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Acidic Task-Specific Ionic Liquid as Catalyst of Microwave-Assisted Solvent-Free Biginelli Reaction*

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Abstract—A simple and effective synthesis of 3,4-dihydropyrimidin-2(1*H*)-one and 3,4-dihydropyrimidine-2(1*H*)-thione derivatives has been developed on the basis of three-component condensation of substituted aromatic and heterocyclic aldehydes, methyl acetoacetate, and urea or thiourea in the presence of 10% of an acidic task-specific ionic liquid ([C_4mim][HSO_4]) as catalyst under microwave irradiation in the absence of a solvent. The proposed procedure ensures short reaction times (4.4–8 min) and good yields after purification by recrystallization.

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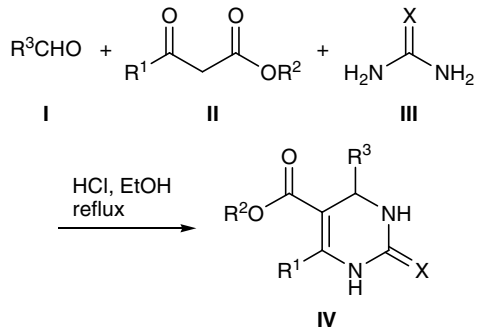
Mullticomponent reactions [1] have become an increasingly important method for developing new potential biologically active substances. Multicomponent condensations involve three or more compounds reacting in a single event, but consecutively to form a new product, which contains the essential parts of all the starting materials. In 1893, Italian chemist Pietro Biginelli anticipated intuitively the synthetic potential of multicomponent reactions [2] by combining in a single flask the reactants of two different reactions leading to the same product. The original Biginelli protocol for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones implied heating a mixture of three components (a1dehyde **I**, β-keto ester **II** and urea **III**) in ethanol containing a catalytic amount of HCl (Scheme 1). The major drawback associated with this protocol is the low yields, particularly for substituted aromatic and aliphatic aldehydes [3]. This has led to the development of multistep synthetic strategies [4].

Scheme 1.



X = O, S.

In the past 10 years, interest in the three-component Biginelli reaction has increased rapidly because of the diverse range of pharmaceutical properties [5] exhibited by dihydropyrimidine derivatives. They have emerged as integral backbones of several calcium channel blockers [6], vasorelaxants [7], α_{1a}-adrenergic receptor antagonists [8], neuropeptide Y (NPY) antagonists [9] and antimitotic agents [10]. In addition, several marine alkaloids containing a dihydropyrimidine-5-carboxylate moiety also showed interesting biological activity [11].

Due to importance of the Biginelli reaction products, much work on improving the yield and reaction conditions has been actively pursued in several decades. The improved synthetic methods involved the use of simple metal (and ammonium) salts with nucleophilic anions, e.g., LiBr [12], NH_4Cl [13], $FeCl_3$ [14] as active catalysts. The catalytic effect of metal cations is even more pronounced in methods based on metal salts with non-nucleophilic anions, such as $LiClO_4$ [15], $Zn(OTf)_2$ [16], $Al(HSO_4)_3$ [17], and various lanthanide trifluoromethanesulfonates $Ln(OTf)_3$ (Ln = Yb, Sc, La) [18]. In other cases, effective Biginelli

* The text was submitted by the authors in English.

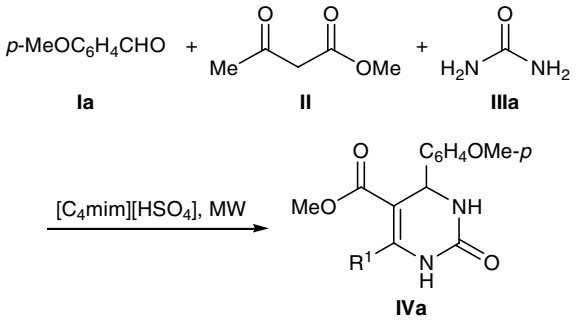
reaction conditions employed stoichiometric reagents like $BF_3 \cdot OEt_2$ and AcOH/CuCl catalyst in boiling THF [19], $KHSO_4$ in glycol [20], H_3BO_3 in glacial AcOH [21]. In addition, the Biginelli reaction can be accomplished with moderate rate enhancement in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) that has a nonacidic counterion [22]. In the present work we showed that this ionic liquid is not very efficient. The use of l-butyl-3-methyl-imidazolium hydrogen sulfate ([bmim][HSO_4]) was also reported for the synthesis of coumarins [23]. In contrast to simple catalytic methods, those employing suitable dehydrating agents proved to be more effective, even in syntheses of more complex dihydropyrimidinones. Thus Kappe and co-workers [24] further improved the Biginelli reaction using microwave irradiation in the presence of ethyl polyphosphate (PPE) to give higher chemical yields of dihydropyrimidinones. In 2002, Ranu et al. reported a noncatalytic Biginelli synthesis [25]; however, our substrates failed to react under these conditions. It should be noted that, despite numerous papers appeared since 2002 in the field of the Biginelli reaction, no noncatalytic conditions were reported again.

Task-specific ionic liquids (TSIL) are those incorporating functional groups designed to exhibit particular properties or reactivities; in the recent years TSILs have attracted considerable attention [26, 27]. Davis et al. reported on TSILs in which the cations were both intrinsically Brønsted acidic and nonvolatile. This was done by covalently tethering an alkanesulfonic acid group to the IL cation [28]. Such sulfonic acid-based TSILs were used simultaneously as solvent and catalyst for Fischer esterification [29], dehydrodimerization of alcohols [27], pinacol–benzopinacol rearrangements [30], and electrophilic substitution of indoles with aldehydes [31].

Another approach developed by our group for the acidic TSILs is to introduce the latent acidity into the anion by anion metathesis from hydrogen sulfate with the corresponding imidazolium [32] or pyridinium halides [33]. These acidic TSILs were used as catalysts for esterification reactions; the resulting esters were insoluble in the TSILs and were isolated in high yields with high purity. In the same manner, Jiang and Han investigated their catalytic activity in Mannich reactions [34].

The utility of microwave irradiation (MW) to carry out organic reactions has now become a regular feature. The main benefits of performing reactions are

Table 1. Catalytic effect of ionic liquid [C_4mim][HSO_4] in model Biginelli reaction[a]



Amounts of reactants		Temperature, °C	Yield,[b] %
[C_4mim][HSO_4], mol %	**IIIa**, equiv		
5	3	140	55
10	3	140	98[c]
20	3	140	98
10	1.5	140	72
10	2.5	140	88
10	3	120	62

[a] Reaction time 4.4 min; the progress was monitored by ^{1}H NMR (200 MHz) in $CDCl_3$ using TMS as internal reference.

[b] The reaction was carried out until disappearance of initial compound **Ia** or **II**.

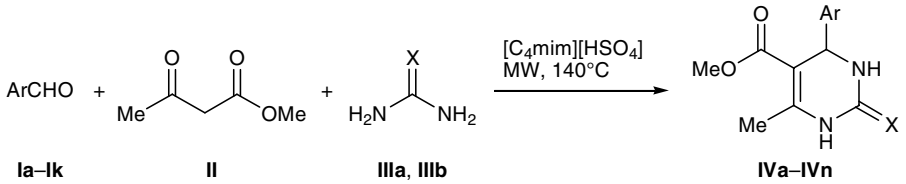
[c] Under conventional heating (on a bath preliminarily heated to the same temperature), the reaction was complete in 16.3 min.

significant rate enhancement and higher yields. A large number of review articles and several books provide extensive coverage of the subject [35]. While performing our research program on the use of microwave dielectric heating in TSIL-catalyzed reactions [36], we presumed that 1-butyl-3-methyl-imidazolium hydrogen sulfate ([C_4mim][HSO_4]) as an acidic TSIL is a potential catalyst for the Biginelli synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones.

The catalyst [C_4mim][HSO_4] was synthesized according to the new two-step process developed in our laboratory [33]. The first step is solvent-free quaternization of commercial 1-methylimidazole with chlorobutane under microwave irradiation [37],** followed by anion metathesis. For anion exchange, the corresponding coordinating anion was HSO_4^- from commercially available sodium hydrogen sulfate. The anion metathesis reaction was carried out in dry acetonitrile by stirring at room temperature under nitrogen for

** Other syntheses of ionic liquids using a commercial multimode microwave reactor were described in [38].

Scheme 2.



I, Ar = 4-$MeOC_6H_4$ (**a**), Ph (**b**), 4-ClC_6H_4 (**c**), 4-$O_2NC_6H_4$ (**d**), pyridin-3-yl (**e**), 4-BrC_6H_4 (**f**), 2-BrC_6H_4 (**g**), 4-$HOCOC_6H_4$ (**h**), 3,4-$OCH_2OC_6H_3$ (**i**), 4-HOC_6H_4 (**j**), 3-FC_6H_4 (**k**); **III**, X = O (**a**), S (**b**); **IV**, Ar = 4-$MeOC_6H_4$, X = O (**a**); Ar = Ph, X = O (**b**); Ar = 4-ClC_6H_4, X = S (**c**); Ar = 4-$O_2NC_6H_4$, X = S (**d**); Ar = 4-$MeOC_6H_4$, X = S (**e**); Ar = 4-$O_2NC_6H_4$, X = O (**f**); Ar = pyridin-3-yl, X = O (**g**); Ar = 4-BrC_6H_4, X = O (**h**); Ar = 2-BrC_6H_4, X = O (**i**); Ar = 4-$HOCOC_6H_4$, X = O (**j**); Ar = 4-ClC_6H_4, X = O (**k**); Ar = 3,4-$OCH_2OC_6H_3$, X = O (**l**); Ar = 4-HOC_6H_4, X = O (**m**); Ar = 3-FC_6H_4, X = O (**n**).

3 days (97%). After removal of insoluble NaCl by filtration, the exchange efficiency was determined by measuring the concentration of HSO_4^- ion in a solution of $[C_4mim][HSO_4]$ by volumetric titration with commercial NaOH solution and phenolphthalein as indicator [33]. The structure of the liquid $[C_4mim][HSO_4]$ was also confirmed by conventional techniques (^1H and ^{13}C NMR and HRMS).

With the desired $[C_4mim][HSO_4]$ catalyst in hand, we started to examine the effect of the amount of $[C_4mim][HSO_4]$ on the reaction of 4-methoxybenzaldehyde (**Ia**, 1 equiv) with methyl acetoacetate (**II**, 1 equiv) and urea (**IIIa**, 1.5–3 equiv) as model process using solvent-free technique under microwave irradiation at 120 and 140°C. The resu1ts are presented in Table 1.

Table 2. Microwave-assisted solvent-free Biginelli reactions catalyzed by $[C_4mim][HSO_4]$

Product no.	Reaction time,[a] min	Yield,[b] %
IVa	4.4	85
IVb	5	80
IVc	5.1	80
IVd	5.5	79
IVe	5.1	82
IVf	5.4	82
IVg	5.1	76
IVh	4.9	87
IVi	6	72
IVj	8	75
IVk	5.4	87
IVl	4.5	82
IVm	5.1	83
IVn	5.1	80

[a] The reactions were performed at 140°C (150 W) until initial compound **I** or **II** disappeared (TLC).

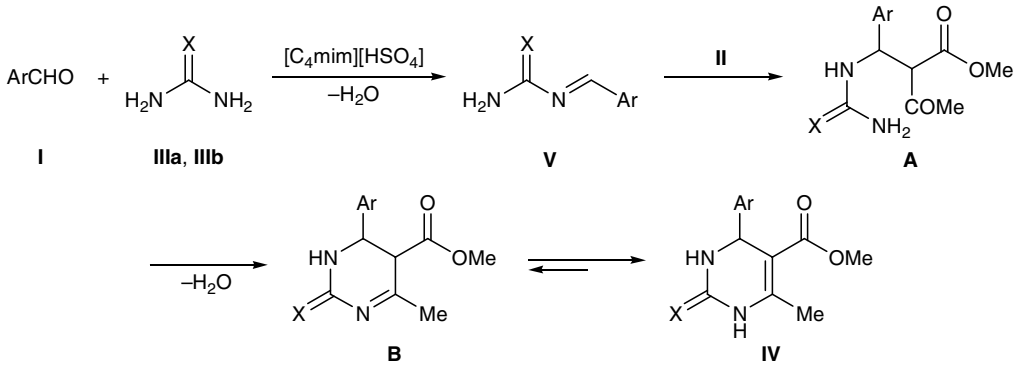
[b] After recrystallization; according to the ^1H NMR spectra of the crude reaction mixtures, the yield was 98% (with respect to 4-H).

The data in Table 1 show that increase in the amount of $[C_4mim][HSO_4]$ at 140°C raises the yield (run nos. 1–3). A slight excess of urea also favors the process (run nos. 4, 5). The yield increases from 62% at 120°C to 98% at 140°C, other conditions being equal. The best yield (98%) and the shortest reaction time (4.4 min) were attained at a **Ia**–**II**–**IIIa**–$[C_4mim]\cdot[HSO_4]$ ratio of 1:1:3:0.1 at 140°C under microwave irradiation (power level 50%, 150 W). No by-products were detected in the crude reaction mixture by ^1H NMR spectroscopy.

On the basis of our results, we focused on the application of $[C_4mim][HSO_4]$ as catalyst in different Biginelli reactions with a variety of substituted aromatic aldehydes. The results are summarized in Table 2. We used aromatic and heterocyclic aldehydes **Ia**–**Ij** having either electron-donating or electron-withdrawing substituents, which afforded good yields (from 75 to 87% after purification by recrystallization) of the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones **IVa**–**IVn** (Scheme 2). It is seen that all microwave-assisted reactions required a short time. This suggests that microwaves enhance the catalytic activity of $[C_4mim]\cdot[HSO_4]$ in the Biginelli reaction. The generally accepted Biginelli reaction mechanism [39] (Scheme 3) involves the formation of C=N bond from initial aldehyde **I** and urea **III**, followed by protic acid-catalyzed addition of acetoacetate **II** to the protonated arylmethylideneurea **V** and cyclodehydration of intermediate **A** to dihydropyrimidone **B** which is tautomeric to **IV**. Presumably, microwave irradiation accelerates the formation of C=N bond as the rate-determining step.

Under the same reaction conditions, aromatic aldehydes reacted with thiourea (**IIIb**) to give the corresponding 3,4-dihydropyrimidine-2(1*H*)-thiones which

Scheme 3.



are also interesting from the viewpoint of their biological activity [40]. Thus the ionic liquid $[C_4mim][HSO_4]$ also exhibits a significant catalytic effect under microwave irradiation in the Biginelli synthesis of dihydropyrimidine-2-thione derivatives with short reaction times (5.1 min for **IVc** and **IVe** and 5.5 min for **IVd**) and the same stoichiometry.

To conclude, we have developed an efficient procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones from aromatic and heterocyclic aldehydes under solvent-free microwave-assisted conditions with short reaction times (<10 min). The process involves an acidic TSIL, $[C_4mim][HSO_4]$, as a readily available catalyst which was used for the first time in heterocyclic chemistry and ensured good to high yields of pure dihydropyrimidinone derivatives. To our knowledge, this rapid and simple procedure [41] has not been reported previously, and it may supplement the existing methods [42].

EXPERIMENTAL

The IR spectra were recorded on a Biorad FTS 175C spectrometer. The ^1H and ^{13}C NMR spectra were measured from solutions in DMSO-d_6 on a Bruker AC 300P spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C). The high-resolution mass spectra (electron impact, 70 eV) were obtained on a Varian MAT-311 mass spectrometer at CRMPQ (Rennes, France).

Microwave-assisted reactions were carried out in a Synthewave® 402 apparatus [43] (Prolabo Merck-Eurolab, France [44]) with variable power output (0 to 300 W). All experiments were performed in an open quartz reactor equipped with a reflux condenser and a stirrer. The required temperature was attained in 3 min, and the irradiation power was held constant to maintain that temperature. The temperature was measured using a Prolabo calibrated infrared sensor [45] (the reaction time included the temperature ramp period).

Solvents were removed on a Buchi rotary evaporator. The melting points were determined on a Kofler hot stage and were not corrected. Thin-layer chromatography was performed on 0.2-mm precoated plates of silica gel 60F-254 (Merck) or neutral aluminum oxide 60F-254 (Merck). Spots were visualized under UV light (λ 254 or 365 nm) or using a fluorescent indicator.

All reagents were commercial products purchased from Acros, Aldrich, and Fluka and were used without additional purification.

General procedure for the synthesis of 3,4-dihydropyrimidin-2-ones(thiones) IVa–IVn under microwave irradiation. A cylindrical quartz reactor (1.8 cm in diameter) was charged with a mixture of 3 mmol of aromatic aldehyde **I**, 3 mmol of methyl acetoacetate **II**, 9 mmol of urea or thiourea **IIIa** or **IIIb**, and 0.3 mmol of $[C_4mim][HSO_4]$, and the reactor was placed in a microwave oven. The mixture was stirred under microwave irradiation at 140°C (150 W) for a time indicated in Table 2 and cooled to room temperature, an ice–water mixture (5:1 by volume) was added, and the mixture was thoroughly stirred to dissolve the catalyst and remove excess urea **III**. The light yellow precipitate was stirred with 10 ml of ice water for 10 min, filtered off, dried in a high vacuum, and recrystallized from ethanol.

Methyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVa). mp 194–196°C; published data [45]: mp 192–194°C. IR spectrum (KBr), ν, cm^{-1}: 3250, 3100, 2951, 2837, 1717, 1655, 1587, 1514. ^1H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 3.54 s (3H, CO_2CH_3), 3.72 s (3H, OCH_3), 5.12 d (1H, 4-H, J = 3.2 Hz), 6.88 d (2H, 3′-H, 5′-H, J = 8.6 Hz), 7.14 d (2H, 2′-H, 6′-H, J = 8.6 Hz),

7.72 br.s (1H, NH), 9.22 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 17.8 (CH_3), 50.7 ($CO_2\mathbf{C}H_3$), 53.2 (C^4), 55.0 (OCH_3), 99.3 (C^5), 113.7 ($C^{3'}$, $C^{5'}$), 127.3 ($C^{2'}$, $C^{6'}$), 136.8 ($C^{1'}$), 148.3 (C^6), 152.2 C^2), 158.4 ($C^{4'}$), 165.8 ($\mathbf{C}O_2CH_3$). Found: M^+ 276.1118. $C_{14}H_{16}N_2O_4$. Calculated: M 276.1110.

Methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVb). mp 211–212°C; published data [46]: mp 210–212°C. IR spectrum (KBr), ν, cm^{-1}: 3158, 3024, 2949, 2902, 1713, 1645, 1433. ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 3.53 s (3H, CO_2CH_3), 5.14 d (1H, 4-H, J = 3 Hz), 7.22–7.35 m (5H, Ph), 7.77 br.s (1H, NH), 9.23 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.3 (CH_3), 51.3 ($CO_2\mathbf{C}H_3$), 54.3 (C^4), 99.1 (C^5), 126.6 ($C^{3'}$, $C^{5'}$), 128.0 ($C^{4'}$), 128.9 ($C^{2'}$, $C^{6'}$), 145.1 ($C^{1'}$), 149.1 (C^6), 152.7 (C^2), 166.3 ($\mathbf{C}O_2CH_3$). Found: M^+ 246.1014. $C_{13}H_{14}N_2O_3$. Calculated: M 246.1011.

Methyl 4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVc). mp 136–138°C. IR spectrum (KBr), ν, cm^{-1}: 3272, 3175, 2998, 2953, 1699, 1572, 1186. ^{1}H NMR spectrum, δ, ppm: 2.29 s (3H, CH_3), 3.56 s (3H, CO_2CH_3), 5.17 d (1H, 4-H, J = 3.5 Hz), 7.23 d (2H, 2′-H, 6′-H, J = 8.4 Hz), 7.42 d (2H, 3′-H, 5′-H, J = 8.4 Hz), 9.70 br.s (1H, NH), 10.42 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 17.71 (CH_3), 51.6 ($CO_2\mathbf{C}H_3$), 53.8 (C^4), 100.5 (C^5), 128.7 ($C^{2'}$, $C^{6'}$), 129.1 ($C^{3'}$, $C^{5'}$), 132.8 ($C^{4'}$), 142.6 ($C^{1'}$), 146.1 ($C^{6'}$), 166.0 ($\mathbf{C}O_2CH_3$), 174.7 (C^2). Found: M^+ 296.0391. $C_{13}H_{13}ClN_2O_2S$. Calculated: M 296.0386.

Methyl 6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVd). mp 122–124°C. IR spectrum (KBr), ν, cm^{-1}: 3178, 3105, 2997, 2952, 1693, 1567, 1516. ^{1}H NMR spectrum, δ, ppm: 2.31 s (3H, CH_3), 3.56 s (3H, CO_2CH_3), 5.30 d (1H, 4-H, J = 2.1 Hz), 7.48 d (2H, 3′-H, 5′-H, J = 8.2 Hz), 8.23 d (2H, 2′-H, 6′-H, J = 8.2 Hz), 9.79 br.s (1H, NH), 10.53 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 17.8 (CH_3), 51.7 ($CO_2\mathbf{C}H_3$), 54.0 (C^4), 99.9 (C^5), 124.5 ($C^{3'}$, $C^{5'}$), 128.2 ($C^{2'}$, $C^{6'}$), 146.7 ($C^{4'}$), 147.4 ($C^{1'}$), 150.6 ($C^{6'}$), 165.8 (CO_2CH_3), 175.0 (C^2). Found: M^+ 307.0622. $C_{13}H_{13}N_3O_4S$. Calculated: M 307.0627.

Methyl 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVe). mp 172–174°C. IR spectrum (KBr), ν, cm^{-1}: 3322, 3287, 3179, 2969, 2934, 1670, 1610, 1560, 1508. ^{1}H NMR spectrum, δ, ppm: 2.29 s (3H, CH_3), 3.55 s (3H, CO_2CH_3), 3.72 s (3H, OCH_3), 5.12 s (1H, 4-H), 6.70 d (2H, 2′-H, 6′-H, J = 7.9 Hz), 7.12 d (2H, 3′-H, 5′-H, J = 7.9 Hz), 9.62 br.s (1H, NH), 10.32 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 17.7 (CH_3), 51.5 ($CO_2\mathbf{C}H_3$), 53.8 (C^4), 55.5 (OCH_3), 101.1 (C^5), 114.4 ($C^{3'}$, $C^{5'}$), 128.0 ($C^{2'}$, $C^{6'}$), 136.0 ($C^{1'}$), 145.5 (C^6), 159.2 ($\mathbf{C}O_2CH_3$), 166.1 ($C^{4'}$), 174.5 (C^2). Found: M^+ 292.0886. $C_{14}H_{16}N_2O_3S$. Calculated: M 292.0882.

Methyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVf). mp 236–238°C; published data [43]: mp 237–238°C. IR spectrum (KBr), ν, cm^{-1}: 3209, 3113, 2967, 2949, 1715, 1693, 1517. ^{1}H NMR spectrum, δ, ppm: 2.27 s (3H, CH_3), 3.54 s (3H, CO_2CH_3), 5.27 d (1H, 4-H, J = 3.1 Hz), 7.50 d (2H, 3′-H, 5′-H, J = 8.6 Hz), 7.91 br.s (1H, NH), 8.21 d (2H, 2′-H, 6′-H, J = 8.6 Hz), 9.38 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.4 (CH_3), 51.3 ($CO_2\mathbf{C}H_3$), 54.0 (C^4), 98.5 (C^5), 124.3 ($C^{3'}$, $C^{5'}$), 128.0 ($C^{2'}$, $C^{6'}$), 147.2 ($C^{4'}$), 150.1 ($C^{1'}$), 152.3 ($C^{6'}$), 152.3 (C^2), 166.0 ($\mathbf{C}O_2CH_3$). Found: M^+ 291.0846. $C_{13}H_{13}N_3O_5$. Calculated: M 291.0855.

Methyl 6-methyl-2-oxo-4-(pyridin-3-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVg). mp 236–238°C. IR spectrum (KBr), ν, cm^{-1}: 3181, 3081, 2946, 2912, 1706, 1675, 1507. ^{1}H NMR spectrum, δ, ppm: 2.27 s (3H, CH_3), 3.53 s (3H, CO_2CH_3), 5.19 s (1H, 4-H), 7.25–7.62 m (2H, 4′-H, 5′-H), 7.84 br.s (1H, NH), 8.32–8.45 m (2H, 2′-H, 6′-H), 9.35 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.3 (CH_3); 51.3 ($CO_2\mathbf{C}H_3$); 53.8 (C^4); 99.0 (C^5); 113.4 ($C^{3'}$); 114.6, 122.6, 131.0, 148.0 ($C^{2'}$, $C^{4'}$, $C^{5'}$, $C^{6'}$); 149.7 (C^6); 152.6 (C^2); 166.2 ($\mathbf{C}O_2CH_3$). Found: M^+ 247.0934. $C_{12}H_{13}N_3O_3$. Calculated: M 247.0957.

Methyl 4-(4-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVh). mp 210–212°C. IR spectrum (KBr), ν, cm^{-1}: 3207, 3105, 2975, 2946, 1715, 1693, 1520. ^{1}H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 3.53 s (3H, CO_2CH_3), 5.12 d (1H, 4-H, J = 3.1 Hz), 7.18 d (2H, 2′-H, 6′-H, J = 8.3 Hz), 7.52 d (2H, 3′-H, 5′-H, J = 8.3 Hz), 7.79 br.s (1H, NH), 9.28 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.3 (CH_3), 51.3 ($CO_2\mathbf{C}H_3$), 53.8 (C^4), 99.0 (C^5), 120.8 ($C^{4'}$), 129.0 (Ar, $C^{2'}$, $C^{6'}$), 131.8 ($C^{3'}$, $C^{5'}$), 144.5 ($C^{1'}$), 149.5 (C^6), 152.5 (C^2), 166.2 ($\mathbf{C}O_2CH_3$). Found: M^+ 324.0130. $C_{13}H_{13}BrN_2O_3$. Calculated: M 324.0109.

Methyl 4-(2-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVi). mp 220–222°C. IR spectrum (KBr), ν, cm^{-1}: 3249, 3210, 3099, 2952, 1706, 1650, 1459. ^{1}H NMR spectrum, δ, ppm: 2.29 s (3H, CH_3), 3.45 s (3H, CO_2CH_3),

5.58 d (1H, 4-H, J = 2.8 Hz), 7.17–7.21 m (1H, 6′-H), 7.29–7.37 m (2H, 4′-H, 5′-H), 7.57 d (1H, 3′-H, J = 7.8 Hz,), 7.71 br.s (1H, NH), 9.32 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.2 (CH_3), 51.2 ($CO_2\mathbf{C}H_3$), 54.4 (C^4), 98.6 (C^5), 122.7 ($C^{2'}$), 129.0 ($C^{5'}$), 129.2 ($C^{6'}$), 129.9 ($C^{4'}$), 133.2 ($C^{3'}$), 143.8 ($C^{1'}$), 149.9 (C^6), 151.9 (C^2), 165.9 ($\mathbf{C}O_2CH_3$). Found: M^+ 324.0980. $C_{13}H_{13}BrN_2O_3$. Calculated: M 324.0110.

4-(5-Methoxycarbonyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl)benzoic acid (IVj). mp 230–232°C. IR spectrum (KBr), ν, cm^{-1}: 3297, 3210, 3147, 2956, 2912, 1712, 1671, 1506. ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 3.53 s (3H, CO_2CH_3), 5.20 s (1H, 4-H), 7.34 d (2H, 2′-H, 6′-H, J = 6.9 Hz), 7.83 br.s (1H, NH), 7.90 d (2H, 3′-H, 5′-H, J = 7 Hz), 9.29 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.3 (CH_3), 51.3 ($CO_2\mathbf{C}H_3$), 54.2 (C^4), 98.9 (C^5), 126.7 ($C^{2'}$, $C^{6'}$), 130.1 ($C^{3'}$, $C^{5'}$), 131.5 ($C^{4'}$), 149.3 ($C^{1'}$), 149.5 (C^6), 152.6 (C^2), 166.2 ($\mathbf{C}O_2CH_3$), 167.9 (CO_2H). Found: M^+ 290.0902. $C_{14}H_{14}N_2O_5$. Calculated: M 290.0903.

Methyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVk). mp 204–206°C; published data [43]: mp 206–208°C. IR spectrum (KBr), ν, cm^{-1}: 3211, 3109, 2974, 2948, 1716, 1690, 1490. ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 3.53 s (3H, CO_2CH_3), 5.14 s (1H, 4-H), 7.24 d (2H, 3′-H, 5′-H, J = 7.7 Hz), 7.39 d (2H, 2′-H, 6′-H, J = 7.7 Hz), 7.80 br.s (1H, NH), 9.28 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.3 (CH_3), 51.3 ($CO_2\mathbf{C}H_3$), 53.7 (C^4), 99.1 (C^5), 128.6 ($C^{2'}$, $C^{6'}$), 128.9 ($C^{3'}$, $C^{5'}$), 132.3 ($C^{4'}$), 144.1 ($C^{1'}$), 149.5 (C^6), 152.5 (C^2), 166.2 ($\mathbf{C}O_2CH_3$). Found: M^+ 280.0604. $C_{13}H_{13}ClN_2O_3$. Calculated: M 280.0615.

Methyl 6-methyl-4-(3,4-methylenedioxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVl). mp 238–240°C. IR spectrum (KBr), ν, cm^{-1}: 3214, 3095, 2951, 2902, 1705, 1646, 1501, 1239. ^{1}H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 3.53 s (3H, CO_2CH_3), 5.06 d (1H, 4-H, J = 3.1 Hz), 5.98 s (2H, OCH_2O), 6.68 d (1H, 5′-H, J = 8.1 Hz), 6.74 s (1H, 2′-H), 6.84 d (1H, 6′-H, J = 7.9 Hz), 7.70 br.s (1H, NH), 9.21 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.3 (CH_3), 51.2 ($CO_2\mathbf{C}H_3$), 54.0 (C^4), 99.5 (C^5), 101.4 (OCH_2O), 107.1 ($C^{2'}$), 108.5 ($C^{5'}$), 119.7 ($C^{6'}$), 139.1 ($C^{1'}$), 146.9 ($C^{3'}$), 147.8 ($C^{4'}$), 149.1 (C^6), 152.6 (C^2), 166.3 ($\mathbf{C}O_2CH_3$). Found: M^+ 290.0902. $C_{14}H_{14}N_2O_5$. Calculated: M 290.0903.

Methyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVm). mp 232–234°C. IR spectrum (KBr), ν, cm^{-1}: 3418, 3239, 3044, 2926, 2849, 1786, 1620, 1556. ^{1}H NMR spectrum, δ, ppm: 2.23 s (3H, CH_3), 3.52 s (3H, CO_2CH_3), 5.03 d (1H, 4-H, J = 3.2 Hz), 6.68 d (2H, 3′-H, 5′-H, J = 8.3 Hz), 7.01 d (2H, 2′-H, 6′-H, J = 8.3 Hz), 7.64 br.s (1H, NH), 9.15 br.s (1H, OH), 9.34 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.3 (CH_3), 51.2 ($CO_2\mathbf{C}H_3$), 53.7 (C^4), 100.0 (C^5), 115.5 ($C^{3'}$, $C^{5'}$), 127.8 ($C^{2'}$, $C^{6'}$), 135.7 ($C^{1'}$), 148.5 (C^6), 152.8 (C^2), 157.0 ($C^{4'}$), 166.4 ($\mathbf{C}O_2CH_3$). Found: M^+ 262.0975. $C_{13}H_{14}N_2O_4$. Calculated: M 262.0954.

Methyl 4-(2-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVn). mp 220–222°C. IR spectrum (KBr), ν, cm^{-1}: 3339, 3295, 3148, 3055, 2953, 1715, 1670, 1587. ^{1}H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 3.54 s (3H, CO_2CH_3), 5.16 d (1H, 4-H, J = 3.3 Hz), 6.98–7.09 m (3H, 4′-H, 5′-H, 6′-H), 7.37–7.39 m (1H, 3′-H), 7.82 br.s (1H, NH), 9.29 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.3 (CH_3), 51.3 ($CO_2\mathbf{C}H_3$), 53.8 (C^4), 99.0 (C^5), 113.4 d ($C^{4'}$, J = 20.8 Hz), 114.6 d ($C^{2'}$, J = 20.8 Hz), 122.6 d ($C^{6'}$, J = 2.6 Hz), 131.0 d ($C^{5'}$, J = 8.1 Hz), 147.9 d ($C^{1'}$, J = 5.8 Hz), 149.7 (C^6), 152.6 (C^2), 162.6 d ($C^{3'}$, J = 244 Hz), 166.2 ($\mathbf{C}O_2CH_3$). Found: M^+ 264.0915. $C_{13}H_{13}FN_2O_3$. Calculated: M 264.0910.

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