# Microwave assisted facile synthesis and anticancer evaluation of novel ethyl 4-(substituted phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

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- **Abstract**
- Herewith, we report the design and synthesis of a series new ethyl 4-(substituted phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(4a-h)** derivatives, obtained by condensation of substituted aldehydes, ethyl 3-oxobutanoate and urea in ethanol as solvent and Potassium tert-butoxide as a catalyst under microwave irradiation for about 2-4 min (800 W). The reaction was perform in mild reaction condition, good to excellent yields, easy workup and easily available starting material make the reaction attractive for the preparation of compounds **4a-h**. Our work is in progress to obtain biological activity in future, such as antimicrobial and anticancer activity.


- **Keywords:** substituted aldehydes; ethyl 3-oxobutanoate; Microwave irradiation; antimicrobial and anticancer activity.

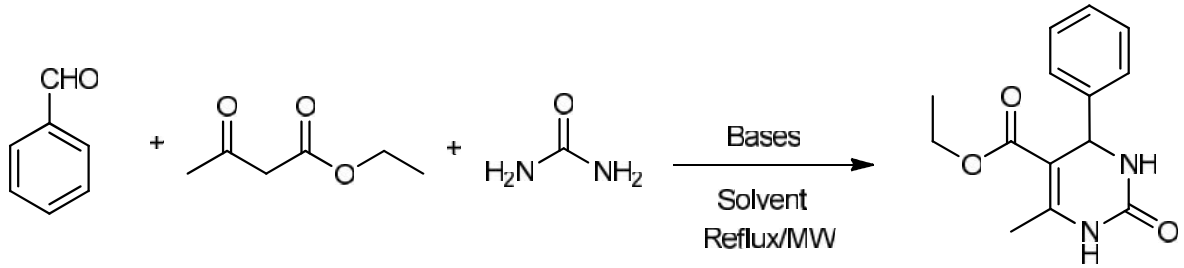
## 1. INTRODUCTION

Pyrimidine moiety is an important class of nitrogen containing heterocycles [1] and is widely used as a key building block for medicinal as well as pharmaceutical agent. Pyrimidine derivatives exhibit antifungal [2], analgesic [3], calcium antagonist [4] and anti-inflammatory activity [5]. The combination of an aldehyde, β-keto ester and urea under acid catalysis to give a dihydropyrimidine was first reported by Pietro Biginelli in 1893 [6] referred to as Biginelli reaction. The original Biginelli reaction was carried out by refluxing a mixture of the three components such as ethyl acetoacetate, benzaldehyde and urea in presence of ethanol catalyzed by small amount of HCl which often result in poor to moderate yields of desired product [7]. The one pot Biginelli protocol for 3,4-dihydropyrimidines synthesis was explored by varying all components and catalyst [8-16] in protic, aprotic solvents, and solvent free condition [17] using ether classical heating, microwave [18,19]. In continuation of our work, [20-28], we have developed the new protocol for the microwave-assisted facile synthesis of novel ethyl 4-(substituted phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate. The substituted benzaldehyde was then subjected to a condensation with the urea and ethyl acetoacetate which was synthesized to provide new series of target compounds **4a-h**. Target compounds were synthesized by microwave irradiation (MW) as well as conventional heating with Potassium tert-butoxide and ethanol.

## 2. RESULT AND DISCUSSION

### 2.1. Chemistry

We have been synthesized and screening of model reaction of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **4a** (Scheme 1, Table 1) and synthesis of ethyl 4-(substituted phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Scheme 2, Table 2) under microwave irradiation as well as conventional method. We would like to mention here we find out best result as a potassium tert-butoxide good base and ethanol good solvent. However, the MW reaction provided cleaner reaction, short reaction time, and the products were only required to be washed with ice-cold water. The yields were good to excellent.

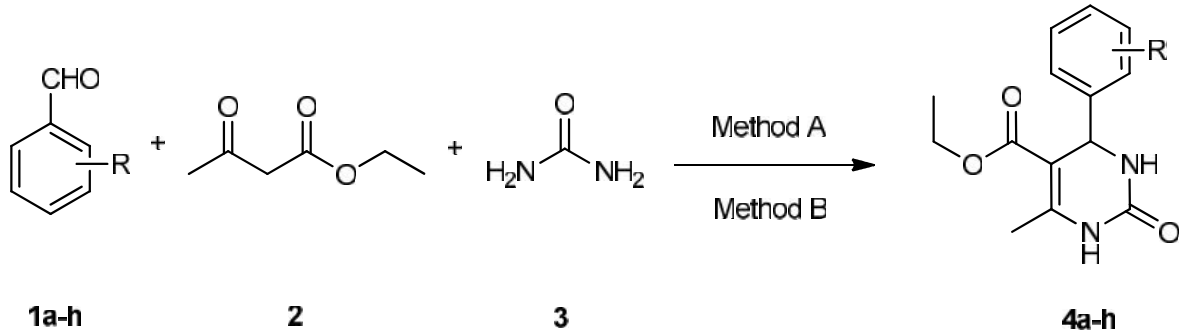



**1a** **2** **3** **4a**

**Scheme 1:** Screening of model reaction of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

[a]**Reaction condition (4a-h):** Benzaldehyde (**1a**) (1 mmol), ethyl 3-oxobutanoate (**2**) (1 mmol), Urea (**3**) (1 mmol), Solvent, bases, reflux 3-7 h**,** / Microwave 3-10 min.

[b]Isolated yield




**1a-h** **2** **3** **4a-h**

**Scheme 2:** Synthesis of ethyl 4-(substituted phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

[a]**Reaction condition (4a-h): Method A:** Compound (**1a-h**) (1 mmol), Compound (**2**) (1 mmol), Compound (**3**) (1 mmol), Ethanol, Potassium tert-butoxide(1 mmol), Microwave 3-4 min.

**Method B:** Compound (**1a-h**) (1 mmol), Compound (**2**) (1 mmol), Compound (**3**) (1 mmol), Ethanol, Potassium tert-butoxide(1 mmol), reflux 3-4 h**.**

[b]Isolated yield

- **2.2. Effect of catalyst and solvents**
- A variety of catalysts were screened under microwave irradiation in order to validate the right choice and the results are shown in Table 1. We have justified the influence of the catalyst; the reaction was carried out in the presence of catalyst potassium tert-butoxide wherein a maximum yield of 95% could be obtained (Table 1, Entry 1). It was further observed that the yield of the reaction hardly improved in the presence of other like sodium acetate and potassium carbonate catalysts (Table 1, Entries 6 and 11), whereas the use of potassium tert-butoxide as catalyst significantly improved the yield to 98% (Table 1, Entry 1) by MW method . Hence potassium tert-butoxide under microwave irradiation was selected for our further studies.
- We synthesized and screening of model reaction under microwave irradiation and conventional method of the compound ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **4a** (Scheme 1, Table 1). The reaction in which the compound **1a** (1 mmol), compound **2** (1 mmol) and the compound **3** (1 mmol), various catalyst and various solvents were selected as a model reaction to optimize the reaction conditions. In terms of the effect of solvents and catalyst on the condensation reaction, potassium tert-butoxide was found to be the better catalyst and ethanol was found to be the best solvent for the reaction (Table 1, entry 1); other solvents, including methanol, acetic acid, N,N-dimethylformamide (DMF) and toluene were less

**Table 1** Screening of catalyst, solvents, reaction time, and yield for the synthesis (**4**)[a]

| Entry | Base | Solvent | Time (h) Conventional method | Time (Min.) Microwave method | Yield[b] (%) Conventional | Yield[b] (%) Microwave |
|---|---|---|---|---|---|---|
| **1** | **Potassium tert-butoxide** | **Ethanol** | **3** | **3** | **95** | **98** |
| 2 | Potassium tert-butoxide | Methanol | 6 | 10 | 80 | 90 |
| 3 | Potassium tert-butoxide | Acetic acid | 6 | 8 | 75 | 85 |
| 4 | Potassium tert-butoxide | DMF | 7 | 9 | 80 | 90 |
| 5 | Potassium tert-butoxide | Toluene | 6 | 10 | 85 | 90 |
| **6** | **Sodium acetate** | **Ethanol** | **5** | **6** | **65** | **85** |
| 7 | Sodium acetate | Methanol | 7 | 8 | 58 | 68 |
| 8 | Sodium acetate | Acetic acid | 7 | 8 | 50 | 70 |
| 9 | Sodium acetate | DMF | 6 | 8 | 55 | 75 |
| 10 | Sodium acetate | Toluene | 7 | 7 | 40 | 70 |
| **11** | **Potassium carbonate** | **Ethanol** | **5** | **6** | **60** | **90** |
| 12 | Potassium carbonate | Methanol | 6 | 10 | 48 | 78 |
| 13 | Potassium carbonate | Acetic acid | 6 | 7 | 50 | 70 |
| 14 | Potassium carbonate | DMF | 6 | 8 | 45 | 75 |
| 15 | Potassium carbonate | Toluene | 7 | 9 | 50 | 70 |

[a] All the reactions were carried out in equimolar amounts of each compounds in 1 mL of solvent

[b] Isolated yield.

**Table 2** Physical data of the synthesized compounds (**4a-h**)[a]

| Compounds | (R) | Time (h) Conventional method | Time (Min.) Microwave method | Yield[b] ( %) CN | Yield[b] ( %) MW | Melting point (°C) |
|---|---|---|---|---|---|---|
| 4a | H | 4 | 3 | 90 | 98 | 200-202 |
| 4b | 4-F | 4 | 3 | 88 | 98 | 175-177 |
| 4c | 4-$NO_2$ | 3 | 3 | 88 | 98 | 233-235 |
| 4d | 4-OH | 4 | 4 | 90 | 98 | 222-224 |
| 4e | 4-OMe | 4 | 3 | 90 | 98 | 198-200 |
| 4f | 4-Me | 4 | 3 | 90 | 97 | 210-212 |
| 4g | 4-Cl | 4 | 4 | 90 | 98 | 215-217 |
| 4h | 2-Cl, 4-Cl | 3 | 4 | 92 | 98 | 240-242 |

[a]Reaction condition (**4a-h**): Compound (**1a-h**) (1 mmol), Compound (**2**) (1 mmol), Compound (**3**) (1 mmol), Ethanol, Potassium tert-butoxide(1 mmol), reflux 3-4 h**,** reflux

[b]Isolated yield

- efficient (Table 1, entries 2–5, 7–10 and 12–15). Rest all of these yields were generally was the best among these solvents (Table 1, entries 1, 6 and 11). To increase the efficiency of the condensation reaction, the effects of different catalyst were investigated (Table 1, entries 1–15). Potassium tert-butoxide exhibited the best performance with used solvents and gave better yield, (Table 1, entries 11–15). Potassium carbonate and sodium acetate gave lower yields with other solvents, but gave better yield in ethanol as a solvent (Table 1, entries 1 and 6). All the reactions were carried out in equimolar amounts of each compound in 1 mL of solvent. Among these reactions same amounts of the solvent, namely 2 mL of ethanol turned out to be the best choice with yields of 98%, 85% and 90% (Table 1, entries 1, 6 and 11).
- We have also synthesized and screening of model reaction under conventional method and the results of these findings are presented in Table 1. The reaction in which the compound **1a** (1 mmol), compound **2** (1 mmol) and the compound **3** (1 mmol), various catalyst and various solvents were selected as a model reaction to optimize the reaction conditions. In terms of the effect of solvents and catalyst on the condensation reaction, potassium tert-butoxide was found to be the better catalyst and ethanol was found to be the best solvent for the reaction (Table 1, entry 1); other solvents, including methanol, acetic acid, DMF and toluene were less efficient (Table 1, entries 2–5, 7–10 and 12–15). Nevertheless, all of these yields were generally low before further optimizations. Ethanol gave the corresponding product in 60–95 % yield, which was the best among these solvents (Table 1, entries 1, 6 and 11). To increase the efficiency of the condensation reaction, the effects of different catalyst were investigated (Table 1, entries 1–15). Potassium tert-butoxide exhibited the best performance with used solvents and gave better yield, (Table 1, entries 11–15). Sodium acetate and Potassium carbonate gave lower yields with other solvents, but gave better yield in ethanol as a solvent (Table 1, entries 6 and 11). All the reactions were carried out in equimolar amounts of each compound in 2 mL of solvent. Among these reactions same amounts of the solvent, namely 2 mL of ethanol turned out to be the best choice with yields of 95%, 65% and 60% (Table 1, entries 1, 6 and 11).

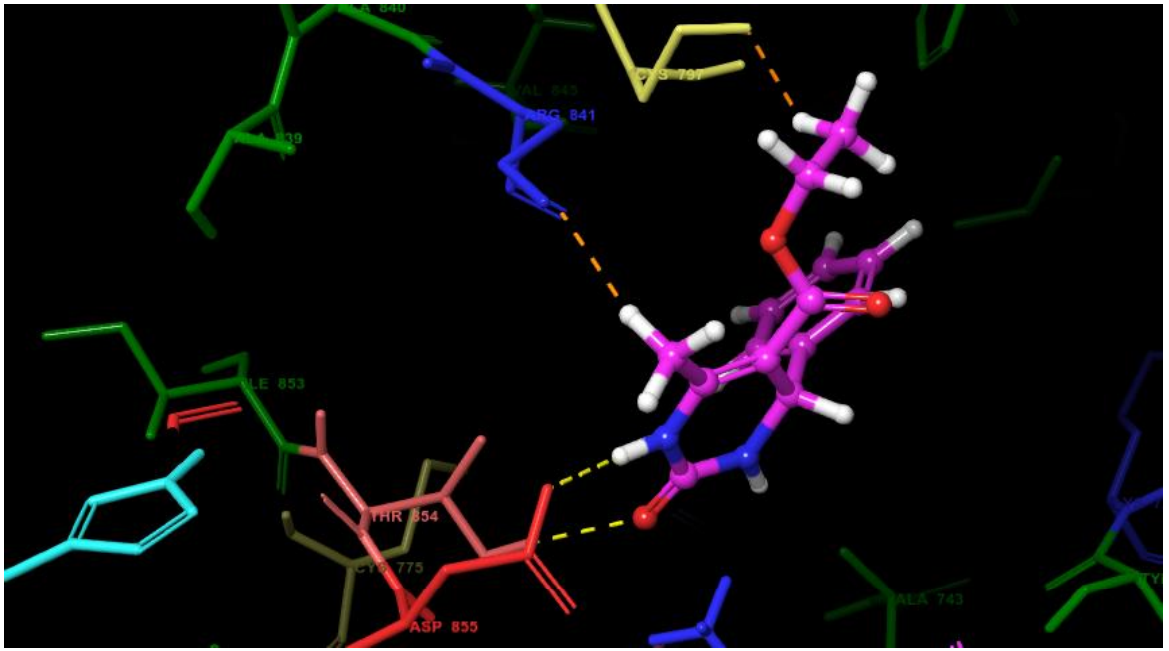



**Figure 1.**

The compound screened during docking was found to attach properly at the binding site of EGFR enzyme. Hydrogen bonding with the amino acids ASP 855, THR 854 and ARG 841 was observed as key interactions. Also compound was found potential to show interactions with amino acid CYS 797 which is key binding site for EGFR kinase enzyme.

- **3. MATERIAL AND METHODS**
- **3.1. Experimental:**
- ***Method A: Microwave-assisted synthesis:***
- In a 100 ml round bottom flask, the compound substituted benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), and urea (1 mmol) with solvent was added and this mixture subjected to MW irradiation (800 W), for 3-4 min. The progress of the reaction was monitored by TLC (20% n-hexane: ethyl acetate). After completion of the reaction, the reaction mixture was concentrated *in vacuo*. The residue was washed with water (2×10 ml) to afford the crude product. The crude product was recrystallized using ethanol as solvent to give yield in the range 97-98 %.
- ***Method B: Conventional synthesis:***
- In a 100 ml round bottom flask, the compound substituted benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), and urea (1 mmol) with solvent was added and this mixture subjected to stirred for 3-4 h at reflux temperature. The progress of the reaction was monitored by TLC (20% n-hexane: ethyl acetate). After completion of the reaction, the reaction mixture was concentrated *in vacuo*. The residue was washed with water (2×10 ml) to afford the crude product. The crude product was recrystallized using ethanol as solvent to give yield in the range 88-92 %.

- **Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a)**

  Yellow solid. Yield 98%, mp 200-202 °C; ES-MS m/z (%):260.29, $^{1}$H NMR (500 MHz, DMSO-*d6*): δ 8.88 (s, 1H), 7.33 – 7.27 (m, 1H), 7.21 (d, J = 7.7 Hz, 1H), 5.32 (dd, J = 7.6, 1.1 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.30 (s, 1H), 1.19 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (125 MHz, DMSO-*d6*): δ= 167.40, 154.78, 148.44, 141.87, 129.12, 128.48, 126.98, 102.90, 60.12, 51.74, 18.97, 14.40.

- **Ethyl 4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b)**

  Yellow solid. Yield 98%, mp 200-202 °C; ES-MS m/z (%): 278.28, $^{1}$H NMR (500 MHz, DMSO-*d6*): δ 8.88 (s, 1H), 7.33 – 7.26 (m, 2H), 7.24 (d, J = 7.7 Hz, 1H), 7.10 – 7.03 (m, 2H), 5.31 (dt, J = 7.5, 0.8 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.30 (s, 1H), 1.19 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (125 MHz, DMSO-*d6*): δ= 167.40, 163.16, 161.15, 154.78, 148.44, 138.45 (d, J = 2.9 Hz), 128.74 (d, J = 8.1 Hz), 116.46, 116.30, 102.49, 60.12, 51.58, 18.97, 14.40.

- **Ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c)**

  Yellow solid. Yield 98%, mp 233-235 °C; ES-MS m/z (%):305.29, $^{1}$H NMR (500 MHz, DMSO-*d6*): δ 8.88 (s, 1H), 8.18 – 8.12 (m, 2H), 7.57 – 7.50 (m, 2H), 7.24 (d, J = 7.5 Hz, 1H), 5.31 (dq, J = 8.0, 1.0 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.30 (s, 1H), 1.19 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (125 MHz, DMSO-*d6*): δ= 167.40, 154.78, 148.44, 146.21, 145.32, 127.62, 124.31, 102.39, 60.12, 51.70, 18.97, 14.40.

## 4. CONCLUSION

In conclusion, we have successfully developed an easy access to a new series of ethyl 4-(substituted phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives by MW irradiation as well as conventional method. The mild reaction conditions, stirring at reflux temperature, good to excellent yields, easy workup, and easily available substrates make the reactions attractive for the preparation of compounds **4a-h**. Efforts towards the synthesis of other important drug molecules with tetrahydropyrimidine-5-carboxylate moiety by MW irradiation as well as conventional method are ongoing in our laboratory. Also work is in progress to obtain biological activity such as anticancer activity of the synthesized compounds.

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# Thank You