CHAPTER 4

A Green Approach for the Synthesis of 2-Oxo-1,2,3,4-Tetrahydropyrimidines through Oxidative Functionalization of Methyl Arenes/Benzyl Derivatives via *in situ* Generated Urea

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4.1 Introduction

The nitrogen-rich heterocyclic compounds constitute a major portion of naturally occurring and biologically active compounds [1], and have recently gained considerable attention in most of biomedical and pharmaceutical industries [2, 3]. Pyrimidine is a prevalent N-heteroaromatic compound with two nitrogen atoms in its backbone. Among them 2-oxo-1,2,3,4-tetrahydropyrimidines are key moieties present in various natural, synthetic and semi-synthetic chemical building blocks [4]. 2-Oxo-1,2,3,4-tetrahydropyrimidines have multiple therapeutic and pharmacological activities including; antimicrobial, antiviral, anticancer, anti-inflammatory action [5, 6], and also include the adrenergic receptor antagonists for prostatic hyperplasia treatment [7]. Oxo-monastrol as the anti-proliferative agent and its substituted compounds such as Fluorastrol, and Nitractin for multiple biological activities and (R)-SQ32926 as the antihypertensive agent [8] (**Figure 4.1**). Many synthetic chemicals like veranal which is used as a sedative and zidovudine [9], an HIV medication, contain tetrahydropyrimidines moiety in their chemical structure. The importance of 2-oxo-1,2,3,4-tetrahydropyrimidines has attracted numerous researchers for its synthesis via various chemical pathways. The Biginelli reaction was the first

multicomponent reaction introduced for synthesizing 2-oxo-1,2,3,4- tetrahydropyrimidines involves the cyclo-condensation of ethyl acetoacetate, benzaldehyde, and urea [10, 11].

In this regard, several homogeneous and heterogeneous acidic catalysts, solvents and approaches have been utilized for improving the yield of Biginelli's reaction product, like ceric ammonium nitrate [12], bismuth nitrate under microwave irradiation [13], 2,4,6-trichloro-1,3,5-triazine (TCT) under ultrasound radiation [14], lewis acid $BF_3.Et_2O$ [15], niobium oxides [16], lanthanide triflates [17], (Bi $(NO_3)_3$) [18], indium chloride [19], antimony chloride [20], barium chloride [21], molecular iodine [22], heteropoly acids [23], copper iodide [24], sodium dodecyl sulphate, (SDS) as an anionic surfactant [25], and $ZrCl_4(THF)_2$ [26] have been used to improve the yield value.

Bio-organic catalyst taurine (2-aminoethanesulfnic acid) [27], and heterogeneous catalysts aluminate sulfonic acid nanoparticles [8], alumina supported MoO_3 [28], amberlyst-70 [29], acidic ionic liquids [30] have also been used. In 2012 Gupta et al., introduced a novel recoverable interphase catalyst sulfonic acid onto silica [31]. Wu Yang Jie et al., 2019 reported an "electrochemical off-on" as an alternative technique for the synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines [32].

However, despite of their potent utility, some of the above methods involved the usage of high-priced catalysts, toxic solvents, strongly-acidic conditions, long-drawn-out reaction, low yield and environmental disposal problems. In addition, the demand of green

chemistry has proposed eco-friendly multicomponent reactions (MCRs) as a best choice for the synthesis of complex molecules with negligible side products [33–35].

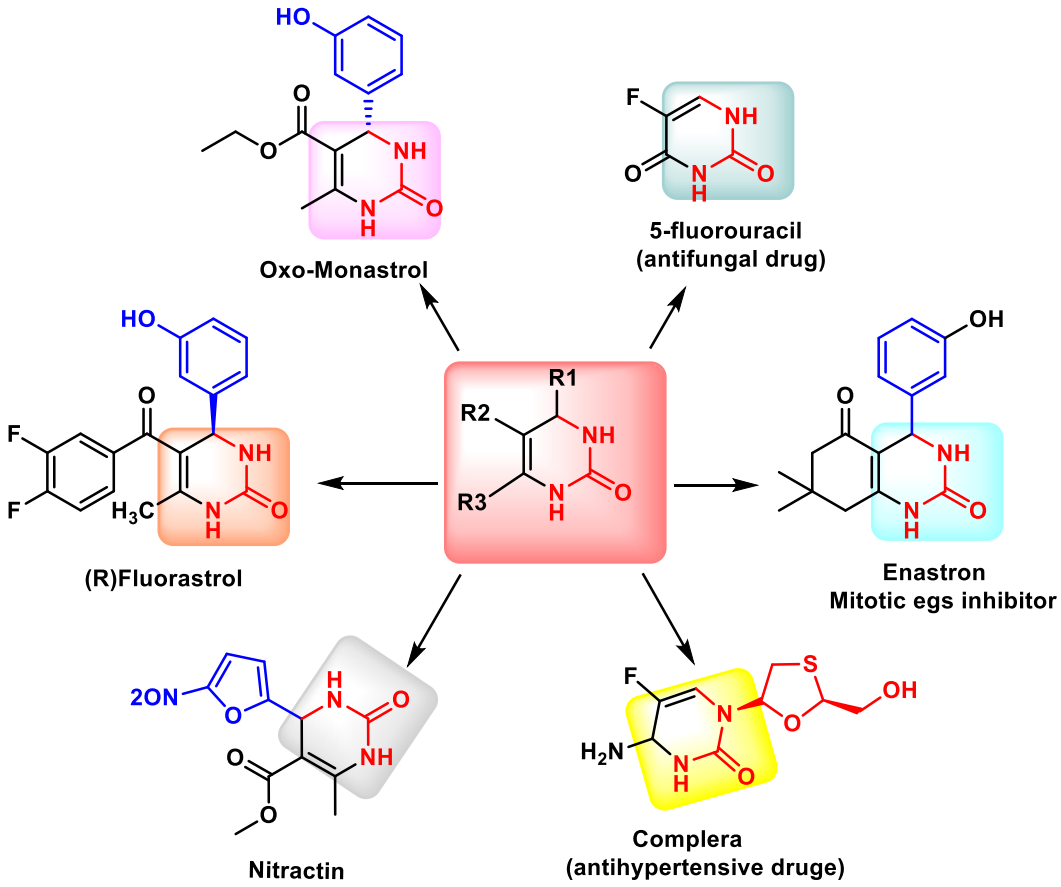


Figure 4.1 Biologically active 2-oxo-1,2,3,4-tetrahydropyrimidines as a key functional moiety.

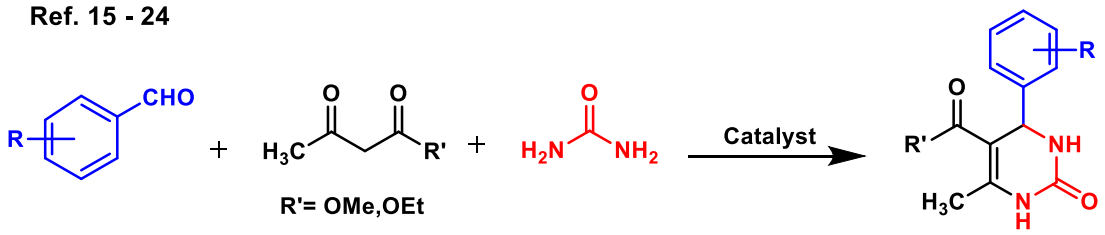
This necessitated the demand of biocompatible, economical, and environmentally safe catalysts, reagents, solvents and starting materials for the synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines. Numerous organic transformations have been already performed for the synthesis of many biomolecules using eco-friendly green solvents like; ionic liquid,

supercritical CO_2, bio-based green solvents or solvent-free conditions etc [36–38]. In addition, solvent-free conditions have also emerged recently as an ideal alternative that not only minimizes environmental pollution but are also cost-effective [39].

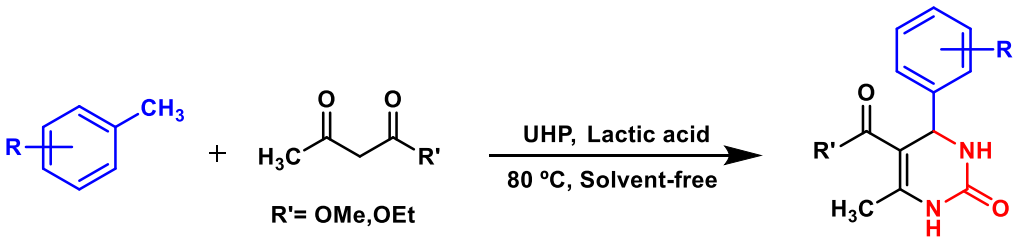
Current work involved the green synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines using methyl arenes as a surrogate of aldehydes. Methyl arenes are cheap and naturally abundant material reported for their use as key starting material in various organic synthesis [40]. In addition to this, urea hydrogen peroxide (UHP) was utilized as an oxidizing reagent. It is a cheap, non-toxic, anhydrous neutral white, and odourless crystalline solid with higher stability than hydrogen peroxide at room temperature [41], it can be employed as a source of water-free hydrogen peroxide for oxidation reactions. Moreover, during oxidation, urea-hydrogen peroxide produces only nontoxic commercial urea as a byproduct, a key advantage of UHP. UHP has been well examined in number of chemical transformations including the chemoselective ipso-hydroxylation of aryl boronic acids [42], a well-known Dakin and Baeyer-Villiger reaction as well as pyranopyrazoles synthesis are also conducted in presence of UHP [43, 44]. Our study also utilized lactic acid as a green catalyst, it is a non-toxic, odourless and bio-based fluid obtained via carbohydrates fermentation. It is biodegradable and diversely used as food, textile, agricultural, pharmaceutical, and cosmetic components [38]. Lactic acid is reported as the potent catalyst as well as a solvent for carrying out various chemical reactions [45]. In 2012, Yanlong Gu and co-workers have revealed the role of lactic acid as a green solvent for carrying out multicomponent reactions (MCRs) with multiple benefits like reusability,

elementary isolation of final products, and high efficiency [46]. In continuation of our research work, we wish to report a simple efficient, environmentally benign synthesis of biologically relevant tetrahydropyrimidine and its derivatives using readily available methyl arenes, alkyl acetoacetate, and urea- hydrogen peroxide (UHP) as starting materials (**Scheme 4.1**). To the best of our knowledge, no such method has been reported where methyl arenes are employed as the source of acyl precursors and UHP for *in situ* generation of urea for synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines in the solvent-free condition.

A) Previous method



B) Present method



Scheme 4.1 Synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines.

4.2 Results and Discussion

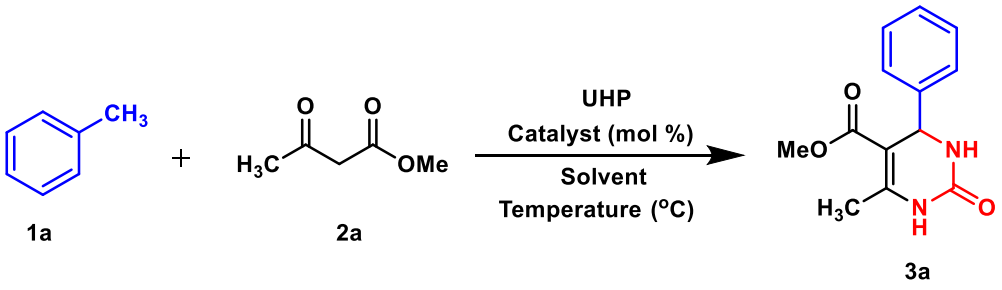
4.2.1 Optimization of Reaction Conditions

The one-pot synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidine (**3a**) (**Scheme 4.1**) was carried out for optimizing the reaction parameters involving experiments with the stoichiometric ratio of toluene (**1a**, 1.0 mmol), methyl acetoacetate (**2a**, 1.0 mmol) and urea-hydrogen peroxide (UHP, 2.0 mmol) as model substrates. The reaction was initiated with reflux in ethanol without catalyst that resulted in only 20% of the product even after 10 h of reaction. However, a similar reaction carried out in ethanol with lactic acid (10 mol %) as a catalyst which was found to increase the yield to 50% in 4 h. Thereafter, the synthesis was carried out for optimizing various reaction parameters like solvents, catalyst loading, the amount of UHP and reaction temperature. To find the appropriate solvent, the reaction was tested in different polar and non-polar solvents at its reflux temperature in the presence of lactic acid (10 mol %) for 4 hrs. The polar solvents like ethanol, methanol, water, 1,4-dioxane, dimethylformamide, dichloromethane and acetonitrile resulted in 3,4-dihydropyrimidine-2(1*H*)-one (**3a**) with 30-50 % yields (**Table 4.1, entries 1-7**). On the other hand, non-polar solvents like xylene, and benzene failed to give the product (**3a**) (**Table 4.1, entries 8, 9**). Further to improve the yield of 2-oxo-1,2,3,4-tetrahydropyrimidine (**3a**), we proceeded the reaction without solvent at 80 ºC with lactic acid that surprisingly improved the yield to 65% in 2.5 h and extending the heating time up to 4 h does not found to have any effect on yield value. Solvent free conditions increase the rate of reaction may be due to increase in

collision frequency which results in decrease the rection time, this could be the reason which resulted in high yield in solvent free conditions. In contrast, the reaction carried out at 80 ºC without lactic acid even for 4 h resulted only in 25% yield. This showed the presence of lactic acid is vital for improving the yield of product (**3a**). Some other readily available acid catalysts like acetic acid and trifluoroacetic acid were also tested in solvent-free condition but the best result was obtained in the presence of lactic acid.

Therefore, the optimized conditions selected for 2-oxo-1,2,3,4-tetrahydropyrimidine (**3a**) synthesis were toluene (**1a**, 1.0 mmol), methyl acetoacetate (**2a**, 1.0 mmol) and urea-hydrogen peroxide (UHP, 3.0 mmol) in the presence of lactic acid (20 mol%) as a catalyst at 80 ºC without solvent. The final product (**3a**) was characterized for its molecular structure and composition by ^{1}H, ^{13}C NMR, and mass spectral (HRMS) analysis.

Table 4.1 Screening of parameters for the synthesis of tetrahydro pyrimidine **3a**[a]



Entry	Solvent	UHP (mmol)	Catalyst (mol%)	Temp. (ºC)	Time (h)	Yield (%)[b]
1	Ethanol	2	Lactic acid (10)	Reflux	4	50
2	Methanol	2	Lactic acid (10)	Reflux	4	43
3	Water	2	Lactic acid (10)	Reflux	4	30
4	1,4 Dioxane	2	Lactic acid (10)	Reflux	4	30

5	DMF	2	Lactic acid (10)	Reflux	4	41
6	DCM	2	Lactic acid (10)	Reflux	4	35
7	Acetonitrile	2	Lactic acid (10)	Reflux	4	30
8	Xylene	2	Lactic acid (10)	Reflux	4	NR
9	Benzene	2	Lactic acid (10)	Reflux	4	NR
10	-	2	Lactic acid (10)	80	2.5	65
11	-	2	-	80	4	25
12	-	2	Acetic acid (10)	80	2.5	50
13	-	2	Trifluoroacetic acid (10)	80	2.5	55
14	-	2	Lactic acid (15)	80	2.5	75
15	-	2	Lactic acid (20)	80	2.5	80
16	-	2	Lactic acid (25)	80	2.5	80
17	**-**	**3**	**Lactic acid (20)**	**80**	**2.0**	**89**
18	-	4	Lactic acid (20)	80	2.0	89
19	-	3	Lactic acid (20)	70	2.0	40
20	-	3	Lactic acid (20)	100	2.0	88
21	Lactic acid	3	-	Reflux	2.0	88

[a] **Reaction conditions**: Toluene (1.0 mmol), methyl acetoacetate (1.0 mmol) and UHP with the lactic acid in 2 ml of the solvents at their refluxed temperature. [b] Isolated yield.

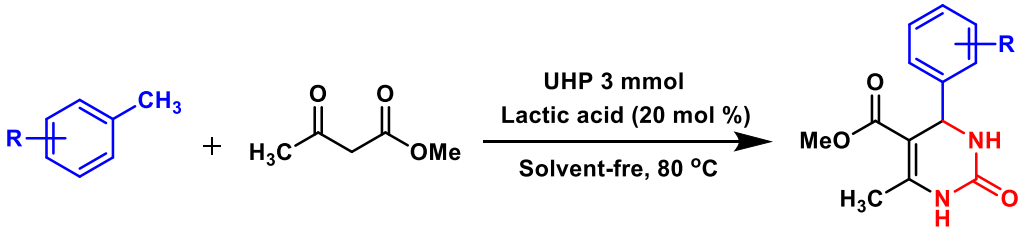
4.2.2 Substrate Scope

Keeping all optimal parameters in hand (**Table 4.1, entry 17**), the suggested methodology's substrate range was investigated using several methyl arene derivatives such as toluene (**1a**), 1-methoxy-4-methylbenzene (**1b**), *N*,*N*,4-trimethylaniline (**1c**),1-chloro-2-methylbenzene (**1d**), 1-bromo-2-methylbenzene(**1e**), 1-fluoro-4-methylbenzene(**1f**), 1-

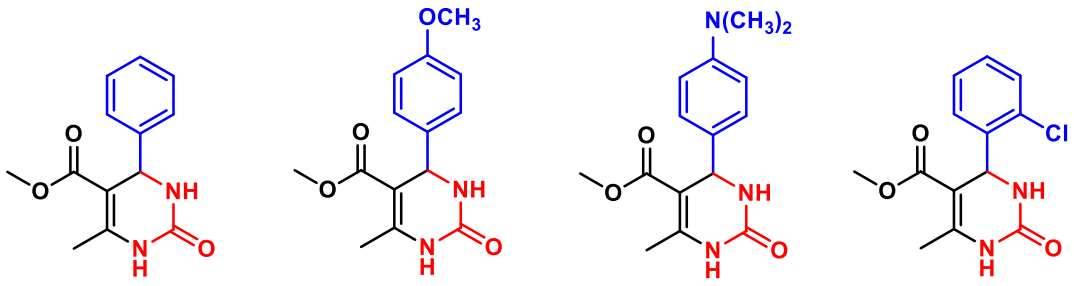
chloro-4-methylbenzene (**1g**), 1-bromo-4-methylbenzene (**1h**), 1-methyl-4-nitrobenzene (**1i**), 2-methylpyridine(**1j**), 2-methylthiophene (**1k**) with methyl acetoacetate (**2a**) and UHP which gave a series of 2-oxo-1,2,3,4-tetrahydropyrimidines derivatives viz. Methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3a**), Methyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3b**), Methyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3c**), Methyl 4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3d**), Methyl 4-(2-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3e**), Methyl 4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3f**), Methyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3g**), Methyl 4-(4-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3h**), Methyl 4-(4-nitrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3i**), Methyl 6-methyl-2-oxo-4-(pyridin-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3j**), Methyl 6-methyl-2-oxo-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3k**) with good to excellent yields (**Table 4.2**). Coincidentally, both methyl arenes linked electron-donating groups (methoxy and N, N-dimethyl) (**Table 4.2, entries 2-3**) and electron-withdrawing groups (nitro, chloro, fluoro and bromo) (**Table 4.2, entries 4-9**) gave substantial yield. pyridine and 2-methyl thiophene were also tested under the same reaction conditions which also gave good yield (**Table 4.2, entries 10-11**). In addition to this ethyl acetoacetate (**2b**) was used and yielded smoothly products Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-

carboxylate (**3l**), Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3m**), Ethyl 4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3n**), Ethyl 4-(2-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3o**), Ethyl 4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3p**), Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3q**), Ethyl 4-(4-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3r**), Ethyl 4-(4-nitrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3s**), Ethyl 6-methyl-2-oxo-4-(pyridin-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3t**), Ethyl 6-methyl-2-oxo-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3u**) in good to excellent yield under optimized reaction conditions (**Table 4.3**). The scope of above established methodology was also evaluated with various benzyl alcohol derivatives such as phenylmethanol (**4a**), (methoxyphenyl)methanol (**4b**), (4-chlorophenyl)methanol (**4c**), (2-chlorophenyl)methanol (**4d**), (4-fluorophenyl)methanol (**4e**) and benzyl bromide derivatives such as 1-bromo-2-(bromomethyl)benzene (**4f**), 1-(bromomethyl)-4-nitrobenzene (**4g**), 1-(bromomethyl)-2-chlorobenzene (**4h**), 1-bromo-4-(bromomethyl)benzene (**4i**) for obtaining Biginelli products. The outcomes showed favorable results with good yield values in shorter reaction time. The chemical structures of the synthesized compounds were established from their spectral data. The structure of the products along with their reaction time and yields are summarized in (**Table 4.4**).

Table 4.2 Substrate scope for the synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines **(3a-k)**[a]



1a-k 2a 3a-k



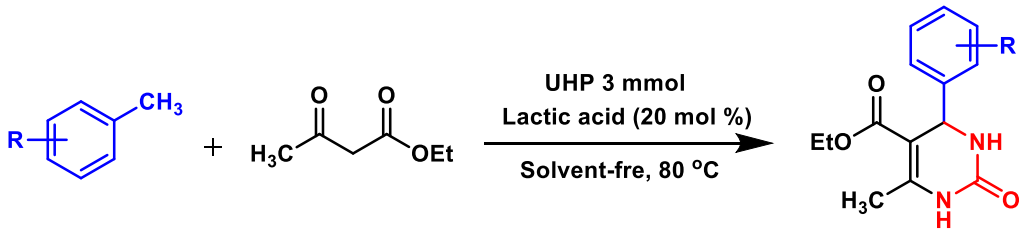
3a; 89% 3b; 85% 3c; 83% 3d; 82%

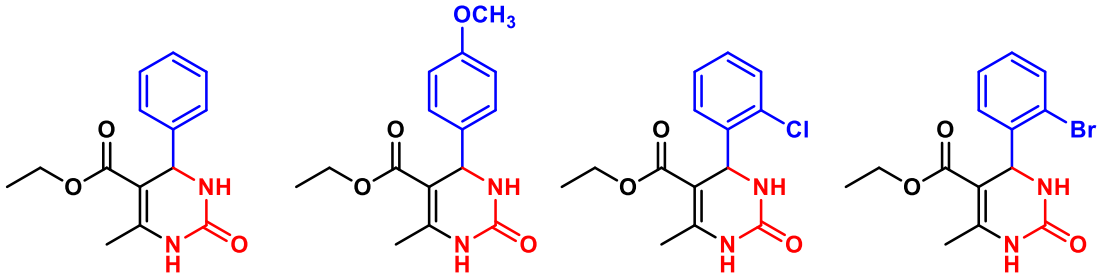
3e; 82% 3f; 87% 3g; 84% 3h; 85%

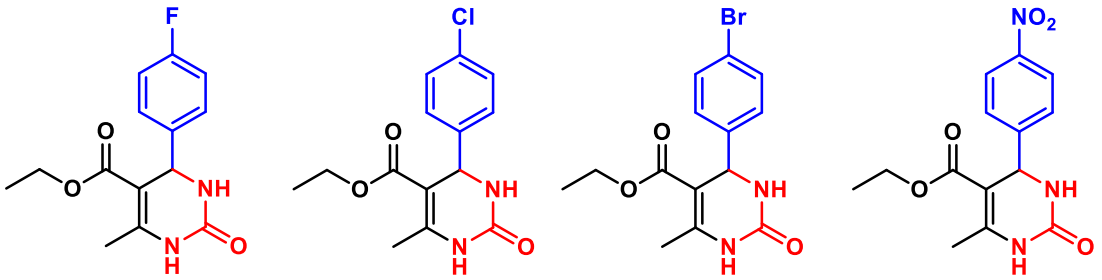
3i; 88% 3j; 80% 3k; 80%

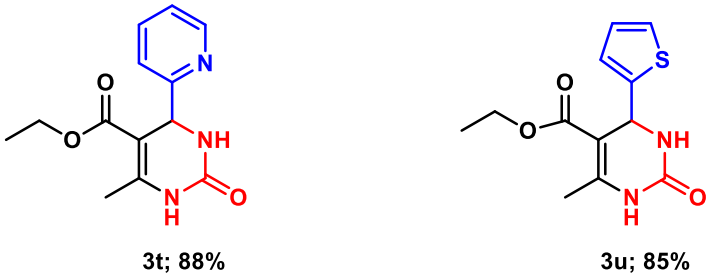
[a]**Reaction conditions:** Methyl arenes (1.0 mmol), methyl acetoacetate (1.0 mmol) and UHP (3.0 mmol) with lactic acid (20 mol%) at 80 ºC.

Table 4.3 Substrate scope for the synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines **(3l-u)**[a]



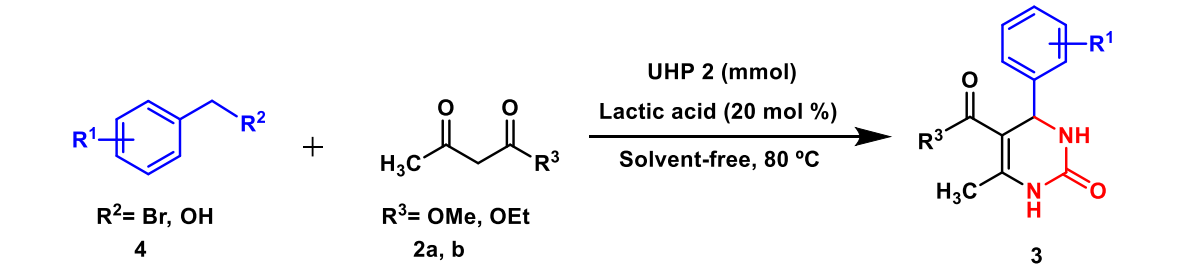


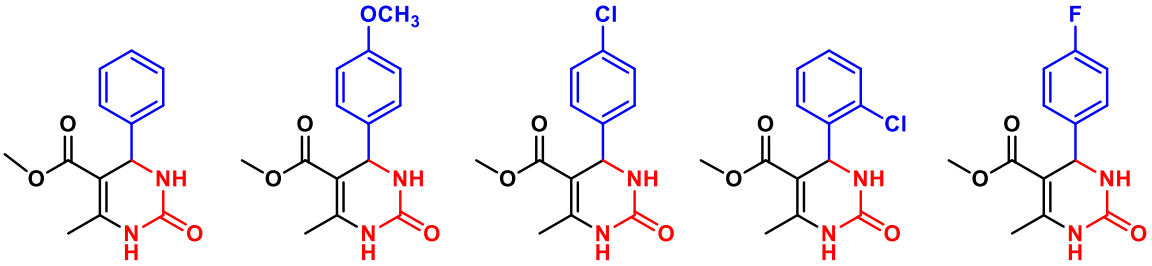


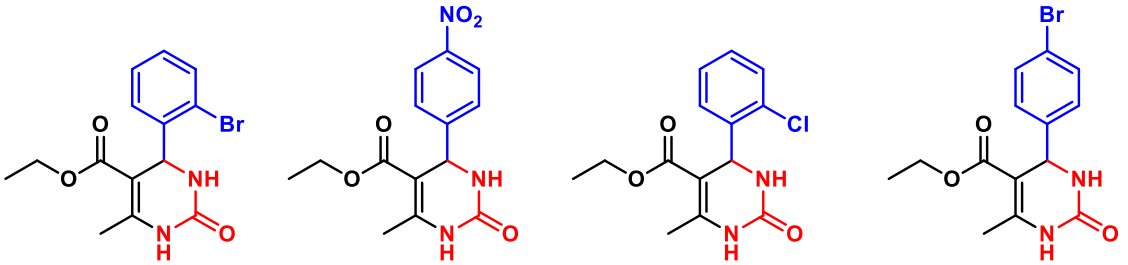


[a]**Reaction conditions:** Methyl arenes (1.0 mmol), ethyl acetoacetate (1.0 mmol) and UHP (3.0 mmol) with lactic acid (20 mol%) at 80 °C.

Table 4.4 Synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines from different benzyl alcohols/benzyl bromides.







[a]**Reaction conditions:** Benzyl alcohol/ Benzyl bromide (1.0 mmol), active methylene compounds (1.0 mmol) and UHP (2.0 mmol) with lactic acid (20 mol%) at 80 °C. [b] Isolated yield.

4.3 Gram-scale synthesis protocol for 2-oxo-1,2,3,4-tetrahydropyrimidine (3a)

To validate the prospective synthetic application of established methodology for 2-oxo-1,2,3,4-tetrahydropyrimidine (**3a**), the experiment was conducted on gram scale using toluene (**1a)** (15.0 mmol, 1.0 equiv.), methyl acetoacetate (**2a)** (15.0 mmol, 1.0 equiv.), UHP (45 mmol, 3.0 equiv.) and lactic acid (20 mol %). The experiment was carried out at 80 ºC without solvent for 2.5 h and the progress was monitored with TLC. After completion of reaction, the mixture was kept aside at room temperature to cool. Then, cold water was added followed by filtration to separate solid residue and washing with cold water. The crude residue obtained was further purified by recrystallization with ethanol to obtain the pure product **(3a)** 87% yield. The experimental work showed a robust and acceptable gram scale method for the synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines (**3**).

4.4 Mechanistic studies

4.4.1 Control experiments

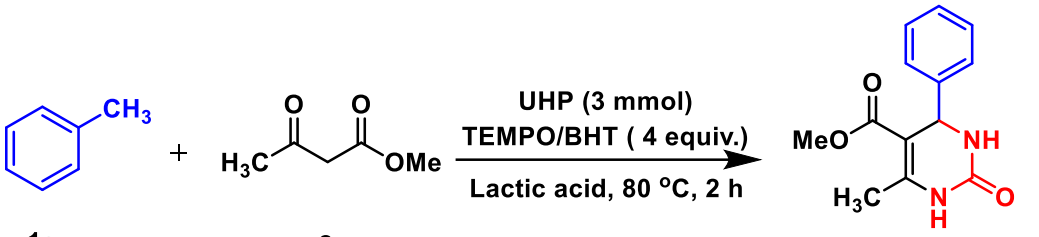
With the aim to determine the plausible reaction mechanism, few controlled experiments were conducted under optimized reaction conditions as presented in (**Scheme 4.2**). Herein, the reaction was performed in the presence of radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-yl) oxy) and BHT (butylated hydroxytoluene) (4 equiv) (**Scheme 4.2, A**) gave less than 10 % yield of the desired product which indicates that the formation of 2-oxo-1,2,3,4-tetrahydropyrimidine involve a radical mechanistic pathway.

Next, the control reaction was carried out between toluene, methyl acetoacetate and urea without UHP which failed to give the product. This indicates that toluene is not oxidized to benzaldehyde without UHP (**Scheme 4.2, B**) suggesting the necessity of UHP for the first step.

Thereafter, the control reaction was executed between benzaldehyde, methyl acetoacetate and UHP under optimized conditions, the reaction proceeded very well with good yield of 90% (**Scheme 4.2, C**). This indicated that decomposition of UHP resulted in hydrogen peroxide and urea, wherein hydrogen peroxide acted as an oxidizing agent for oxidizing toluene to benzaldehyde while remaining urea was utilized in the cyclo condensation reaction. The above results revealed the role of UHP for the oxidation of methyl arene to aldehyde as well as the source of urea. No significant change in the yield was observed when the above experiment was performed with radical scavenger, TEMPO and BHT (**Scheme 4.2, D**) that shows 2-oxo-1,2,3,4-tetrahydropyrimidines formation through the non-radical mechanistic pathway after the oxidation of methyl arenes.

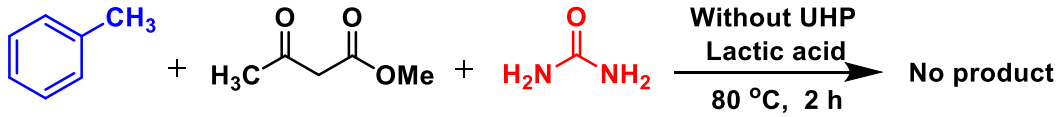
Now, to find out the steps where lactic acid works like a catalyst, each step of synthesis was examined with and without lactic acid. The lactic acid was not found to affect the first step of oxidation of toluene to benzaldehyde in the presence of UHP, while all the next steps were found to be catalyzed by lactic acid. Lactic acid may form perlactic acid in the presence of H_2O_2 generally it is more reactive species. To know whether the rection is catalyzed by lactic acid or per lactic acid we designed (**Scheme 4.2, E**) no change in the yield was obtained this indicates reaction may be catalyzed by lactic acid.

(A)



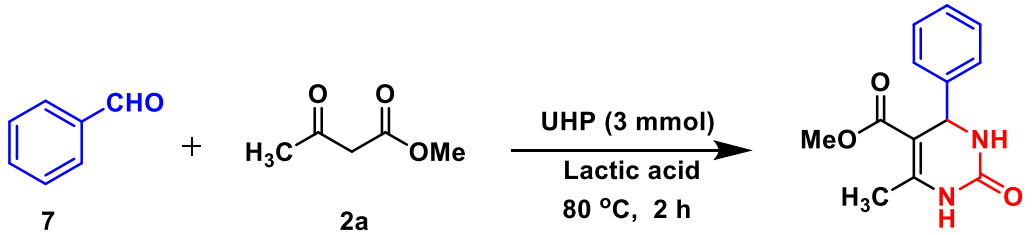
1a 2a 3a, < 10 % yield

(B)



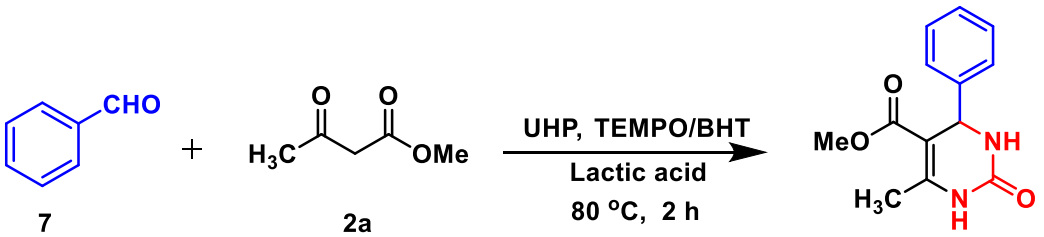
1a 2a 6

(C)



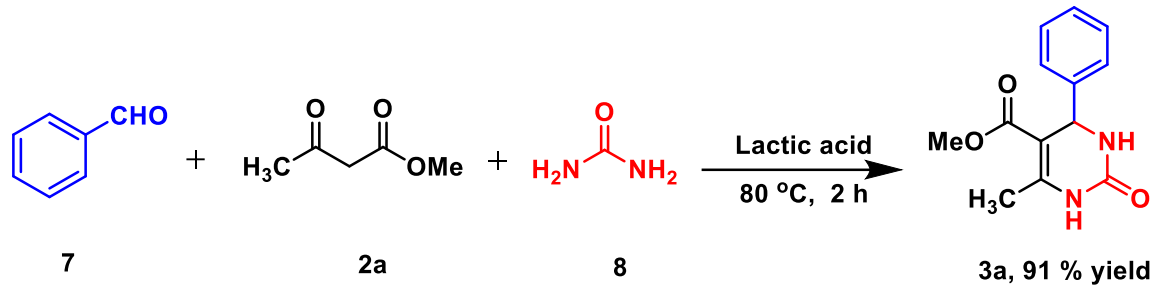
7 2a 3a, 90 % yield

(D)



7 2a 3a, 90 % yield

(E)



Scheme 4.2 Control experiments in support of the mechanism.

4.4.2 Proposed Mechanism

Combining all the above results along with previously reported literatures, a plausible mechanism for the reaction is predicted as shown in (**Figure 4.2**). The reaction is induced by the oxidation of methyl arene derivatives that selectively produces aldehyde derivatives (**I**) [36, 47]. Similarly, when the reaction starts from benzyl bromide in the presence of urea hydrogen peroxide, it gave benzyl alcohol and HOBr. The reactive species HOBr selectively oxidizes benzylic alcohols to benzaldehyde (**I**) [48, 49]. Thereafter, the lactic acid will activate the carbonyl group of the aldehyde, further attacked by amino groups of urea. The reaction further proceeds with removal of water to form an imine intermediate (**II**), which subsequently condenses with β-keto ester and form an intermediate (**III**). Finally, the *in situ* intermolecular cyclization gives the target product (**IV**).

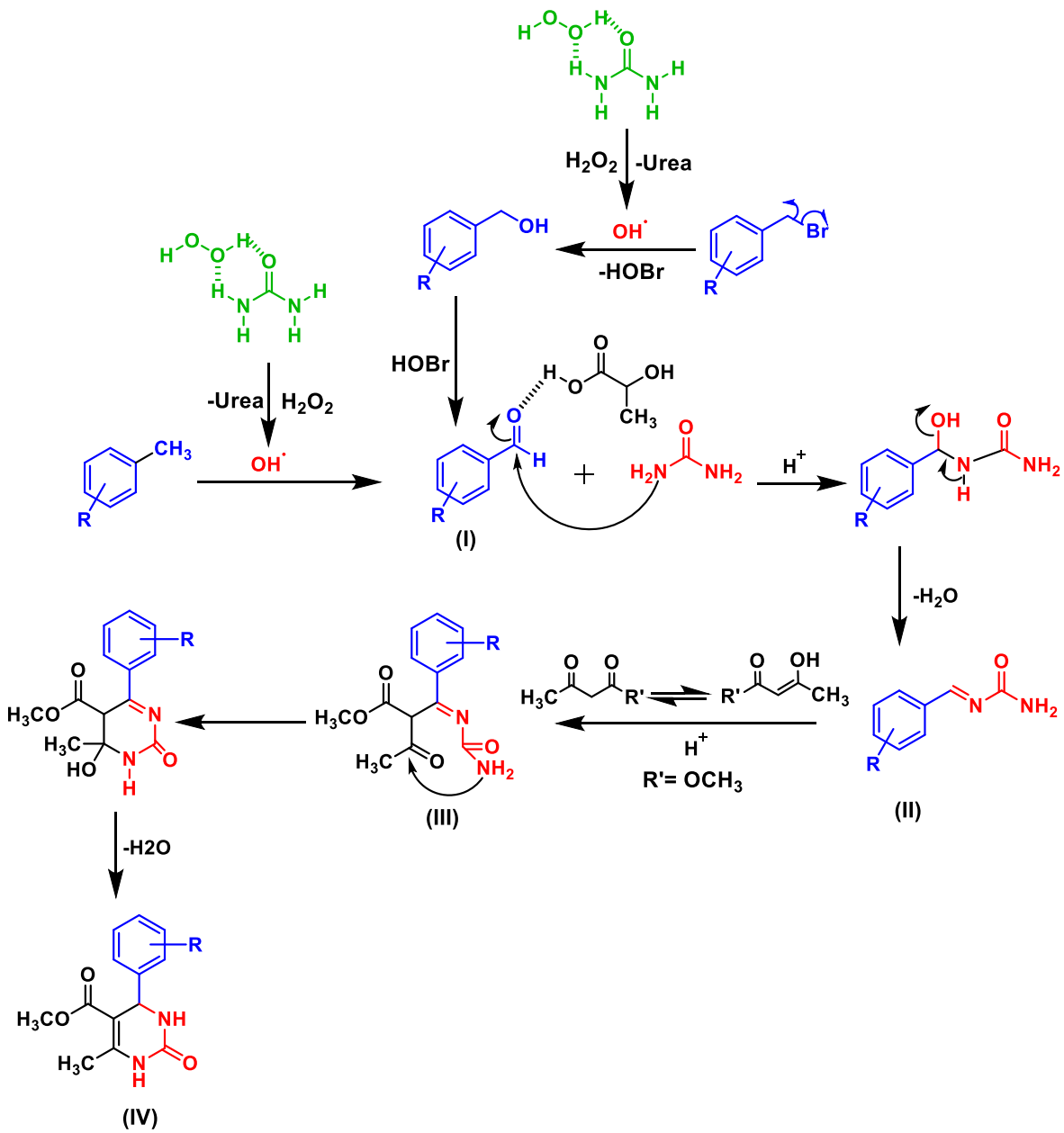
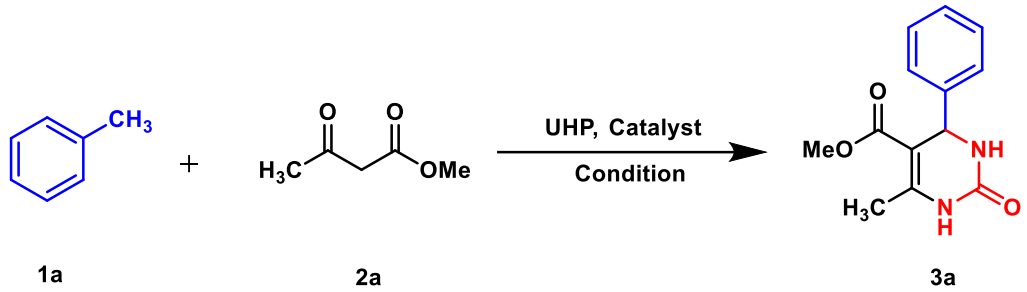


Figure 4.2 Probable mechanism for the synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines.

Table 4.5 Comparison of the results of the reaction of toluene (**1a**), methyl acetoacetate (**2a**), and UHP using lactic acid with those obtained by reported catalysts



1a 2a 3a

Entry	Substrate	Catalyst/Conditions	Time (h)	Yield (%)	Ref.
1.	Methyl arynes	Lactic acid/Solvent-free, 80 ºC	2	89	Current work
2.	Aromatic aldehyde	$NH_4H_2PO_4$-MCM-41/solvent-free 100 ºC	5	68	[50]
3.	Aromatic aldehyde	Iron (III) tosylate/octane, 125 ºC	17	65	[51]
4.	Aromatic aldehyde	B F_3.Et_2O/ CuCl/ Glacial acetic acid/60 ºC	8-18	82	[15]
5.	Aromatic aldehyde	Poly (SIL)/EtOH, 80 ºC	7	91	[52]
6.	Aromatic aldehyde	$SbCl_3$/acetonitrile, reflux	20	77	[20]
7.	Aromatic aldehyde	$FeCl_3$/DMAP/EtOH, reflux	5	76	[53]
8.	Aromatic aldehyde	I_2/ acetonitrile, reflux	7	86	[22]
9.	Aromatic aldehyde	ZnO or nano-ZnO/solvent-free, 60 ºC	10	95	[54]
10.	Aromatic aldehyde	Bovine serum albumin (BSA)/EtOH, 60 ºC	8	78	[55]

11.	Aromatic aldehyde	β-Cyclodextrin/solvent-free, 100 ºC	3	86	[56]
12.	Aromatic aldehyde	$InCl_3$/THF, reflux	6-9	75	[19]
13.	Aromatic aldehyde	Amberlyst-70/water, 90 ºC	3	81	[29]

With the aim of showing the benefit of the catalyst and comparison of the efficiency of the lactic acid catalyst with other catalysts in the synthesis of 2-oxo-1,2,3,4-tetrahydro pyrimidines, the results of the reaction of toluene (**1a**), methyl acetoacetate (**2a**), and UHP are shown in (**Table 4.5**). As presented in (**Table 4.5**), lactic acid is comparable to the formerly reported approaches in terms of reaction times and yields.

4.5 Experimental Section

4.5.1 General procedure for the synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines (3a)

A mixture of methyl arenes (1 mmol), methyl acetoacetate (1 mmol), UHP (3 mmol) and lactic acid (20 mol %) was heated at 80 ºC on an oil bath in solvent-free conditions for the times reported in (**Tables 4.1**). The progress of the reaction was followed by TLC. After the reaction was completed, the mixture was cooled to room temperature and crushed ice was added. The precipitate was filtered, and washed with cold water, to remove lactic acid because lactic acid is soluble in water and dried under a vacuum. The products were

purified by recrystallization from ethanol and dried to afford the pure products. All the products were characterized based on ^{1}H-NMR, ^{13}C-NMR and HR-MS.

4.6 Analytical data

Methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3a) Light yellow solid; yield 89%; m.p. 210−211 °C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.17 (s, 1H, NH), 7.73 (s, 1H, NH), 7.34−7.31 (m, 2H, Ar-H), 7.25−7.23 (m, 3H, Ar-H,), 5.15 (d, J = 3.8 Hz, 1H, CH), 4.0 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 165.9, 152.6, 148.7, 145.2, 128.8, 127.7, 126.6, 99.7, 59.1, 54.4, 18.2; **HR-MS** (ESI) for $C_{13}H_{14}N_2O_3$ (m/z) $[M + H]^+$ calcd: 247.1004, found: 247.1077.

Methyl4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3b) Yellow solid; yield 85%; m.p. 191-193 °C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.14 (s, 1H, NH), 7.66 (s, 1H, NH), 7.14−7.15 (m, J = 7.6 Hz, 2H, Ar-H), 6.86−6.88 (m, J = 7.6 Hz, 2H, Ar-H), 5.10 (d, J = 3.4 Hz, 1H, CH), 3.99 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 165.9, 158.9, 152.7, 148.9, 137.6, 127.9, 114.1, 100.0, 59.7, 55.6, 53.8, 18.2; **HR-MS** (ESI) for $C_{14}H_{16}N_2O_4$ (m/z) $[M + H]^+$ calcd: 277.1110, found: 277.1178.

Methyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3c) Yellow solid; yield 83%; m.p. 235-237 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 9.46 (s, 1H, NH), 8.17–8.23 (d, j = 8.4Hz 2H, Ar-H), 7.99 (s, 1H, NH), 7.74 – 7.79

(d, *j* = 8.4Hz, 2H, Ar-H), 5.38 (d, *J* = 3.4 Hz, 1H, CH), 3.44 (s, 3H, OCH_3), 2.35 (m, 6H, $N(CH_3)_2$), 1.17 (s, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$): δ 165.2, 152.0, 149.6, 147.2, 133.2, 130.4, 121.2, 98.5, 59.6, 53.7, 51.1, 18.3; **HR-MS** (ESI) for $C_{15}H_{19}N_3O_3$ (m/z) $[M + H]^+$ calcd : 290.1426, found:290.1457.

Methyl 4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3d) White solid; yield 82%; m.p. 225 °C; **^{1}H NMR** (500 MHz, DMSO- *d*$_6$): δ 9.29 (s, 1H, NH), 7.70 (s, 1H, NH), 7.42 −7.40 (m, 1H, Ar-H), 7.33−7.29 (m, d, *J* =7.6 Hz, 3H, Ar-H), 5.62 (d, *J* = 3.1 Hz, 1H, CH), 3.46 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$): δ 166.0, 152.9, 150.0, 142.0, 132.1, 130.0, 129.6, 129.1, 128.2, 98.2, 51.9, 51.2, 18.2; **HR-MS** (ESI) for $C_{13}H_{13}ClN_2O_3$ (m/z) $[M + H]^+$ calcd: 281.0614, found: 281.0657.

Methyl 4-(2-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3e) White solid; yield 82%; m.p. 219-221 °C; **^{1}H NMR** (500 MHz, DMSO-*d*$_6$): δ 9.28 (s, 1H, NH), 7.68 (s, 1H, NH), 7.41−7.39 (m, 1H, Ar-H), 7.32−7.27 (m, 3H, Ar-H), 5.61 (d, *J* = 3.1 Hz, 1H, CH), 3.45 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$): δ 166.0, 151.8, 150.0, 142.0, 132.1, 129.9, 129.5, 129.1, 128.2, 98.2, 51.9, 51.1, 18.2; **HR-MS** (ESI) for $C_{13}H_{13}BrN_2O_3$ (m/z) $[M + H]^+$ calcd: 325.0109, found: 325.0162.

Methyl 4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3f) White solid; yield 87%; m.p. 290-292 ^{o}C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.32 (s, 1H, NH), 7.75 (s, 1H, NH), 7.27 (d, J = 8.4 Hz, 2H, Ar-H), 7.14 (d, J = 8.4 Hz, 2H, Ar-H), 5.15 (d, J = 3.2 Hz, 1H, CH), 3.52 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 166.2, 162.8, 152.5, 149.2, 141.3, 128.7, 115.8, 99.1, 53.2, 51.3, 18.1; **HR-MS** (ESI) for $C_{13}H_{13}FN_2O_3$ (m/z) $[M + H]^+$ calcd: 265.0910, found: 265.0980.

Methyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3g) White solid; yield 84%; m.p. 204-206 ^{o}C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.26 (s, 1H, NH), 7.79 (s, 1H, NH), 7.40 (d, J = 8.4 Hz, 2H, Ar-H), 7.26 (d, J = 8.4 Hz, 2H, Ar-H), 5.15 (d, J = 3.2 Hz, 1H, CH), 3.53 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 166.2, 152.4, 149.4, 144.1, 132.3, 129.0, 128.5, 99.1, 53.8, 51.3, 18.3; **HR-MS** (ESI) for $C_{13}H_{13}ClN_2O_3$ (m/z) $[M + H]^+$ calcd: 281.0614, found: 281.0679.

Methyl 4-(4-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3h) White solid; yield 85%; m.p. 208-210 ^{o}C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.24 (s, 1H, NH), 7.77 (s, 1H, NH), 7.52 (d, J = 8.0 Hz, 2H, Ar-H), 7.20 (d, J = 8.0 Hz, 2H, Ar-H), 5.14 (d, J = 3.2 Hz, 1H, CH), 3.53 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 166.2, 152.4, 149.4, 144.4, 131.9, 129.0, 120.9, 99.1, 53.9, 51.3, 18.2; **HR-MS** (ESI) for $C_{13}H_{13}BrN_2O_3$ (m/z) $[M + H]^+$ calcd: 325.0109, found: 325.0149.

Methyl 4-(4-nitrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3i Yellow solid; yield 88%; m.p. 235-237 °C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.37 (s, 1H, NH), 8.22−8.20 (m, *J* = 8.4 Hz, 2H, Ar-H), 7.90 (s, 1H, NH), 7.52−7.50 (m, *J* = 8.4 Hz, 2H, Ar-H), 5.29 (d, *J* = 3.5 Hz, 1H, CH), 3.54 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 166.0, 152.2, 150.1, 147.2, 146.6, 128.0, 124.3, 98.5, 54.0, 51.3, 18.3; **HR-MS** (ESI) for $C_{13}H_{13}N_3O_5$ (m/z) $[M + H]^+$ calcd: 292.0855, found: 292.0920.

Methyl 6-methyl-2-oxo-4-(pyridin-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3j Yellow solid; yield 80%; m.p. 236-238 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.15 (s, 1H, NH), 8.51 (s, 1H, NH), 7.74−7.24 (4H, *J* = 8.6 Hz m, Ar-H), 5.22 (d, *J* = 3.5 Hz, 1H, CH), 3.52 (s, 3H, OCH_3), 2.23 (s, 3H, CH_3); ^{13}C NMR (126 MHz, DMSO-d_6): δ 166.3, 162.7, 152.8, 149.8, 149.6, 137.1, 123.1, 121.2, 98.4, 55.9, 51.1, 18.3; HR-MS (ESI) for $C_{12}H_{13}N_3O_3$ (m/z) $[M + H]^+$ calcd: 248.0956, found: 248.0989.

Methyl 6-methyl-2-oxo-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3k) White solid; Yield 80%; m.p. 223-225 ^{o}C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.32 (s, 1H, NH), 7.90 (s, 1H, NH), 7.34 – 6.89 (m, *J* = 8.6 Hz 3H, Ar-H), 5.42 (d, *J* = 3.2 Hz, 1H, CH), 3.59 (s, 3H, OCH_3), 2.22 (s, 3H, CH_3); **^{13}C NMR (**126 MHz, DMSO-d_6**)**: δ 165.9, 152.4, 151.7, 149.4, 127.2, 125.1, 124.0, 100.1, 51.4, 49.8, 18.2; **HR-MS** (ESI) for $C_{11}H_{12}N_2O_3S$ (m/z) $[M + H]^+$ calcd: 252.0568, found: 252.0598.

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3l) White solid; yield 88%; m.p. 203 ^{o}C; **^{1}H NMR** (500 MHz, DMSO- d_6): δ 9.17 (s, 1H, NH), 7.73

(s, 1H, NH), 7.33 –7.23 (m, *J* = 8.4 Hz 5H, Ar-H), 5.15 (d, *J* = 3.6 Hz 1H, CH), 3.99 (q, *J* = 7.1 Hz, 2H, CH_2), 2.25 (s, 3H, CH_3), 1.10 (t, *J* = 7.1 Hz, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 165.8, 152.6, 148.8, 145.3, 128.9, 127.8, 126.8, 99.8, 59.6, 54.4, 18.2, 14.5; HR-MS (ESI) for $C_{14}H_{16}N_2O_3$ (m/z) [M + H]+ calcd: 261.1160, found: 261.1223.

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3m) White solid; yield 87%; m.p. 198-200 ^{o}C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.14 (s, 1H, NH), 7.66 (s, 1H, NH), 7.16 (d, *J* = 8.1 Hz, 2H, Ar-H), 6.88 (d, *J* = 8.1 Hz, 2H, Ar-H), 5.10 (d, *J* = 3.6 Hz 1H, CH), 3.99 (q, *J* = 6.8 Hz, 2H, CH_2), 3.72 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3), 1.12 (t, *J* = 6.8, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 165.9, 158.9, 159.6, 152.6, 148.5, 137.5, 127.9, 114.2, 100.0, 59.6, 53.8, 18.2, 14.6; **HR-MS** (ESI) for $C_{15}H_{18}N_2O_4$ (m/z) $[M + H]^+$ calcd: 291.1266, found: 291.1234.

Ethyl 4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3n) White solid; yield 84%; m.p. 213 °C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.26 (s, 1H, NH), 7.69 (s, 1H, NH), 7.41-7.27 (m, *J* = 8.6 Hz 4H, Ar-H), 5.64 (d, *J* =2.7Hz, 1H, CH), 3.90 (q, *J* =7.1Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.0 (t, *J* =7.1Hz, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 165.5, 151.8, 149.8, 142.1, 132.2, 129.8, 129.6, 129.2, 128.2, 98.4, 59.6, 52.0, 18.1, 14.4; **HR-MS** (ESI) for $C_{14}H_{15}N_2O_3$ (m/z) $[M + H]^+$ calcd: 295.0771, found: 295.0840.

Ethyl 4-(2-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3o) White solid; yield 84%; m.p. 205-207 °C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ in ppm =

9.26 (s, 1H, NH), 7.69 (s, 1H, NH), 7.41 - 7.39 (m, 1H, Ar-H), 7.33-7.31 (m, *J* = 7.2 Hz, 3H, Ar-H), 5.64 (d, *J* =2.4Hz, 1H, CH), 3.90 (q, *J* =7.1Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.01 (t, *J* =7.1Hz, 3H, CH_3), **^{13}C NMR** (126 MHz, DMSO-d_6): δ 165.0, 151.4, 149.3, 141.8, 133.2, 131.8, 129.4, 128.9, 127.8, 98.0, 59.1, 51.6, 17.7, 14.0; **HR-MS** (ESI) for $C_{14}H_{15}BrN_2O_3$ (m/z) $[M + H]^+$ calcd: 339.0266, found: 339.0318.

Ethyl 4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3p) White solid; yield 82%; m.p. 173-175 ^{o}C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.21 (s, 1H, NH), 7.74 (s, 1H, NH) 7.26 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.17 (d, *J* = 8.4 Hz, 2H, Ar-H), 5.15 (d, *J* = 2.6 Hz, 1H, CH), 3.98 (q, *J* = 7.1 Hz, 2H, CH_2), 2.25 (s, 3H, CH_3), 1.09 (t, *J* = 7.1 Hz, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 165.7, 152.0, 152.4, 149.0, 141.6, 128.7, 115.7, 99.6, 59.7, 53.8, 18.2, 14.5; HR-MS (ESI) for $C_{14}H_{15}FN_2O_3$ (m/z) $[M + H]^+$ calcd: 279.1066, found: 279.1098.

Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3q) White solid; yield 85%; m.p. 213 ^{o}C; **^{1}H NMR** (500 MHz, DMSO-d_6): *δ* 9.24 (s, 1H, NH), 7.77 (s, 1H, NH), 7.39 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.26 (d, *J* = 8.0 Hz, 2H, Ar-H), 5.15 (d, *J* = 2.6 Hz, 1H, CH), 4.01-3.96 (q, *J* = 6.8 Hz, 2H, CH_2), 2.26 (s, 3H, CH_3), 1.11 (t, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6): *δ* 165.7, 152.4, 149.2, 144.2, 132.3, 128.9, 128.7, 99.3, 59.8, 53.9, 18.2, 14.5; **HR-MS** (ESI) for $C_{14}H_{15}ClN_2O_3$ (m/z) $[M + H]^+$ calcd: 295.0771, found: 295.0832.

Ethyl 4-(4-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3r) White solid; yield 84%; m.p. 195-197 ^{o}C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.23 (s, 1H, NH), 7.76 (s, 1H, NH), 7.54 (d, J = 7.2 Hz, 2H, Ar-H), 7.20 (d, J = 7.2 Hz, 2H, Ar-H), 5.14 (d, J = 7.3 Hz, 1H, CH), 4.01 (q, J = 6.4 Hz, 2H, CH_2), 2.47 (s, 3H, CH_3), 1.10 (t, J = 6.8 Hz, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 165.7, 152.4, 149.2, 144.7, 131.8, 129.0, 120.8, 98.3, 59.8, 54.0, 17.3, 14.5; **HR-MS** (ESI) for $C_{14}H_{15}N_2O_3$ (m/z) $[M + H]^+$ calcd: 339.0266, found: 339.0322.

Ethyl 4-(4-nitrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3s) White solid; yield 88%; m.p. 204-206 ^{o}C; **^{1}H-NMR** (500 MHz, DMSO-d_6): δ 9.34 (s, 1H, NH), 8.22 (d, J = 8.4 Hz, 2H, Ar-H), 7.89 (s, 1H, NH), 7.52 (d, J = 8.4 Hz, 2H, Ar-H), 5.29 (s, J = 2.6 Hz, 1H, CH), 4.00 (q, J = 7.1 Hz, 2H, CH_2), 2.27 (s, 3H, CH_3), 1.10 (t, J = 7.1 Hz, 3H, CH_3); **^{13}C-NMR** (126 MHz, DMSO-d_6): δ 165.5, 152.5, 151.9, 147.9, 147.2, 127.7, 123.9, 98.7, 59.9, 54.2, 18.3, 14.5; **HR-MS** (ESI) for $C_{14}H_{15}N_3O_5$ (m/z) $[M + H]^+$ calcd: 306.1011, found: 306.1079.

Ethyl 6-methyl-2-oxo-4-(pyridin-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3t) White solid; yield 85%; m.p. 212-214; ^{o}C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.12 (s, 1H, NH), 8.51 (s, 1H, NH), 7.76 –7.25 (m, J = 8.6 Hz, 4H, Ar-H), 5.22 (d, J = 3.6 Hz, 1H, CH), 3.99 (q, J = 7.2 Hz, 2H, CH_2), 2.23 (s, 3H, CH_3), 1.09 (t, J = 7.2 Hz, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 165.8, 162.8, 152.8, 149.8, 146.3, 137.1, 123.1, 121.4, 98.5, 59.6,

56.1, 18.3, 14.5; **HR-MS** (ESI) for $C_{13}H_{15}N_3O_3$ (m/z) $[M + H]^+$ calcd: 262.1113, found: 262.1188.

Ethyl 6-methyl-2-oxo-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3u) Brown solid; yield 88%; m.p. 216 ^oC; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.31 (s, 1H, NH), 7.90 (s, 1H, NH), 7.35 (s, 1H, Ar-H), 6.95 (m, J = 8.6 Hz 2H, Ar-H), 5.43 (d, J = 3.6 Hz, 1H, CH), 4.06 (q, J = 7.2 Hz, 2H, CH_2), 2.23 (s, 3H, CH_3), 1.19 (t, J = 7.2 Hz, 3H, CH_3); **^{13}C NMR (**126 MHz, DMSO-d_6**)**: δ 165.4, 160.6, 152.6, 149.1, 127.0, 125.0, 123.8, 100.2, 59.7, 49.7, 18.0, 14.5; **HR-MS** (ESI) for $C_{12}H_{14}N_2O_3S$ (m/z) $[M + H]^+$ calcd: 267.0725, found: 267.0781.

4.7 Spectra of few 2-oxo-1,2,3,4-tetrahydropyrimidine derivatives

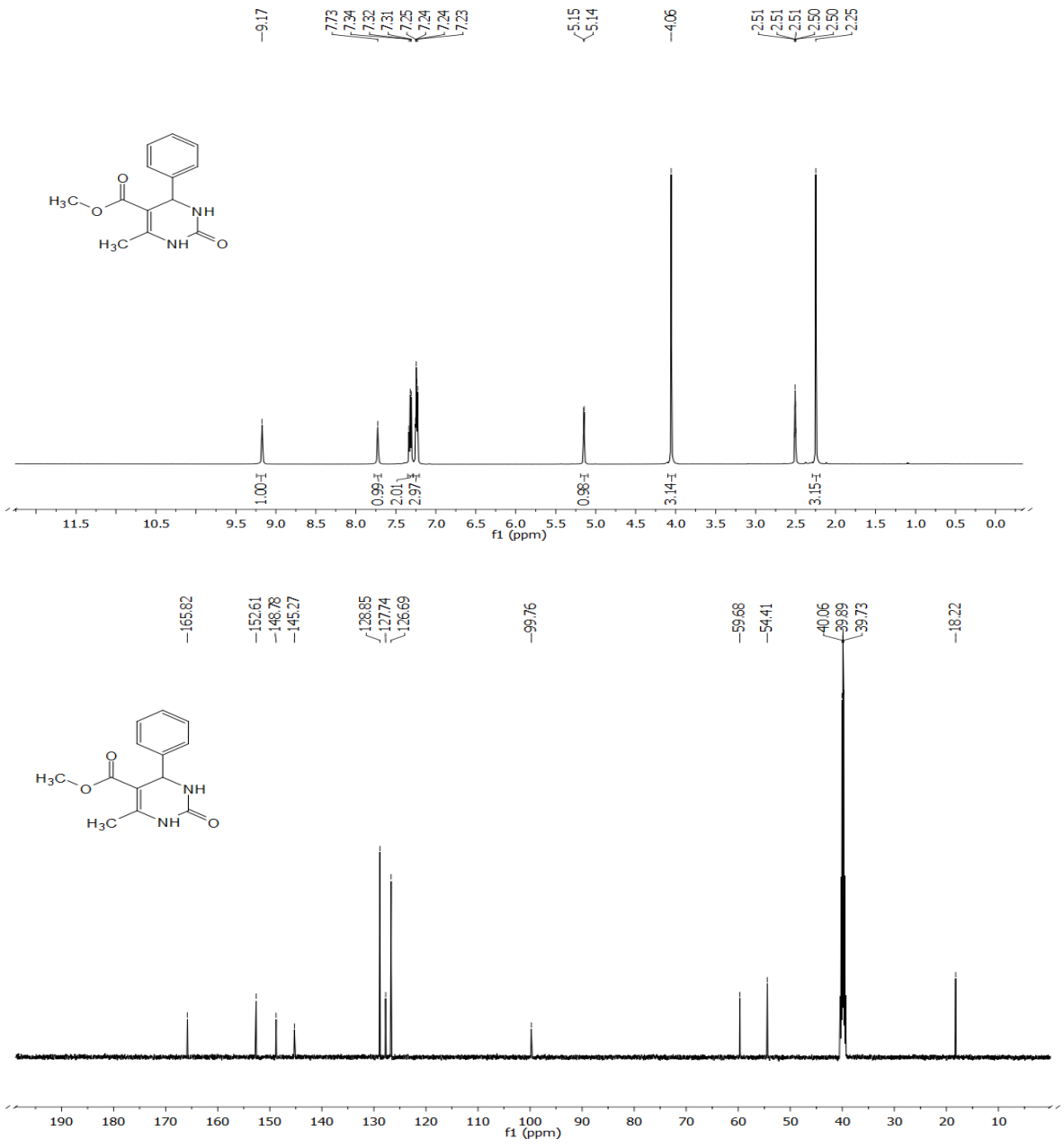


Figure 4.3 ^{1}H and ^{13}C NMR spectra of Methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3a**)

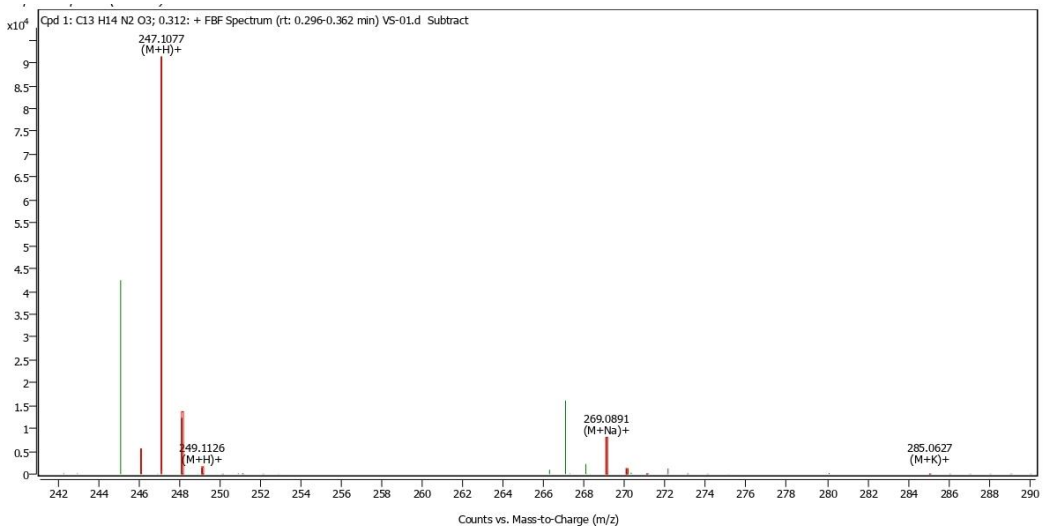


Figure 4.4 Mass spectra of Methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3a**)

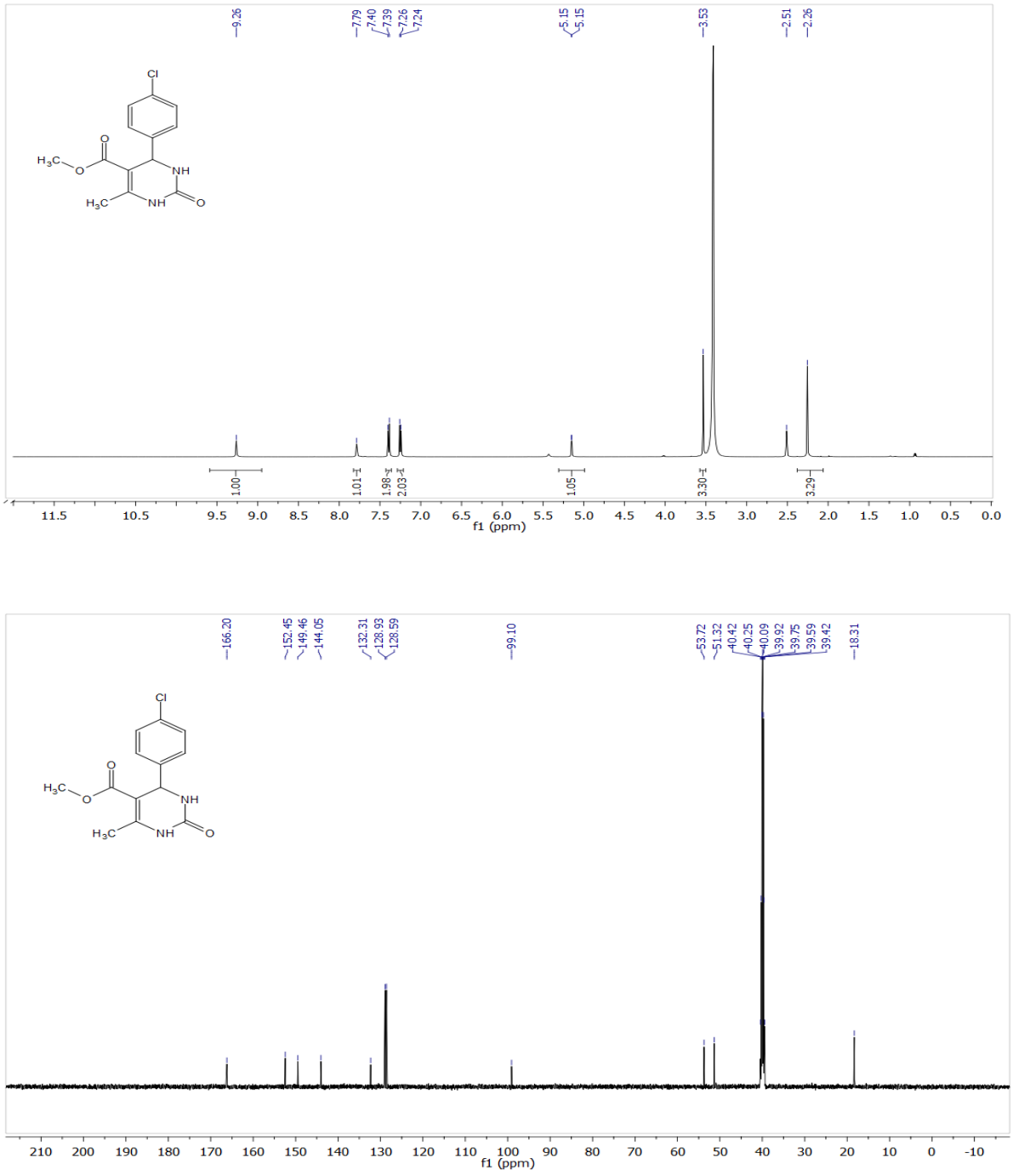


Figure 4.5 ^{1}H and ^{13}C NMR spectra of Methyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3g**)

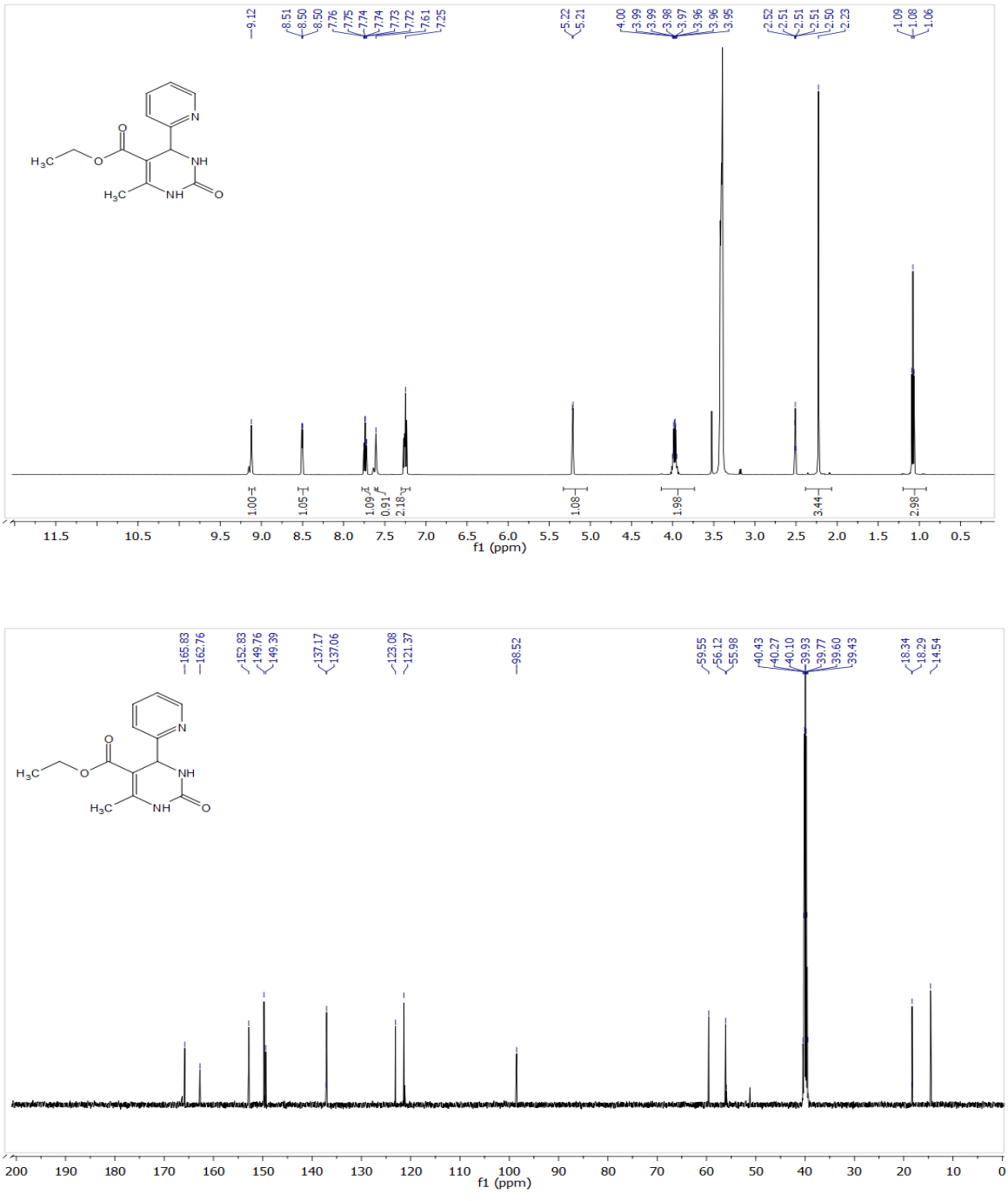


Figure 4.6 ^{1}H and ^{13}C NMR spectra of Ethyl 6-methyl-2-oxo-4-(pyridin-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3t**)

4.8 References

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