1.1. Introduction

Dihydropyrimidinones (DHPMs), commonly known as Biginelli compounds, have attained unprecedented attention due to its greater biological, pharmaceutical and therapeutic properties. In 1893, Pietro Biginelli reported the first synthesis of 3,4-dihydroprimidin-2(1H)ones (DHPM) by a very simple one-pot condensation reaction of an aromatic aldehyde, urea and ethyl acetoacetate in ethanolic solution (Scheme 1.1). This efficient approach to partly reduced pyrimidines, termed the Biginelli reaction or condensation, was largely ignored in the following years, and therefore, also the synthetic potential of these multi-functionalized dihydropyrimidines remained unexplored. In recent years, however, interest in these compounds has increased rapidly, and the scope of the original cyclocondensation reaction has been widely extended by variation of all three components.

Scheme 1.1. Classical Biginelli condensation reaction.

The simple MCR for dihydropyrimidinone synthesis reported by Biginelli is being extensively exploited nowadays to have the maximum benefit to the scientific field especially in biological field. The synthesis and utilization of these multi-disciplined moieties is in full swing for the last few decades, which is clearly evident from the increasing number of publications and patents. The properties of these compounds can be changed considerably by varying the reactants of the reaction, which is of profound interest to contemporary scientific community.
1.2. Review of Literature

Although the most straightforward protocol to synthesize DHPMs is the one-pot acid-catalyzed Biginelli condensation shown above (Scheme 1), this protocol—using ethanol and catalytic amounts of HCl—often provides only low to moderate yields of the desired target molecules, in particular, when substituted aromatic aldehydes or thioureas are employed.\textsuperscript{2,3} This has led to the recent disclosure of several improved reaction protocols for the synthesis of DHPMs, either by modification of the classical one-pot Biginelli approach itself,\textsuperscript{13} or by the development of novel, but more complex multistep strategies.\textsuperscript{4}

1.2.1. Structural Variations of Reactants

The original cyclocondensation reaction has been extended widely to include variations in all three components. Of these, the aldehyde component has been varied to the largest extent and now includes not only many aromatic,\textsuperscript{5,6,7,9} but also aliphatic\textsuperscript{7-13} and heterocyclic aldehydes.\textsuperscript{14} Of particular interest are reactions where the aldehyde component is derived from a carbohydrate\textsuperscript{15} (Figure 1.1). Another unusual substitute for an aldehyde in the standard Biginelli reaction is $\alpha, \beta$-dichloroethyl ethyl ether\textsuperscript{16} (Figure 1.1). The 4-unsubstituted derivative is prepared by reaction of methyleneurea with ethyl acetoacetate.\textsuperscript{1,5,17} In some cases aldehyde diacetates have been used instead of the unprotected aldehydes.\textsuperscript{11,14}

Figure 1.1. Substitute for aldehydes in Biginelli reaction

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Figure 1.1. Substitute for aldehydes in Biginelli reaction}
\end{figure}
Apart from common alkyl acetoacetates which are employed frequently as the β-ketoester component, other acetoacetic acid esters such as benzyl acetoacetate, methyl acetoacetate, β-chloroethyl acetoacetate, 2-furanyl methyl acetoacetate and ethylthioacetoacetate and benzoylacetic acid esters have been used successfully in the Biginelli reaction. Similarly, ethyl 4-bromoacetoacetate and ethyl trifluoromethylacetoacetate afford the corresponding 6-functionalized dihydropyrimidinones. Liang et al. used simple ketones instead of diketones to form DHPMs under a solvent free microwave assisted condition (Scheme 1.2).

Scheme 1.2. Simple Ketones for Dihydropyrimidinones

The diketones are substituted by spiro-fused heterocycles and α-substituted ketoacids for the successful formation of biginelli compounds as given in Scheme 1.3. Primary, secondary, and tertiary acetoacetamides have been used in place of esters to produce pyrimidine-5-carboxamides.
Scheme 1.3. Spiro Fused Heterocycles and α-Ketoacids as Substitutes for Diketones in Biginelli reaction

Substituted ureas and thioureas can replace the urea component. It should be emphasized that monosubstituted ureas or thioureas form exclusively N-1 substituted dihydropyrimidines.\textsuperscript{25-27} The N-3 alkylated products cannot be obtained by the standard Biginelli reaction or by alkylation of unsubstituted derivatives. N,N’-disubstituted ureas do not react at all under these conditions. Nilsson and Overman\textsuperscript{28} effectively utilized the guanidine derivatives instead of urea for the formation of biologically active dihydropyrimidinones (Scheme 1.4).

Scheme 1.4. Guanidine Derivatives as Substitute for Urea in Biginelli Reaction
1.2.2. Variation of the Reagents and Methods

The classical Biginelli condensation was catalyzed by mineral acids. Later the mineral acids have been replaced successfully by various Lewis acids and metallic salts, polymer supported reagents, ionic liquids, non-metallic reagents and solid catalysts such as clay, dowex, silica etc. These reagents have been used under conventional as well as modern experimental conditions. The modern methodologies used for the Biginelli reaction involves the microwave assisted organic synthesis, ionic liquid phase organic synthesis and sonochemical techniques. Also combinatorial approaches towards DHPMs have been advanced, under solid phase, or fluorous phase reaction conditions.

1.2.3. Alternative Synthetic Strategies

1.2.3.1. The Atwal Modification

Although the classical Biginelli reaction has been used widely in the past decades it is not always reliable and often gives only moderate yields, in particular when aliphatic or ortho-substituted aromatic aldehydes are employed. A more reliable approach to Biginelli compounds was reported in 1987 by K. Atwal and co-workers (Scheme 1.5). In the first step an unsaturated ketoester (14) is condensed with a suitable protected urea (15a) or thiourea derivative (15b) in the presence of sodium bicarbonate. The reaction presumably proceeds through a Michael addition product and affords dihydropyrimidines (16a,b). Deprotection with HCl (for 16a) or trifluoroacetic acid/ethanethiol (for 16b) leads to the desired Biginelli compounds (17a,b) in high overall yield. Although this method requires prior synthesis of the unsaturated ketosters (14), its reliability and broad applicability makes it an attractive alternative to the standard Biginelli condensation.
Scheme 1.5. Atwal Modification for Biginelli Compounds.

Similar results are obtained when 14 is condensed with guanidine or N,N-dimethylguanidine to give 2-amino-substituted pyrimidines, 16 (XR^2=NH_2, NMe_2).^{43,44}

1.2.3.2. Other Procedures

Apart from the procedure described in Scheme 1.1, there are a few other methods that lead to Biginelli compounds. Most of them, however, are limited in their scope and are hardly ever used for synthetic purposes. Thus, substituted acetoacetate can react with urea with elimination of MeSH to furnish dihydropyrimidinones (Scheme 1.6).^{45} The same compound is obtained upon hydrogenation of pyrimidine with H_2/Pt.^{46}

Scheme 1.6

A route leading to dihydropyrimidinones, having a hydrogen atom in position 6 is shown in Scheme 1.7.^{47}
Scheme 1.7

Another route leading to Biginelli compounds with a hydrogen atom in position 6 is the condensation of ethyl propiolate (H-C≡C-CO₂Et) with N-methyl urea and benzaldehyde (Scheme 1.8).⁴⁸

Scheme 1.8

Yet another novel approach to DHPMs has been described by Shutalev et al.⁴⁴ and is outlined below (Scheme 1.9). This synthesis is based on the condensation of readily available α-tosyl-substituted (thio) ureas with the (in situ prepared) enolates of aceto-acetates or 1,3-dicarbonyl compounds to give hexahydro pyrimidines which is then converted directly into DHPMs. This method works particularly well for aliphatic aldehydes and thioureas and produces high overall yields of the desired target compounds.

Scheme 1.9. Shutalev’s Method for Dihydropyrimidinones
1.2.4. Mechanistic Aspects

Several research groups have investigated the mechanism of the Biginelli reaction. Its dependence upon acid catalysis has been experimentally established\textsuperscript{3-5} and a mechanism proposed by Folkers and co-workers\textsuperscript{50} in 1933 was accepted. In the proposed mechanism, the first step is believed to be the condensation between the aldehydes and urea with some similarities to the Mannich condensation. The iminium intermediate generated act as an electrophile for the nucleophilic addition of the ketoester enol, and the ketone carbonyl of the resulting adduct undergoes condensation with the urea-NH$_2$ to give the cyclised product. The schematic representation of the mechanism is given in Scheme 1.10.

**Scheme 1.10. Mechanism Proposed by Folkers for Acid Catalysed Biginelli Reaction.**

The reaction mechanism was further reinvestigated by Sweet and Fissekis.\textsuperscript{50} These authors suggested that an aldol condensation is the first and limiting step of the reaction, eventually leading to carbenium ion which was proposed as the key intermediate in the reaction. Interception of cation by urea affords an intermediate ready for cyclization to dihydropyrimidine as depicted in Scheme 1.11.
Scheme 1.11. Mechanism Proposed by Sweet And Fissekis.

A reexamination of the mechanism by Kappe et al.\textsuperscript{51} later showed that
the original mechanistic proposal put forward by Folkers and Johnson in
1933, involving an aldehyde-urea condensation product as key intermediate
in the Biginelli condensation is essentially correct. On the basis of the
experimental evidences Hu et al.\textsuperscript{3a} also established the same mechanism.

1.2.5. Biological Activity

Biginelli compounds show a diverse range of biological activities. As
early as 1930 simple derivatives such as 33 were patented as agents for the
protection of wool against moths.\textsuperscript{52} Later, interest focused on the antiviral
activity of Biginelli compounds,\textsuperscript{53} eventually leading to the development of
nitractin (34), which has excellent activity against the viruses of the trachoma
group.\textsuperscript{14,54} The Biginelli compounds also exhibits modest antibacterial
activity.\textsuperscript{55} Dihydropyrimidinone 1 and some of its analogs were screened as
antitumor agents and found to be active against Walker carcinosarcoma in rats
and mice.\textsuperscript{55-57} Pyrimidine 5-carboxamides of type 35 are reported to possess
anticarcinogenic\textsuperscript{58} activity. Antinflammatory,\textsuperscript{9,59} antioxidant,\textsuperscript{59b} analgesic,\textsuperscript{9}
and blood platelet aggregation inhibitory activity\textsuperscript{8} was found in a number of
derivatives. 1,4 Dihydropyrimidine \( \text{36} \) is useful as platelet- activating factor antagonist.\(^{60} \) Other Biginelli compounds were shown to inhibit the uptake of adenosine by thrombocytes.\(^{61} \)

**Figure 1.2.**

Dihydropyrimidinones have found widespread use in cardiovascular medicine\(^ {7,9,19} \) and have served as important tools for the study of calcium channel structure and function.\(^ {62} \) Structural modification of the substituent at N-3 of DHPMs led to the development of orally effective long-lasting antihypertensive agents (\( \text{37} \)).\(^ {65,66} \) Another derivative, \( \text{38} \) containing a basic amino group in the N-3 substituent was identified as a ‘lead compound’ for drug discovery.\(^ {67} \)

**Figure 1.3.**

Betzelladine alkaloid

\( \text{39} \)
Rovnyak reported a general structure-activity relationship of dihydropyrimidinone calcium channel blockers. Apart from their use as antihypertensive agents dihydropyrimidinone calcium channel blockers are also of interest as agents for treating anxiety, and optic nerve dysfunction. Several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have recently been isolated. Most notable among these are the batzelladine alkaloids which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy.

1.3. Results and Discussion

Since the first report on the synthesis of dihydropyrimidinones by Biginelli in 1893, many improved procedures, have been developed for their formation under conventional, microwave assisted and ultrasonic pathways. Most of these methods reported describe the use of Lewis acids and salts, which mainly contain heavy metals. Other promoters include chloroacetic acid, ammonium chloride, tungstophosphoric acid, propane phosphonic acid anhydride, montmorillonite KSF clay, ZrO$_2$-pillard clay etc.

Although many revised protocols are available for the formation of dihydropyrimidinones, most of them suffer from low yields, long reaction time and cumbersome work up. In the present study we have devised tributylborate catalyzed two new synthetic strategies under microwave-assisted and reflux condition. The electron deficiency of boron and its ability to co-ordinate with the lone pair containing atoms or group make this reagent more efficient. Only very few boron-based reagents have been reported that catalyse the formation of DHPMs and they include BF$_3$-Etherate/CuCl/
HOAc, boric acid in glacial acetic acid, phenyl boronic acid, 1-n-butyl-3-methylimidazolium tetrafluoroborate and HBF₄.

It is noteworthy that tributylborate is a mild, efficient, cost-effective and non-metallic catalyst used for the first time to generate DHPMs library under conventional as well as microwave assisted conditions. To the best of our knowledge, it has not been much utilized as a catalyst in organic multicomponent reactions. In very few reactions it is used as a mild water scavenger⁷².

In the present investigation my interest was to synthesis the pharmacologically active dihydropyrimidinone moieties without the possibility of any metallic contamination, which may alter its biological activity. Reports show that mono or di-substituted amide bearing DHPMs have the potential therapeutic properties such as anticancer, antioxidant, antibacterial, analgesic, antihypertensive activities etc. With this basic knowledge I have synthesized some DHPMs with a secondary amide unit and screened for their bioactivity. The results of the biological studies have been discussed in Part 5.

The current studies were started by exposing a mixture of methyl acetoacetate (40), urea (41), benzaldehyde (42) and tributylborate to microwave in the absence of a solvent for 3 minutes at a power 390 W. It gave the target dihydropyrimidinone 43 in efficient yield of 95% (Scheme 1.12). A number of 1,3-diketones, urea/thiourea and aldehydes were found to be the suitable substrates for DHPMs synthesis under these conditions.

**Scheme 1.12. Reaction of Methylacetoacetate, Urea And Benzaldehyde in Presence of Tributylborate.**
In the first part of the study, I have synthesized only known compounds to ascertain its applicability under different set of substrates and their melting points and other spectroscopic data are compared with that reported in the literature (Table 1.1). The microwave method gave good yields under micro-scale synthesis. However, in bulk synthesis the yield of the target compound was not very efficient. Hence, for large scale preparations, the reflux method has also been employed.

In the reflux method, the reaction was carried out in a dimethylformamide (DMF)-methanol solvent mixture at room temperature as well as under reflux condition. The summary of the optimization experiment carried out on the synthesis of compound 43 under conventional conditions has been shown in Table 1.2. From the table it could be understood that the room temperature experiments are not giving any satisfactory results. At the same time under reflux condition considerable yield was obtained. Also 1:1 DMF-methanol mixture was found to be a good solvent system for the reaction. All the compounds synthesized under solvent-free microwave assisted conditions have also been prepared under reflux condition and the yields are compared (Table 1.2).

From a comparative analysis of the microwave method and the reflux protocol for the synthesis of DHPMs, it is clear that the microwave method has merit over the other one in reaction time and yield. Also, the work up under microwave method is very simple, easy and less time consuming than that of the reflux protocol. As the microwave strategy did not use any volatile
organic solvents for synthesis it is an eco-friendly method. Except a few, most of the compounds are obtained in 95% purity. The formation of byproducts was almost negligible and the reaction was complete within 4-12 minutes. Although the microwave-assisted methods have many merits compared to the tributylborate catalyzed reflux technique, the latter is advantageous over the former when a large-scale synthesis is concerned. Though it is a time consuming process, the reflux method provides reasonable yields of DHPMs.

**Table 1.1. Formation of DHPMs catalyzed by tributylborate.**

![Chemical reaction diagram]

**Table 1.2. Optimization experiments under solution phase conditions.**

<table>
<thead>
<tr>
<th>Entries</th>
<th>R₁</th>
<th>R₂</th>
<th>X</th>
<th>Time (A: hours; B: min)</th>
<th>Yield (%)</th>
<th>Melting point (°C)</th>
<th>Exptl.</th>
<th>Reported</th>
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<tr>
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<td>O</td>
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<td>72/87</td>
<td>174-176</td>
<td>178-180</td>
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<tr>
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<td>2-Cl-C₅H₄</td>
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<td>O</td>
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<tr>
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<td>OEt</td>
<td>O</td>
<td>6 4</td>
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<tr>
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<td>O</td>
<td>9 7</td>
<td>70/86</td>
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<tr>
<td>6</td>
<td>2-OH-C₅H₄</td>
<td>OEt</td>
<td>O</td>
<td>10 6</td>
<td>68/69</td>
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<td>65/79</td>
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**Table 1.2. Optimization experiments under solution phase conditions.**

<table>
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<tr>
<th>Time (hours)</th>
<th>Yield (%)</th>
<th>A Time (hours)</th>
<th>Yield (%)</th>
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---

A – Reflux method; B – Microwave assisted method

5
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<tr>
<td>3</td>
<td>Ethyl acetate</td>
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<td>32</td>
<td>10</td>
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<tr>
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<td>Acetonitrile</td>
<td>24</td>
<td>42</td>
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<tr>
<td>5</td>
<td>Toluene</td>
<td>26</td>
<td>12</td>
<td>14</td>
<td>52</td>
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<tr>
<td>6</td>
<td>DMF</td>
<td>16</td>
<td>41</td>
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<td>79</td>
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<td>DMF + Methanol (1:1)</td>
<td>15</td>
<td>48</td>
<td>8</td>
<td>82</td>
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</table>

The purification procedure for the dihydropyrimidinones are simple as the impurities in the reaction product can be easily removed by repeated washing with cold solvents such as alcohols, ethyl acetate, acetonitrile, toluene, chloroform etc. since the dihydropyrimidinones are insoluble in above mentioned cold solvents, at the same time impurities are perfectly soluble. The final purification could be done by crystallization from hot alcohol or alcohol-DMF mixture. Hence it is clear that the protocol using tributylborate reagent, as a promoter for the Biginelli multicomponent reaction is very adaptable and could be used with different substrates. The aromatic aldehydes with both electron withdrawing and electron donating functionalities behave efficiently and even the acid sensitive aldehydes such as furfuraldehyde and thiophene-2-carbaldehyde also form DHPMs with considerable yields.

A plausible mechanism proposed for this tributylborate mediated Biginelli reaction is depicted in scheme 1.13. The water scavenging nature of the reagent may enhance the rate of condensation of aldehydes with the urea to form an acyliminium derivative 44. Also the boron atom of the reagent co-ordinates with the diketone, which will convert it into a nucleophilic keto-enolic structure and thus promote its nucleophilic addition to the acyliminium derivative to form the intermediate 45. The final condensation-cyclisation of
45 to 47 is also speeded up by tributylborate. The excess reagent, if any, can be easily removed by the aqueous workup.

Scheme 1.13. Feasible Mechanism for Dihydropyrimidinone Formation in Presence of Tributylborate \([\text{B(OBu)}_3]\).

In the second part of our study, new dihydropyrimidinones were synthesized using tributylborate both under reflux and microwave assisted method. The diketones mainly used are acetoacatanilide, benzoyl acetone and methyl acetoacetate. To the best of my knowledge, acetoacatanilide was rarely used for the DHPMs synthesis. The aldehydes utilized for the library synthesis of pyrimidinones were hydroxyl, chloro, methoxy, nitro and amino derivatives of benzaldehyde. Apart from these, heterocyclic aldehydes such as furfuraldehyde, thiophene-2-carbaldehyde and polynuclear aldehydes like naphthaldehyde have been successfully exploited. The details of the compounds are shown in Table 1.3.

Table 1.3. Synthesis of new dihydropyrimidinones
A representative compound is discussed below.

All the newly synthesized compounds have been characterized by IR, NMR and Mass spectrometric techniques. Characterization of one representative compound is discussed below.

\[
\text{R}_1 \text{O} + \text{H}_2\text{N} - \text{NH}_2 + \text{O} = \text{O} \rightarrow \text{O} \text{O} \text{O} + \text{H}_2\text{N} - \text{NH}_2 + \text{O} = \text{O} \text{O} \text{O}
\]

A- Reflux method; B- microwave assisted method
1.3.1 Characterisation

The dihydropyrimidinone synthesized were characterized by the conventional spectroscopic techniques. For the spectroscopic discussion let the compound U48 may be selected as a representative molecule. The tentative structure of the compound is shown in Figure 1.4. For convenience let the molecule may be numbered as shown in Figure 1.4.

Figure 1.4. 5-Methoxy carbonyl-4-(N, N-dimethylamino phenyl)-6-methyl-3, 4-dihydro – 1(H)-pyrimidin-2-one

In the infrared spectrum of the compound U48, the major absorption were seen at 3234.47, 3109.04, 1712.67, 1645, 1620, 1303.79 and 1180 cm\(^{-1}\). The peaks at 3234.47 and 3109.04 cm\(^{-1}\) are due to the absorption of the two amide NH groups. The absorption of the ester carbonyl group (C\(_8\)) occurs at 1712 cm\(^{-1}\) and that of the ring carbonyl group (C\(_2\)) at 1645 cm\(^{-1}\). The vibration due to the C=C (between C\(_5\) and C\(_6\)), C-N and C-O of esters appears at 1620, 1379 and 1180 cm\(^{-1}\) respectively. The IR spectrum of the compound is shown in Figure 1.5.
Figure 1.5. IR spectrum of the compound U48
In the $^1$H NMR spectrum there are seven distinct proton resonances. The down field resonances at $\delta$ 9.08 and $\delta$ 7.582 are ascribed to the two NH protons at position 1 and 3 of the pyrimidone ring. The NH proton at position 1 is more deshielded than the NH at position 3, as the former is flanked by an electron withdrawing carbonyl group and an electronegative sp$^2$ carbon, while the latter is near to a carbonyl group and an sp$^3$ carbon, which is less electronegative than C$_6$. The aromatic protons resonate at 7.0 and 6.6 ppm. The doublet at $\delta$ 7.0 is attributed to the protons on C$_{12}$ and C$_{16}$ of the aromatic ring. These protons are coupled to the protons at C$_{13}$ and C$_{15}$ with a coupling constant $J = 7$ Hz. Similarly the proton at C$_{13}$ and C$_{15}$ appears as a doublet at 6.6 ppm with a coupling constant $J = 7.2$ Hz. The similar J values for these protons confirm the mutual $^3$J coupling with a coupling constant ~ 7 Hz. The proton on the tertiary carbon C$_4$ resonates at $\delta$ 5.068. In the present compound under consideration the peak of the proton on C$_4$ appears as a singlet. But in the spectra of most of the other dihydropyrimidinones (Appendix I) it appears as a doublet with a coupling constant $J = 2-3$ Hz. This splitting is due to the amide NH near to C$_4$. A singlet peak at 3.54 ppm is attributed to proton on C$_{10}$ (-OCH$_3$). Similarly a singlet peak at $\delta$2.864 is ascribed to the resonance of protons of the methyl groups at C$_{17}$ and C$_{18}$. The methyl protons of C$_7$ resonate at 2.251 ppm. The proton NMR spectra of the compound U48 is shown in Figure 1.6.
Figure 1.6. a. H NMR spectrum of the compound U48
Figure 1.6.b. H NMR spectrum (Expanded) of the compound U48
The $^1$H-$^1$H COSY (Homonuclear Correlation Spectroscopy) spectrum of the compound U48 is shown in Figure 1.7. From the figure, it is clear that the proton correlation is between $H_{12}$ and $H_{13}$ or $H_{15}$ and $H_{16}$, in which $H_{12}$ & $H_{16}$ and $H_{13}$ & $H_{15}$ are equivalent protons. Another correlation is observed between $H_3$ and $H_4$.

**Figure 1.7.a. H-H COSY spectrum of the compound U48**

**Figure 1.7.b. H-H COSY spectrum (expanded) of the compound U48**
The $^{13}$C-$^1$H COSY spectrum (Heteronuclear Multiple Quantum Coherence, HMQC) shows the direct correlation of different protons with carbons to which they are attached. The correlation obtained from the C-H COSY spectra are $(C_{12}, H_{12})/(C_{16}, H_{16})$, $(C_4, H_4)$, $(C_{10}, H_{10})$, $(C_{18}, H_{18})/(C_{17}, H_{17})$ and $(C_7, H_7)$. The C-H COSY spectrum is shown in Figure 1.8.

Figure 1.8. C-H COSY spectra of the compound U48

The $^{13}$C NMR spectrum is shown in Figure 1.9. From the $^{13}$C NMR and C-H COSY spectra the chemical shift values are ascribed to the carbon as shown in the Table 1.4.

Table 1.4

<table>
<thead>
<tr>
<th>Carbons</th>
<th>C_7</th>
<th>C_{17} &amp; C_{18}</th>
<th>C_4</th>
<th>C_{10}</th>
<th>C_6</th>
<th>C_{12} &amp; C_{13}</th>
<th>C_{12} &amp; C_{14}</th>
<th>C_{11}</th>
<th>C_2</th>
<th>C_6</th>
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<td>Chemical shift ($\delta$ ppm)</td>
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<td>40.145</td>
<td>53.172</td>
<td>50.653</td>
<td>99.669</td>
<td>126.848</td>
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<td>147.737</td>
<td>149.668</td>
<td>165.972</td>
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</tbody>
</table>
Figure 1.9. $^{13}$C NMR spectrum of compound U48
The resonance of the N-methyl carbon is not seen in Figure 1.9, as it is merged with the solvent (DMSO) peak. But it is clearly visible in the DEPT spectrum (Figure 1.10).

The DEPT 135 spectrum of the compound is shown in Figure 1.10. The upward peaks at 17.708 ppm, 40.145 ppm, 50.651 ppm and 53.162 ppm represent the methyl carbons of C7, C17 & C18, C4 and C10 respectively. The aromatic CH group at (C12 & C16) and (C13 & C15) are represented by the upward peaks at δ112.142 and δ 126.845 ppm.

**Figure 1.10. The DEPT 135 spectrum of the compound U48**

The Heteronuclear Multiple Bond Correlation (HMBC) spectrum of the compound shows the correlation of the protons with carbon separated by more than one bond. The different multiple bond correlations are (H16, C15), (H16, C12), (H16, C14), (H15, C11), (H15, C13), (H17/ H18, C14), (H7, C6), and (H7, C5). The HMBC spectrum is shown in Figure 1.11.
Figure 1.11.a. HMBC spectrum of the compound U48

Figure 1.11.b. HMBC (expanded) spectrum of the compound U48
On the basis of the one and two-dimensional NMR experiments the chemical shift values ascribed to the protons are shown in Figure 1.12.

**Figure 1.12. The NMR chemical shift values of the compound U48.**

The structure is further confirmed by the mass spectrum. The molecular ion peak is obtained at m/z 289.40 and the base peak at m/z 154. The possible fragmentation pattern for the molecule is shown in scheme 1.14. The FAB mass spectrum of the compound U48 is shown in Figure 1.13.
Figure 1.13. FAB mass spectrum of the compound U48

The spectroscopic details of all other compounds are given in experimental section 1.4 and the spectra are shown in the Appendix I.

When terephthalaldehyde was made to react with acetoacetanilide and urea (1:2:2) in refluxing DMF-methanol mixture a double Biginelli condensation occurred to form a symmetric bi-dihydropyrimidinone as shown in Scheme 1.15. NMR and mass spectra confirmed the structure of the compound.
The spectra of this compound are shown in the Appendix I and the spectral data are given below.

Melting point - 327-329°C; IR ($\nu_{\text{max}}$, KBr, cm$^{-1}$) 3394 (NH), 3271.05 (NH) 3116.75 (NH), 1666 (C=O), 1630 (ring C=O), 1527 (N-H bend), 1328 (C-N), $^1$HNMR ($\delta$ppm, 300 MHz, DMSO-d$_6$) 9.329 (s, 2H, two NH), 8.420 (s, 2H, Ar), 7.2-7.1 (m, 4H, Ar), 7.0 (m, 4H, Ar) 5.50 (s, 2H, 3°C-H), 2.121 (s, 6H, CH$_3$). $^{13}$CNMR ($\delta$ppm, 75 MHz, DMSO-d$_6$), 164.643, 152.327, 137.826, 137.452, 127.451, 125.765, 122.346, 118.906, 104.798, 55.256, 17.313; MS (FAB) m/z - 537.40 (M+1, 10), 444.4 (100), 429 (55) 323.25 (35), 217.16 (40).

1.4. Experimental

1.4.1. Materials and Methods

All the known compounds reported herein are characterized by comparing their melting points, NMR and mass spectroscopic data with those reported in the literature. The new compounds synthesized are characterized by IR, NMR (one dimensional and two dimensional) and FAB mass spectra. All the chemicals used are of synthetic grade and are purified before use. The melting points are determined using a GUNF melting point apparatus and are uncorrected. The IR spectra are recorded on a SHIMADZU FTIR 8400S and
JASCO FT/IR-4100 Spectrophotometer in KBr medium, NMR spectra are recorded on a BRUKER AVANCE DPX 300 MHz Spectrometer in DMSO-d$_6$ using TMS as the internal standard and high-resolution mass spectra recorded on a JEOL JMS600 instrument.

1.4.2. General Synthetic Procedure

1.4.2.1. Synthesis of 5-methoxycarbonyl-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (43) under solvent free microwave assisted condition.

Methyl acetoacetate (0.69 g, 6 mmol), urea (0.48 g, 8 mmol), benzaldehyde (0.53 g, 5 mmol) and tributylborate (0.48 g, 2 mmol) are taken in a loosely stoppered borosil vessel and irradiated with microwave at a power level 390 W for 3 minutes, intermittently (6 x 30 seconds). The reaction mixture is transferred into crushed ice and stirred vigorously for 30 minutes. The crude solid separated is vacuum filtered, washed repeatedly with ice-cold ethyl acetate-petroleum ether mixture (1:1) and finally with distilled water. The dried product is further purified by crystallization from hot ethanol to obtain the pure product. The yield is 95%. Melting point - 206-207°C.

For the synthesis of all other compounds the above procedure was followed with respective substrates, reagents and time as shown in Table 1.1 and 1.3.

1.4.2.2. Synthesis of 5-methoxycarbonyl-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one(43) using tributyl borate as catalyst under the reflux method.

Methyl acetoacetate (0.69 g, 6 mmol), urea (0.48 g, 8 mmol), benzaldehyde (0.53 g, 5 mmol) and tributylborate (0.48 g, 2 mmol) are mixed in 5 ml dry solvent and stirred at room temperature/ refluxed for specified time as is indicated in Table 1.1. The reaction mixture is then poured into crushed ice and stirred vigorously for 1 hour keeping the temperature below
5°C. The solid separated out is vacuum filtered, washed repeatedly with ice-cold ethyl acetate and finally with distilled water. The crude product obtained is dried under vacuum and re-crystallised from ethanol for pure crystals. The yield is 85%.

In order to synthesis other compounds given Table 1.1 and 1.3 this procedure was adopted with appropriate substrates and reagents mentioned therein.

1.4.3. Spectroscopic Details

The spectral details of newly synthesized compounds are shown below

<table>
<thead>
<tr>
<th>Compound</th>
<th>Spectroscopic Data of the New Dihydropyrimidinones</th>
</tr>
</thead>
<tbody>
<tr>
<td>T21</td>
<td>IR ($\nu_{\text{max}}$, KBr, cm$^{-1}$) 3278.76 (NH), 3186.18 (NH), 1674 (Carbonyl group) 1627 (C=S), 1334.65 (C-N), 1203 (C-O) HNMR (δ ppm, 300 MHz, DMSO-D$_6$) 9.415 (s, 1H, NH), 9.014 (s, 1H, NH), 8.8 (s, 1H, NH), 7.5 (m, 2H, Ar) 7.3 - 7.2 (m, 8H, Ar), 7.034 (m, 1H, Ar), 5.5 (d, J=2.4 Hz, 1H, 3°C-H), 2.186 (s, 3H, CH$_3$). $^{13}$CNMR (δ ppm, 75 MHz, DMSO-D$_6$) - 173.915, 164.6, 141.9, 137.8, 135.2; 128.24, 128.03, 127.474, 126.10, 123.22, 119.539, 106.991, 55.517, 16.420, MS (FAB) m/z - 324.24 (M+1, 100), 217.16 (58), 172.25 (25), 149.16 (58).</td>
</tr>
<tr>
<td>U21</td>
<td>IR ($\nu_{\text{max}}$, KBr, cm$^{-1}$) 3278 (NH), 3109 (NH), 1681(C=O), 1635(C-N) $^1$HNMR (δ ppm, 300 MHz, DMSO-d$_6$) 8.584 (s, 1H, NH) 7.2 (d, J=8.4 Hz, 2H, Ar), 7.1 (d, J=7 Hz, 2H, Ar) 7.09-6.9 (m, 5H, Ar), 6.7 (s, 1H, Ar) 5.27 (s, 1H, 3°C-H) 1.925 (s, 3H, CH$_3$); $^{13}$CNMR (δ ppm, 75 MHz, DMSO-d$_6$). 165.0, 153.09, 142.8, 137.9, 128.1, 127.9, 127.2, 125.91, 123.030, 119.462, 105.280, 55.406, 16.822; MS (FAB) m/z-308.41 (M+1; 100), 265.35 (10), 215.24 (40), 172.28 (25).</td>
</tr>
</tbody>
</table>
U22 IR (ν_{max}, KBr, cm^{-1}) 3278.76 (NH), 3116.75(NH), 1700 and 1674 (C=O), 1630 (C=N), 1512 (NH-bend), 1326 (C-N) 1242.07 (C-O); HNMR (δ ppm, 300 MHz, DMSO-\textsubscript{d6}), 8.594 (s, 1H, NH), 8.438 (s, 1H, NH), 7.4 (d, J=7.8 Hz, 2H, Ar), 7.3 (d, J=8.7 Hz, 2H, Ar), 7.2 (t, J= 8 Hz, 2H, Ar), 7.0 (t, J= 7Hz, 1H, Ar), 6.8 (d, J= 8.7 Hz, 2H, Ar), 3.7 (s, 3H, OCH\textsubscript{3}), 2.181 (s, 3H, CH\textsubscript{3}); \textsuperscript{13}C NMR (δ ppm, 75 MHz, DMSO-\textsubscript{d6}) 165.014, 158.616, 152.926, 138.311, 137.948, 135.022, 128.05, 127.3; 123.1, 119.4, 113.5, 105.2, 55.03, 54.656, 16.924; MS (FAB) m/z - 338.30 (M+1, 100), 245.25 (43), 230.24 (85) 217.20 (45).

U24 IR (ν_{max}, KBr, cm^{-1}) 3286.48 (OH) 3209.33 (NH), 3093.61 (NH) 1681 (C=O), 1645 (C=O), 1272 (C-N), 1126 (C-O), HNMR (δ ppm, 300 MHz, DMSO-\textsubscript{d6}) 9.312 (s, 1H, NH), 8.890 (s, 1H, OH), 8.556 (s, 1H, NH), 7.866 (s, 1H, NH) 7.5 (d, J=7.8 Hz, 2H, Ar), 7.2 (s, 2H, Ar), 7.0 (m, 1H, Ar) 6.9 (s, 1H, Ar), 6.7 (m, 2H, Ar); 5.4 (s, 1H, CH), 2.1 (s, 3H, CH\textsubscript{3}); \textsuperscript{13}C NMR (δ ppm, 75 MHz, DMSO-\textsubscript{d6}) 164.57, 152.04, 146.3, 144.6, 137.54, 136.63, 133.67, 127.208, 122.136, 118660, 117.568, 114.054, 109.14, 104.718, 54.396, 54.173, 15.877; MS (FAB) m/z - 354.28 (M+1, 45), 230.21 (24), 217.20 (100).

U25 IR (ν_{max}, KBr, cm^{-1}) 3247.9, (NH), 1681 (C=O), 1527 (N-H bend) 1326 (C-N), 1249 (C=O), 756 (C-Cl), HNMR (δ ppm, 300 MHz, DMSO-\textsubscript{D6}) 8.9 (s, 1H, NH) 8.6 (s, 1H, NH), 6.5 (s, 1H, NH), 7.5 (m, 1H, Ar) 7.49 (d, J=7.5 Hz, 2H, Ar), 7.3 (d, J=7.5 Hz, 1H, Ar), 7.3-7.2 (m, 4H, Ar), 7.014 (m, 1H, Ar) \textsuperscript{13}C NMR (δ ppm, 75 MHz, DMSO-\textsubscript{D6}) 164.51, 152.51, 139.84, 138.33, 137.91, 131.62, 129.08, 128.74, 128.47, 127.92, 127.0, 123.0, 119.4, 103.3, 52.337, 16.822; MS (FAB) m/z 342.44 (m+1, 100), 299.35 (15), 249.32 (35), 206.26 (25).

U26 IR (ν_{max}, KBr, cm^{-1}) 3286.48 (NH), 3116 (NH) 1700 (C=O), 1674 (C=O), 1627 (C=C), 1326 (C-N) 1242 (C-O); \textsuperscript{1}HNMR (δ ppm, 300 MHz, DMSO-\textsubscript{d6}) 9.111 (s, 1H, NH) 8.536 (s, 1H,
N), 7.5 (d, J=7.8 Hz, 2H, Ar) 1.098 (S, 1H, NH), 7.2 (m, 2H, Ar), 7.09-7.0 (m, 2H, Ar), 6.3 (d, J=1.5 Hz, 2H, Ar), 5.5 (d, J=2.7 Hz, 1H, 3°CH), 2.191 (s, 3H, CH₃); ¹³CNMR (δppm, 75 MHz, DMSO-d₆) 164.553, 154.345, 152.896, 141.419, 140.628, 138.014, 127.778, 122.762, 119.347, 109.618, 105.418, 102.163, 48.607, 16.738; MS (FAB) m/z - 298.27 (M+1, 100), 230.24 (75), 205.25 (30).

NH), 8.827 (s, 1H, NH), 7.467 (d, J=7.8 Hz, 2H, Ar), 7.2-7.1 (m, 4H, Ar) 7.0-6.9 (m, 2H, Ar), 6.7 (d, 1H, Ar); ¹³CNMR (δ ppm, 75 MHz, DMSO-d₆) 164.936, 156.227, 152.677, 137.853, 137.707, 133.463, 127.787, 127.109, 122.784, 119.238, 114.956, 105.202, 54.785, 16.582; MS (FAB) m/z- 324.33 (M+1), 217.20 (100), 197.18 (20), 149.19 (15).

IR (νmax, cm⁻¹, KBr) 3425.34, (NH), 3247 (NH), 3116.75 (NH), 1700 (C=O), 1674 (C=O), 1519 (N-H bend), 1326 (C-N) 1249 (C-O); HNMR (δ ppm, 300 MHz, DMSO-d₆) 9.241 (s, 1H, NH), 8.827 (s, 1H, NH), 8.462 (s, 1H, NH), 7.467 (d, J=7.8 Hz, 2H, Ar), 7.2-7.1 (m, 4H, Ar) 7.0-6.9 (m, 2H, Ar), 6.7 (d, 1H, Ar); ¹³CNMR (δ ppm, 75 MHz, DMSO-d₆) 165.137, 153.932, 146.69, 137.29, 134.54, 129.83, 128.12, 123.85, 123.47, 122.66, 119.63, 21.948; MS (FAB) m/z- 354.19 (M+1, 25) 276.21 (100), 217.20 (100), 197.18 (20), 149.19 (15).

IR (νmax, cm⁻¹) 3278.76, 3070 (NH), 1650 (C=O) 1596 (C=C), 1535.23 (N=O), 1342 (C-N), HNMR (δ ppm, 300 MHz, DMSO-d₆) 10.142 (s; 1H, NH) 8.5 (S, 1H, NH), 8.05 (d, J=8.4 Hz, 1H, Ar), 7.9 (d, J=7.8 Hz, 1H, Ar) 7.5 (m, 2H, Ar), 7.3 (d, J=8.1 Hz, 2H, Ar), 7.2 (m, 2H, Ar) 7.0 (m, 1H, Ar), 4.83 (s, 1H, 3°C-H), 2.6 (s, 3H, CH₃) ¹³C NMR (δ ppm, 75 MHz, DMSO-d₆) 165.137, 153.932, 146.69, 137.29, 134.54, 129.83, 128.12, 123.85, 123.47, 122.66, 119.63, 21.948; MS (FAB) m/z- 354.19 (M+1, 25) 276.21 (100), 217.20 (45).

IR (νmax, KBr, cm⁻¹) - 3402.2 (NH), 3294 (NH), 3232.47 (NH), 1700 (C=O), 1596 (C=C), 1311 (C-N), HNMR (δ ppm, 300 MHz, DMSO-d₆) 7.8-7.7 (m, 2H, Ar), 7.5-7.4 (m, 7H, Ar), 7.2 (m, 2H, Ar) 7.0 (t, J=7.2 Hz, 1H, Ar), 5.6 (d, J= 2.1Hz, 1H, 3°C -H) 2.1 (s, 3H, CH₃); ¹³C NMR (δ ppm, 75MHz, DMSO-d₆) 164.563, 152.261, 139.942, 137.553, 137.025, 131.767, 131.411, 127.253, 126.691, 126.230,
124.960, 124.709, 123.783, 123.604, 122.233, 118.821, 104.632, 54.676, 16.045; MS (FAB) m/z- 358.22 (M+1, 100), 265.22 (35), 222.19 (30)

U217
IR (ν _max_, cm⁻¹, KBr). 3471.63 (NH), 3394.48 (NH), 3263.33 (NH), 1666 (C=O), 1527 (N-H bend) 1319.22 (C-N); ¹H NMR (δ ppm, 300 MHz, DMSO-d₆). 8.62 (s, 1H, NH), 8.414 (s, 1H, NH), 7.5, 7.4 (m, 2H, Ar) 7.2 (m, 3H, Ar), 7.0 (m, 1H, Ar), 7.016 (s, 1H, NH), 6.9 (m, 2H, Ar), 5.7 (d, J = 2.7 Hz, 1H, 3°C-H), 2.212 (s, 3H, CH₃)

¹³CNMR (δ ppm, 75 MHz, DMSO-d₆) 164.727, 152.778, 147.293, 139.501, 138.059, 128.211, 126.487, 124.816, 123.972, 119.700, 105.19, 5.98, 17.189; MS (FAB) m/z- 314 (M+1), 230.24, 217.2, 181.17.

U44
IR (ν _max_, KBr, cm⁻¹) 3386.7 (OH), 3255.6 (NH), 3132.18 (NH), 1740 (C=O), 1674.10 (C=O), 1350 (C-N), 1234.36 (C-O); ¹H NMR (δ ppm, 300 MHz, DMSO-d₆) 9.111 (s, 1H, NH), 9.019 (s, 1H, NH), 7.636 (S, 1H, OH), 6.813 (S, 1H, Ar), 6.689 (d, J = 8.1 Hz, 1H, Ar) 6.6 (d, J = 8.7 Hz, 1H, Ar); ¹³CNMR (δ ppm, 75 MHz, DMSO-d₆) 167.597, 165.942, 152.318, 148.057, 147.234, 145.669, 135.595, 118.098, 115.109, 110.630, 99.328, 55.327, 53.390, 17.712.

U47
IR (ν _max_, KBr, cm⁻¹) 3579.64 (OH), 3240 (NH), 3116 (NH) 1681 (C=O), 1320 (C-N), 1234 (C-O); ¹H NMR (δ ppm, 300 MHz, DMSO-d₆) 9.164 (s, 1H, NH), 8.873 (s, 1H, NH), 7.190 (s, 1H, OH), 7.1 (d, J = 8.4 Hz, 2H, Ar), 6.7 (d, J = 8.4 Hz, 2H, Ar), 5.2 (d, J = 3 Hz, 1H, 3°C-H) 3.6 (s, 3H, OCH₃ - it is found merged with the solvent peak), 2.3 (s, 3H, CH₃); ¹³CNMR (δ ppm, 75 MHz, DMSO-d₆) 167.208, 165.355, 155.59, 152.04, 146.553, 134.357, 126.588, 114.219, 99.350, 53.043, 17.567; MS (FAB) m/z- 263.40 (M+1), 154.86 (100).

U411
IR (ν _max_, KBr, cm⁻¹) 3317.34 (NH), 3201.6 (NH), 1670 (C=O)
1342.36 (C-N), 1249.79 (C-O); $^1$HNMR ($\delta$ppm, 300 MHz, DMSO-d$_6$) 9.262 (s, 1H, NH), 7.683 (s, 1H, NH), 7.9-7.8 (m, 5H, Ar) 7.5-7.4 (m, 7H, Ar), 5.364 (s, 1H, 3°C-H) 3.5 (s, 3H, OCH$_3$), 2.315 (s, 3H, CH$_3$); $^{13}$CNMR ($\delta$ppm, 75 MHz, DMSO-d$_6$) 165.882, 152.167, 148.737, 141.780, 132.646, 128.299, 127.779, 126.216, 125.874, 124.356, 98.884, 50.777, 17.831; MS (FAB) m/z - 297.37 (M+1), 217.24 (100), 181.24, 149.16.

**U417**

IR ($\nu$$_\text{max}$, KBr, cm$^{-1}$) 3332.76 (NH), 3247.9 (NH), 1689.53 (C=O), 1643 (C=C), 1311.5 (C-N), 1226.6 (C-O); $^1$HNMR ($\delta$ppm, 300 MHz, DMSO-d$_6$) 9.167 (s, 1H, NH), 1.016 (s, 1H, NH), 7.1 (d, J= 4.5 Hz 1H, Ar), 7.0 (d, J= 4.8 Hz, 1H, Ar) 6.8 (t, J= 4.2 Hz, 1H, Ar), 5.5 (d, J=3.3 Hz, 1H, 3°C-H), 3.6 (s, 3H, OCH$_3$), 2.3 (s, 3H, CH$_3$) $^{13}$CNMR ($\delta$ppm, 75 MHz, DMSO-d$_6$) 166.229, 164.523, 151.583, 147.370, 145.081, 125.219, 122.855, 122.238, 121.088, 100.222, 49.412, 17.078; MS (FAB) m/z - 253.20 (M+1, 100), 224.18, 217.16.

**U56**

IR ($\nu$$_\text{max}$, KBr, cm$^{-1}$) 3325.05 (NH), 3271.05 (NH) 1689.5 (C=O), 1612 (C=C), 1334 (C-N), 1242 (C-O), $^1$HNMR ($\delta$ppm, 300 MHz, DMSO-d$_6$) 8.876 (s, 1H, NH), 7.5-7.3 (m, 6H, Ar) 7.040 (s, 1H, NH) 6.2 (d, J=1.5 Hz, 1H, -H), 6.1 (d, J=2.7, 1H, fufuryl-H), 5.543 (s, 1H, 3°C-H), 1.787 (S, 3H, CH$_3$) $^{13}$CNMR ($\delta$ppm, 75 MHz, DMSO-d$_6$) 194.043, 154.635, 152.659, 145.458, 141.2, 140.2, 130.8, 127.7, 127.3, 109.6, 106.9, 105.17, 49.18, 18.19; MS (FAB) m/z 283.15 (M+1), 217.13 (100), 181.14, 149.1.

**U57**

IR ($\nu$$_\text{max}$, cm$^{-1}$, KBr), 3350 (OH) 3224.76 (NH), 3109 (NH), 1681 (C=O), 1612 (C=C) 1334 (C-N); $^1$HNMR ($\delta$ppm, 300 MHz, DMSO-d$_6$) 8.957 (s, 1H, NH), 8.831 (s, 1H, NH), 7.4 (d, J= 6.6 Hz, 2H, Ar), 7.3 (m, 2H, Ar), 6.7(d, J= 8.4 Hz, 2H, Ar), 5.4 (s, 1H, 3°C-H), 1.728 (s, 3H, CH$_3$) $^{13}$CNMR ($\delta$ ppm, 75 MHz, DMSO-d$_6$) 194.625, 155.955, 152.429, 142.32, 140,
159, 133.938, 130.769, 127.621, 126.885, 114.625, 109.991, 55.135, 17.872; MS (FAB) m/z 309.60 (M+1), 253.6, 169.44 (100).

IR ($\nu_{max}$, KBr, cm$^{-1}$) 3294 (NH), 3201(NH), 1704.96(C=O), 1596 (C=O), 1360 (C-N) $^1$HNMR ($\delta$ppm, 300 MHZ, DMSO-d$_6$), 9.079 (NH), the other NH peak has been merged with the aromatic protons, 7.8 - 7.3 (m, 12H, Ar) 5.6 (d, 1H, 3°C-H), 1.748 (s, 3H, CH$_3$), $^{13}$CNMR ($\delta$ppm, 75 MHZ, DMSO-d$_6$) 193.86, 15.181, 143.53, 140.24, 139.92, 131.77, 131.44, 130.32, 127.26, 126.71, 126.31, 124.98, 124.69, 123.71, 108.8, 55.13; 17.652.

IR ($\nu_{max}$ KBr, cm$^{-1}$) - 3294.1 (NH), 3186.18 (NH), 1700 (C=O), 1581.5 (C=C), 1473 (N-H bend), 1357 (C-N), $^1$HNMR ($\delta$ppm, 300 MHz, DMSO-d$_6$) 9.077 (s, 1H, NH), 8.9 (s, 1H, NH), 7.6-7.3, (m, 5H, Ar), 7.2 (d, J=6 Hz, 1H, Thiophenyl-H), 7.0 (d, J=3.1 Hz, 1H, Thiophenyl-H), 6.7 (t, 1H, Thiophenyl-H) 5.7 (d, J=3.3 Hz, 1H, 3°C-H), 1.9 (s, 3H, CH$_3$) $^{13}$CNMR ($\delta$ppm, 75 MHZ, DMSO-d$_6$) 195.585, 151.750, 147.194, 142.970, 140.022, 139.941, 130.016, 127.342, 126.850, 126.764, 125.466, 109.341, 50.066, 17.853; MS (FAB) m/z- 299.26 (M+1), 221.22, 157.12 (100).

1.5. Conclusions

In the present work I have adopted a new synthetic strategy for the dihydropyrimidinones under a solvent free microwave assisted green approach. Compared to the solution phase mode, the microwave-assisted method is found to be more advantageous. It is simple, easy, fast and high yielding. The workup procedure is simple and in most cases the products are obtained in high purity just by washing with cold solvents. The strategy is very versatile as it provides for any variation in the components of the reaction.
The method so far developed for the synthesis of Biginelli compounds extensively made use of metal containing reagents that may contaminate the highly pharmacologically active pyrimidinone moiety. Hence our aim was to use a mild and efficient non-metallic reagent for the DHPM synthesis. Thus, a new boron-based reagent has been introduced for the expeditious synthesis of dihydropyrimidinones under the microwave-assisted protocol. The reagent can be successfully used under solution conditions also. Herein we have synthesized the DHPMs both under microwave assisted and solution phase experimental conditions and the yields were compared. As far as yield is concerned the two methodologies are almost equally efficient with slight predominance for the microwave method. But when rapidity and simplicity are considered the microwave method is the better of the two. The reactions, which require 5-12 hours under solution method, could be completed within 4-10 minutes by the microwave-assisted protocol. The main disadvantage with microwave method is the scaling up process. The method as such cannot be used for the large-scale synthesis with in the limitation of microwave synthesis.

The present protocol can adjust with the change in any components of the reaction. Five diketones, nine aromatic and two heterocyclic aldehydes, urea and thiourea have been used to generate a variety of DHPMs under the current experimental conditions. Twenty new compounds have been added to the Biginelli library using the new protocol. All the aromatic aldehydes with electron withdrawing and electron donating functional groups on the ring reacted effectively to give the desired product. Even acid sensitive heterocyclic aldehydes such as furan-2-carbaldhyde and thiophene-2-carbaldehyde formed DHPMs by this novel method.

From the pharmaceutical point of view, as the method does not involve the use of any heavy metal species, the products may be obtained free of any heavy metal contamination. Also when the reaction is followed by microwave-assisted route for synthesis, the product could be obtained by a
simple, easy, fast, economic and clean strategy. The process is solvent-free and the simple workup procedure affords pure product. The quantity and numbers of byproducts formed are negligible and could be removed by solvent washing. Hence this methodology may be claimed to be an eco-friendly ‘green protocol’ for Biginelli reaction.
1.6. References


