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D-xylonic Acid: A Solvent and Effective Biocatalyst for Three-component Reaction

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Abstract

A simple and effective synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones and their derivatives from aldehydes, β-dicarbonyl compounds and urea or thiourea using D-xylonic acid both as a green solvent and an effective catalyst is described. Taking the environment and economy into account, the work presented here has the merits of environmental friendliness, easy operation, simple work-up, excellent yields, the avoidance of the organic solvents and inexpensive catalysts. In addition, the good property of D-xylonic acid has also been validated by synthesis of 5-phenyl-1(4-methoxyphenyl)-3[(4-methoxyphenyl)-amino]-1H-pyrrol-2(5H)-one and 12-phenyl-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one. The synthesized compounds were characterized by FT-IR, $^1$H NMR, $^{13}$C NMR and melting point.

Key words: D-xylonic acid; green catalyst; green solvent; Biginelli reaction; 3,4-dihydropyrimidin-2-(1H)-ones/thiones
Introduction

The development of efficient, practical and environmentally friendly synthetic methodology for organic reactions is one of the latest challenges to all organic chemists. Considering the pollution and economy of many synthetic organic processes with organic solvents, the development of a clean, safe, and efficient synthetic methodology for organic reactions in green solvents is a focal point of modern organic synthesis. The most commonly used green reaction media are supercritical fluids, ionic liquids, and water. Recently, bio-based solvents such as glycerol, gluconic acid aqueous solution, and meglumine aqueous solution or their mixtures have also increasingly attracted attention. As a new kind of green reaction media, bio-based solvents are not only wildly available in nature, but also environmentally benign, and even some of them have played a dual role as both of a reaction medium and a catalyst in organic synthesis. In recent years, the application of green reaction media in organic synthesis is not only valuable for the atom economy, but also avoids using hazardous solvents. On the other hand, taking various factors of catalysts into consideration, the applications of various metal-free, eco-friendly, inexpensive and readily available catalysts are also a focus in organic reactions.

Multicomponent reaction (MCR) is a valuable tool for the synthesis of structurally diverse chemical libraries of heterocyclic compounds. To date, this type of reaction has been used successfully in many fields, especially in the area of drug discovery, organic synthesis, and material science. Dihydropyrimidinones (DHPMs) and their derivatives (a series of heterocyclic organic compounds) are one of the most widely distributed classes of natural compounds, which have gained extensive interests due to their wide range of biological properties and important applications in medicine. Multicomponent one-pot strategy to access DHPMs has attracted considerable attention over the years. Recently, this important class of heterocyclic compounds exhibits a wide spectrum of biological activities, including antiviral, antimitotic, anticarcinogenic, and antihypertensive effects. Some functionalized DHPMs also have been used as calcium channel modulators, alpha-1a-antagonists, and neuropeptide Y (NPY) antagonists. In addition, some marine alkaloids containing the dihydropyrimidione-5-carboxylate core unit possess interesting biological properties. In particular, Batzelladine A and B have been found to be potent HIV gp-120-CD4 inhibitors.
The first simple and straightforward strategy to synthesize DHPMs is the Biginelli reaction via one-pot condensation reaction of β-dicarbonyl compounds with aldehydes (aromatic or aliphatic aldehydes) and urea or thiourea. This kind of reaction is usually carried out in organic solvents at a reflux temperature in the presence of acid catalyst. Products with low yields (20–50%) are also generally observed when substituted aromatic or aliphatic aldehydes are used. Although more multistep reactions have been developed to increase product yields, these processes are complex.

In recent years, enormous progresses have been made to develop novel procedures under milder conditions by employing a wide array of acid catalysts, such as HCl, silica gel-supported L-pyrrolidine-2-carboxylic acid-4-hydrogen sulfate, silica gel-supported sodium hydrogensulfate, MNPs-IL-HSO₄, L-tyrosine, solid acids, Lewis acids, and basic catalysts. Many of these new catalytic materials and synthetic methods, however, have many limitations such as longer reaction time, harsher reaction condition, expensive and complex catalysts, and generation of noticeable amount of side products. These catalysts also suffer from other drawbacks, such as strongly acidic media, high temperature, tedious work-up or purification. When the environmental effects are taken into consideration, new and efficient procedures in ionic liquids, or eutectic mixtures, by microwave or ultrasonic assistance, have been reported. However, there are still some drawbacks, for examples, volatile organic solvents, toxic and hazardous transition metals, side products, and harsh or sensitive reaction conditions. Thus, there is ample scope for the development of greener new synthetic protocols to assemble such compounds.

Currently, several new methodologies have shown that natural catalysts (vitamin B1, tartaric acid, citric acid, bovine serum albumin, baker’s yeast, and even phytic acid, etc.) could be used for the three-component condensation reaction. Moreover, using heterogeneous Bronsted acid, carboxylic acids, and phosphoric acids as mild and efficient catalysts for the reaction also captured our interest. It is envisioned that the ubiquitous carboxylic acid D-xylonic acid could be a potential catalyst in organic transformations. D-xylonic acid is a versatile platform chemical derived from renewable hemicellulose, which can be used as complexing agent, chelator, or precursor for synthesizing polyesters, hydrogels or copolyamides and 1,2,4-butanezil. With increasing glucose prices, D-xylonic acid may provide a cheap, non-food derived alternative for gluconic acid. Large-scale production of D-xylonic acid has not been developed, reflecting the
current limited market for D-xylonic acid. To the best of our knowledge, there has not been a
report about the synthesis of DHPMs and their derivatives catalyzed by D-xylonic acid. In
continuation of our work on the applications of heterogeneous catalysts in organic
transformations,40 we not only explored the possibility of using D-xylonic acid as both of a
biocatalyst and green reaction medium for one-pot three-component condensation reaction to
3,4-dihydropyrimidin-2(1H) ones/thiones (Scheme 1), but also investigated the feasibility of the
synthesis of 5-phenyl-1(4-methoxyphenyl)-3[(4-methoxyphenyl)-amino]-1H-pyrrol-2(5H)-one
and 12-phenyl-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one. The results showed that
D-xylonic acid exhibited desired catalytic performances.

Experimental section

Materials

Aldehyde and 1,3-dicarbonyl compound are analysis grade and purchased from Aladdin Industrial
Corporation. D-xylonic acid with a purity of 96% is provided by Guangzhou Chemical Reagent
Factory, China. Urea, thiourea, and other reagents used are analysis grade and also provided by
Guangzhou Chemical Reagent Factory, China. All the reagents were employed without further
purification.

General procedure for the synthesis of dihydropyridine-2(1H)-ones using D-xylonic acid
catalyst

In a typical experimental procedure, a mixture of aldehyde (5 mmol), 1,3-dicarbonyl compound (6
mmol), urea (or thiourea) (7.5 mmol), and D-xylonic acid (6.5 mol% to all of the reactants) was
charged into a 35 mL pressure flask with a magnetic stirring bar. Then the reaction system was
placed in an oil-bath (100 °C) for 5 h with magnetic stirring. Upon the completion of the reaction,
the resulting solid product with pale yellow color was cooled to room temperature. Ice water or a
mixture of ethanol and water was then added and fully crushed, rested for a period of time, and the
product was then washed with ice water for several times, filtered and dried in vacuum for 10 h to
afford the crude product. Finally, the pure product was obtained by recrystallization of the crude
product in anhydrous ethanol.

Synthesis of 5-phenyl-1(4-methoxyphenyl)-3[(4-methoxyphenyl)-amino]-1H-pyrrol-2(5H)
one using D-xylonic acid catalyst

A mixture of 4-methoxyaniline (2 mmol), benzaldehyde (1 mmol), ethyl pyruvate (1.5 mmol) and
D-xylonic acid (12 mol% to all of the reactants) was stirred at room temperature for 2 h. Upon the completion of the reaction, absolute ethyl alcohol (5 mL) was added, and the reaction continued to whisk for further 3-4 minutes until smooth. Then the reaction mixture was filtered, and the solid product was washed with absolute ethyl alcohol and diethyl ether for several times. Finally, the solid product was dried in vacuum, and the product was confirmed by NMR spectral.

**Synthesis of 12-phenyl-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one using D-xylonic acid catalyst**

In a typical experimental procedure, a mixture of benzaldehyde (1.0 mmol), 2-hydroxynaphthalene (1.0 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1.2 mmol) and D-xylonic acid (4 mol% to all of the reactants) was charged into a 35 mL pressure flask with a magnetic stirring bar. The reaction system was placed in an oil-bath (90 °C) for 2 h with magnetic stirring. Upon the completion of the reaction, ethyl acetate (5 mL) was added and the reaction mixture was filtered. Then the catalyst was washed with ethyl acetate (10 mL) for two times. The pure product was afforded by evaporation of the solvent, followed by recrystallization from ethanol or by column chromatography on silica gels using ethyl acetate/hexane as the eluent. Finally, the product was confirmed by NMR spectral.

**Characterization**

In the pertinent literatures, the information on the characterization of the products was almost retrieved. In this work, the identifications of the products including FT-IR, $^1$H NMR, $^{13}$C NMR, and melting points (mp) measurements were conducted. A Nicolet 750 spectrophotometer (Thermo Fisher Nicolet, Florida, USA) was used to record FT-IR spectra using a KBr disc containing 1% (w/w) of finely ground sample. The melting points were determined on a BUCHI Melting Point B-545. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AVIII 600 MHz spectrometer (Bruker Corporation, Rheinstetten, Gemery) by using DMSO-$d_6$ as a solvent. $^1$H NMR spectral measurements were performed at 600 MHz using TMS as the internal standard, and $^{13}$C NMR spectral measurements were at 151 MHz with complete proton decoupling.

**Results and discussion**

**Optimization of the reaction conditions**

Initially, the three-component Biginelli condensation reaction of benzaldehyde (5 mmol) with ethyl acetoacetate (5 mmol) and urea (5 mmol) in the presence of D-xylonic acid (6.5 mol% to all of the
reactants) at 100 °C for different times was studied to give the desired product 5a. It was observed that when the reaction time increased, the yield of 5a increased at first and then decreased (Table 1, entries 1-5). The largest output of 5a occurred in 5 h and thus this period of time was chosen as the optimum reaction time for further reactions. Subsequently, the stoichiometric of the reactants for the synthesis of 5a as a model was investigated. As can be seen from Table 1, with the increase in the amount of urea, the yield of 5a increased (Table 1, entries 4, 6 and 7). However, under the same reaction condition, the amount of 5a was firstly increased and then slightly decreased with the raising of the dosage of ethyl acetoacetate (Table 1, entries 6, 8 and 9). The maximum production rate was observed when benzaldehyde, ethyl acetoacetate and urea were used at a mole ratio of 1:1.2:1.5, as illustrated in Table 1. 

Next, in order to explore the effect of reaction temperature on the field of the product, the reaction was carried out from 60 °C to 120 °C. The output of 5a increased along with the temperature raising from 60 °C to 100 °C (Table 2, entries 1-5). However, the yield of the product 5a had no obvious increase as the reaction temperature raised from 100 °C to 120 °C (Table 2, entries 6-7). Therefore, the optimum temperature for the synthesis of 5a by the catalysis of D-xylonic acid was observed at 100 °C. Finally, the effect of the amount of D-xylonic acid on the Biginelli reaction was explored. Based on the data in the Table 2, as the quantity of D-xylonic acid was increased from 1.6 mol% to 6.5 mol%, the yield of 5a increased from 83% to 87%. However, no obvious increase of the yield was observed as excessive D-xylonic acid was used (Table 2, entries 10-12). Furthermore, as the reaction was carried out with the same reagents and conditions in the absence of D-xylonic acid, the yield of 5a was only 37%, which demonstrated that D-xylonic acid was an efficient catalyst for this reaction. Therefore, according to the results discussed above, the optimal results for the three-component Biginelli condensation reaction was observed at a molar ratio of benzaldehyde, ethyl acetoacetate, and urea of 1:1.2:1.5 for 5 h at 100 °C in the presence of D-xylonic acid (6.5 mol% to all of the reactants).

To have a better understanding of the catalytic system, the effectiveness of D-xylonic acid was compared to those of the catalysts reported previously, and the results are listed in Table 3. D-xylonic acid is an efficient catalyst for the synthesis of DHPMs with a high yield in a relatively short period (Table 3, entries 1-4). Although some of them have excellent yields, additional solvents (water and ethanol) were used (Table 3, entries 3, 5, and 6), or the reaction
time was relatively long (Table 3, entry 3). In the case of Cu@PMO-IL, the yield obtained was as high as that from D-xylonic acid, and the reaction time was short, but the synthesis of the catalyst was very tedious (Table 3, entry 7). Obviously, D-xylonic acid catalyst system was much better than the other catalysts reported due to its non-toxic, inexpensiveness, and biodegradable, etc.

Reaction medium is a main factor influencing the selectivity of organic synthesis. In this work, the effect of D-xylonic acid for the synthesis of DHPMs under different reaction media was explored. As can be seen from Table 4, the yield of the three-component condensation reaction in only D-xylonic acid system was higher than those of other systems, and additional solvents in the reaction system not only caused environmental pollution, but also waste resources. In addition, the liquid D-xylonic acid had strong nominal stickiness, which could be considered as a green reaction medium for three-component condensation reaction.

**The scope of the substrates**

To examine the extent of the application of this catalyst in condensation reaction, the three-component Biginelli reaction of a variety of aldehydes with 1,3-dicarbonyl compounds (ethyl acetoacetate, methyl acetoacetate and acetylacetone) and urea or thiourea in the presence of D-xylonic acid (6.5 mol% to all of the reactants) was also investigated at the optimal condition (Table 5). For all cases, D-xylonic acid could catalyze the reaction smoothly in green reaction media to give the corresponding DHPMs and their derivatives with yields of 23~93%. Many aromatic aldehydes with electro-donating groups, such as 4-methyl-benzaldehyde, 4-chloro-benzaldehyde, 4-bromo-benzaldehyde and 4-fluoro-benzaldehyde, could be converted to corresponding DHPMs and their derivatives in high yields with 1,3-dicarbonyl compounds (ethyl acetoacetate, methyl acetoacetate and acetylacetone) and urea (Table 5, entries 11, 12, 14-21 and 27-28). Many aromatic aldehydes including 4-hydroxy-benzaldehyde, 4-nitro-benzaldehyde, 4-methoxy-benzaldehyde, 3-methoxy-4-hydroxybenzaldehyde, 3-methoxybenzaldehyde with electro-withdrawing groups could also give excellent yields under the same condition (Table 5, entries 2, 3, 5, 7, 13, 20, 21 and 28). Moreover, this work also explored the effect of D-xylonic acid by three-component Biginelli condensation reaction among aliphatic aldehyde, ethyl acetoacetate and urea on the yield. It found that the yield of aliphatic aldehyde was lower as compared with the aromatic aldehydes (Table 5, entries 22-26). In addition, thiourea was also
successfully used to produce the corresponding 3,4-dihydropyrimidin-2(1H)-thiones (Table 5, entries 4, 8 and 9). However, under the same condition, the yields of the products with thiourea were slightly lower than those with urea (Table 5, entries 1 and 4, 5 and 8, 6 and 9).

Due to the excellent activity of D-xylonic acid, it is worth to explore its catalytic activity for the synthesis of pyrroles. Pyrroles and their analogs, are a general class of important five-member N-heterocyclic compounds in the aspect of synthesis of pharmacologically significant molecules and natural products.\textsuperscript{43} Moreover, 1,5-dihydro-2H-pyrrol-2-ones compounds are a fascinating family of lactams.\textsuperscript{44} Thus, synthesis of this class of N-heterocyclic compounds has gained intensive interest for organic chemists.\textsuperscript{45} Xanthenes, an important group of O-heterocyclic compounds, were widely employed in laser technique\textsuperscript{46} and biological molecular fluorescent tags\textsuperscript{47} as a source for chemical fluorescent dyes. It was found that xanthenes, especially benzoxanthene derivatives, possess favorable biological and pharmaceutical properties, such as analgesic,\textsuperscript{48} antiviral,\textsuperscript{49} and antibacterial.\textsuperscript{50} Moreover, these kinds of compounds can also be employed as antagonists in photodynamic therapy.\textsuperscript{51} Therefore, the synthesis of xanthenes and benzoxanthene derivatives is of great importance. For pyrroles synthesis, the condensation reaction was carried out by mixing 4-methoxyaniline, benzaldehyde and ethyl pyruvate with 78% yield (Scheme 2), while for xanthenes, the condensation reaction among benzaldehyde, 2-hydroxynaphthalene, and 5,5-dimethyl-1,3-cyclohexanedione gave product 3 with 89% yield (Scheme 3). Furthermore, when a new reaction is discovered or observed, it is necessary to explore the plausible pathway for the reaction. Today, the hotly debated mechanism for the Biginelli condensation reaction mainly includes three types: Knoevenagel mechanism, enamine mechanism and iminium mechanism. In 1973, Sweet and Fissekis\textsuperscript{52} presented the Knoevenagel mechanism (Scheme 4) based on their findings. However, as time goes on, further study indicated that the Knoevenagel mechanism was not the preferred reaction pathway. In 1933, Folkers and coworkers\textsuperscript{53} advanced the enamine mechanism (Scheme 5), which was the first attempt to illustrate mechanism of the Biginelli condensation reaction. However, the reports including Folkers,\textsuperscript{53} Johnson,\textsuperscript{53} and Kappe\textsuperscript{54} have only supposed a plausible mechanism without any real proof. The good news was that the work of Cepanec and coworkers\textsuperscript{55} which used SbCl\textsubscript{3} as the catalyst showed that the Biginelli condensation reaction went through the enamine mechanism. The work of Litvic\textsuperscript{56} also returned similar results, in accordance with the description of Cepanec.\textsuperscript{55}
Iminium mechanism of the Biginelli condensation reaction (Scheme 6) was reported by Kappe\textsuperscript{54} based on NMR experiments. Lately, Souza and coworkers\textsuperscript{57} also investigated the mechanism of the Biginelli reaction using Bronsted acid catalysis (formic acid). The work\textsuperscript{57} not only detected and characterized the structure of intermediate by using ESI-MS/MS, but also won the support of thermodynamic and kinetics from DFT calculations. According to the data from \textsuperscript{1}H and \textsuperscript{13}C NMR,\textsuperscript{54} ESI-MS/MS\textsuperscript{57} and DFT calculation,\textsuperscript{57} the iminium mechanism could be highly favored and the Knoevenagel and enamine pathways could be discarded. Herein, based on the former literatures,\textsuperscript{23a, 52-58} a plausible reaction mechanism for the synthesis of DHPMs catalyzed by D-xylonic acid was proposed in Scheme 7. N-acyl iminium intermediates might generate via cyclocondensation of aldehyde and urea in the presence of D-xylonic acid during the reaction. Subsequently, 1,3-dicarbonyl compounds were added to the reaction system, followed by cyclization and dehydration procedures under the acidic condition. Finally the corresponding 3,4-dihydropyrimidin-2(1H)-ones/thiones and their derivatives were obtained.

Conclusions

In summary, D-xylonic acid was proved to be both an effective biocatalyst and a green reaction medium for one-pot three-component Biginelli condensation reaction to give 3,4-dihydropyrimidin-2(1H)-ones/thiones and their derivatives. The natural abundance, ease of use, eco-friendliness, biodegradability, as well as air, water, and substrate tolerances make it an excellent catalyst and solvent for Biginelli condensation reaction. Moreover, D-xylonic acid was also used in the synthesis of 5-phenyl-1(4-methoxyphenyl)-3[(4-methoxyphenyl)-amino]-1H-pyrrrol-2(5H)-one and 12-phenyl-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[\textalpha]xanthen-11-one with excellent yields.

Acknowledgements

The project is supported by the National Natural Science Foundation of China (21404043, 31430092 and 21336002), Pearl River S&T Nova Program of Guangzhou (2014J2200063), Science and Technology Project of Guangdong Province (2015A010105005), Research Fund for the Doctoral Program of Higher Education (201301721200240), Fundamental Research Funds for the Central Universities.

Notes

The authors declare no competing financial interest.
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The Characterization of the Products

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (5a)

$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm = 9.17 (brs, 1H, NH), 7.72 (brs, 1H, NH), 7.33-7.23 (m, 5H, Ar5H), 5.14 (d, $J = 3.0$ Hz, 1H, CH), 3.98 (q, $J = 7.2$ Hz, 2H, OCH$_2$CH$_3$), 2.25 (s, 3H, CH$_3$), 1.08 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$);

$^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 165.31, 152.09, 148.32, 144.84, 128.36, 127.23, 126.22, 99.25, 59.16, 53.94, 17.76, 14.06; IR (KBr): v (cm$^{-1}$) 3245, 3115, 2979, 1725, 1702, 1649; mp (°C): 208-210.

5-Ethoxycarbonyl-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5b)

$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm = 9.32 (s, 1H, OH), 9.10 (brs, 1H, NH), 7.61 (brs, 1H, NH), 7.02 (d, $J = 9.0$ Hz, 2H, Ar5H), 6.68 (d, $J = 8.4$ Hz, 2H, Ar5H), 5.04 (d, $J = 3.6$ Hz, 1H, CH), 3.97 (q, $J = 7.2$ Hz, 2H, OCH$_2$CH$_3$), 2.23 (s, 3H, CH$_3$), 1.09 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$);

$^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 165.03, 151.97, 151.71, 149.36, 146.70, 127.63, 123.81, 98.17, 59.37, 53.67, 17.85, 14.04; IR (KBr): v (cm$^{-1}$) 3284, 3111, 2973, 1691, 1652, 1606; mp (°C): 232-234.

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (5c)

$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm = 9.34 (brs, 1H, NH), 8.22 (d, $J = 9.0$ Hz, 2H, Ar5H), 7.88 (brs, 1H, NH), 7.50 (d, $J = 9.0$ Hz, 2H, Ar5H), 5.27 (d, $J = 3.6$ Hz, 1H, CH), 3.99 (q, $J = 7.2$ Hz, 2H, OCH$_2$CH$_3$), 2.27 (s, 3H, CH$_3$), 1.09 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$);

$^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 165.05, 151.97, 151.71, 149.36, 146.70, 127.63, 123.81, 98.17, 59.40, 53.68, 17.89, 14.06; IR (KBr): v (cm$^{-1}$) 3225, 3118, 2981, 1705, 1641, 1522; mp (°C): 210-212.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione (5d)

$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm = 10.33 (brs, 1H, NH), 9.65 (brs, 1H, NH), 7.36-7.21 (m, 5H, Ar5H), 5.17 (d, $J = 3.6$ Hz, 1H, CH), 4.01 (q, $J = 7.2$ Hz, 2H, OCH$_2$CH$_3$), 2.29 (s, 3H, CH$_3$), 1.10 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$);

$^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 174.22, 165.12, 145.04, 143.49, 128.57, 127.69, 126.38, 100.70, 59.60, 54.04, 17.17, 14.02; IR (KBr): v (cm$^{-1}$) 3248, 3113, 2954, 1716, 1684,1652; mp (°C): 205-206.

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5e)

$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm = 9.14 (brs, 1H, NH), 7.14 (d, $J = 8.4$ Hz, 2H, Ar-H), 6.87 (d, $J = 8.4$ Hz, 2H, Ar-H), 5.09 (d, $J = 3.0$ Hz, 1H, CH), 3.98 (q, $J = 7.2$ Hz, 2H, OCH$_2$CH$_3$), 2.29 (s, 3H, CH$_3$), 1.10 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$); $^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 174.22, 165.12, 145.04, 143.49, 128.57, 127.69, 126.38, 100.70, 59.60, 54.04, 17.17, 14.02; IR (KBr): v (cm$^{-1}$) 3248, 3113, 2954, 1716, 1684,1652; mp (°C): 205-206.
(q, J = 7.2 Hz, 2H, OCH₂CH₃), 3.72 (s, 3H, OCH₃), 2.24 (s, 3H, CH₃), 1.10 (t, J = 7.2 Hz, 3H, OCH₂CH₃); ¹³C NMR (151 MHz, DMSO-d₆, δ ppm): 165.36, 158.42, 152.13, 147.99, 137.04, 127.37, 113.69, 99.56, 59.14, 53.32, 17.75, 14.10; IR (KBr): ν (cm⁻¹) 3244, 3111, 2956, 1706, 1650, 1614; mp (°C): 203.52-205.

5-Methoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (5f)

¹H NMR (DMSO-d₆, 600 MHz, Me₄Si, 25 °C): δ ppm = 9.21 (brs, 1H, NH), 7.74 (brs, 1H, NH), 7.33-7.23 (m, 5H, Ar-H), 5.14 (d, J = 3.6 Hz, 1H, CH), 3.53 (s, 3H, OCH₃), 2.25 (s, 3H, CH₃); ¹³C NMR (151 MHz, DMSO-d₆, δ ppm): 165.82, 152.14, 148.64, 144.66, 128.44, 127.27, 126.15, 99.00, 53.77, 50.79, 17.83; IR (KBr): ν (cm⁻¹) 3332, 3224, 3107, 2947, 1706, 1668; mp (°C): 212-213.

5-Methoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5g)

¹H NMR (DMSO-d₆, 600 MHz, Me₄Si, 25 °C): δ ppm = 9.17 (brs, 1H, NH), 7.68 (brs, 1H, NH), 7.14 (d, J = 9.0 Hz, 2H, Ar-H), 6.87 (d, J = 8.4 Hz, 2H, Ar-H), 5.09 (d, J = 3.6 Hz, 1H, CH), 3.72 (s, 3H, OCH₃), 3.52 (s, 3H, OCH₃), 2.24 (s, 3H, CH₃); ¹³C NMR (151 MHz, DMSO-d₆, δ ppm): 165.85, 158.45, 152.15, 148.32, 136.84, 127.32, 113.76, 99.28, 55.05, 53.18, 50.76, 17.80; IR (KBr): ν (cm⁻¹) 3246, 3111, 2949, 2840, 1720, 1655; mp (°C): 197.5-200.

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (5h)

¹H NMR (DMSO-d₆, 600 MHz, Me₄Si, 25 °C): δ ppm = 10.28 (brs, 1H, NH), 9.59 (brs, 1H, NH), 7.13 (d, J = 8.4 Hz, 2H, Ar-H), 6.90 (d, J = 8.4 Hz, 2H, Ar-H), 5.11 (d, J = 3.6 Hz, 1H, CH), 4.00 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 3.72 (s, 3H, OCH₃), 2.28 (s, 3H, CH₃); ¹³C NMR (151 MHz, DMSO-d₆, δ ppm): 174.02, 165.15, 158.73, 144.73, 135.70, 127.60, 113.86, 100.97, 59.54, 55.10, 53.45, 17.14, 14.04; IR (KBr): ν (cm⁻¹) 3313, 3172, 3000, 1667, 1575, 1458; mp (°C): 151-153.
$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm = 10.26 (brs, 1H, NH), 9.56 (brs, 1H, NH), 9.42 (s, 1H, OH), 7.01 (d, $J = 8.4$ Hz, 2H, Ar-H), 6.71 (d, $J = 8.4$ Hz, 2H, Ar-H), 5.06 (d, $J = 3.6$ Hz, 1H, CH), 3.54 (s, 3H, OCH$_3$), 2.28 (s, 3H, CH$_3$).

$^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 173.90, 165.71, 156.93, 144.82, 133.89, 127.58, 115.21, 100.81, 53.42, 51.04, 17.19; IR (KBr): v (cm$^{-1}$) 3310, 3124, 1665, 1567, 1448, 1341, 1192; mp (°C): 246-248.

5-Ethoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5k)

$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm = 9.14 (brs, 1H, NH), 7.67 (brs, 1H, NH), 7.12 (s, 4H, Ar-H), 5.10 (d, $J = 3.6$ Hz, 1H, CH), 3.98 (q, $J = 7.2$ Hz, 2H, OCH$_2$CH$_3$), 2.26 (s, 3H, CH$_3$), 2.24 (s, 3H, CH$_3$), 1.10 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$);

$^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 165.34, 152.15, 148.11, 141.94, 136.34, 128.86, 126.12, 99.41, 59.14, 53.62, 20.63, 17.74, 14.09; IR (KBr): v (cm$^{-1}$) 3246, 3115, 2972, 1716, 1644, 1460; mp (°C): 216-218.

5-Methoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5l)

$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm = 9.17 (brs, 1H, NH), 7.69 (brs, 1H, NH), 7.11 (s, 4H, Ar-H), 5.10 (d, $J = 3.6$ Hz, 1H, CH), 3.52 (s, 3H, OCH$_3$), 2.26 (s, 3H, CH$_3$), 2.24 (s, 3H, CH$_3$);

$^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 165.84, 152.17, 148.44, 141.76, 136.40, 128.94, 126.07, 99.15, 53.49, 50.74, 20.63, 17.80; IR (KBr): v (cm$^{-1}$) 3242, 3113, 2934, 1703, 1644, 1514; mp (°C): 234-236.

5-Ethoxycarbonyl-4-(4-hydroxyphenyl-3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5m)

$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm = 9.10 (s, 1H, OH), 8.89 (brs, 1H, NH), 7.61 (brs, 1H, NH), 6.80-6.60 (m, 3H, Ar-H), 5.06 (d, $J = 3.0$ Hz, 1H, CH), 3.99 (q, $J = 7.2$ Hz, 2H, OCH$_2$CH$_3$), 3.72 (s, 3H, OCH$_3$), 2.23 (s, 3H, CH$_3$), 1.11 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$);

$^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 165.44, 152.21, 147.86, 147.24, 145.78, 135.91, 118.28, 115.26, 110.89, 99.55, 59.11, 55.57, 53.55, 17.73, 14.15; IR (KBr): v (cm$^{-1}$) 3245, 3114, 2948, 1717, 1647, 1433; mp (°C): 225-226.

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5n)

$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm = 9.23 (brs, 1H, NH), 7.39 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.25 (d, $J = 8.4$ Hz, 2H, Ar-H), 5.14 (d, $J = 3.0$ Hz, 1H, CH), 3.98 (q, $J = 7.2$ Hz, 2H, OCH$_2$CH$_3$), 2.25 (s, 3H, CH$_3$), 1.09 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$);

$^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 165.19, 151.91, 148.70, 143.78, 131.77, 128.38, 128.17, 98.83,
4-(4-Chlorophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5o)

1H NMR (DMSO-d6, 600 MHz, Me4Si, 25 °C): δ ppm = 9.27 (brs, 1H, NH), 7.78 (brs, 1H, NH), 7.39 (d, J = 8.4 Hz, 2H, Ar-H), 7.25 (d, J = 9.0 Hz, 2H, Ar-H), 5.14 (d, J = 3.6 Hz, 1H, CH), 3.53 (s, 3H, OCH3), 2.25 (s, 3H, CH3); 13C NMR (151 MHz, DMSO-d6, δ ppm): 165.70, 151.96, 148.98, 143.59, 131.82, 128.44, 128.11, 98.61, 53.27, 50.82, 17.85; IR (KBr): v (cm⁻¹) 3241, 3114, 2968, 1713, 1645, 1469; mp (°C): 201-217.

4-(4-Bromophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5p)

1H NMR (DMSO-d6, 600 MHz, Me4Si, 25 °C): δ ppm = 9.24 (brs, 1H, NH), 7.77 (brs, 1H, NH), 7.53 (d, J = 8.4 Hz, 2H, Ar-H), 7.19 (d, J = 8.4 Hz, 2H, Ar-H), 5.12 (d, J = 3.6 Hz, 1H, CH), 3.98 (q, J = 7.2 Hz, 2H, OCH2CH3), 2.24 (s, 3H, CH3), 1.09 (t, J = 7.2 Hz, 3H, OCH2CH3); 13C NMR (151 MHz, DMSO-d6, δ ppm): 165.18, 151.90, 148.72, 144.18, 131.30, 128.53, 120.29, 98.76, 53.48, 17.80, 14.07; IR (KBr): v (cm⁻¹) 3244, 3116, 2968, 1717, 1648, 1471; mp (°C): 223-225.

4-(4-Bromophenyl)-5-methylcarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5q)

1H NMR (DMSO-d6, 600 MHz, Me4Si, 25 °C): δ ppm = 9.27 (brs, 1H, NH), 7.78 (brs, 1H, NH), 7.52 (d, J = 8.4 Hz, 2H, Ar-H), 7.18 (d, J = 8.4 Hz, 2H, Ar-H), 5.12 (d, J = 3.0 Hz, 1H, CH), 3.53 (s, 3H, OCH3), 2.25 (s, 3H, CH3); 13C NMR (151 MHz, DMSO-d6, δ ppm): 165.69, 151.94, 149.00, 144.00, 131.37, 128.47, 120.35, 98.54, 53.33, 50.84, 17.87; IR (KBr): v (cm⁻¹) 3363, 3222, 3106, 2953, 1720, 1633; mp (°C): 225-227.

4-(4-Fluorophenyl)-5-methylcarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5r)

1H NMR (DMSO-d6, 600 MHz, Me4Si, 25 °C): δ ppm = 9.26 (brs, 1H, NH), 7.78 (brs, 1H, NH), 7.27-7.13 (m, 4H, Ar-H), 5.14 (d, J = 3.0 Hz, 1H, CH), 3.53 (s, 3H, OCH3), 2.25 (s, 3H, CH3); 13C NMR (151 MHz, DMSO-d6, δ ppm): 165.76, 162.14, 160.53, 152.02, 148.89, 131.88, 128.18 (d, J = 11.28 Hz), 115.20 (d, J = 21.29 Hz), 98.89, 53.17, 50.84, 17.87; IR (KBr): v (cm⁻¹) 3327, 3223, 3106, 2948, 1680, 1423; mp (°C): 202-203.

4-(4-Fluorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5s)

1H NMR (DMSO-d6, 600 MHz, Me4Si, 25 °C): δ ppm = 9.21 (brs, 1H, NH), 7.73 (brs, 1H, NH), 7.27-7.13 (m, 4H, Ar-H), 5.14 (d, J = 3.0 Hz, 1H, CH), 3.98 (m, 2H, OCH2CH3), 2.25 (s, 3H,
CH₃), 1.09 (t, J = 7.2 Hz, 3H, OCH₂CH₃); ¹³C NMR (151 MHz, DMSO-δ₆, δ ppm): 165.23, 162.10, 160.49, 151.94, 148.51, 141.12 (d, J = 3.02 Hz), 128.23 (d, J = 8.15 Hz), 115.10 (d, J = 21.29 Hz), 99.11, 59.20, 53.33, 17.78, 14.06; IR (KBr): ν (cm⁻¹) 3243, 3120, 2971, 1717, 1646, 1461; mp (°C): 184.5-186.5.

5-Ethoxycarbonyl-4-(3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5t)

¹H NMR (DMSO-δ₆, 600 MHz, Me₄Si, 25 °C): δ ppm = 9.19 (brs, 1H, NH), 7.73 (brs, 1H, NH), 7.24 (t, J = 7.8 Hz, Ar-H), 6.80 (m, 3H, Ar-H), 5.11 (d, J = 3.0 Hz, 1H, CH), 3.99 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 3.72 (s, 3H, OCH₃), 2.24 (s, 3H, CH₃), 1.11 (t, J = 7.2 Hz, 3H, OCH₂CH₃); ¹³C NMR (151 MHz, DMSO-δ₆, δ ppm): 165.35, 159.20, 152.20, 148.45, 146.34, 129.57, 112.39, 112.13, 99.13, 59.23, 54.98, 53.74, 17.78, 14.13; IR (KBr): ν (cm⁻¹) 3254, 3109, 2952, 1704, 1638, 1451; mp (°C): 229.5-231.

5-Methylcarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (5u)

¹H NMR (DMSO-δ₆, 600 MHz, Me₄Si, 25 °C): δ ppm = 9.37 (brs, 1H, NH), 8.21 (d, J = 8.4 Hz, 2H, Ar-H), 7.90 (brs, 1H, NH), 7.50 (d, J = 8.4 Hz, 2H, Ar-H), 5.27 (d, J = 3.6 Hz, 1H, CH), 3.54 (s, 3H, OCH₃), 2.27 (s, 3H, CH₃); ¹³C NMR (151 MHz, DMSO-δ₆, δ ppm): 165.55, 151.79, 151.77, 149.62, 146.73, 127.57, 123.86, 97.98, 53.53, 50.91, 17.92; IR (KBr): ν (cm⁻¹) 3364, 3223, 3113, 2958, 1714, 1638, 1516; mp (°C): 241.5-243.5.

5-Ethoxycarbonyl-4,6-dimethyl-3,4-dihydropyrimidin-2(1H)-one (5v)

¹H NMR (DMSO-δ₆, 600 MHz, Me₄Si, 25 °C): δ ppm = 8.96 (s, 1H, NH), 7.18 (s, 1H, NH), 4.13-4.06 (m, 2H, OCH₂CH₃), 4.06-4.01 (m, 1H, CH), 2.15 (s, 3H, CH₃), 1.19 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 1.10 (d, J = 6.6 Hz, 3H, CH₃); ¹³C NMR (151 MHz, DMSO-δ₆, δ ppm): 165.32, 152.48, 147.70, 100.47, 59.03, 46.28, 23.38, 17.65, 14.22; IR (KBr): ν (cm⁻¹) 3251, 3116, 2978, 2937, 1705, 1656; mp (°C): 288-290.

5-Ethoxycarbonyl-6-methyl-4-ethyl-3,4-dihydropyrimidin-2(1H)-one (5w)

¹H NMR (DMSO-δ₆, 600 MHz, Me₄Si, 25 °C): δ ppm = 8.91 (s, 1H, NH), 7.27 (s, 1H, NH), 4.11-4.06 (m, 2H, OCH₂CH₃), 4.06-4.01 (m, 1H, CH), 2.16 (s, 3H, CH₃), 1.44-1.39 (m, 2H, CH₂CH₃), 1.18 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 0.79 (t, J = 7.2 Hz, 3H, CH₂CH₃); ¹³C NMR (151 MHz, DMSO-δ₆, δ ppm): 165.96, 153.29, 148.86, 99.25, 59.48, 51.83, 30.09, 18.17, 14.68, 9.00; IR (KBr): ν (cm⁻¹) 3249, 3121, 2961, 2936, 1724, 1704; mp (°C): 191-192.

5-Ethoxycarbonyl-6-methyl-4-propyl-3,4-dihydropyrimidin-2(1H)-one (5x)
$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm= 8.92 (s, 1H, NH), 7.32 (s, 1H, NH), 4.11-4.06 (m, 2H, OCH$_2$CH$_3$), 4.06-4.01 (m, 1H, CH), 2.16 (s, 3H, CH$_3$), 1.43-1.20 (m, 4H, (CH$_2$)$_2$CH$_3$), 1.18 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$), 0.84 (t, $J = 7.2$ Hz, 3H, (CH$_2$)$_2$CH$_3$); $^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 165.42, 152.87, 148.19, 99.48, 59.01, 49.83, 39.07, 17.66, 17.00, 14.18, 13.71; IR (KBr): v (cm$^{-1}$) 3251, 3120, 2958, 2935, 1721, 1704; mp (°C): 192-193.

5-Ethoxycarbonyl-6-methyl-4-heptyl-3,4-dihydropyrimidin-2(1H)-one (5y)

$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm= 8.91 (s, 1H, NH), 7.31 (s, 1H, NH), 4.10-4.07 (m, 2H, OCH$_2$CH$_3$), 4.07-4.02 (m, 1H, CH), 2.16 (s, 3H, CH$_3$), 1.38-1.22 (m, 12H, (CH$_2$)$_2$CH$_3$), 1.18 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$), 0.85 (t, $J = 7.2$ Hz, 3H, (CH$_2$)$_2$CH$_3$); $^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 165.40, 152.79, 148.18, 99.43, 59.00, 50.06, 36.67, 31.20, 28.74, 28.62, 23.66, 22.07, 17.65, 14.17, 13.89; IR (KBr): v (cm$^{-1}$) 3240, 3113, 2952, 2927, 2859, 1706; mp (°C): 138-139.

5-Ethoxycarbonyl-6-methyl-4-decyl-3,4-dihydropyrimidin-2(1H)-one (5z)

$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm= 8.90 (s, 1H, NH), 7.30 (s, 1H, NH), 4.10-4.03 (m, 2H, OCH$_2$CH$_3$), 4.03-4.00 (m, 1H, CH), 2.15 (s, 3H, CH$_3$), 1.39-1.23 (m, 18H, (CH$_2$)$_9$CH$_3$), 1.18 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$), 0.85 (t, $J = 7.2$ Hz, 3H, (CH$_2$)$_9$CH$_3$); $^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 165.89, 153.23, 148.69, 99.90, 59.45, 50.52, 37.15, 31.75, 29.46, 29.43, 29.42, 29.23, 29.17, 24.12, 22.55, 18.14, 14.66, 14.39; IR (KBr): v (cm$^{-1}$) 3244, 3122, 2921, 2852, 1730, 1706; mp (°C): 142-143.

5,6-Dimethyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (5a')

$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm = 9.19 (brs, 1H, NH), 7.83 (brs, 1H, NH), 7.34-7.23 (m, 5H, Ar$_5$H), 5.27 (d, $J = 3.6$ Hz, 1H, CH), 2.29 (s, 3H, CH$_3$), 2.10 (s, 3H, CH$_3$); $^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 194.26, 152.15, 148.11, 144.25, 128.52, 127.34, 126.43, 109.60, 53.85, 30.32, 18.92; IR (KBr): v (cm$^{-1}$) 3408, 2936, 1745, 1636, 1510, 1458; mp (°C): 239-241.

5,6-Dimethyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (5b')

$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm = 9.34 (brs, 1H, NH), 8.20 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.98 (brs, 1H, NH), 7.50 (d, $J = 9.0$ Hz, 2H, Ar-H), 5.39 (d, $J = 3.6$ Hz, 1H, CH), 2.31 (s, 3H, CH$_3$), 2.18 (s, 3H, CH$_3$); $^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 193.91, 151.98, 151.56, 149.05, 146.68, 127.67, 123.81, 109.46, 53.16, 30.63, 19.11; IR (KBr): v (cm$^{-1}$) 3269, 2943, 1716,
5-Phenyl-1(4-methoxyphenyl)-3(4-methoxyphenyl)-amino-1H-pyrrol-2(5H)-one

$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm= 7.85 (s, 1H), 7.47 (d, $J = 9.0$ Hz, 2H), 7.26 (d, $J = 7.2$ Hz, 2H), 7.22-7.19 (m, 5H), 6.85 (dd, $J_1 = 9.6$ Hz, $J_2 = 9.0$ Hz, 4H), 6.11 (d, $J = 2.4$ Hz, 1H), 5.92 (d, $J = 2.4$ Hz, 1H), 3.69 (s, 6H); $^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 166.31, 156.17, 153.36, 138.26, 135.48, 132.64, 130.18, 127.63, 126.80, 123.50, 118.28, 114.31, 113.86, 107.24, 62.81, 55.17, 55.10; mp (°C): 254-256.

12-Phenyl-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one

$^1$H NMR (DMSO-$d_6$, 600 MHz, Me$_4$Si, 25 °C): δ ppm= 8.04 (d, $J = 8.4$ Hz, 2H), 7.92-7.90 (m, 2H), 7.50-7.41 (m, 3H), 7.30-7.29 (m, 2H), 7.19-7.16 (m, 2H), 7.06-7.03 (m, 1H), 5.58 (s, 1H), 2.63 (dd, $J_1 = 17.4$ Hz, $J_2 = 16.2$ Hz, 2H), 2.34-2.32 (m, 2H), 1.06 (s, 3H), 0.88 (s, 3H); $^{13}$C NMR (151 MHz, DMSO-$d_6$, δ ppm): 196.31, 164.25, 147.64, 145.33, 131.55, 131.11, 129.55, 129.00, 128.60, 128.59, 127.60, 126.66, 125.43, 123.73, 117.77, 117.62, 113.70, 50.60, 40.73, 34.59, 32.36, 29.30, 26.69; mp (°C): 197-199.
Scheme 1 Synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones using D-xylonic acid as both a catalyst and a green reaction medium.
Scheme 2 D-xylonic acid catalyzed for the synthesis of 5-phenyl-l(4-methoxyphenyl)-3[(4-methoxyphenyl)-amino]-1H-pyrrol-2(5H)-one.
Scheme 3 D-xylonic acid catalyzed for the synthesis of 12-phenyl-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one.
Scheme 4 The Knoevenagel mechanism for the Biginelli reaction.
Scheme 5 The enamine-based mechanism for the Biginelli reaction.
Scheme 6 The iminium mechanism for the Biginelli reaction.
Scheme 7 A plausible mechanism of D-xylonic acid-catalyzed three-component Biginelli condensation reaction.
Table 1. Optimizations of reaction time and the stoichiometric ratio of the reactants for the synthesis of 5a catalyzed by D-xylonic acid.a

![Reaction Scheme]

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*Experimental condition: Various stoichiometric of the reactants at 100 °C for various reaction times in the presence of D-xylonic acid (6.5 mol% to all of the reactants).

b The ratio order of reactants is benzaldehyde to ethyl acetoacetate to urea (5 mmol benzaldehyde, 1 equiv).

c Isolated yields.
Table 2. Effects of reaction temperature and the dosage of D-xylonic acid on the synthesis of 5a.  

![Chemical structure of 5a]

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<tr>
<td>8</td>
<td>100</td>
<td>1.6</td>
<td>83</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td>3.3</td>
<td>84</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>9.8</td>
<td>85</td>
</tr>
<tr>
<td>11</td>
<td>100</td>
<td>13.0</td>
<td>84</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
<td>16.0</td>
<td>83</td>
</tr>
</tbody>
</table>

a Benzaldehyde, ethyl acetoacetate, and urea in equimolar ratio (1:1.2:1.5) at various reaction temperatures for 5 h in the presence of D-xylonic acid.

b Isolated yields.
Table 3. Various catalysts for the synthesis of 5a in their own appropriate reaction medium.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst$^a$</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D-xylonic acid</td>
<td>D-xylonic acid</td>
<td>5</td>
<td>87</td>
<td>This work</td>
</tr>
<tr>
<td>2</td>
<td>PPF-SO$_3$H$^b$</td>
<td>ethanol</td>
<td>8</td>
<td>81</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>Fe$_3$O$_4$@mesoporous SBA-15</td>
<td>ethanol</td>
<td>6</td>
<td>85</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>BSA$^c$</td>
<td>ethanol</td>
<td>8</td>
<td>83</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>IBX$^d$</td>
<td>water</td>
<td>2.5</td>
<td>90</td>
<td>35b</td>
</tr>
<tr>
<td>6</td>
<td>DSA$^e$</td>
<td>water</td>
<td>2.4</td>
<td>91</td>
<td>35a</td>
</tr>
<tr>
<td>7</td>
<td>Cu@PMO-IL$^f$</td>
<td>solvent-free</td>
<td>0.83</td>
<td>97</td>
<td>42</td>
</tr>
</tbody>
</table>

$^a$ The specific information of catalysts was shown in the corresponding papers.

$^b$ PPF-SO$_3$H: Sulfonic acid-functionalized polypropylene fiber.

$^c$ BSA: Bovine serum albumin.

$^d$ IBX: Iodoxy benzoic acid.

$^e$ DSA: Dodecyl sulfonic acid.

$^f$ Cu@PMO-IL: Ionic liquid-based ordered mesoporous organosilica-supported copper.
Table 4. Three-component reaction catalyzed by D-xylonic acid in various solvents.\textsuperscript{a}

\[
\begin{align*}
\text{Entry} & & \text{Solvent} & & \text{Temperature (°C)} & & \text{Time (h)} & & \text{Yield (\%)} \\
1 & & \text{D-xylonic acid} & & 100 & & 5 & & 87 \\
2 & & \text{EtOH} & & 78 & & 5 & & 62 \\
3 & & \text{Toluene} & & 110 & & 5 & & 66 \\
4 & & \text{CH}_2\text{Cl}_2 & & 60 & & 5 & & 32 \\
5 & & \text{Water} & & 100 & & 5 & & 57 \\
\end{align*}
\]

\textsuperscript{a}Reaction condition: 5 mmol aldehyde, 6 mmol 1,3-dicarbonyl compound and 7.5 mmol urea or thiourea, 6.5 mol\% (to all of the reactants) D-xylonic acid, 5 h.

\textsuperscript{b}Isolated yields.
Table 5. Synthesis of dihydropyrimidin-2(\(H\))-ones and thiones catalyzed by D-xylonic acid at 100°C.\(^a\)

$$
\text{R}^1 + \text{R}^2 + \text{R}^3 \xrightarrow{\text{D-xylonic acid}} \text{Product 5}
$$

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R(^1)</th>
<th>X</th>
<th>Product 5</th>
<th>Yield (%, (\text{b/c}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>OEt</td>
<td>O</td>
<td>5a</td>
<td>87/97</td>
</tr>
<tr>
<td>2</td>
<td>4-HO-(\text{C}_6\text{H}_4)</td>
<td>OEt</td>
<td>O</td>
<td>5b</td>
<td>87/95</td>
</tr>
<tr>
<td>3</td>
<td>4-NO(_2)-(\text{C}_6\text{H}_4)</td>
<td>OEt</td>
<td>O</td>
<td>5c</td>
<td>84/99</td>
</tr>
<tr>
<td>4</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>OEt</td>
<td>S</td>
<td>5d</td>
<td>76/88</td>
</tr>
<tr>
<td>5</td>
<td>4-MeO-(\text{C}_6\text{H}_4)</td>
<td>OEt</td>
<td>O</td>
<td>5e</td>
<td>81/91</td>
</tr>
<tr>
<td>6</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>OMe</td>
<td>O</td>
<td>5f</td>
<td>83/92</td>
</tr>
</tbody>
</table>
7  4-MeO-C₆H₄  OMe  O  88/99

8  4-MeO-C₆H₄  OEt  S  65/83

9  C₆H₅  OMe  S  83/92

10  4-HO-C₆H₄  OMe  S  84/96

11  4-Me-C₆H₄  OEt  O  81/90

12  4-Me-C₆H₄  OMe  O  81/93

13  3-MeO-4-HO-C₆H₅  OEt  O  86/95
14  4-Cl-C₆H₄  OEt  O  89/99

15  4-Cl-C₆H₄  OMe  O  90/98

16  4-Br-C₆H₄  OEt  O  92/99

17  4-Br-C₆H₄  OMe  O  93/99

18  4-F-C₆H₄  OMe  O  77/90

19  4-F-C₆H₄  OEt  O  80/91

20  3-MeO-C₆H₄  OEt  O  75/96
a Reaction condition: 5 mmol Aldehyde, 6 mmol 1, 3-dicarbonyl compound and 7.5 mmol urea or thiourea, 6.5 mol% (to all of the reactants) D-xylonic acid at 100 °C for 5 h.

b Isolated yields: the yields of products with recrystallization.

c Isolated yields: crude.
Graphical Abstract

D-xylonic acid was used as both a biocatalyst and a solvent for the three-component reaction.