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Trifluoroethanol as a Metal-Free, Homogeneous, and Recyclable Medium for the Efficient One-Pot Synthesis of Dihydropyrimidones

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TRIFLUOROETHANOL AS A METAL-FREE, HOMOGENEOUS, AND RECYCLABLE MEDIUM FOR THE EFFICIENT ONE-POT SYNTHESIS OF DIHYDROPYRIMIDONES

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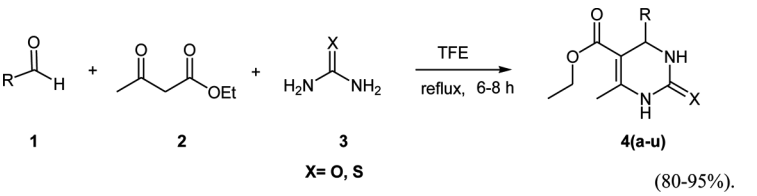
GRAPHICAL ABSTRACT



Abstract *Trifluoroethanol is an efficient and recyclable medium in promoting one-pot, three-component condensation reactions of β-ketoesters, aldehydes, and urea (or thiourea) to afford the corresponding dihydropyrimidones in good yields. This protocol does not require the use of an acid or base catalyst.*

Keywords Biginelli reaction; cyclization; homogeneous catalysis; multicomponent; trifluoro ethanol

INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry.[1,2] MCR strategies offer significant advantages over conventional linear-type syntheses. In such reactions, three or more reactants come together in a single reaction vessel to form new products that contain portions of all the components.[3,4] Aryl substituted 3,4-dihydropyrimidine-2-ones (DHPMs) and their derivates have been receiving much attention in the recent years owing to their applications in the field of drugs and pharmaceuticals.[5–7] They occupy an important place in the realm of natural and synthetic organic chemistry because of their broad range of biological activities, including antiviral, antitumor, antibacterial, and anti-inflammatory activities, and use as anti-HIV agents.[8–12] They also attract

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considerable interest because of their promising activities as calcium channel blockers and orally active antihypertensive agents. A very recent important highlight in this aspect is the identification of the structurally simple DHPM monstrol as a mitotic kinesis EG_5 motor protein inhibitor and as a potential new lead for the development of anticancer drugs.[12,13] In 1893, Italian chemist Pietro Biginelli first reported the synthesis of DHPMs by multi component cyclocondensation,[14a] which involves a reaction of a β-keto ester, an aldehyde, and urea or thiourea under strongly acidic conditions. Under strongly acidic conditions, the yields are very poor (around 20%).[14b–d]

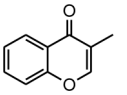
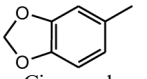
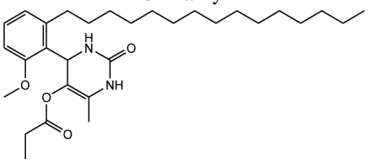
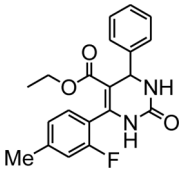
To enhance the efficiency of the Biginelli condensation, various catalysts and reaction conditions have been studied including classical conditions, microwave-assisted irradiation, solid support, ionic liquids,[15] and Lewis acid as well as protic acid promoters such as $BF_3 \cdot OEt$,[16] $InCl_3$,[17] $LaCl_3 \cdot 7H_2O$,[18,19] $FeCl_3 \cdot 6H_2O$, $Mn(OAc)_2$, $Cu(OTf)_2$, $LiClO_4$, $Cu(NO_3)_2 \cdot 3H_2O$, and H_2SO_4.[20–24] Homogeneous catalyst supported on the solid matric has also been used for the synthesis of DHPMs.[25] However, some of these one-pot procedures generally require strong protic or Lewis acids, prolonged reaction time, high temperature, drastic reaction conditions, tedious work up procedure, and the use of toxic and inflammable solvents while giving poor yields or several side reactions. These factors caused us to search for better catalysts. The discovery of a milder and more efficient procedure for the synthesis of DHPMs is of prime importance. There is need to develop new methods using less hazardous solvents.

Herein, we report a novel trifluoroethanol (TFE)- and hexafluoroisopropanol (HFIP)-catalyzed Biginelli reaction applied to the one-pot, three-component condensation of aldehyde, β-keto ester, and urea or thiourea to synthesize DHPMs, which is simple and high yielding. To best of our knowledge, there have been no reports for the synthesis of DHPMs catalyzed by TFE. Treatment of aldehyde (2 mmol), ethyl aectoacetate (2 mmol), and urea (3 mmol) in TFE at reflux temperature for 4–5 h afforded the corresponding 3,4-DHPMs. After the reaction was complete, the solvent was evaporated, and the products were isolated with acceptable purity [by liquid chromatography–mass spectrometry (LCMS) and NMR]. The 98% recovery of the TFE by fractional distillation below 80 °C was sufficient for its reuse. For example, the reaction of benzaldehyde, β-ketoester, and urea or thiourea gave corresponding DHPMs in 95%, 95% and 93%, yields over three cycles. Thus we explored the effectiveness of TFE as reusable solvent and catalyst for generation of DHPMs. The highlight of this procedure is the tolerance of acid-sensitive aldehydes such as cinnamaldehyde and furfuralhyde without formation of side products. The crude products are obtained are highly pure (>95% by LCMS). Another, important feature of this protocol is survival of a variety of functional groups such as OCH_3, OH, NO_2, F, Cl, and conjugated C=C double bond under the reaction conditions. In general, the products were obtained in good yields with an environmentally friendly process. New compounds were adequately characterized by physical and spectral data, and data of known compounds are in good agreement with those reported in the literature. Spectral data of new compounds are shown.

RESULTS AND DISCUSSION

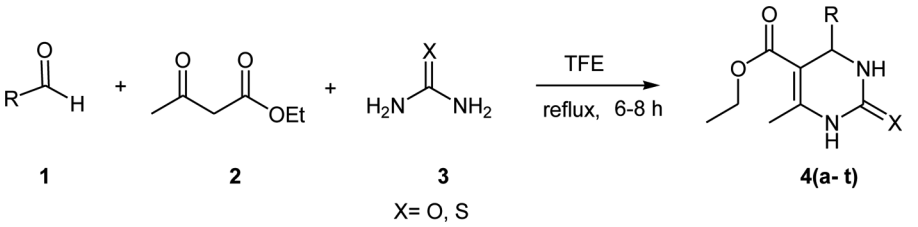
Fluorinated alcohols possess interesting physiochemical properties, which include lower boiling points and higher melting points than their nonfluorinated

Table 1. TFE-catalyzed synthesis of dihydropyrimidones **4a–y** in reflux conditions

Entry	Product	R	X	Yield[a] (%)	Ref.
1	**4a**	Ph	O	95	25
2	**4b**	4-(OMe)-C_6H_4	O	94	25
3	**4c**	4-(OH)-C_6H_4	O	92	25
4	**4d**	2-(Cl)-C_6H_4	O	94	25
5	**4e**	4-(Cl)-C_6H_4	O	86	25
6	**4f**	4-(NO_2)-C_6H_4	O	90	25
7	**4g**	2-Furfuryl	O	87	26
8	**4h**	Ph	S	90	26
9	**4i**	4-(NO_2)-C_6H_5)	S	84	26
10	**4j**	2-(Br)-C_6H_5	O	94	26
11	**4k**	4-(isobutyl)-C_6H_5	O	85	New
12	**4l**	4-(OPr)-C_6H_4	O	90	New
13	**4m**	3-C_6H_4N	O	92	New
14	**4n**	4-Thiazole	O	94	New
15	**4o**	4-(NMe_2) C_6H_4	O	95	25
16	**4p**		O	82	New
17	**4q**	1-Bipheynyl	O	90	New
18	**4r**		O	90	New
19	**4s**	Cinnamyl	O	80	26
20	**4t**			90	New
21	**4u**	2-Thienyl	O	82	26
22	**4v**	5-Thiazole	O	86	New
23.	**4x**	n-Propyl	O	84	New
24.	**4y**			90	New

[a]Yields refer to those of pure isolated products characterized by IR, ^{1}H NMR, LCMS, and elementary analysis.

counterparts and high polarity, strong hydrogen bond donation properties, and the ability to solvate water. The electron-withdrawing character of CF_3 confers high acidity to the hydrogen of the hydroxyl group. Besides these properties, fluorinated alcohols are not nucleophiles or hydrogen bond acceptors. The main advantage of TFE is operational simplicity; the reaction was carried out in the absence of promoting agents. (These reactions usually require the aid of Lewis acids or catalysts.) This constitutes an improvement from an environmental point of view, with suffression of effluents, in particular, heavy metals. In addition to this, TFE was separated easily



Scheme 1.

from the reaction mixture for subsequent reuse. It is also important to note that the workup of the reaction mixture is very simple. The Biginelli reactions were strongly facilitated by the acidic character and strong hydrogen bond donor ability of TFE. The solvent was recovered once the reaction was completed and reused. The results are summarized in Table 1.

Table 1 shows the generality of the present protocol, which is equally effective for urea and thiourea. In most cases, the reactions proceeded smoothly to produce the corresponding DHPMs in good yields. Aromatic aldehydes containing either electron-donating or electron-withdrawing substitutes, heterocyclic, and aliphatic aldehydes all produced improved yields compared to the classical Biginelli protocol; surprisingly, even sterically hindered aldehyde gave the corresponding DHPM **4t**.

CONCLUSION

We have developed a simple, convenient, and practical method for the synthesis of DPHMs and their derivatives using substituted aldehydes, β-ketoester, and urea or thiourea at reflux temperature using TFE a reusable, ecofriendly, homogeneous solvent and catalyst. This method is applicable to a wide range of substrates including aromatic, aliphatic, heterocyclic, and α,β-unsaturated aldehydes. This method is not only simple but clean with good yield (80–95%) and greatly decreases environmental pollution because TFE as a reusable solvent and catalyst (Scheme 1).

EXPERIMENTAL

Prepration of Dihydropyrimidinones: General Procedure for the Synthesis of 3,4-Dihydropiridinones and -Thiones

A mixture of β-keto ester (2 mmol), corresponding aldehyde (2 mmol), and urea or thiourea (3 mmol in TFE was stirred rapidly and heated to 80 °C in preheated oil bath for 4–6 h (completion of the reaction was monitored by thin-layer chromatography, TLC). The TFE was separated by distillation. The solid product was filtered and passed through a column of silica gel of 60–120 mesh to get the pure product. All the products were identified by comparing their spectral and physical data with those of authentic samples.

Selected Data

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (4a). Mp 202–204 °C, lit.[25] 202–204 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.20 (s, 1H, N*H*), 7.74 (s, 1H, N*H*), 7.25 (s, 5H, C_6H_5), 5.14 (s, 1H, C*H*), 3.97 (q, J = 6.5 Hz, 2H, OCH_2CH$_3$), 2.24 (s, 3H, CH_3), 1.08 (t, J = 6.5 Hz, 3H, OCH$_2$CH_3).

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4b). Mp 202–204 °C, lit.[25] 201–203 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.14 (s, 1H, N*H*), 7.66 (s, 1H, N*H*), 7.15–6.84 (m, 4H, C_6H_4), 5.07 (s, 1H, C*H*), 3.96 (q, J = 6.8 Hz, 2H, OCH_2CH$_3$), 3.70 (s, 3H, OCH_3), 2.23 (s, 3H, CH_3), 1.09 (t, J = 6.8 Hz, 3H, OCH$_2$CH_3).

5-Ethoxycarbonyl-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4c). Mp 230–232 °C, lit.[25] 230–232 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.34 (s, 1H, O*H*), 9.10 (s, 1H, N*H*), 7.64 (s, 1H, N*H*), 7.03–6.65 (m, 4H, C_6H_4), 5.02 (s, 1H, C*H*), 3.96 (q, J = 7.0 Hz, 2H, OCH_2CH$_3$), 2.21 (s, 3H, CH_3), 1.08 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3).

4-(2-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4d). Mp 222–224 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.25 (s, 1H, N*H*), 7.70 (s, 1H, N*H*), 7.37–7.29 (m, 4H, C_6H_4), 5.61 (s, 1H, C*H*), 3.87 (q, J = 6.9 Hz, 2H, OCH_2CH$_3$), 2.28 (s, 3H, CH_3), 0.97 (t, J = 6.9 Hz, 3H, OCH$_2$CH_3); IR (KBr): 3150, 1688, 1626 cm^{-1}, Calcd. for $C_{14}H_{15}O_3N_2Cl$: C, 57.03; H, 5.13; N, 9.51. Found: C, 56.89; H, 5.44; N, 9.30.

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4e). Mp 212–214 °C, lit,[25] 213–215 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.24 (s, 1H, N*H*), 7.78 (s, 1H, N*H*), 7.40–7.21 (m, 4H, C_6H_4), 5.12 (s, 1H, C*H*), 3.97 (q, J = 6.9 Hz, 2H, OCH_2CH$_3$), 2.24 (s, 3H, CH_3), 1.08 (t, J = 6.9 Hz, 3H, OCH$_2$CH_3).

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4f). Mp 207–209 °C, lit.[25] 208–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.35 (s, 1H, N*H*), 7.89 (s, 1H, N*H*), 8.23–7.47 (m, 4H, C_6H_4), 5.26 (s, 1H, C*H*), 3.97 (q, J = 7.0 Hz, 2H, OCH_2CH$_3$), 2.25 (s, 3H, CH_3), 1.08 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3).

5-Ethoxycarbonyl-4-(2-furfuryl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4g). Mp 208–211 °C; lit.[25] 209–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.24 (s, 1H, N*H*), 7.75 (s, 1H, N*H*), 7.54 (s, 1H, C*H*-Ar.), 6.34 (s, 1H, C*H*-Ar), 6.08 (s, 1H, C*H*-Ar.), 5.19 (s, 1H, C*H*), 4.01 (q, J = 6.9 Hz, 2H, OCH_2CH$_3$), 2.22 (s, 3H, CH_3), 1.12 (t, J = 6.9 Hz, 3H, OCH$_2$CH_3); IR (KBr): 3320, 3225, 3100, 1695, 1640 cm^{-1}.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione (4h). Mp 151–153 °C; lit.[26] 150–152 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.33 (s, 1H, N*H*), 9.64 (s, 1H, N*H*), 7.35–7.19 (m, 5H, C_6H_5), 5.16 (d, J = 3.5 Hz, 1H, C*H*), 4.00 (q, J = 7.0 Hz, 2H, OCH_2CH$_3$), 2.28 (s, 3H, CH_3), 1.09 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3).

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (4i). Mp 209–211 °C; lit.[26] 209–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.40 (s, 1H, N*H*), 9.62 (s, 1H, N*H*), 8.25–7.45 (m, 4H, C_6H_4), 5.26 (s, 1H, C*H*), 4.00 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 2.30 (s, 3H, CH_3), 1.12 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3).

Ethyl 4-(2-(bromophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate (4j). Mp 210–212 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.26(s, 1H, N*H*), 7.68 (d, 1H, N*H*), 7.55 (d, J = 5.9, 1H, Ar-*H*), 7.35 (m, 2H, C_6H_4), 7.17 (m, J = 12.5 Hz, 1H, C_6H_4), 5.58 (s, 1H, C*H*), 3.87 (q, J = 6.8 Hz, 2H, OCH_2-CH$_3$), 2.29 (s, 3H, CH_3), 0.95 (t, 3H, J = 7.1 Hz, OCH$_2$-CH_3); IR (KBr): 3340, 3208, 3106, 2972, 1685, 1633, 1367, 1249 cm^{-1}; MS (ESI +ion): m/z = 340, 341.0. Anal. (%) calcd. for $C_{14}H_{15}O_3N_2Br$: C, 49.58; H, 4.46; N, 8.26. Found: C, 49.62; H, 4.53; N, 8.33.

Ethyl 1,2,3,4-tetrahydro-4-(isobutylphenyl)-6-methyl-2-oxopyrimdidine-5-carboxylate (4k). Mp 172.8–174.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.12 (s, 1H, N*H*), 7.64 (d, 1H, N*H*), 7.11 (d, J = 6.5 Hz, 2H, C_6H_4), 6.83 (d, J = 6.2 Hz, 2H, C_6H_4), 5.06 (s, 1H, C*H*), 3.93–3.99(q, J = 6.8 Hz, 2H, OCH_2-CH$_3$), 3.85–3.88 (t, J = 6.9 Hz, 2H, OCH$_2$-CH_3), 1.66–1.71 (q, 2H, CH$_3$), 1.10 (t, 3H, CH$_3$-CH$_2$), 0.95 (t, 3H, CH_3-CH$_2$); IR (KBr): 3237, 3113, 2952, 1698, 1643, 1217 cm^{-1}; MS (ESI +ion): m/z 317.2. Anal. (%) calcd. for $C_{18}H_{24}O_3N_2$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.35; H, 7.68; N, 8.92.

Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-(propoxyphenyl)pyrimidine-3-yl)pyrimidine-5-carboxylate (4l). Mp 166–168 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.12(s, 1H, N*H*), 7.64 (s, 1H, N*H*), 7.11 (d, 2H, C_6H_4), 6.83 (d, 2H, C_6H_4), 5.06 (s, 1H, CH), 3.93–3.99 (q, J = 6.6 Hz, 2H, OCH_2-CH$_3$), 3.85–3.88 (t, J = 6.9 Hz, 2H, OCH$_2$-CH_3), 2.23 (s, 3H, CH$_3$), 1.66–1.71 (q, 2H, -CH$_2$-CH$_2$-), 1.10 (t, 3H, OCH$_3$-CH$_3$), 0.95 (t, 3H, CH$_2$-CH_3); IR (KBr): 3215, 3113, 2966, 1703, 1644, 1511, 1219, 1089 cm^{-1}; MS (ESI +ion): m/z = 319.2. Anal. (%) calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.16; H, 6.93; N, 8.89.

Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-(pyridine-3-yl)pyrimidine-5-carboxylate (4m). Mp 217–218 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.31(s, 1H, N*H*), 8.39–8.45 (m, 2H, C_6H_4), 7.79 (d, 1H, N*H*, C_6H_4), 7.60 (d, J = 2.7 Hz, 1H, C_6H_4), 7.34–7.37 (q, 1H, C_6H_4), 5.17 (s, 1H, CH), 3.91–4.02(q, J = 6.9 Hz, 2H, OCH_2CH$_3$), 2.25 (s, 3H, CH$_3$), 1.06 (t, J = 7.1 Hz, 3H, OCH_2-CH$_3$); IR (KBr): 3339, 3215, 3100, 2972, 1679, 1636, 1222, 1114 cm^{-1}; MS (ESI +ion): m/z = 262.2. Anal. (%) calcd. for $C_{13}H_{15}O_3N_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.81; H, 5.82; N, 16.12.

Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-(thiazol-4-yl)pyridine-3-yl) pyrimidine-5-carboxylate (4n). Mp 226–228 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.15(s, 1H, N*H*), 8.98 (d, 1H, Ar*H*), 7.65 (s, 1H, N*H*), 7.32 (d, 1H, Ar*H*), 5.31 (s, 1H, CH), 3.96–4.03 (q, 2H, J = 6.7 Hz, OCH_2-CH$_3$), 2.21 (s, 3H, CH_3), 1.11 (t, J = 6.9 Hz, 3H, OCH$_2$-CH_3). IR (KBr): 3196, 3093, 1699, 1660, 1370, 1246, 1091 cm^{-1}; MS (ESI +ion): m/z = 268. Anal. (%) calcd. for $C_{11}H_{13}O_3N_3S$: C, 49.43; H, 4.90; N, 15.72. Found: C, 49.52; H, 4.88; N, 15.68.

Ethyl 4-(4-(dimethylamin)phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate (4o). Mp 255–256 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.05$(s, 1H, N*H*), 7.58 (s, 1H, N*H*), 7.0 (d, $J = 6.5$ Hz, 2H, C_6H_4), 6.64 (d, 2H, C_6H_4), 5.01 (s, 1H, C*H*) 3.93–3.99 (q, $J = 7.0$ Hz, 2H, OCH_2CH_3), 2.83 [s, 6H, $N(CH_3)_2$], 2.21 (s, 3H, CH_3), 1.11 (t, $J = 6.5$ Hz, 3H, OCH_2CH_3); IR (KBr): 3236, 3110, 2928, 2806, 2214, 1698, 1562, 1216, 1085 cm^{-1}; MS (ESI + ion): $m/z = 304.2$. Anal. (%) calcd. for $C_{16}H_{21}O_3N_3$: C, 63.35, H, 6.98; N, 13.85. Found: C, 63.36; H, 6.96; N, 13.79.

Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-(4-oxo-4*H*-chromen-3-yl) pyrimidine-5-carboxylate (4p). Mp 266–268 °C; ^{1}H NMR(400 MHz, DMSO-d_6): $\delta = 9.24$(s, 1H, N*H*), 8.28 (d, 1H, C_6H_4), 8.17 (s, 1H, N*H*), 8.08 (d, 1H, C_6H_4), 7.79–7.83 (t, $J = 6.5$ Hz, 1H, C_6H_4), 7.65 (d, $J = 6.2$ Hz, 1H, C_6H_4), 7.50 (t, 1H, C_6H_4), 7.26 (s, 1H, C_6H_4), 6. 95 (t, 1H, C_6H_4), 5.23 (s, 1H, CH), 3.93–4.00 (q, 2H, OCH_2-CH_3), 2.22 (s, 2H, CH_3), 1.08 (t, 3H, OCH_2-CH_3), IR (KBr): 3274, 3212, 3093, 2966, 1706, 1663, 1634, 1461, 1350, 1234, 1088, 759 cm^{-1}; MS (ESI +ion): $m/z = 329$. Anal. (%) calcd. for $C_{17}H_{16}O_3N_2O_5$: C, 62.19, H, 4.91; N, 8.53. Found: C, 62.23; H, 4.96; N, 8.62.

Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-bipheylpyrimidine-5-carboxylate (4q). Mp 216–217 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.04$ (s, 1H, N*H*), 9.22 (d, 1H, C_6H_4), 7.99 (s, 1H, N*H*), 7.90 (d, 1H, C_6H_4), 7.77 (t, $J = 6.84$ Hz, Hz, 4H, C_6H_4), 7.62 (t, 2H, C_6H_4), 7.50 (t, 1H, C_6H_4), 7.45 (t, 2H, C_6H_4), 7.30–7.35 (t, 3H, C_6H_4), 5.18 (s, 1H, C*H*), 4.00 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 2.25 (s, 3H, CH_3), 1.11 (t, $J = 6.8$ Hz 3H, OCH_2-CH_3); IR (KBr): 3233, 3095, 2974, 1697, 1675, 1259 cm^{-1}; (ESI +ion): $m/z = 337$. Anal. (%) calcd. for $C_{20}H_{20}O_3N_2$: C, 71.41, H, 5.99; N, 8.33. Found: C, 71.44; H, 5.96; N, 8.28.

Ethyl 4-(benzo[d][1,3]dixol-5-yl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carbxoylate (4r). Mp 189–191 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.16$(s, 1H, N*H*), 7.66 (s, 1H, N*H*), 6.83 (d, $J = 5.97$ Hz, 1H, C_6H_4), 6.72 (s, 1H, C_6H_4), 6.67 (d, $J = 7.2$ Hz, 1H, C_6H_4), 5.97 (s, 1H, -O*CH2O*-), 5.05 (s, 1H, C*H*), 3.97 (q, $J = 6.5$ Hz, 2H, OCH_2-CH_3), 2.23 (s, 3H, CH_3), 1.09 (t, $J = 6.8$ Hz,3H, Hz,3H, OCH_2-CH_3); IR (KBr): 3354, 3217, 3094, 2975, 1692, 1638, 1218, 1089 cm^{-1}; MS (ESI +ion): $m/z = 305.2$. Anal. calcd. for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21. Found: C, 59.14; H, 5.36; N, 9.28.

Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-styrylpyrimidine-5-carboxylate (4s). Mp 189–191 °C; lit.[27] 189–192 °C; ^{1}H NMR(400 MHz, DMSO-d_6): $\delta = 9.16$ (s, 1H, N*H*), 7.66 (d, 1H, C_6H_4), 6.83 (d, $J = 5.97$ Hz, 1H, C_6H_4), 6.72 (s, 1H, C_6H_4), 6.67 (d, $J = 7.2$ Hz, 1H, C_6H_4), 5.97 (d, 1H, C_6H_4), 5.05 (s, 1H, C*H*), 3.97 (q, $J = 6.5$ Hz, 2H, OCH_2-CH_3), 2.23 (s, 3H, CH_3), 1.09 (t, 3H, OCH_2-CH_3).

1,2,3,4-tetrahydro-4-(2-metoxy-6-pentacecylphenyl)-6-methyl-2-oxopyrimidin-5-yl propionate (4t). Mp 250–253 °C; ^{1}H NMR (400 MHz, D_2O): 7.086 (t, 1H, C_6H_3), 6.76 (d, 1H, C_6H_4), 6.66 (d, 1H, C_6H_3), 5.61 (s, 1H, C*H*), 3.80 (q, $J = 6.5$ Hz, 2H, OCH_2-CH_3), 3.77 (s, 3H, OCH_3), 2.11 (s, 3H, CH_3), 1.45 (q, 2H, (CH_2-CH_3), 1.04–1.26 [m, 26H, $-(CH_2)_{15}$], 0.929 (t, 3H, CH_3-CH_2-), 0.80 (t, 3H, -CH_3-CH_2-); IR (KBr): 3354, 3217, 3094, 2975, 1692, 1638, 1218,

1089 cm^{-1}; MS (ESI +ion): $m/z = 501.34$. Anal. calcd. for $C_{30}H_{48}N_2O_4$; C, 72.12; H, 9.67; N, 5.60. Found: C, 72.15, H, 9. 69; N, 5.68.

Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-(thiophen-2-yl)pyrimidine-5-carboxylate (4u). Mp 209–211 °C; lit.[26] 209–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.13$ (s, 1H, N*H*), 7.70 (s, 1H, N*H*), 7.12 (s, 1H, Ar-H), 6.96 (9d, 1H, Ar-H), 5.12 (s, 1H, C*H*), 4.02 (q, $J = 7.1$ Hz, 2H, OCH_2CH$_3$), 2.19 (s, 3H, CH_3), 1.13 (t, 3H, OCH$_2$-CH_3).

Materials and Methods

All analytical TLC was performed with E. Merck silica-gel 60 F_{254} aluminum sheets and was visualized with ultraviolet (UV) light. The following mobile phases were employed for TLC: chloroform/methanol and hexane/ethyl acetate in different ratios.

The instrumental techniques employed for the characterization of the newly synthesized compounds include ^{1}H NMR and mass spectroscopy. The details of instrumentation is briefly given below. ^{1}H (400-MHz) spectra were recorded on $CDCl_3$ solution in a 5-mm tube on a Bruker AMX 400 and 300 Fourier transform (FT) spectrophotometer (at SIF, Indian Institute of Science, Bangalore, India) with tetramethylsilane (TMS) as internal standard. The spectrophotometer was internally locked to the deuterium frequency of the solvent. Chemical shifts were recorded in parts per million (ppm) relative to tetramethylsilane (TMS). Mass and purity were recorded on a LC–MSD-Trap-XCT.

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