

Green Protocol for the Biginelli Three-Component Reaction: $\text{Ag}_3\text{PW}_{12}\text{O}_{40}$ as a Novel, Water-Tolerant Heteropolyacid for the Synthesis of 3,4-Dihydropyrimidinones

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Biginelli three-component condensation of an aldehyde, β -keto ester, and urea proceeds smoothly on the surface of the silver salt of heteropolyacid (HPA), i.e. $\text{Ag}_3\text{PW}_{12}\text{O}_{40}$, in water to afford the corresponding 3,4-dihydropyrimidinones in high-to-quantitative yields under mild conditions. The heterogeneous solid acid provides ease of separation of the catalyst and isolation of the products. The recovered catalyst can be recycled in subsequent reactions with consistent activity.

Compared to the classical Biginelli reaction conditions, this new method has the advantages of improved yields, reusability of the catalyst, an eco-friendly solvent, ease of isolation of products, and simplicity in the experimental procedure.

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Introduction

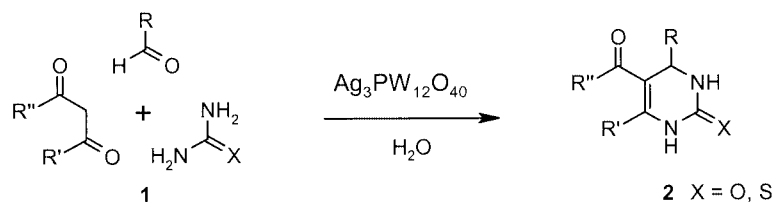
Aryl-3,4-dihydropyrimidinones have recently received great attention because of their wide range of therapeutic and pharmacological properties, such as antiviral, anti-tumor, antibacterial, and antiinflammatory behaviour.^[1] Furthermore, these compounds have emerged as the integral backbones of several calcium channel blockers, antihypertensives, α_{1a} -adrenergic antagonists, and neuropeptide Y (NPY) antagonists.^[2] Moreover, several alkaloids containing the dihydropyrimidine core structure have been isolated from marine sources and also exhibit interesting biological properties. Most notably among these are the batzelladine alkaloids, which are found to be potent HIV gp-120-CD₄ inhibitors.^[3] Thus, the synthesis of this heterocyclic nucleus is of much current importance. The simplest and the most straightforward procedure, originally reported by Biginelli,^[4] involves the three-component, one-pot condensation of an aldehyde, β -keto ester, and urea under strongly acidic conditions. This so-called Biginelli reaction often suffers, however, from low yields of products, particularly in case of substituted aromatic and aliphatic aldehydes.^[5] This problem has led to the development of multi-step synthetic strategies that produce relatively higher yields, but lack the simplicity of the original one-pot-Biginelli protocol.^[6] Thus,

the Biginelli reaction has received renewed interest from researchers interested in discovering milder and more-efficient procedures that are applicable to a wide range of substituents in all three components and proceed in better yields. As a result, several improved procedures have been reported recently using Lewis acids, as well as protic acids, as promoters.^[7,8] Asymmetric versions of the Biginelli reaction have also been reported using Garner aldehyde or a sugar-derived aldehyde, β -keto ester and urea to produce optically active 3,4-dihydropyrimidinones.^[9] Recently, environmentally benign approaches have been developed using solvent-free conditions.^[10] Much attention, however, has been focussed on the use of water as a green solvent in organic synthesis. In addition to its abundance, economy and safety, water has become a natural substitute and an alternative environmentally benign solvent in organic synthesis.^[11] The use of an aqueous medium as solvent also reduces the harmful effects of organic solvents on the environment. These advantages become even more attractive if such reactions can be performed using reusable catalysts.

Heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be reused after activation or without activation, thereby making the process economically viable.^[12] In many cases, heterogeneous catalysts can be recovered with only minor changes in activity and selectivity so that they can be used conveniently in continuous-flow reactions. Among various heterogeneous catalysts, heteropolyacids are most attractive because of their reusability, flexibility in modifying the acid

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Scheme 1

strength, ease of handling, environmental compatibility, non-toxicity and experimental simplicity.^[13]

Results and Discussion

In this report, we disclose an efficient and high-yielding protocol for the synthesis of 3,4-dihydropyrimidinones involving the three-component, one-pot condensation of an aldehyde, β -dicarbonyl compounds and urea using heteropolyacids as novel and environmentally benign, heterogeneous, solid acid catalysts. Thus, treatment of benzaldehyde, ethyl acetoacetate and urea in the presence of the silver salt of 12-tungstophosphoric acid^[14] in water at 80 °C resulted in the formation of 4-phenyl-3,4-dihydropyrimidinone in 92% yield (Scheme 1).

In a similar fashion, a variety of aromatic, aliphatic, and heterocyclic aldehydes underwent three-component condensation smoothly to afford a wide range of substituted dihydropyrimidinones. Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency by using this procedure (Table 1). Most importantly, aromatic aldehydes carrying either electron-donating or -withdrawing substituents reacted well under the reaction conditions to give the corresponding dihydropyrimidinones in high-to-quantitative yields with high purity. Acid-sensitive furfural also worked well without the formation of any side products (entry **j**, Table 1). Another important feature of this method is survival of a variety of functional groups, such as olefin, nitro, halide, ether, and ester groups, under the reaction conditions. This method is even effective with aliphatic and α,β -unsaturated aldehydes, which normally show extremely low conversions in the Biginelli reaction (entries **h** and **t**, Table 1). Unlike most of the reported methods, this procedure does not require any additives or activators or anhydrous conditions. Some other methods require the use of toxic reagents in combination with Brønsted acids, such as hydrochloric acid and acetic acid, as additives.^[7e] This procedure not only preserves the simplicity of the Biginelli reaction, but also produces excellent yield of the products with high purity. Thiourea has been used with similar success to produce the corresponding thio derivatives of dihydropyrimidinones, which are also of much interest with respect to their biological activities (entries **n**, **o**, and **p**, Table 1).^[1] Decreased reaction times and improved yields are realised as a result of the increased reactivity of the substrates on the surface of heteropolyacid. By using heteropolyacid as catalyst, the yields of the one-pot Biginelli re-

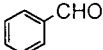
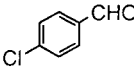
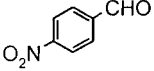
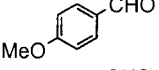
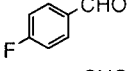
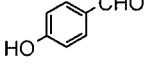
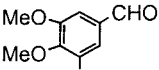
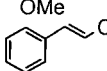
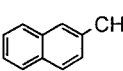
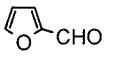
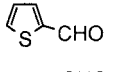
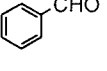
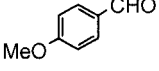
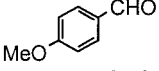
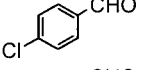
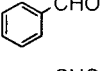
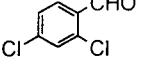
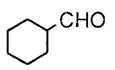
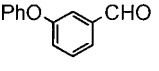
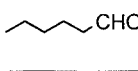
action^[4] can be increased from 20–60% to 82–96% while the reaction times are shortened from 18 h to 3.0–4.5 h. To optimize the conditions, we carried out the reactions using different quantities of reactants. The best results were obtained using a 0.1:1.0:1.0:2.0 ratio of $\text{Ag}_3\text{PW}_{12}\text{O}_{40}$, aldehyde, 1,3-dicarbonyl compound, and urea or thiourea. In the absence of the heteropolyacid, the products were obtained in low yields (20–30%) after long reaction times (8–12 h) when the reactions were carried out in water at 80 °C. The efficacy of other solid acids, such as KSF clay, acid resin (Amberlyst-15) and acid-washed silica gel ($\text{H}_2\text{SO}_4\text{-SiO}_2$), were also studied for this reaction. Among these catalysts, the silver(I) salt of heteropolyacid was found to be superior in terms of conversion and reaction time. Comparable yields and reaction rates were also obtained when using 30-wt% of silver heteropolyacid supported on silica. For example, treatment of a mixture of benzaldehyde and ethyl acetoacetate with urea in the presence of 30-wt% $\text{Ag}_3\text{PW}_{12}\text{O}_{40}/\text{SiO}_2$ resulted in the formation of 4-phenyl-3,4-dihydropyrimidinone in 93% yield after stirring in water at 80 °C for 2.5 h. Thus, this procedure provides easy access to the preparation of substituted pyrimidinones having a wide range of substitution patterns on all three components. The results obtained in the recycling experiments of benzaldehyde, ethyl acetoacetate, and urea are presented in Table 2.

The scope and generality of this process is illustrated with respect to the various 1,3-diketones and aldehydes that are tolerated; the results are presented in Table 1. Finally, the catalyst was recovered by simple filtration and reused in subsequent reactions with consistent activity.

Conclusion

In summary, we have found that heteropolyacids are extremely useful and highly efficient heterogeneous solid acids for the synthesis of biologically potent aryl 3,4-dihydropyrimidinones by means of three-component condensations of an aldehyde, 1,3-dicarbonyl compound, and urea or thiourea in a one-pot operation. This method is applicable to a wide range of substrates, including aromatic, aliphatic, α,β -unsaturated, and heterocyclic aldehydes, and provides a variety of biologically relevant dihydropyrimidinones in high-to-quantitative yields after short reaction times. The combination of the water-tolerant heteropolyacid as a recyclable catalyst and water as a green solvent makes this method convenient, economic and environmentally friendly.

Table 1. Ag₃PW₁₂O₄₀-catalyzed synthesis of Biginelli 3,4-dihydropyrimidinones

Entry	Aldehyde	X	R'	R''	Conversion (%) ^b	H ₂ O		EtOH	
						Time (h)	Yield (%) ^c	Time (h)	Yield (%) ^c
a		O	Me	OEt	100	4.0	92	3.0	95
b		O	Me	OEt	99	3.5	93	3.5	96
c		O	Me	OEt	99	4.5	91	4.0	93
d		O	Me	OEt	100	3.5	92	3.0	95
e		O	Me	OEt	99	3.5	93	3.0	93
f		O	Me	OEt	100	3.0	90	3.0	95
g		O	Me	OEt	100	3.5	92	3.0	96
h		O	Me	OEt	97	4.5	88	4.0	91
i		O	Me	OEt	100	3.5	90	3.0	93
j		O	Me	OEt	99	3.0	92	2.5	95
k		O	Me	OEt	100	3.5	90	3.0	92
l		O	Ph	OEt	100	3.0	93	3.0	95
m		O	Me	Me	97	4.5	85	4.0	87
n		S	Me	OEt	99	4.0	90	3.5	91
o		S	Me	OEt	100	4.0	89	4.0	93
p		S	Me	Me	97	4.5	86	4.0	89
q		O	Me	OMe	100	3.5	90	3.0	92
r		O	Me	OEt	99	4.0	89	3.5	93
s		O	Me	OEt	100	4.0	92	4.0	95
t		O	Me	OEt	98	4.5	82	4.0	86

^a All the products were characterized by ¹H-NMR, IR and mass spectroscopy.^b Conversions were determined by GC analysis (conversions in water).^c Yield refers to the isolated pure products after recrystallization.

Table 2. Recycling experiments of benzaldehyde, ethyl acetoacetate, and urea

Recycle no.	Solvent	Reaction temp. [°C]	Reaction Time [h]	Yield [%]
1	EtOH	80	3.0	95
2	EtOH	80	3.0	93
3	EtOH	80	3.0	95
4	EtOH	80	3.0	94
5	EtOH	80	3.0	93
1	water	80	4.0	92
2	water	80	4.0	92
3	water	80	4.0	91
4	water	80	4.0	90

Experimental Section

General Remarks: Melting points are uncorrected. IR spectra were recorded on a refractive spectrophotometer using KBr optics. ^1H and ^{13}C NMR spectra were recorded in $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$ using TMS as the internal standard. Mass spectra were recorded using a mass spectrometer operating at 70 eV. TLC was conducted on 0.25-mm pre-coated silica gel plates (60F-254). The catalyst was prepared according to the procedure reported in literature.^[14]

General Procedure: A mixture of aldehyde (5 mmol), ethyl acetoacetate (5 mmol), urea (10 mmol), and $\text{Ag}_3\text{PW}_{12}\text{O}_{40}$ (10% w/w of aldehyde) in water or ethanol (10 mL) was stirred at 80 °C for the appropriate time (Table 1). On completion of the reaction, as indicated by TLC, the reaction mixture was lyophilized to remove the water. The resulting product was separated from the catalyst by washing with methanol. The product thus obtained was recrystallized from methanol to yield pure dihydropyrimidinone. The recovered catalyst was dried in an oven at 120 °C for 3–5 h and reused in subsequent reactions. The products obtained were identified by comparison of their NMR, IR, and mass spectra and physical data, and analysis by TLC and mixed TLC, with authentic samples. The spectroscopic data of all the products were identical with those of authentic samples.^[7,8,15]

Ethyl 6-Methyl-2-oxo-4-phenyl-3,4-dihydropyrimidine-5-carboxylate (2a): Colorless crystals, m.p. 201–203 °C. IR (KBr): $\tilde{\nu}$ = 3520, 3230, 3150, 1705, 1690 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 8.05 (br. s, 1 H, NH), 7.22–7.30 (m, 5 H, Ar), 5.50 (br. s, 1 H, NH), 5.35 (s, 1 H, -CH-), 4.03 (q, J = 7.1 Hz, 2 H, -OCH₂-), 2.36 (s, 3 H, CH₃), 1.09 (t, J = 7.1 Hz, 3 H, CH₃) ppm. ^{13}C NMR (50 MHz, $[\text{D}_6]\text{DMSO}$): δ = 163.5, 150.4, 143.3, 126.4, 125.5, 124.5, 97.6, 57.3, 52.2, 16.0, 12.2 ppm. EIMS: m/z (%) = 261 [M^+] (100), 243 (52), 213 (15), 217 (15), 148 (32).

Ethyl 4-(4-Chlorophenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (2b): Colorless crystals, m.p. 213–215 °C. IR (KBr): $\tilde{\nu}$ = 3233, 3093, 2976, 2933, 1701, 1643 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 8.01 (br. s, 1 H, NH), 7.25 (m, 4 H, Ar), 5.60 (br. s, 1 H, NH), 5.35 (s, 1 H, -CH-), 4.10 (q, J = 7.1 Hz, 2 H, -OCH₂-), 2.35 (s, 3 H, -CH₃), 1.19 (t, J = 7.1 Hz, 3 H, -OCH₂CH₃) ppm. ^{13}C NMR (50 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 151.8, 143.7, 128.2, 128.1, 98.7, 59.1, 53.3, 17.7, 13.9 ppm. EIMS: m/z (%) = 265 [M^+] (60), 221 (35), 183 (100), 155 (42), 137 (35), 136 (48).

Ethyl 6-Methyl-4-(4-nitrophenyl)-2-oxo-3,4-dihydropyrimidine-5-carboxylate (2c): Colorless solid, m.p. 208–211 °C. IR (KBr): $\tilde{\nu}$ =

3230, 3109, 2977, 1701, 1641, 1591, 1520 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 9.10 (br. s, 1 H, NH), 8.20 (d, J = 8.5 Hz, 2 H, Ar), 7.60 (d, J = 8.5 Hz, 2 H, Ar), 5.24 (br. s, 1 H, NH), 5.20 (s, 1 H, -CH-), 4.05 (q, J = 7.0 Hz, 2 H, -OCH₂-), 2.27 (s, 3 H, -CH₃), 1.09 (t, J = 7.0 Hz, 3 H, -OCH₂CH₃) ppm. ^{13}C NMR (50 MHz, $[\text{D}_6]\text{DMSO}$): δ = 164.9, 151.7, 149.3, 146.6, 127.5, 123.7, 59.3, 53.6, 17.8, 13.9 ppm. EIMS: m/z (%) = 276 [M^+] (75), 183 (100), 169 (30), 155 (40), 137 (18).

Ethyl 4-(4-Methoxyphenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (2d): Colorless crystals, m.p. 203–205 °C. IR (KBr): $\tilde{\nu}$ = 3225, 3098, 2928, 2835, 1710, 1651, 1613, 1583, 1513 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 8.40 (br. s, 1 H, NH), 7.22 (d, J = 8.7 Hz, 2 H, Ar), 6.80 (d, J = 8.7 Hz, 2 H, Ar), 5.60 (br. s, 1 H, NH), 5.30 (s, 1 H, -CH-), 4.01 (q, J = 7.1 Hz, 2 H, -OCH₂-), 3.80 (s, 3 H, -OCH₃), 2.36 (s, 3 H, CH₃), 1.20 (t, J = 7.1 Hz, 3 H, -OCH₂CH₃) ppm. ^{13}C NMR (50 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 165.3, 158.0, 152.0, 147.5, 136.9, 127.3, 113.6, 99.9, 59.0, 53.2, 17.0, 14.0 ppm. EIMS: m/z (%) = 261 [M^+] (100), 217 (70), 183 (52), 155 (50), 137 (25).

Ethyl 4-(4-Fluorophenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (2e): Colorless crystals, m.p. 175–177 °C. IR (KBr): $\tilde{\nu}$ = 3243, 1698, 1638 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 9.0 (br. s, 1 H, NH), 7.80 (br. s, 1 H, NH), 7.20 (m, 2 H, Ar), 6.98 (m, 2 H, Ar), 5.21 (s, 1 H, -CH-), 4.05 (q, J = 7.1 Hz, 2 H, -OCH₂-), 2.25 (s, 3 H, -CH₃), 1.15 (t, J = 7.1 Hz, 3 H, -OCH₂CH₃) ppm. ^{13}C NMR (50 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 165.3, 162.9, 159.8, 152.0, 148.6, 141.1, 128.3, 115.1, 99.2, 59.3, 53.3, 17.8, 14.1 ppm. EIMS: m/z (%) = 278 [M^+] (12), 249 (100).

Ethyl 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (2f): Colorless solid, m.p. 198–200 °C. IR (KBr): $\tilde{\nu}$ = 3520, 3230, 3150, 1705, 1690 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 8.80 (br. s, 1 H, NH), 7.09 (d, J = 8.5 Hz, 2 H, Ar), 7.0–7.05 (br. s, 1 H, NH), 6.60 (d, J = 8.5 Hz, 2 H, Ar), 5.09 (br. s, 1 H, NH), 3.90 (q, J = 7.0 Hz, 2 H, -OCH₂-), 2.20 (s, 3 H, -CH₃), 2.50 (br. s, 1 H, OH), 1.18 (t, J = 7.0 Hz, 3 H, -OCH₂CH₃) ppm. EIMS: m/z (%) = 276 [M^+] (10), 248 (100), 231 (28), 204 (80), 168 (87), 136 (48).

Ethyl 6-Methyl-2-oxo-4-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidine-5-carboxylate (2g): Colorless crystals, m.p. 217–219 °C. IR (KBr): $\tilde{\nu}$ = 3300, 1735, 1705 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 8.85 (br. s, 1 H, NH), 7.25 (s, 2 H, Ar), 5.21 (br. s, 1 H, NH), 5.19 (s, 1 H, -CH-), 4.10 (q, J = 7.0 Hz, 2 H, -OCH₂-), 3.75 (s, 6 H, -OCH₃), 3.70 (s, 3 H, -OCH₃), 2.10 (s, 3 H, -CH₃), 1.09 (t, J = 7.0 Hz, 3 H, -OCH₂CH₃) ppm. ^{13}C NMR (50 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 165.6, 153.7, 153.2, 146.2, 139.3, 103.5, 101.1, 60.6, 59.9, 56.0, 55.6, 18.4, 14.1 ppm. EIMS: m/z (%) = 350 (68) [M^+], 335 (9), 321 (50), 304 (23), 277 (41), 261 (22), 238 (69), 222 (22), 195 (100), 183 (72), 168 (23), 155 (45), 137 (75), 125 (52), 110 (40), 77 (32), 66 (41).

Ethyl 6-Methyl-2-oxo-4-(4-styryl)-3,4-dihydropyrimidine-5-carboxylate (2h): Colorless crystals, m.p. 232–235 °C. IR (KBr): $\tilde{\nu}$ = 3241, 1704, 1650 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 8.90 (br. s, 1 H, NH), 7.85 (br. s, 1 H, NH), 7.27 (m, 5 H, Ar), 6.45 (d, J = 14.4 Hz, 1 H, -CH=CH-Ph), 6.15 (dd, J = 14.5, 4.1 Hz, 1 H, -CH=CH-), 5.30 (d, J = 4.1 Hz, 1 H, -CH-), 4.10 (q, J = 7.0 Hz, 2 H, -OCH₂-), 2.23 (s, 3 H, -CH₃), 1.13 (t, J = 7.0 Hz, 3 H, -CH₃) ppm. ^{13}C NMR (50 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 165.1, 152.6, 148.5, 136.2, 130.0, 128.6, 128.1, 127.5, 126.2, 97.8, 59.2, 51.8, 17.7, 14.2 ppm. EIMS: m/z (%) = 286 [M^+] (17), 259 (100).

Ethyl 6-Methyl-4-(2-naphthyl)-2-oxo-3,4-dihydropyrimidine-5-carboxylate (2i): Solid, m.p. 247–248 °C. IR (KBr): $\tilde{\nu}$ = 3245, 3118, 2977, 1698, 1647, 1431, 1231, 1088, 790 cm^{-1} . ^1H NMR ($[\text{D}_6]\text{DMSO}$): δ = 9.10 (br. s, NH), 8.30 (d, J = 8.2 Hz, 1 H), 7.85 (d, J = 8.2 Hz, 1 H), 7.80 (t, J = 8.2 Hz, 1 H), 7.40–7.55 (m, 5 H), 6.10 (s, 1 H), 3.90 (q, J = 7.0 Hz, 2 H), 2.40 (s, 3 H), 0.90 (t, J = 7.0 Hz, 3 H) ppm. EIMS: m/z (%) = 310 $[\text{M}^+]$ (30), 217 (15), 176 (100), 133 (65), 119 (20), 91 (100), 69 (70).

Ethyl 4-(2-Furyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (2j): Colorless solid, m.p. 209–211 °C. IR (KBr): $\tilde{\nu}$ = 3280, 3126, 2920, 1720, 1650, 1580, 1265, 1130 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 9.0 (br. s, 1 H, NH), 7.80 (br. s, 1 H, NH), 6.25 (m, 2 H, Ar), 6.10 (s, 1 H, Ar), 5.25 (br. s, 1 H, NH), 5.30 (s, 1 H, -CH-), 4.10 (q, J = 7.1 Hz, 2 H, -OCH₂-), 2.23 (s, 3 H, -CH₃), 1.12 (t, J = 7.1 Hz, 3 H, -OCH₂CH₃) ppm. ^{13}C NMR (50 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 165.0, 155.9, 152.4, 149.2, 142.1, 110.3, 105.2, 96.8, 59.2, 47.7, 17.7, 14.1 ppm. EIMS: m/z (%) = 250 $[\text{M}^+]$ (80), 221 $[\text{M} - \text{C}_2\text{H}_5]^+$ (99), 177 (100).

Ethyl 6-Methyl-2-oxo-4-(2-thienyl)-3,4-dihydropyrimidine-5-carboxylate (2k): Colorless crystals, m.p. 215–217 °C. IR (KBr): $\tilde{\nu}$ = 3165, 1680, 1633 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 9.0 (br. s, 1 H, NH), 7.50 (br. s, 1 H, NH), 7.13 (d, J = 8.1 Hz, 2 H, Ar), 6.85–6.90 (m, 2 H, Ar), 5.55 (s, 1 H, -CH-), 4.15 (q, J = 7.1 Hz, 2 H, -OCH₂-), 2.30 (s, 3 H, -CH₃), 1.13 (t, J = 7.1 Hz, -OCH₂CH₃) ppm. EIMS: m/z (%) = 266 $[\text{M}^+]$ (84), 237 (100), 193 (91).

Ethyl 2-Oxo-4,6-diphenyl-3,4-dihydropyrimidine-5-carboxylate (2l): Colorless crystals, m.p. 157–159 °C. IR (KBr): $\tilde{\nu}$ = 3214, 3086, 2980, 1699, 1651 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 7.92 (br. s, 1 H, NH), 7.15–7.30 (m, 10 H, Ar), 5.53 (br. s, 1 H, NH), 5.13 (s, 1 H, -CH-), 4.05 (q, J = 7.1 Hz, 2 H, -OCH₂-), 2.30 (s, 3 H, CH₃), 1.20 (t, J = 7.1 Hz, -OCH₂CH₃) ppm. ^{13}C NMR (50 MHz, $[\text{D}_6]\text{DMSO}$): δ = 165.3, 153.2, 147.1, 143.5, 135.1, 129.5, 128.8, 128.2, 128.1, 128.0, 126.6, 102.4, 60.0, 55.8, 13.6 ppm. EIMS: m/z (%) = 322 $[\text{M}^+]$ (45), 294 (20), 278 (50), 249 (35), 185 (60), 157 (15), 138 (70), 91 (85), 77 (65), 69 (100).

5-Acetyl-4-(4-methoxyphenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine (2m): Colorless crystals, m.p. 166–168 °C. IR (KBr): $\tilde{\nu}$ = 3242, 1714, 1624 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 9.03 (br. s, 1 H, NH), 7.45 (br. s, 1 H, NH), 7.18 (d, J = 8.7 Hz, 2 H, Ar), 6.85 (d, J = 8.7 Hz, 2 H, Ar), 5.20 (s, 1 H, -CH-), 3.75 (s, 3 H, -COCH₃), 2.23 (s, 3 H, -OCH₃), 1.90 (s, 3 H, -CH₃) ppm. ^{13}C NMR (50 MHz, $[\text{D}_6]\text{DMSO}$): δ = 194.4, 158.5, 152.1, 147.8, 136.4, 127.7, 113.9, 109.6, 55.1, 53.3, 30.2, 18.8 ppm. EIMS: m/z (%) = 260 $[\text{M}^+]$ (44), 259 (100).

Ethyl 4-(4-Methoxyphenyl)-6-methyl-2-thioxo-3,4-dihydropyrimidine-5-carboxylate (2n): Colorless crystals, m.p. 150–152 °C. IR (KBr): $\tilde{\nu}$ = 3250, 1651, 1598, 1561 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 9.90 (br. s, 1 H, NH), 9.21 (br. s, 1 H, NH), 7.15 (d, J = 8.1 Hz, 2 H, Ar), 6.67 (d, J = 8.1 Hz, 2 H, Ar), 5.15 (s, 1 H, -CH-), 4.03 (q, J = 7.1 Hz, 2 H, -OCH₂-), 2.23 (s, 3 H, -CH₃), 1.15 (t, J = 7.1 Hz, 3 H, -OCH₂CH₃) ppm. ^{13}C NMR (50 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 173.7, 174.0, 165.2, 158.8, 144.7, 135.8, 127.7, 113.9, 101.1, 59.6, 55.1, 53.5, 17.2, 14.1 ppm. EIMS: m/z (%) = 306 $[\text{M}^+]$ (82), 277 (80), 32 (100).

Ethyl 4-(4-Chlorophenyl)-6-methyl-2-thioxo-3,4-dihydropyrimidine-5-carboxylate (2o): Colorless crystals, m.p. 192–194 °C. IR (KBr): $\tilde{\nu}$ = 3255, 1657, 1560 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 10.0 (br. s, 1 H, NH), 9.30 (br. s, 1 H, NH), 7.15 (m, 4 H, Ar), 5.25 (s, 1 H, -CH-), 4.10 (q, J = 7.1 Hz, 2 H, -OCH₂-

), 2.41 (s, 3 H, CH₃), 1.13 (t, J = 7.1 Hz, 3 H, -OCH₂CH₃) ppm. ^{13}C NMR (50 MHz, $[\text{D}_6]\text{DMSO}$): δ = 174.3, 165.0, 145.3, 142.4, 132.3, 128.6, 128.4, 100.4, 59.7, 53.5, 17.2, 14.0 ppm. EIMS: m/z (%) = 310 $[\text{M}^+]$ (99), 281 (82), 199 (100).

5-Acetyl-6-methyl-4-phenyl-2-thioxo-3,4-dihydropyrimidine (2p): Colorless crystals, m.p. 220–222 °C. IR (KBr): $\tilde{\nu}$ = 3282, 1615, 1575 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 8.40 (br. s, 1 H, NH), 7.35 (m, 5 H, Ar), 6.09 (br. s, 1 H, NH), 4.98 (s, 1 H, -CH-), 2.60 (s, 3 H, -COCH₃), 2.38 (s, 3 H, -CH₃) ppm. ^{13}C NMR (50 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 195.1, 174.1, 144.9, 143.2, 129.0, 128.0, 126.9, 110.8, 54.1, 30.8, 18.0 ppm. EIMS: m/z (%) = 246 $[\text{M}^+]$ (10), 233 (15), 168 (30), 141 (20), 94 (100), 76 (80), 43 (95).

Methyl 4-(2,4-Dichlorophenyl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (2q): Solid, m.p. 241–243 °C. IR (KBr): $\tilde{\nu}$ = 3384, 3232, 3105, 2960, 1700, 1640, 1612 cm^{-1} . ^1H NMR (200 MHz, $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$): δ = 9.10 (br. s, 1 H, NH), 7.30 (s, 1 H, Ar), 7.15–7.25 (m, 2 H, Ar), 6.98 (br. s, 1 H, NH), 5.62 (s, 1 H, -CH-), 3.55 (s, 3 H, -COOCH₃), 2.33 (s, 3 H, -CH₃) ppm. EIMS: m/z (%) = 314 $[\text{M}^+]$ (26), 299 (85), 279 (100), 255 (98), 219 (8), 183 (66), 170 (100), 137 (93), 110 (32), 67 (11), 42 (50).

Ethyl 4-Cyclohexyl-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate (2r): Solid, m.p. 235–236 °C. IR (KBr): $\tilde{\nu}$ = 3236, 3118, 2920, 2850, 1726, 1702, 1647, 1450, 1230, 1095, 789 cm^{-1} . ^1H NMR ($[\text{D}_6]\text{DMSO}$): δ = 8.45 (br. s, NH), 6.15 (br. s, NH), 4.15 (m, 3 H), 2.30 (s, 3 H), 1.75 (m, 4 H), 1.45 (m, 3 H), 1.25 (t, J = 6.8 Hz, 3 H), 1.05 (m, 4 H) ppm. EIMS: m/z (%) = 266 $[\text{M}^+]$ (40), 183 (35), 137 (100), 155 (70), 40 (55).

Ethyl 6-Methyl-2-oxo-4-(3-phenoxyphenyl)-3,4-dihydropyrimidine-5-carboxylate (2s): Solid, m.p. 193–194 °C. IR (KBr): $\tilde{\nu}$ = 3243, 3113, 2981, 1712, 1654, 1582, 1487, 1245, 1097, 785 cm^{-1} . ^1H NMR ($[\text{D}_6]\text{DMSO}$): δ = 8.40 (br. s, NH), 7.45 (m, 3 H), 7.05 (m, 5 H), 6.85 (m, 1 H), 5.80 (br. s, NH), 5.35 (s, 1 H), 4.10 (q, J = 6.8 Hz, 2 H), 2.35 (s, 3 H), 1.15 (t, J = 6.8 Hz, 3 H) ppm. EIMS: m/z (%) = 352 $[\text{M}^+]$ (35), 323 (60), 279 (15), 183 (100), 155 (90), 137 (45), 91 (70), 69 (30).

Ethyl 6-Methyl-2-oxo-4-pentyl-3,4-dihydropyrimidine-5-carboxylate (2t): Solid, m.p. 151–153 °C. IR (KBr): $\tilde{\nu}$ = 3249, 2933, 1730, 1646, 1433, 1331, 1288, 1086, 779 cm^{-1} . ^1H NMR ($[\text{D}_6]\text{DMSO}$): δ = 8.55 (br. s, NH), 6.05 (br. s, NH), 4.25 (m, 1 H), 4.15 (m, 2 H), 2.30 (s, 3 H), 1.55 (m, 2 H), 1.25–1.40 (m, 9 H), 0.95 (t, J = 6.8 Hz, 3 H) ppm. EIMS: m/z (%) = 254 $[\text{M}^+]$ (25), 209 (30), 183 (45), 155 (100), 137 (15), 91 (65), 40 (70).

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