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β-Cyclodextrin-assisted synthesis of Biginelli adducts under solvent-free conditions

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ABSTRACT

A simple, green and efficient protocol was developed using β-cyclodextrin as a solid catalyst for the solvent-free synthesis of various Biginelli adducts. The advantages of our protocol included the following: (i) a metal-free methodology; (ii) high yields; (iii) simple and efficient work-up procedures; (iv) improved results under solvent-free conditions. β-cyclodextrin-catalyzed the Biginelli reactions for various aldehydes, demonstrating that it is an efficient and eco-friendly catalyst for the preparation of heterocyclic compounds.

1. Introduction

In recent years, multicomponent reactions (MCRs) have emerged as a powerful synthetic tool for generating structurally complex molecular entities with fascinating biological properties through the formation of several carbon–carbon and carbon–heteroatom bonds in a one-pot operation. The convergent character, atom economy, ease of a one-pot operation, and access to structurally diverse libraries of compounds provided by MCRs is advantageous compared to linear multistep synthesis.[1]

3,4-Dihydropyrimidin-2(1*H*)-one/-thione derivatives, also named Biginelli adducts, have attracted much attention as important structural motifs in medicinal chemistry because of their significant therapeutic and biological activities, such as antihypertensive, potassium channel antagonist, antiepileptic, antimalarial, antimicrobial, antitumor, antibacterial, anticancer, and antiflammatory properties.[2]

During the last few years, numerous catalytic methods have been developed to improve the reaction yield, lower the reaction time and/or broaden the scope of the Biginelli reaction. Although numerous methods for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/-thiones are known, few use Brønsted-Lowry or Lewis acids as catalysts for the Biginelli reaction.[3] The use of ionic liquids,[4] microwave irradiation,[5] solid phase reagents,[6] baker's yeast,[7] polymer-supported catalysts,[8] zeolite,[9] surfactants,[10] and PEG[11] has also been reported. Only a few examples of organocatalysts have been described for the Biginelli reaction.[12] However, most of these methods require expensive reagents, long reaction times, harsh reaction conditions, and tedious work-up procedures or provide unsatisfactory yields.

Cyclodextrins (CDs), obtained from the enzymatic degradation of starch, are cyclic oligosaccharides that catalyze a wide range of chemical reactions through the formation of a reversible host–guest complex via non-covalent interactions.[13] Recently, Luo and co-workers described the use of hydrochloric acid-β-cyclodextrin catalysts in the Biginelli reaction and excellent yields were obtained.[14] Tajbakhsh and co-workers disclosed the use of sulfonated β-cyclodextrin as an efficient and recyclable heterogeneous catalyst for Biginelli reactions.[15] However, the first method required a co-catalyst, HCl, and the second method requires the sulfonation of β-cyclodextrin using chlorosulfonic acid, a hazardous and corrosive reagent, to prepare the catalyst.

Herein, we have disclosed a simple, effective and eco-friendly approach to the synthesis of Biginelli adducts using β-cyclodextrin (β-CD) as a reusable catalyst under solvent-free conditions.

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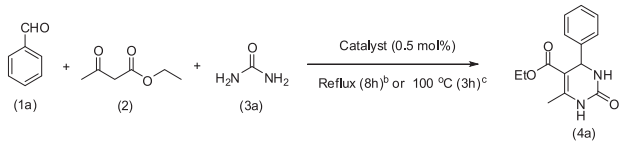
2. Results and discussion

We first examined the reaction with a series of cyclodextrins (catalysts) and solvents as well as performing the reaction under solvent-free conditions. In these reactions we studied the Biginelli one-pot condensation reaction of benzaldehyde (**1a**; 3.0 mmol), ethyl acetoacetate (**2**; 4.5 mmol), and urea (**3**; 4.5 mmol) using 0.5 mol % of different cyclodextrins [α-cyclodextrin (α-CD); β-cyclodextrin (β-CD), γ-cyclodextrin (γ-CD), 2-hydroxypropyl-β-cyclodextrin (HP-β-CD), and methyl-β-cyclodextrin (Me-β-CD)] as the catalysts (Table 1). Similar results were obtained under solvent-free conditions employing α-, β- and γ-CD as the catalysts (Table 1, entries 6, 12 and 18, respectively). These results indicate that the size of the cyclodextrin cavities (α- for the hexamer, β- for the heptamer and γ- for the octamer) does not have a significant effect on their catalysis of Biginelli reactions.

Table 1
Effect of solvents on the yield of cyclodextrin-catalyzed Biginelli reactions[a]

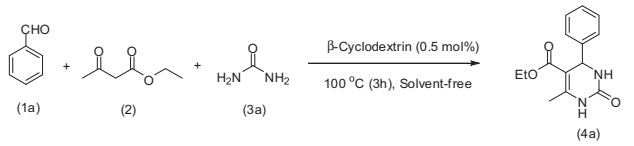


Entry	Solvent	Catalyst	Yield[d] (%)
1	Methanol[b]	α-CD	45
2	Ethanol[b]	α-CD	35
3	Acetonitrile[b]	α-CD	24
4	DMSO[b]	α-CD	41
5	Water[b]	α-CD	40
6	—[c]	α-CD	82
7	Methanol[b]	β-CD	18
8	Ethanol[b]	β-CD	6
9	Acetonitrile[b]	β-CD	21
10	DMSO[b]	β-CD	43
11	Water[b]	β-CD	20
12	—[c]	β-CD	83
13	Methanol[b]	γ-CD	44
14	Ethanol[b]	γ-CD	12
15	Acetonitrile[b]	γ-CD	39
16	DMSO[b]	γ-CD	41
17	Water[b]	γ-CD	21
18	—[c]	γ-CD	79
19	Methanol[b]	HP-β-CD	21
20	Ethanol[b]	HP-β-CD	23
21	Acetonitrile[b]	HP-β-CD	9
22	DMSO[b]	HP-β-CD	42
23	Water[b]	HP-β-CD	26
24	—[c]	HP-β-CD	64
25	Methanol[b]	Me-β-CD	11
26	Ethanol[b]	Me-β-CD	26
27	Acetonitrile[b]	Me-β-CD	29
28	DMSO[b]	Me-β-CD	60
29	Water[b]	Me-β-CD	23
30	—[c]	Me-β-CD	64

[a] Reagents and conditions: benzaldehyde/ethyl acetoacetate/urea (molar ratio=3:4.5:4.5). Catalysts: α-CD: α-cyclodextrin; β-CD: β-cyclodextrin; γ-CD: γ-cyclodextrin; HP-β-CD: 2-hydroxypropyl-β-cyclodextrin; or Me-β-CD: methyl-β-cyclodextrin.
[b] These reactions were carried out for 8 h at the boiling point of the solvent.
[c] These reactions were carried out under solvent-free conditions at 100 °C for 3 h.
[d] The yields are those of the purified Biginelli adduct **4a**.

Using the optimized reactions conditions, we then evaluated the effect of the catalytic load of β-CD on the yield of the Biginelli adduct (Table 2). The use of 0.5 mol % β-CD as a catalyst is sufficient to promote the reaction with excellent yields (Table 2, entry 4). No improvement in the reaction rates and yields was observed from increasing or decreasing the amount of the catalyst from 0.5 mol % (Table 2). The yield of Biginelli reaction without β-CD furnished the desired product with lower yield than 30% (Table 2, entry 1).

Table 2
Screening the catalyst load of β-cyclodextrin in the Biginelli reaction[a]

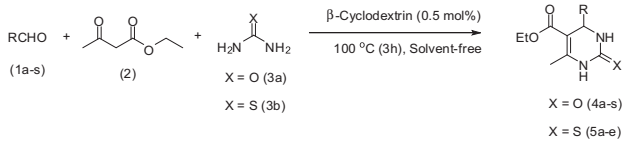


Entry	β-CD (mol %)	Yield[b] (%)
1	—	29
2	0.15	77
3	0.25	79
4	0.50	83
5	1.00	85
6	2.00	71

[a] Reagents: benzaldehyde/ethyl acetoacetate/urea (molar ratio=3:4.5:4.5).
[b] The yields correspond to the purified Biginelli adduct **4a**.

Having optimized the reaction conditions for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using β-CD as the catalyst under solvent-free conditions, we subsequently applied the optimized reaction conditions to various aldehydes to explore the generality of the reaction system. As shown in Table 3, Biginelli reactions produced excellent product yields for a wide range of aromatic aldehydes bearing both electron-donating and electron-withdrawing substituents. Non-aromatic and heteroaromatic aldehydes, however, were less reactive producing only moderate yields (Table 3). Both urea and thiourea were suitable substrates as demonstrated from the yields of the corresponding Biginelli adducts (Table 3).

Table 3
Use of different aldehydes in β-CD-catalyzed Biginelli reactions[a]



Product	R	X	Yield[b] (%)
4a	C_6H_5	O	85
5a	C_6H_5	S	67
4b	3-OHC_6H_4	O	82
5b	3-OHC_6H_4	S	71
4c	4-OHC_6H_4	O	78
5c	4-OHC_6H_4	S	61
4d	4-FC_6H_4	O	83
5d	4-FC_6H_4	S	73
4e	4-NCC_6H_4	O	71
5e	4-NCC_6H_4	S	70
4f	4-$O_2NC_6H_4$	O	91
4g	3- $O_2NC_6H_4$	O	78
4h	4-ClC_6H_4	O	85
4i	4-$CO_2HC_6H_4$	O	83
4j	3-OMe–4-OHC_6H_4	O	88
4k	3,5-OMe–4-OHC_6H_4	O	75
4l	3-$OMeC_6H_4$	O	75
4m	4-$OMeC_6H_4$	O	86
4n	4-MeC_6H_4	O	83
4o	4-$(N(CH_3)_2)C_6H_4$	O	60
4p	C_4H_4O	O	28
4q	C_4H_4S	O	26
4r	$CH_3CH_2CH_2$	O	38
4s	CH_3	O	26

[a] Reagents and conditions: benzaldehyde/ethyl acetoacetate/urea or thiourea (molar ratio=3:4.5:4.5).
[b] The reaction shows no stereoselectivity.

In all cases, the pure product was isolated by simple filtration, without chromatography or a cumbersome work-up procedure. After the reaction, the catalyst can be easily separated from the product and reused without a significant decrease in its catalytic

activity. For example, the reaction of benzaldehyde (**1a**), ethyl acetoacetate (**2**), and urea (**3**) produced the corresponding 3,4-dihydropyrimidine-2(1*H*)-one **4a** in good yield even after five cycles (Fig. 1).

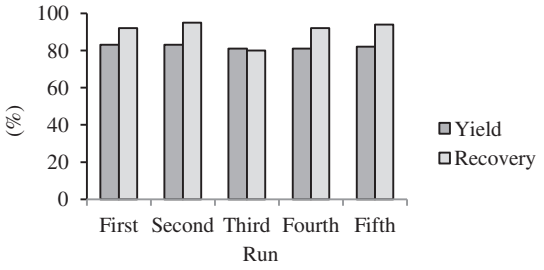


Fig. 1. Reuse of β-cyclodextrin (β-CD) in the Biginelli reaction.

3. Conclusions

In conclusion, we describe a novel protocol for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones/-thiones using the three-component Biginelli reactions of aldehydes, ethyl acetocetate, and urea or thiourea under solvent-free conditions. This procedure offers several notable advantages including operational simplicity, reuse of the catalyst (β-CD), good or high yields, solvent-free conditions, and recrystallization from ethanol, all of which contribute to the minimization of waste. Therefore, it can be considered a green transformation. Hence, the solvent-free Biginelli reaction using β-CD is a useful method for the synthesis of these heterocyclic compounds.

4. Experimental section

4.1. General techniques

Unless noted, all commercial reagents were used as purchased without further purification. The reaction monitoring was accomplished by layer chromatography (TLC) was carried out using 0.2 mm Kieselgel F_{254} (Merck) silica plates and compounds were visualized using UV irradiation at 365 nm. Melting points were measured by an MQAPF-301 Microquímica micromelting point apparatus and are uncorrected. Infrared spectra were recorded as neat using an FT-IR Varian 660 Fourier Transform Infrared spectrometer. Values are expressed in wavenumbers (cm^{-1}) and recorded in a range of compound 4000 to 450 cm^{-1}. NMR spectra were recorded at 25 °C in DMSO-d_6 on a Varian Mercury 300 spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C. All chemical shifts are reported in parts per million (ppm) and were measured relative to the solvent in which the sample was analyzed (DMSO-d_6, δ 2.49 for ^1H NMR and δ 39.5 for ^{13}C NMR). Coupling constants (*J*) are reported in hertz (Hz).

4.2. General procedure for the synthesis of 3,4-dihydropyrmidin-2(1*H*)-ones/-thiones Biginelli reactions

Aldehyde (3 mmol), ethyl acetoacetate (0.586 g, 4.5 mmol), urea (0.270 g, 4.5 mmol) or thiourea (0.343 g, 4.5 mmol), and β-cyclodextrin (17 mg, 0.5 mol %) were mixed in a 25 mL round bottom flask for 3 h at a temperature of 100 °C. The reaction mixture was cooled and the solid was solubilized in ethanol and the addition of few drops of cold water to precipitate the product. The precipitated solid was filtered on sintered funnel. The crude product was further purified by recrystallization from ethanol to afford pure 3,4-dihydropyrimidin-2(1*H*)-ones. After separation of the product by filtration, the filtrate was washed with ethyl acetate and the aqueous phase was concentrated on rotary evaporator obtaining the catalyst.

*4.2.1. Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4a**).* Yield (0.664 g, 85%) as a yellow solid; mp 202.9–204.3 °C (lit.: 203–205 °C).[16] ^1H NMR (300 MHz, DMSO-d_6) δ 1.07 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 2.22 (s, 3H, CH_3), 3.96 (q, 2H, *J*=7.1 Hz, OCH_2CH_3), 5.12 (d, 1H, *J*=3.2 Hz, CH), 7.40–7.12 (m, 5H, aromatic), 7.73 (br s, 1H, NH), 9.18 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.7, 18.5, 54.6, 59.9, 99.9, 126.9, 127.9, 129.1, 145.5, 149.0, 152.8, 166.0. FTIR (ATR, cm^{-1}): 3236, 3109, 2978, 1722, 1697, 1645, 1560, 1368, 1312, 1291, 1216, 1087, 1025, 755.

*4.2.2. Ethyl 4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4b**).* Yield (0.679 g, 67%) as a yellow solid; mp 164.4–166.2 °C (lit.: 164–168 °C).[17] ^1H NMR (300 MHz, DMSO-d_6) δ 1.12 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 2.24 (s, 3H, CH_3), 3.97 (dd, 2H, *J*=7.1, *J*=3.2 Hz, OCH_2CH_3), 5.03 (d, 1H, *J*=3.2 Hz, CH), 6.59–6.46 (m, 3H, CH, CH, CH), 6.94 (t, 1H, *J*=8.0 Hz), 8.76 (br s, 1H, NH), 9.10 (s, 1H, OH), 9.36 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.9, 18.9, 54.3, 59.6, 102.4, 113.3, 114.9, 118.7, 129.0, 145.8, 149.5, 157.4, 157.9, 167.8. FTIR (ATR, cm^{-1}): 3351, 3242, 2973, 2703, 1644, 1595, 1449, 1369, 1215, 1090, 1018, 872.

*4.2.3. Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4c**).* Yield (0.646 g, 78%) as a yellow solid; mp 226.5–228.3 °C (lit.: 227–229 °C).[18] ^1H NMR (300 MHz, DMSO-d_6) δ 1.06 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 2.21 (s, 3H, CH_3), 3.95 (q, 2H, *J*=7.1 Hz, OCH_2CH_3), 5.01 (d, 1H, *J*=3.2 Hz, CH), 6.65 (d, 2H, *J*=8.5 Hz), 6.83 (d, 2H, *J*=8.5 Hz, CH, CH), 7.61 (br s, 1H, NH), 9.09 (s, 1H, NH), 9.32 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 18.4, 54.1, 59.8, 100.3, 115.6, 128.1, 136.1, 148.4, 152.7, 157.3, 166.1. FTIR (ATR, cm^{-1}): 3280, 3097, 2169, 1712, 1681, 1651, 1511, 1446, 1319, 1223, 1172, 1093, 782, 667.

*4.2.4. Ethyl 4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4d**).* Yield (0.696 g, 83%) as a yellow solid; mp 181.1–181.8 °C (lit.: 180–182 °C).[19] ^1H NMR (300 MHz, DMSO-d_6) δ 1.09 (t, 3H, *J*=6.9 Hz, OCH_2CH_3), 2.23 (s, 3H, CH_3), 3.98 (q, 2H, *J*=6.9 Hz, OCH_2CH_3), 5.11 (br s, 1H, CH), 7.27–7.09 (m, 4H, aromatic), 7.75 (br s, 1H, NH), 9.22 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.7, 18.5, 53.9, 59.9, 99.7, 115.8, 128.9, 141.8, 149.2, 152.6, 163.6, 165.9. FTIR (ATR, cm^{-1}): 3228, 3122, 2978, 2162, 1725, 1697, 1643, 1505, 1290, 1214, 1082, 1011, 844, 764, 658.

*4.2.5. Ethyl 4-(4-cyanophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4e**).* Yield (0.606 g, 71%) as a yellow solid; mp 217.8–218.5 °C (lit.: 219–221 °C).[20] ^1H NMR (300 MHz, DMSO-d_6) δ 1.07 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 2.24 (s, 3H, CH_3), 3.96 (q, 2H, *J*=7.2 Hz, OCH_2CH_3), 5.74 (s, 1H, CH), 6.86 (s, 1H, NH), 7.57–7.27 (m, 4H, aromatic), 9.32 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.6, 19.1, 55.3, 59.5, 98.5, 110.3, 119.6, 127.7, 132.8, 146.5, 149.3, 158.3, 161.9. FTIR (ATR, cm^{-1}): 3451, 3348, 3292, 3097, 2232, 1650, 1602, 1546, 1405, 1362, 1274, 1205, 1152, 1100, 1017, 861, 825, 777.

*4.2.6. Ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4f**).* Yield (0.834 g, 91%) as a yellow solid; mp 198.4–199.5 °C (lit.: 200–203 °C).[21] ^1H NMR (300 MHz, DMSO-d_6) δ 1.09 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 2.24 (s, 3H, CH_3), 3.96 (q, 2H, *J*=7.1 Hz, OCH_2CH_3), 5.25 (d, 1H, *J*=3.2 Hz, CH), 7.48 (d, 2H, *J*=8.7 Hz, CH, CH), 8.20 (d, 2H, *J*=8.7 Hz, CH, CH), 7.89 (br s, 1H, NH), 9.35 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.7, 18.5, 54.3 60.1, 98.8, 124.5, 128.3, 147.4, 150.1, 152.4, 152.7, 165.7. FTIR (ATR, cm^{-1}): 3224, 3114, 2985, 2169, 1729, 1698, 1642, 1518, 1288, 1212, 1085, 1014, 777, 698.

*4.2.7. Ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4g**).* Yield (0.711 g, 78%) as a white solid; mp 228.1–229.0 °C (lit.: 228–230 °C).[12] ^1H NMR (300 MHz, DMSO-d_6) δ 1.10 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 2.26 (s, 3H, CH_3), 3.96 (q,

2H, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 5.28 (d, 1H, *J*=3.3 Hz, CH), 7.84–7.41 (m, 2H, CH, CH), 7.90 (br s, 1H, NH), 8.34–7.91 (m, 2H, CH, CH), 9.37 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.7, 18.9, 54.2, 59.9, 99.1, 121.8, 122.6, 130.3, 133.8, 147.0, 147.6, 150.1, 158.2, 167.2. FTIR (ATR, cm^{-1}): 3320, 3212, 3087, 2965, 1701, 1677, 1620, 1517, 1458, 1428, 1378, 1341, 1260, 1215, 1110, 1081, 1003, 904, 819, 789, 735.

*4.2.8. Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4h**).* Yield (0.748 g, 85%) as a yellow solid; mp 209.4–211.4 °C (lit.: 209–211 °C).[22] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 2.23 (s, 3H, CH$_3$), 3.93 (q, 2H, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 5.12 (d, 1H, *J*=3.3 Hz, CH), 7.77–7.20 (m, 4H, aromatic), 7.77 (br s, 1H, NH), 9.25 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ=14.7, 18.5, 54.1, 59.9, 99.4, 128.8, 129.1, 132.4, 144.4, 149.4, 152.6, 165.8. FTIR (ATR, cm^{-1}): 3232, 3113, 2978, 2169, 1722, 1699, 1644, 1488, 1289, 1218, 1089, 1012, 958, 779, 684.

*4.2.9. 4-(5-(Ethoxycarbonyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl)benzoic acid (**4i**).* Yield (0.759 g, 83%) as a yellow solid; mp 277.1–278.8 °C (lit.: not found). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.05 (t, 3H, *J*=7.0 Hz, OCH$_2$C*H*$_3$), 2.23 (s, 3H, CH$_3$), 3.96 (q, 2H, *J*=7.0 Hz, OC*H*$_2$CH$_3$), 5.18 (br s, 1H, CH), 7.33 (d, 2H, *J*=8.3 Hz, CH, CH), 7.80 (br s, 1H, NH), 7.89 (d, 2H, *J*=8.3 Hz, CH, CH), 9.26 (s, 1H, NH), 10.07 (sl, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.7, 18.5, 54.5, 59.3, 99.3, 127.2, 130.4, 149.5, 150.2, 152.6, 165.8, 167.7, 171.1. FTIR (ATR, cm^{-1}): 3286, 3215, 3074, 2929, 2166, 1702, 1646, 1609, 1579, 1421, 1386, 1316, 1274, 1223, 1169, 1123, 1085, 907, 861, 770.

*4.2.10. Ethyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4j**).* Yield (0.806 g, 88%) as a yellow solid; mp 224.9–226.9 °C (lit.: 226–228 °C).[21] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.07 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 2.21 (s, 3H, CH$_3$), 3.34 (s, 3H, OCH$_3$), 3.97 (q, 2H, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 5.03 (d, 1H, *J*=3.1 Hz, CH), 6.69–6.56 (m, 2H, CH, CH), 6.78 (s, 1H, CH), 7.63 (br s, 1H, NH), 8.91 (s, 1H, NH), 9.11 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 18.4, 54.2, 56.2, 59.8, 100.2, 111.4, 115.9, 118.9, 136.6, 146.6, 147.9, 148.6, 152.9, 166.1. FTIR (ATR, cm^{-1}): 3286, 3215, 3074, 2929, 2166, 1702, 1646, 1609, 1579, 1421, 1386, 1316, 1274, 1223, 1169, 1123, 1085, 907, 861, 770.

*4.2.11. Ethyl 4-(4-hydroxy-3,5-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4k**).* Yield (0.762 g, 75%) as a yellow solid; mp 169.8–171.7 °C (lit.: not found). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 2.22 (s, 3H, CH$_3$), 3.68 (s, 6H, OCH$_3$, CH$_3$), 3.99 (q, 2H, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 5.07 (d, 1H, *J*=3.2 Hz, CH), 6.46 (s, 2H, CH, CH), 7.64 (br s, 1H, NH), 8.32 (s, 1H, NH), 9.13 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.9, 18.4, 54.4, 56.6, 59.8, 99.4, 104.4, 135.6, 148.4, 148.7, 152.9, 166.1. FTIR (ATR, cm^{-1}): 3610, 3228, 3119, 2981, 2162, 1726, 1706, 1648, 1517, 1426, 1319, 1283, 1217, 1119, 1091, 1024, 777, 698.

*4.2.12. Ethyl 4-(3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4l**).* Yield (0.655 g, 75%) as a yellow solid; mp 220.4–221.4 °C (lit.: 220–221 °C).[23] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.09 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 2.22 (s, 3H, CH$_3$), 3.70 (s, 3H, OCH$_3$), 3.97 (q, 2H, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 5.09 (d, 1H, *J*=3.2 Hz, CH), 6.86–6.68 (m, 3H, CH, CH, CH), 7.22 (t, 1H, *J*=7.5 Hz, CH), 7.72 (br s, 1H, NH), 9.19 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 18.4, 54.4, 55.6, 59.9, 99.8, 112.8, 113.0, 118.9, 130.3, 146.9, 149.1, 152.8, 159.8, 166.0. FTIR (ATR, cm^{-1}): 3235, 3097, 2937, 2841, 2191, 1699, 1648, 1597, 1493, 1427, 1329, 1276, 1255, 1222, 1119, 1037, 862, 772, 751.

*4.2.13. Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4m**).* Yield (0.745 g, 86%) as a yellow solid; mp 203.2–205.1 °C (lit.: 203–205 °C).[19] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.08 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 2.22 (s, 3H, CH3), 3.69 (s, 3H, OCH3), 3.95 (q, 2H, *J*=7.1 Hz, OCH$_2$CH$_3$), 5.07 (d, 1H, *J*=3.0 Hz, CH), 6.85 (d, 2H, *J*=8.7 Hz, CH, CH), 7.12 (d, 2H, *J*=8.7 Hz, CH, CH), 7.67 (br s, 1H, NH), 9.15 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 18.4, 53.9, 55.7, 59.8, 100.2, 114.3, 128.1, 137.7, 148.7, 152.8, 159.1, 166.0. FTIR (ATR, cm^{-1}): 3237, 3105, 2960, 2837, 2160, 1722, 1647, 1613, 1583, 1511, 1366, 1277, 1256, 1218, 1174, 1085, 1030, 953, 834, 778.

*4.2.14. Ethyl 6-methyl-2-oxo-4-p-tolyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4n**).* Yield (0.684 g, 83%) as a yellow solid; mp 215.4–216.4 °C (lit.: 214–216 °C).[24] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.09 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 2.23 (s, 3H, CH$_3$), 2.49 (s, 3H, CH$_3$), 3.37 (q, 2H, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 5.09 (d, 1H, *J*=3.3 Hz, CH), 7.10 (s, 4H, aromatic), 7.68 (br s, 1H, NH), 9.15 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 18.4, 21.3, 54.3, 59.9, 100.1, 126.8, 129.6, 137.1, 142.6, 148.8, 152.9, 166.1. FTIR (ATR, cm^{-1}): 3234, 3109, 2977, 2929, 2166, 1699, 1644, 1459, 1365, 1285, 1216, 1085, 956, 776.

*4.2.15. Ethyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4o**).* Yield (0.548 g, 60%) as a yellow solid; mp 248.5–250.6 °C (lit.: 249–250 °C).[23] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 2.21 (s, 3H, CH$_3$), 3.33 (s, 6H, N(C*H*$_3$)$_2$), 3.97 (q, 2H, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 5.01 (d, 1H, *J*=3.2 Hz, CH), 6.63 (d, 2H, *J*=8.7 Hz, CH, CH), 7.02 (d, 2H, *J*=8.7 Hz, CH, CH), 7.58 (br s, 1H, NH), 9.08 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 18.4, 43.4, 53.9, 59.8, 100.5, 112.9, 127.5, 133.3, 148.2, 150.4, 152.9, 166.1. FTIR (ATR, cm^{-1}): 3236, 3105, 2968, 2809, 2160, 1700, 1698, 1644, 1617, 1514, 1364, 1216, 1167, 1084, 1024, 990, 781, 659.

*4.2.16. Ethyl 4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4p**).* Yield (0.210 g, 28%) as a yellow solid; mp 215.4–216.4 °C (lit.: 214–216 °C).[25] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.12 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 2.21 (s, 3H, CH$_3$), 4.01 (q, 2H, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 5.17 (br s, 1H, CH), 6.07 (br s, 1H, *J*=3.2 Hz, CH), 6.34 (s, 1H, CH), 7.54 (d, 2H, *J*=1.8 Hz, CH), 7.75 (br s, 1H, NH), 9.25 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 18.4, 48.3, 59.9, 97.4, 105.9, 111.0, 142.8, 149.9, 153.1, 156.6, 165.5. FTIR (ATR, cm^{-1}): 3339, 3215, 3095, 2991, 2902, 2162, 1696, 1642, 1455, 1417, 1364, 1313, 1295, 1228, 1144, 1096, 1009, 923, 881, 730.

*4.2.17. Ethyl 6-methyl-2-oxo-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4q**).* Yield (0.207 g, 26%) as a yellow solid; mp 210.0–211.5 °C (lit.: 209–210 °C).[19] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.16 (t, 3H, *J*=7.2 Hz, OCH$_2$C*H*$_3$), 2.21 (s, 3H, CH$_3$), 4.06 (q, 2H, *J*=7.2 Hz, OC*H*$_2$CH$_3$), 5.40 (d, 1H, *J*=3.6 Hz, CH), 7.00–6.81 (m, 1H, CH), 7.33 (d, 1H, *J*=1.3 Hz, CH), 7.35 (d. 1H, *J*=1.3 Hz, CH), 7.92 (br s, 1H, NH), 9.31 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 18.4, 50.0, 60.0, 100.1, 124.2, 125.3, 127.4, 149.5, 149.4, 152.9, 165.7. FTIR (ATR, cm^{-1}): 3330, 3232, 3105, 2159, 2034, 1696, 1450, 1364, 1225, 1158, 1094, 1023, 778, 706.

*4.2.18. Ethyl 4-butyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4r**).* Yield (0.276 g, 38%) as a yellow solid; mp 164.1–165.7 °C (lit.: 165–167 °C).[26] ^{1}H NMR (300 MHz, DMSO-d_6DMSO-d_6) δ 0.82 (t, 3H, *J*=6.6 Hz, CH$_3$), 1.22–1.08 (m, 7H, H-10, H-11, OCH$_2$C*H*$_3$), 1.42–1.25 (m, 2H, CH$_2$), 2.14 (s, 3H, CH$_3$), 4.09–3.94 (m, 3H, H-4, OC*H*$_2$CH$_3$), 7.32 (br s, 1H, NH), 8.93 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.4, 14.9, 17.7, 18.4, 39.6, 50.4, 59.7, 100.0, 148.9, 153.5, 166.1. FTIR (ATR, cm^{-1}): 3242, 3113, 2932, 2161, 1717, 1700, 1671, 1643, 1462, 1391, 1367, 1332, 1281, 1230, 1219, 1087, 884, 775.

*4.2.19. Ethyl 4-ethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4s**).* Yield (0.167 g, 26%) as a yellow solid; mp 181.0–182.3 °C (lit.: 180–183 °C).[27] ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (t, 3H, *J*=6.6 Hz, H-10), 1.06 (t, 3H, *J*=6.6 Hz, OCH$_2$C*H*$_3$), 1.17 (q, 2H, *J*=6.6 and 1.8 Hz, CH$_2$), 2.15 (s, 3H, CH$_3$), 4.11–4.01(m, 3H, H-4, OC*H*$_2$CH$_3$), 7.20 (br s, 1H, NH), 8.98 (s, 1H, NH). ^{13}C NMR (75 MHz,

DMSO-d_6) δ 15.1, 18.3, 18.7, 23.9, 46.9, 59.7, 100.9, 146.3, 153.2, 166.0. FTIR (ATR, cm^{-1}): 3346, 3239, 2981, 2159, 1698, 1651, 1490, 1386, 1366, 1324, 1286, 1227, 1167, 1133, 1100, 1019, 769.

*4.2.20. Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**5a**).* Yield (0.561 g, 67%) as a yellow solid; mp 204.5–205.6 °C (lit.: 204–206 °C).[28] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.09 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.27 (s, 3H, CH_3), 4.00 (q, 2H, J=7.1 Hz, OCH_2CH_3), 5.15 (d, 1H, J=2.9 Hz, CH), 7.39–7.13 (m, 5H, aromatic), 9.64 (s, 1H, NH), 10.32 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.7, 17.8, 54.7, 60.3, 101.3, 127.0, 128.4, 129.2, 144.1, 145.7, 165.8, 174.8. FTIR (ATR, cm^{-1}): 3324, 3170, 3097, 1665, 1572, 1463, 1369, 1283, 1193, 1174, 1116, 1023, 757, 722.

*4.2.21. Ethyl 4-(3-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**5b**).* Yield (0.614 g, 71%) as a yellow solid; mp 180.2–182.1 °C (lit.: 180–182 °C).[29] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.12 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.26 (s, 3H, CH_3), 4.00 (q, 2H, J=7.1 Hz, OCH_2CH_3), 5.10 (d, 1H, J=3.4 Hz, CH), 6.75–6.57 (m, 3H, CH, CH, CH), 7.10 (t, 1H, J=7.9 Hz), 9.42 (s, 1H, NH), 9.58 (s, 1H, OH), 10.27 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.7, 17.8, 54.6, 60.3, 101.4, 113.9, 115.3, 117.8, 130.1, 145.5, 158.1, 165.8, 174.8, 184.5. FTIR (ATR, cm^{-1}): 3271, 3173, 2046, 1655, 1589, 1453, 1369, 1273, 1182, 1096, 865, 780, 696.

*4.2.22. Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**5c**).* Yield (0.534 g, 61%) as a yellow solid; mp 190.5–192.3 °C (lit.: 192–193 °C).[30] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.08 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.23 (s, 3H, CH_3), 3.98 (q, 2H, J=7.1 Hz, OCH_2CH_3), 5.04 (d, 1H, J=3.6 Hz, CH), 6.66 (d, 2H, J=8.3 Hz, CH, CH), 6.99 (d, 2H, J=8.3 Hz, CH, CH), 9.54 (s, 1H, OH), 9.77 (br s, 1H, NH), 10.24 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 4.7, 17.8, 54.1, 60.2, 101.7, 115.8, 116.5, 128.3, 132.8, 145.2, 157.6, 165.8, 174.5. FTIR (ATR, cm^{-1}): 3177, 2981, 2162, 1977, 1713, 1683, 1659, 1573, 1510, 1445, 1314, 1255, 1169, 1082, 1028, 826, 748.

*4.2.23. Ethyl 4-(4-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**5d**).* Yield (0.644 g, 73%) as a yellow solid; mp 187.3–189.5 °C (lit.: 191–192 °C).[31] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.09 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.28 (s, 3H, CH_3), 3.98 (q, 2H, J=7.1 Hz, OCH_2CH_3), 5.15 (d, 1H, J=3.6 Hz, CH), 7.65–6.98 (m, 4H, aromatic), 9.66 (br s, 1H, NH), 10.37 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 17.8, 54.0, 60.3, 101.2, 116.05, 129.1, 140.4, 145.9, 160.6, 165.7, 174.8. FTIR (ATR, cm^{-1}): 3325, 3171, 2981, 2029, 1679, 1603, 1573, 1464, 1368, 1334, 1282, 1192, 1115, 853, 789, 755.

*4.2.24. Ethyl 4-(4-cyanophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**5e**).* Yield (0.627 g, 70%) as a yellow solid; mp 237.8–239.6 °C (lit.: 239–242 °C).[32] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.14 (t, 3H, J=7.0 Hz, OCH_2CH_3), 2.20 (s, 3H, CH_3), 3.95 (q, 2H, J=7.0 Hz, OCH_2CH_3), 5.23 (d, 1H, J=3.6 Hz, CH), 7.38 (d, 2H, J=8.3 Hz, CH, CH), 7.84 (d, 2H, J=8.3 Hz, CH, CH), 9.73 (s, 1H, NH), 10.47 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.6, 17.2, 54.2, 60.5, 100.5, 109.6, 121.8, 123.2, 131.1, 148.5, 161.8, 165.5, 175.1. FTIR (ATR, cm^{-1}): 3290, 3176, 2977, 2227, 1681, 1605, 1555, 1454, 1368, 1311, 1169, 1094, 1014, 834, 734.

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Supplementary data

Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **4a**–**4s** and **5a**–**5e**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.07.024.

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