):

General Procedure:
To a magnetically stirred suspension of 36b (0.5gm, 2.1 mmole) and K$_2$CO$_3$ (0.28gm 2.1 mmole) in DMF (4 mL) was added 39 (2.2 mmole). This suspension was further stirred at room temperature for 12 hrs (TLC check, chloroform: methanol, 9:1) and the reaction mixture was then quenched in ice-cold water. The solid obtained was collected, washed with water, dried and was recrystallized from dichloromethane: heptane (2:8) to give compounds 40 as colorless solids in 60-95% yields.

2-(5-Acetyl-3-benzyl-4-imino-2-oxo-3,4-dihydro-2H-pyrimidin-1-yl)-N-(4-chloro-3-trifluoromethyl-phenyl)-acetamide (40a)
m.p. 145-148 °C; Yield 0.59 g, (60 %); IR (KBr): 3464,3268, 3196,3122, 3075,1696, 1658, 1597 cm$^{-1}$; $^1$H NMR (DMSO-d$_6$) δ 10.85(bs,1H,NH), 8.59(s, 1H, olefinic,CH), 8.15(bs, 1H, NH), 7.70 (dd, $J$ =2.4 & 8.7Hz, 2H, Ar-H), 7.29(s, 1H, Ar-H), 7.26(m, 5H, ArH), 5.00(s,
2H, -N CH₂), 4.84(s, NCH₂), 2.50(s, 3H, CH₃) ppm; ¹³C NMR (DMSO-d₆): δ 198.2, 165.5, 160.4, 151.8, 150.0, 141.2, 137.1, 132.5, 128.5, 127.7, 127.2, 127.0, 126.4, 126.2, 124.1, 123.2, 120.2, 117.7, 115.1, 52.8, 44.3, 30.2 ppm; MS: 477(M-1), 278, 221, 195, 133, 91, 77, 65, 43.

Anal. Calcd. for C₂₂H₁₈ClF₃N₄O₃: C, 55.18; H, 3.79; N, 11.70.

Found: C, 55.43; H, 4.06; N, 11.55.

2-(5-Acetyl-3-benzyl-4-imino-2-oxo-3,4-dihydro-2H-pyrimidin-1-yl)-N-(4-fluoro-phenyl)-acetamide (40b)
m.p. 158-160 °C; Yield 0.65g, (80 %); IR (KBr): 3455,3266, 3147,3115, 3075,1697, 1657 cm⁻¹; ¹H NMR (DMSO-d₆) δ 10.68 (bs, 1H,-NH), 9.63(s, 1H, =CH), 8.50(bs, 1H, -NH), 7.58(m, 2H, Ar-H), 7.25(m, 7H, Ar-H), 5.13(s, 2H, -CH₂), 4.65 (s, 2H, N-CH₂), 2.36(s, 3H,-CH₃) ppm;
¹³C NMR (DMSO-d₆): δ 196.2, 165.2, 159.2, 156.2, 153.2, 149.2, 137.1, 134.5, 128.4, 128.2, 127.4, 126.8, 126.0, 121.1, 120.5, 115.7, 115.3, 112.2, 51.8, 43.3, 26.2 ppm;
MS: 393(M-1), 242, 133, 111, 91, 77, 43.


Found: C, 63.82; H, 4.95; N, 14. 13.

2-(5-Acetyl-3-benzyl-4-imino-2-oxo-3,4-dihydro-2H-pyrimidin-1-yl)-N-(4-methyl-phenyl)-acetamide (40c)
m.p. 186-188 °C; Yield 0.62 g, (78 %); IR (KBr): 3451,3274, 3149,3111, 3077,1691,1591 cm⁻¹; ¹H NMR (DMSO-d₆) δ 10.30(bs, 1H,-NH), 9.62(s, 1H, =CH), 8.51(bs, 1H,-NH), 7.46(d, 2H, J = 8.1 Hz, Ar-H), 7.25(m, 5H, Ar-H), 7.10(d, 2H, J = 8.1 Hz, Ar-H), 5.13(s, 2H, -CH₂), 4.65(s, 2H, N-CH₂), 2.36(s, 3H,CH₃), 2.24(s, 3H, CH₃) ppm; ¹³C NMR (DMSO-


Found: C, 67.52; H, 5.79; N, 14.6

2-(5-Acetyl-3-benzyl-4-imino-2-oxo-3,4-dihydro-2H-pyrimidin-1-yl)-N-(2-chloro-6-fluoro-phenyl)-acetamide (40d)
m.p. 230-232 °C; Yield 0.84 g, (96 %); IR (KBr): 3457,3280, 3144,3118, 3078,1695, 1654 cm⁻¹; ¹H NMR (DMSO-d₆) δ 10.15(bs, IH, -NH), 9.60 (s, IH, =CH), 8.54(bs,1H, -NH), 7.46(m, 3H, ArH), 7.20(m, 5H, Ar-H), 5.14(s, 2H, -CH₂), 4.74(s, 2H, N-CH₂), 2.30(s, 3H, -CH₃) ppm;
²C NMR (DMSO-d₆): δ 195.8, 168.3, 160.5, 153.2, 149.4, 144.2, 132.4, 131.2, 128.8, 128.5, 127.8, 127.2, 126.6, 122.4, 118.4, 115.2, 116.6, 113.5, 53.6, 45.8, 28.2 ppm;
MS: 427(M-1), 242, 145, 106, 91, 77, 65, 43.

Anal. Calcd. for C₂₁H₁₈ClF₄N₄O₃: C, 58.82; H, 4.23; N, 13.06.

Found: C, 59.04; H, 4.14; N, 13.25.

2-(5-Acetyl-3-benzyl-4-imino-2-oxo-3,4-dihydro-2H-pyrimidin-1-yl)-N-(2,5-bis-trifluoromethyl-phenyl)-acetamide (40e)
m.p. 168-171 °C; Yield 0.78 g, (74 %); IR (KBr): 3485,3288, 3145,3110,1690, 1591 cm⁻¹; ¹H NMR (DMSO-d₆) δ 10.22 (bs, 1H, NH), 9.65(s, 1H, =CH), 8.56(bs, 1H, -NH), 7.52(m, 3H, Ar-H), 7.17(m, 5H, Ar-H), 5.19(s, 2H, -CH₂), 4.82 (s, 2H, N-CH₂), 2.32(s, 3H, -CH₃) ppm;
$^{13}$C NMR (DMSO-$d_6$): δ 192.2, 166.8, 158.5, 151.3, 150.9, 148.8, 141.4, 138.2, 134.2, 133.8, 133.1, 129.2, 125.8, 124.9, 124.2, 123.8, 121.8, 117.2, 115.8, 114.2, 54.6, 44.8, 26.2 ppm; MS: 511(M-1), 285, 257, 132, 124, 91, 82, 65, 43.

Anal. Calcd. for C$_{23}$H$_{18}$F$_6$N$_4$O$_3$: C, 53.91; H, 3.54; N, 10.93.

Found: C, 54.15; H, 3.36; N, 11.16.

2-(5-Acetyl-3-benzyl-4-imino-2-oxo-3,4-dihydro-2H-pyrimidin-1-yl)-N-(2,4-dichlorophenyl)acetamide (40f)

m.p. 130-133 °C; Yield 0.84 g, (91 %); IR (KBr): 3485,3288, 3145,3110, 3085,1690, 1655, 1591 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) δ 10.05 (bs, 1H,-NH), 9.60(s, 1H, =CH), 8.51(bs, 1H,-NH), 7.78(d, 1H, J = 8.4 Hz, Ar-H), 7.68(s, 1H,Ar-H), 7.42(d, 1H, J=8.7 Hz Ar-H), 7.23(m, 5H, Ar-H), 5.13(s, 2H, -CH$_2$), 4.76(s, 2H, N-CH$_2$), 2.36(s, 3H, -CH$_3$) ppm; $^{13}$C NMR (DMSO-$d_6$): δ 198.1, 168.8, 153.5, 151.9, 149.3, 148.1, 141.2, 137.1, 133.5, 131.9, 131.2, 130.6, 129.6, 128.8, 127.2, 126.8, 124.2, 116.9, 51.3, 43.5, 26.9 ppm; MS: 443(M-1), 242, 161, 133, 123, 106, 91, 77, 65, 43.

Anal. Calcd. for C$_{21}$H$_{18}$Cl$_2$N$_4$O$_3$: C, 56.64; H, 4.07; N, 12.58.

Found: C, 56.62; H, 4.08; N, 12.32.

2-(5-Acetyl-3-benzyl-4-imino-2-oxo-3,4-dihydro-2H-pyrimidin-1-yl)-N-(4-chlorophenyl)acetamide (40g)

m.p. 168-170 °C; Yield 0.78 g, (92 %); IR (KBr): 3489,3281, 3156,3115, 3089,1698, 1659, 1593 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) δ 10.50(bs, 1H, NH), 9.60(s, 1H =CH), 8.51(bs, 1H, -NH), 7.60(d, 2H, J = 8.7 Hz), 7.38(d, 2H, J = 8.7 Hz, Ar-H), 7.26(m, 5H, Ar-H), 5.13(s, 2H, -CH$_2$), 4.66(s, 2H, N-CH$_2$), 2.36(s, 3H,CH$_3$) ppm; $^{13}$C NMR (DMSO-$d_6$): δ 195.8, 165.2,
153.9, 149.8, 137.8, 135.6, 131.9, 131.1, 131.2, 128.8, 128.6, 127.5, 127.0, 126.9, 126.9, 120.2, 106.9, 54.3, 51.5, 43.7, 26.9 ppm; MS: 409(M-1), 242, 123, 106, 91, 77, 65, 43.

Anal. Calcd. for C_{21}H_{19}ClN_{4}O_{3}: C, 61.39; H, 4.66; N, 13.64.

Found: C, 61.65; H, 4.56; N, 13.72.

1.7 REFERENCES


Nucleosides Nucleotides, 1993, 12, 225.


