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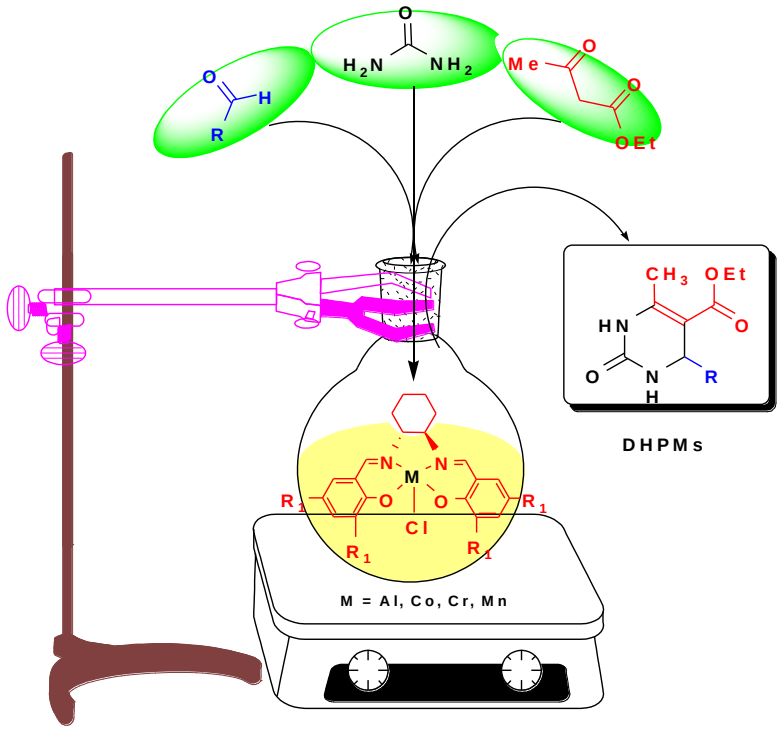
# Jacobsen Metal Complex catalyzed One-Pot Multicomponent Biginelli reaction: An Efficient Synthesis of Dihydropyrimidin-2-(1*H*)-ones

Soundararajan Karthikeyan,[1*] Sethupathy Alaguraja[2]
[*1]Assistant Professor, *Department of Chemistry, Nagarathinam Angalammal Arts and Science College, Madurai, Tamil Nadu, India.*
[2]Assistant Professor, *Department of Chemistry, Nagarathinam Angalammal Arts and Science College, Madurai, Tamil Nadu, India.*
***Corresponding Author**: Soundararajan Karthikeyan*

**GRAPHICAL ABSTRACT**




**Advantages**
- ✓ One-pot reaction
- ✓ Mild condition
- ✓ High yield

***Abstract***
*Here we report an efficient synthetic way to the construction of pharmacologically active dihydropyrimidin-2-(1H)-one (DHPMs) via Biginelli reaction catalyzed by chiral (salen)chromium(III) metal catalyst. The developed synthetic methodology is smoothly proceeds to afford high yields of DHPMs derivatives under mild reaction condition. All the synthesized compounds are characterized and confirmed by using NMR and HR-Mass analysis.*

***Keywords**: Chromium catalyst, one-pot multicomponent reaction, dihydropyrimidin-2-(1H)-one.*

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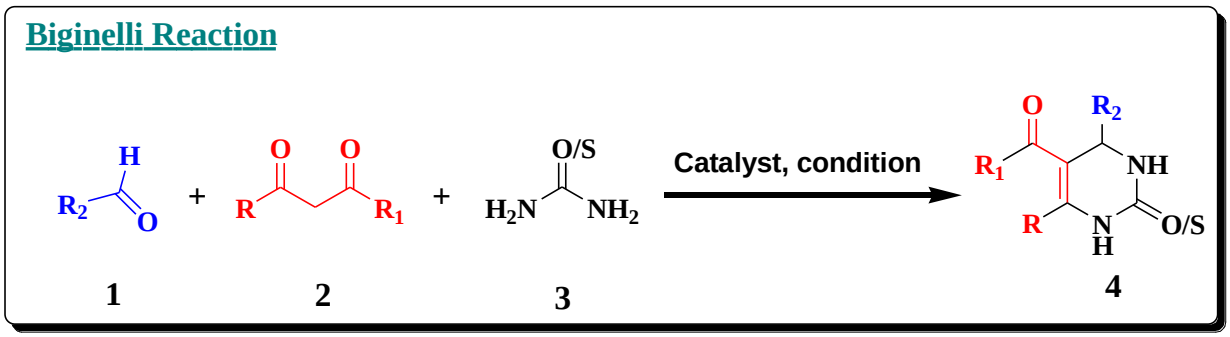
## I. INTRODUCTION

Organic synthesis is one of the most successful and useful disciplines of science and mainly involves the formation of carbon-carbon bond(s), carbon-heteroatom bond(s) and cleavage of the bonds. [1,2] From this perspective, the multi-component reaction is the best way to access complex as well as structurally diverse molecules through simple starting substrates. [3] In past decades, synthetic organic chemists are more focused to describe an effective multicomponent reaction (MCR) is also known as tandem reactions such as Ugi reaction,[4] Passerini reaction,[5] Baylis-Hillman reaction [6-8], Bucherer–Bergs [9-14], Gewald reaction [15-21], Hantzch [22-24]. Among them, Biginelli reaction is an efficient one-pot multicomponent approach discovered in 1891 by Pietro Biginelli. [25]




**Scheme 1**: General reaction of Biginelli MCR reaction.

The Biginelli reaction is widely used to construct the heterocyclic system consisting of nitrogen atoms, such as of 3,4-dihydropyrimidin-2(1*H*)-ones (or -thiones), which are also referred to as DHPMs (**Scheme 1**). [26] The simple as well as structural fulfillment of DHPMs and its analogues are an important class of nitrogen heterocyclic molecules comprising significant pharmacological activity against enormous biological disorders like malaria, HIV and tuberculosis, etc. [27-28] In recent years, synthetic chemists are successfully reported to examine the wide range of synthetic protocols towards DHPMs by using various catalysts such as lewis acids, lewis bases, heteropoly acids, nanocatalysts and baker's yeast, etc. [29-33] In this point of view, we also endeavour to describe the facile synthetic approach to the construction of DHPMs *via* Biginelli reactions by using different metal catalysts. Among these catalytic systems, the chromium based Jacobsen catalyst has efficiently promote this one-pot multicomponent Biginelli condensation with a high yield in mild condition.

## II. MATERIALS AND METHODS

The following chemicals urea, ethylacetoacetate, benzaldehyde, 4-bromo Benzaldehyde, 4-chloro benzaldehyde, 4-fluoro benzaldehyde and 4-methyl benzaldehyde were purchased from Sigma-Aldrich and Sisco Research Laboratories Private Limited, India. (*R*,*R*)-N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2 cyclohexanediamino chromium(III)chloride,(*R*,*R*)-(-)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride and (*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminoaluminum(III) chloride were purchased from Sigma-Aldrich Chemicals Private Limited, India. Solvents were purchased from Merck Life Science Private Limited and Central Drug House Private Limited, India. The thin-layer chromatography plates and column silica gel were purchased from Merck Life Science Private Limited, India.

***Purification method***: The monitoring of the reaction was carried by using silica gel-G. All the synthesized products were purified by column chromatography using chloroform/ methanol as solvent.

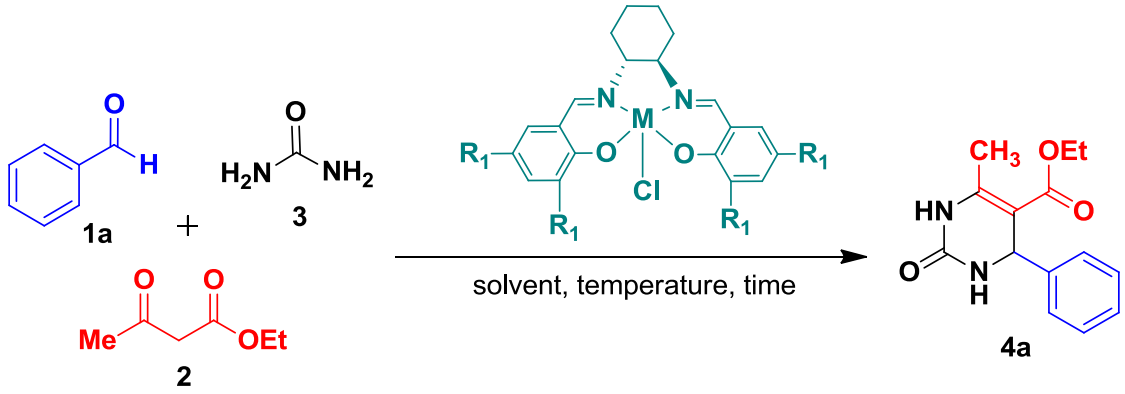
***Instrumental methods***: The $^{1}H$ & $^{13}C$ NMR spectra were recorded in $CDCl_3$ solution on a Bruker Avance 300 MHz spectrometer at Madurai Kamaraj University, Madurai, India. Tetramethylsilane (TMS) was used as an internal standard. The splitting patterns are designated as s (singlet), d (doublet), q (quartet) and m (multiplet) and coupling constants are expressed in Hz. High-resolution mass spectra were recorded on Waters XEVO-G2-XS-QToF at Vellore Institute of Technology, India. Melting points were determined in open capillary tubes, expressed in degree Celsius (°C) and are uncorrected.

## III. RESULTS AND DISCUSSION

We first examined the reaction of benzaldehyde **1a** (**1 mmol**), ethyl acetoacetate **2** (**1.2 mmol**) with urea **3 (1 mmol**) by employing different metal catalysts such as manganese (III), aluminium (III), cobalt (II) and chromium (III), which affords the moderate yield of **4a** (28-53 %) when using 10 mol % of catalyst loading (**Table 1**, **entries 1-4**). In addition, we also focused on discovering an excellent solvent to provide a high yield of product **4a** (**Table 1, entries 5-11**). It is evident that the reaction proceeded smoothly when the 15 mol %

chromium catalyst was used in dichloromethane as a solvent at room temperature (**Table 1, entry 12**). Next, we only observed a 79% yield by using 20 mol % of chromium catalyst (**Table 1, entry 13**). Moreover, we also demonstrated the yield of **4a** by the utilization of a 15 mol % chromium catalyst at elevated reaction time and temperature (**Table 1, entries 14-16**). But

**Table 1: Optimization of one-pot three component Biginelli condensation**



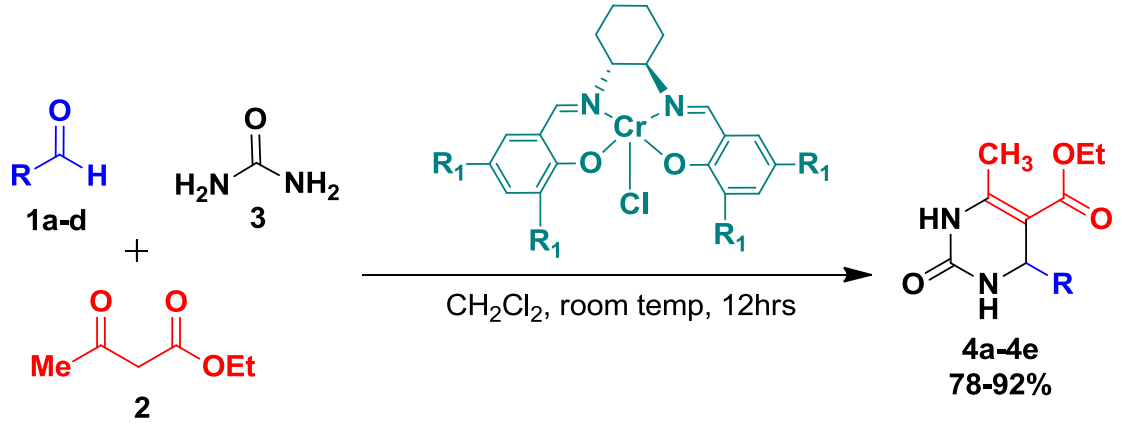

| Entry | Jacobsen metal complexes (M) (mol %) | solvent | time (hours) | yield (%) |
|---|---|---|---|---|
| 1 | Mn(III)salen (10) | $CH_2Cl_2$ | 8 | 41 |
| 2 | Co(II)salen (10) | $CH_2Cl_2$ | 8 | 37 |
| 3 | Al(III)salen (10) | $CH_2Cl_2$ | 8 | 28 |
| 4 | Cr(III)salen (10) | $CH_2Cl_2$ | 8 | 53 |
| 5 | Cr(III)salen (15) | $CH_2Cl_2$ | 8 | 68 |
| 6 | Cr(III)salen (15) | $CH_3CN$ | 8 | 60 |
| 7 | Cr(III)salen (15) | THF | 8 | 57 |
| 8 | Cr(III)salen (15) | EtOH | 8 | 52 |
| 9 | Cr(III)salen (15) | DMSO | 8 | 42 |
| 10 | Cr(III)salen (15) | toluene | 8 | 58 |
| 11 | Cr(III)salen (15) | $CH_2Cl_2$ | 10 | 68 |
| **12** | **Cr(III)salen (15)** | **$CH_2Cl_2$** | **12** | **92** |
| 13 | Cr(III)salen (20) | $CH_2Cl_2$ | 12 | 79 |
| 14 | Cr(III)salen (15) | $CH_2Cl_2$ | 16 | 81 |
| 15 | Cr(III)salen (15) | $CH_2Cl_2$ | 24 | 76 |
| 16 | Cr(III)salen (15) | $CH_2Cl_2$ | 12 | 75[a] |

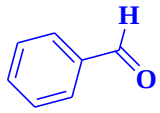
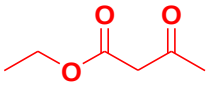
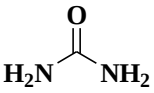
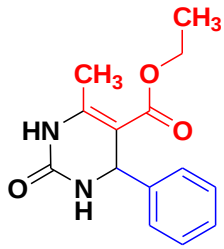
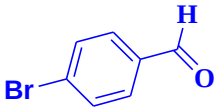
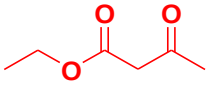
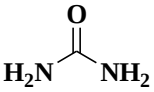
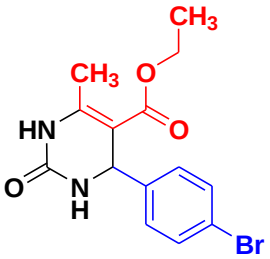
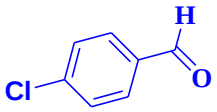
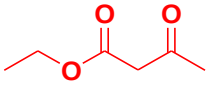
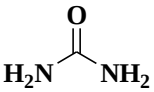
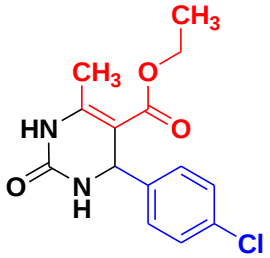
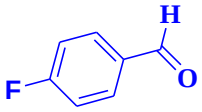
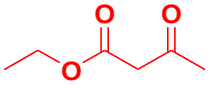
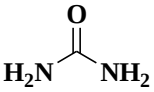
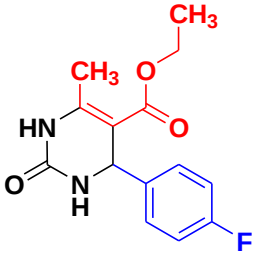
**Note**: [a]Reaction carried at 80 °C; $CH_3CN$- acetonitrile, $CH_2Cl_2$- dichloromethane, DMSO- dimethylsulfoxide, EtOH- ethanol, $CHCl_3$- chloroform.

it also gives only the moderate yield of DHPMs (**4a**) in the range of 75 to 81%. Finally, we concluded that chiral (salen)chromium(III) was found to be the most suitable catalyst for the synthesis of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4a**) with a high yield at mild temperature (**Table 1, entry 12**).

Inspired by this result, we decided to survey the scope of this optimized reaction condition (**Table 1, entry 12**) by using various substituted benzaldehydes (**Table 2, entries 1-5**) with ethyl acetoacetate (**2**) and urea (**3**), which yielded a high percentage of dihydropyrimidin-2-(1*H*)-one (DHPMs) derivatives (**4a-4e**) ranging from 78 to 92 % (**Table 2 entries 1-5**).

**Table 2: Synthesis of DHPMs by one-pot Biginelli condensation**




| Entry | 1a-1e | 2 | 3 | 4a-4e | yield(%)[a] |
|---|---|---|---|---|---|
| 1 |  |  |  |  | 92 |
| 2 |  |  |  |  | 78 |
| 3 |  |  |  |  | 86 |
| 4 |  |  |  |  | 89 |

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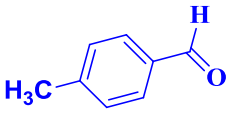
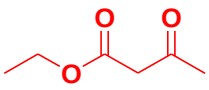
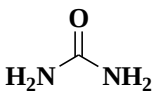
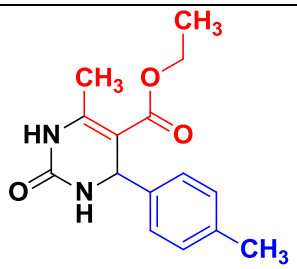
| 5 |  |  |  |  | 87 |

All reactions were carried at room temperature with aldehydes (1.0 mmol), ethyl acetoacetate (1.2 mmol), urea (1 mmol) and catalyst loading of 15 mol % unless otherwise noted. [a] Isolated yields.

## IV. CONCLUSION

In summary, we have reported an effective protocol for the synthesis of DHPMs derivatives (**4a-4e**) by using Jacobsen chromium catalyzed. The present synthetic approach allows to accesses the formation of DHPMs when 15 mol% of chromium metal complex. In addition, this methodology is most attractive for its mild reaction condition and gave high yields of DHPMs (**4a-4e**) in one-pot three component reaction.

## V. EXPERIMENTAL SECTION

***General procedure to synthesis of DHMPs derivatives (4a-4e)*:** To a solid of chromium catalyst (**15 mol %**) were added to the dichloromethane solution (3mL) containing oven dried reaction tube at room temperature. Then, the reactants of aldehydes (**1a-1e, 1 mmol**), ethyl acetoacetate (**2, 1.2 mmol**) and urea (**3, 1 mmol**) was added to the reaction tube consisting chromium catalyst. The resulted reaction mixture is stirred at room temperature for 12 hours and monitored by thin layer chromatography. Next, the reaction mixture was quenched with water (**20-30mL**), the filtrate was extracted with dichloromethane (**20-30mL**), dried over anhydrous $MgSO_4$. Finally, the resulting solvent was concentrated under vacuo followed by column chromatography over silica gel using $CHCl_3$:MeOH as eluent to affords the desired DHMPs (**4a-4e, 78-92%**).

**5-(ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one** (**4a**)**:** Yellow solid; mp 201-204 °C; $^1$H NMR: ($CDCl_3$, 300 MHz), $\delta_H$ = 9.18 (s, 1H, N**H**), 7.71 (s, 1H, N**H**), 7.28-7.13 (m, 5H, Aro-**H**), 5.15 (s, 1H, NH-C**H**-Aro), 4.00-3.97 (q, J = 3Hz, 2H, -COOC**H$_2$**CH$_3$), 2.25 (s, 3H, NH-C-C**H$_3$**), 1.10-1.08 (t, J = 3Hz, 3H, -COOCH$_2$C**H$_3$**); HRMS: m/z Calculated for $C_{14}H_{16}N_2O_3$ $[M+H]^+$: 260.29; found: 261.35.

**4-(4-bromophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4b):** Yellow solid; mp 213-215 °C; $^1$H NMR: ($CDCl_3$, 300 MHz), $\delta_H$ = 9.20 (s, 1H, N**H**), 7.93 (s, 1H, N**H**), 7.40-7.38 (d, J = 6Hz, 2H, Aro-**H**), 7.24-7.26 (d, J = 6Hz, 2H, Aro-**H**), 5.15 (s, 1H, NH-C**H**-Aro), 4.01-3.97 (q, J = 3Hz, 2H, -COOC**H$_2$**CH$_3$), 2.25 (s, 3H, NH-C-C**H$_3$**), 1.11-1.08 (t, J = 3Hz, 3H, -COOCH$_2$C**H$_3$**); HRMS: m/z Calculated for $C_{14}H_{15}BrN_2O_3$ $[M+H]^+$: 339.18; found: 340.30.

**4-(4-chlorophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4c):** Yellowish white solid; mp 210-212 °C; $^1$H NMR: ($CDCl_3$, 300 MHz), $\delta_H$ = 7.84 (s, 1H, N**H**), 7.25 (s, 1H, N**H**), 7.23-7.19 (m, 4H, Aro-**H**), 5.33 (s, 1H, NH-C**H**-Aro), 4.04-4.01 (q, J = 3Hz, 2H, -COOC**H$_2$**CH$_3$), 2.29 (s, 3H, NH-C-C**H$_3$**), 1.11-1.08 (t, J = 3Hz, 3H, -COOCH$_2$C**H$_3$**). $^{13}$C NMR: ($CDCl_3$, 300 MHz), $\delta_C$ = $\delta_C$ 167.96 (1C, NH-**C**=O), 146.79 (1C, NH-**C**-CH$_3$), 144.72 (1C, Aro-**C**), 132.05-128.30 (5C, Aro-**C**), 104.03 (1C, CH-**C**-CO-CH$_2$CH$_3$), 60.22 (1C, NH-**C**H), 39.63 (1C, CH-C-CO-**C**H$_2$CH$_3$), 19.79 (1C, NH-C-**C**H$_3$), 14.65 (1C, CH-C-CO-CH$_2$**C**H$_3$); HRMS: m/z Calculated for $C_{14}H_{15}ClN_2O_3$ $[M+H]^+$: 294.73; found: 295.84.

**4-(4-fluorophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4d):** Yellow solid; mp 175-177 °C; $^1$H NMR: ($CDCl_3$, 300 MHz), $\delta_H$ = 7.22 (s, 1H, N**H**), 7.20-7.03 (m, 4H, Aro-**H**), 4.92 (s, 1H, NH-C**H**-Aro), 4.03-4.00 (q, J = 3Hz, 2H, -COOC**H$_2$**CH$_3$), 2.25 (s, 3H, NH-C-C**H$_3$**), 1.13-1.16 (t, J = 3Hz, 3H, -COOCH$_2$C**H$_3$**); HRMS: m/z Calculated for $C_{14}H_{15}FN_2O_3$ $[M+H]^+$: 278.28; found: 279.32.

**4-(4-methylphenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4e):** Yellowish white solid; mp 168-170 °C; $^1$H NMR: ($CDCl_3$, 300 MHz), $\delta_H$ = 9.20 (s, 1H, N**H**), 7.73 (s, 1H, N**H**), 7.53-7.51 (d, J = 6Hz, 2H, Aro-**H**), 7.19-7.18 (d, J = 3Hz, 2H, Aro-**H**), 5.13 (s, 1H, NH-C**H**-Aro), 4.01-3.96 (q, J = 6Hz, 2H, -COOC**H$_2$**CH$_3$), 2.49 (s, 3H, Aro-C**H$_3$**), 2.24 (s, 3H, NH-C-C**H$_3$**), 1.11-1.08 (t, J = 3Hz, 3H, -COOCH$_2$C**H$_3$**); HRMS: m/z Calculated for $C_{15}H_{18}N_2O_3$ $[M+H]^+$: 274.32; found: 273.28.

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**SUPPORTING INFORMATION**

Proton NMR spectrum of 5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (**4a**)

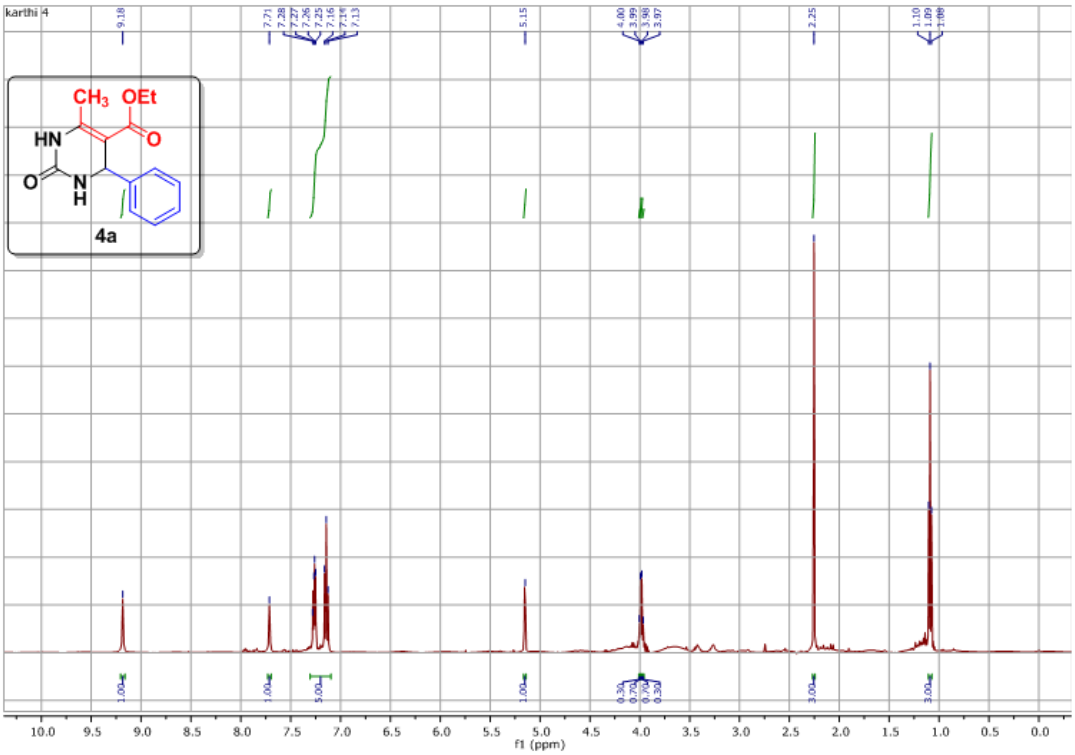
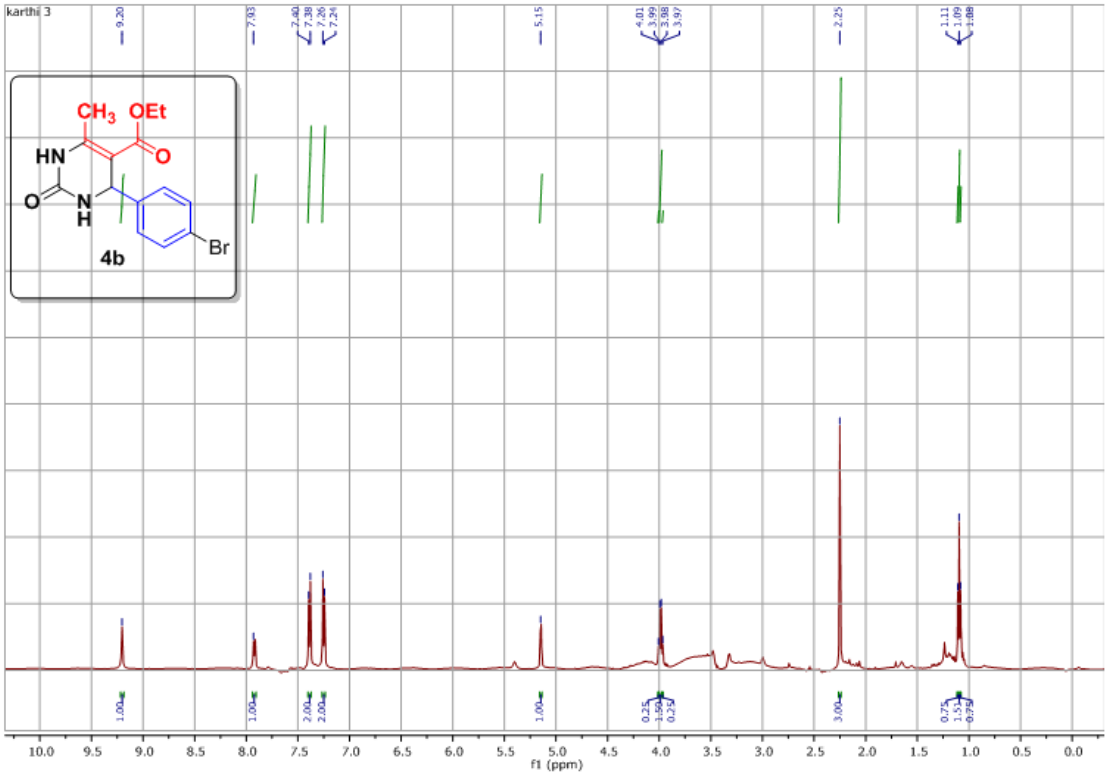



**Fig. 1** $^{1}$H NMR spectrum of 5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (**4a**).

Proton NMR spectrum of 4-(4-Bromophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4b**)

**Fig. 2** $^{1}$H NMR spectrum of 4-(4-Bromophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4b**).



Proton NMR spectrum of 4-(4-chlorophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4c**)

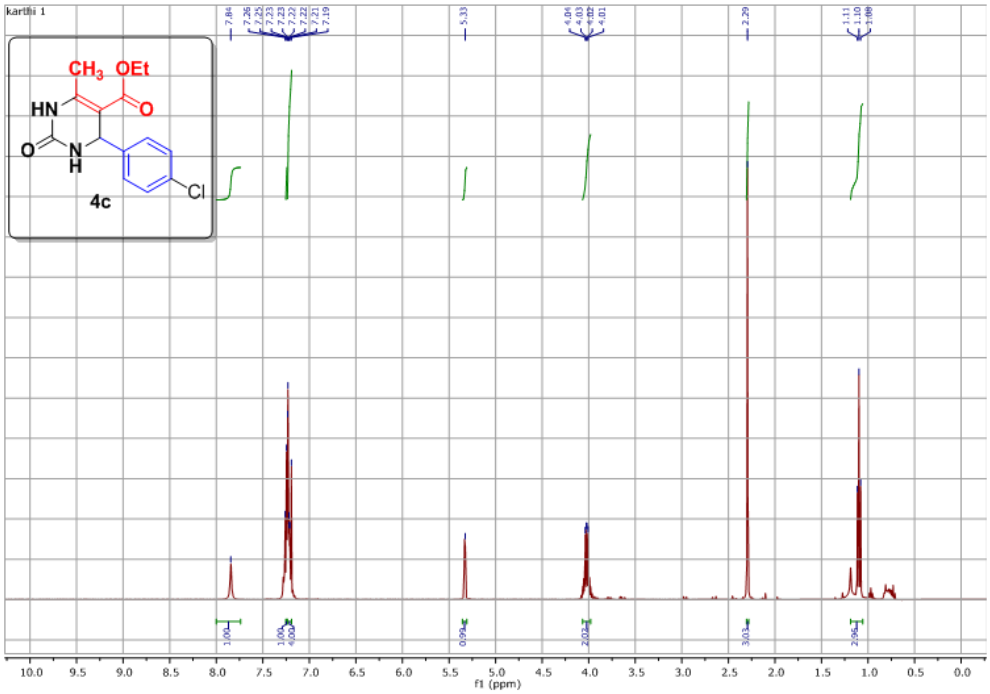



**Fig. 3** $^{1}$H NMR spectrum of 4-(4-chlorophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4c**).

Carbon NMR spectrum of 4-(4-chlorophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4c**)

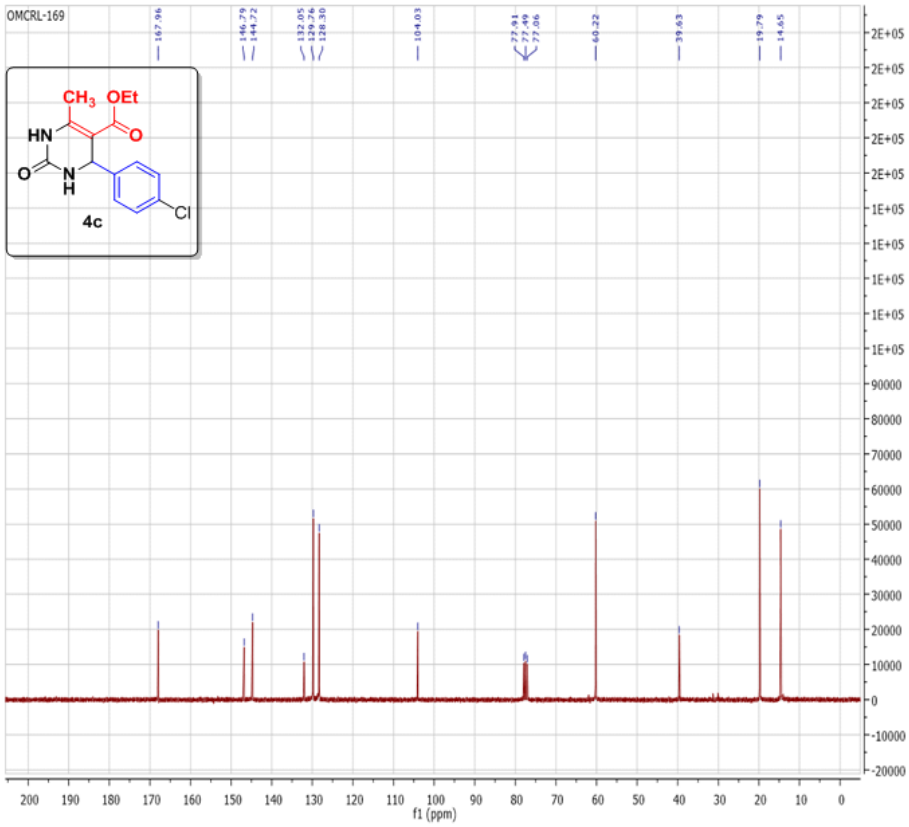



**Fig. 4** $^{13}$C NMR spectrum of 4-(4-chlorophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4c**).

Proton NMR spectrum of 4-(4-fluorophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4d**)

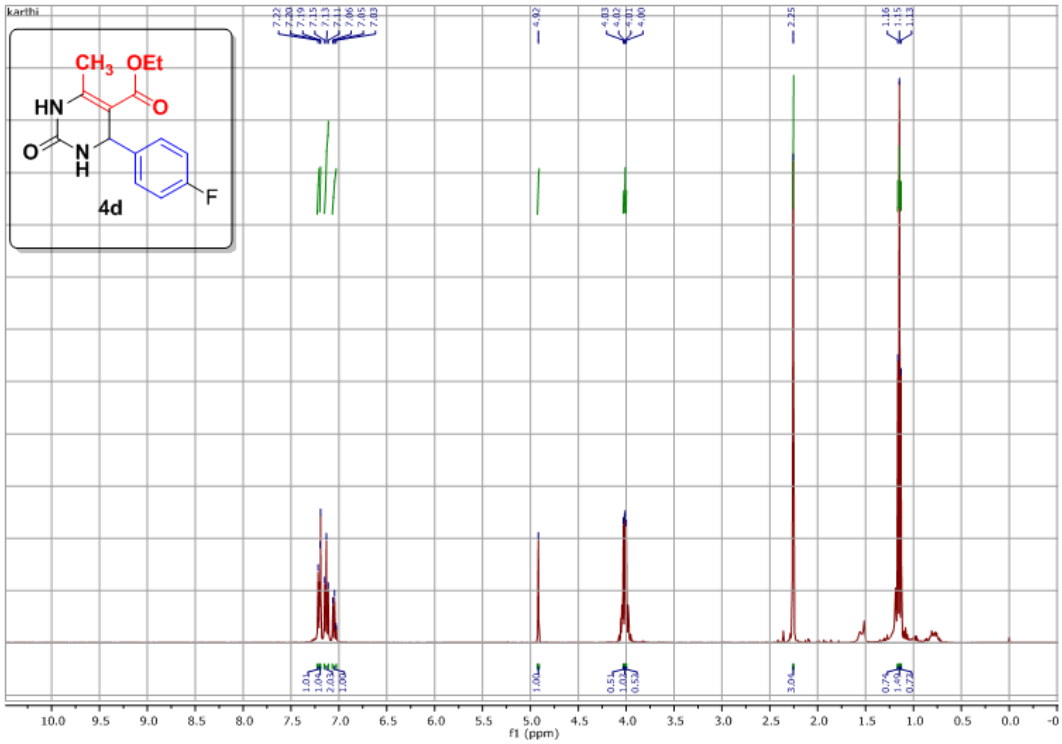



**Fig. 5** $^{1}$H NMR spectrum of 4-(4-fluorophenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4d**).

Proton NMR spectrum of -(4-methylphenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4e**)

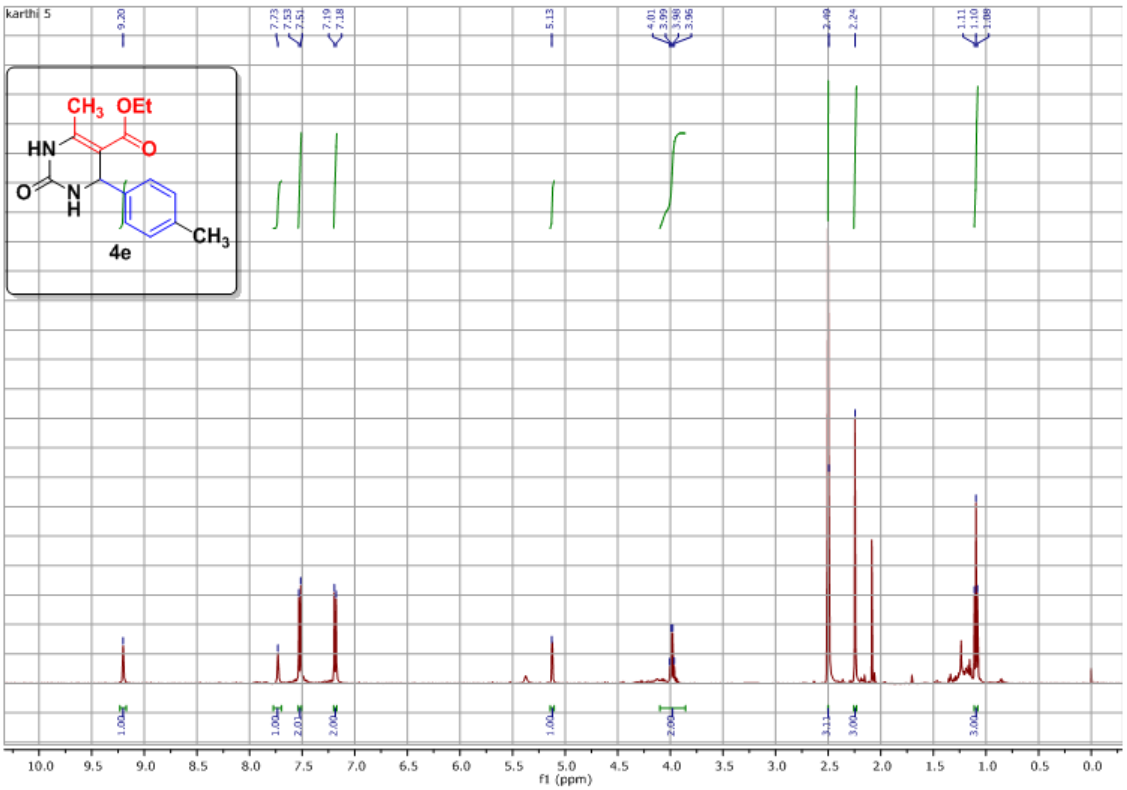



**Fig. 6** $^{1}$H NMR spectrum of 4-(4-methylphenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4e**).