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HMF in multicomponent reactions: utilization of 5-hydroxymethylfurfural (HMF) in the Biginelli reaction†

Weigang Fan, Yves Queneau * and Florence Popowycz *

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The use of the renewable platform molecule 5-hydroxymethylfurfural (HMF) in the multi-component Biginelli reaction has been investigated. Multicomponent reactions (MCR) using HMF offer straightforward access to novel fine chemicals. However, the peculiar reactivity and lower stability of HMF have limited its use in such strategies. In this paper, we report our results on the use of HMF in 3-component Biginelli reactions, leading in one single step to a series of functionalized dihydropyrimidinones obtained in moderate to good yields, with a broad substrate scope of 1,3-dicarbonyl compounds and urea building blocks. This is the first report on the use of HMF in this reaction. The CH_2OH motif found in HMF provides useful functionalization for the target molecules, which cannot be offered by simpler aldehydes such as furfural.

Biomass is a widely available carbon source apart from oil and coal in nature, which has been an important resource for the production of chemicals and fuels.[1] 5-Hydroxymethylfurfural (HMF) is regarded as one of the most promising biomass-derived platform chemicals due to its rich chemistry and ready availability from carbohydrates.[2] HMF is the dehydration product of hexoses, and is obtained under heating with the assistance of acidic catalysis. Its formation is easier from fructose, but cheaper resources such as glucose, sucrose, cellulose and inulin can also be used. Processes including a first isomerisation step from the hexose to fructose appear to be the most efficient and current industrial processes as its production uses a large collection of acidic catalysts.[2,3]

In recent years, considerable efforts have been devoted to the development of efficient methods for the HMF synthesis and manufacture, and to its conversion to value-added fine chemicals. A wide range of chemicals can be obtained from HMF such as 2,5-diformylfuran,[4] 2,5-furandicarboxylic acid,[5] 2,5-dihydroxymethylfuran[4c,6] and 2,5-bis(aminomethyl) furan,[7] designed notably to be used as monomers. In fine chemistry, complex furan-based molecules or heterocycles have also been prepared, as well as furan opening derivatives such as levulinic acid.[8] In this respect, multicomponent reactions (MCR) represent a powerful synthetic tool allowing the straightforward formation of complex molecules directly from simple starting materials.[9] They have many advantages over stepwise reactions, such as high atom economy, less waste generation and high convergence. However, to our knowledge, the direct utilization of HMF in MCR strategies has been only scarcely explored. The Biginelli reaction, involving aldehydes, C–H acidic carbonyl compounds and urea-type building blocks, has shown its strong vitality since its discovery more than 120 years ago. 3,4-Dihydropyrimidin-2-ones (DHPMs), produced by one-pot condensation, show, for instance, potent anti-viral, anti-tumour, anti-bacterial and anti-inflammatory activities.[10] In addition to the large use of these molecules in medicinal chemistry, DHPMs have also been used as functional polymers.[11] Interestingly, although several pieces of work have reported the use of furfural in Biginelli reactions, none of them included HMF as a potential substrate, likely due to its sensitivity to acidic conditions.[12] However, HMF, with its CH_2OH motif in the target Biginelli products, can offer much more useful and interesting structural content than furfural in such reactions, as this available primary alcohol which is kept intact can be used as a position for further transformation and substitution, essential in strategies related to the applications of DHPMs.

As a continuation of on-going projects on HMF[13] and on widening the scope of its use towards fine chemicals, we investigated the possibility of obtaining Biginelli products directly from HMF, by finding the appropriate reaction conditions among a variety of acidic catalysts, including Brønsted acids[14] (either homogeneous or solid-supported) and mild Lewis acids.[15]

Université de Lyon, INSA Lyon, ICBMS, Equipe Chimie Organique et Bioorganique, UMR 5246 CNRS, Université Lyon 1, CPE Lyon, Bâtiment Jules Verne, 20 Avenue Albert Einstein, F-69621 Villeurbanne Cedex, France.
E-mail: yves.queneau@insa-lyon.fr, florence.popowycz@insa-lyon.fr

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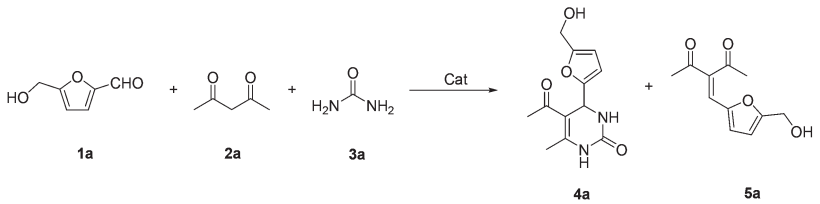
Table 1 Optimization of the Biginelli reaction of HMF[a]



Entry	Catalyst	Solvent	Temperature	Time	^{1}H NMR ratio[b] **1a**/**4a**/**5a**
1	Conc. HCl (2 drops)	EtOH	Reflux	24 h	Messy
2	CF_3COOH (50 μL)	MeCN	Reflux	24h	Messy
3	Amberlyst-15 (50 mg)	EtOH	Reflux	24 h	14/59/27
4	$ZnCl_2$ (20 mol%)	EtOH	Reflux	24 h	6/65/29
5	$ZnCl_2$ (20 mol%)	MeCN	Reflux	24 h	2/77/21
6	$ZnCl_2$ (20 mol%)	Neat	80 °C	4 h	0/94/6
7[c]	$ZnCl_2$ (20 mol%)	Neat	80 °C	4 h	0/88/12
8	$ZnCl_2$ (10 mol%)	Neat	80 °C	4 h	0/87/13
9	$ZnCl_2$ (5 mol%)	Neat	80 °C	4 h	0/84/16
10	$ZnBr_2$ (20 mol%)	Neat	80 °C	4 h	0/93/7
11	$Zn(ClO_4)_2{\cdot}6H_2O$ (20 mol%)	Neat	80 °C	4 h	0/78/22
12	—	Neat	80 °C	4 h	3/55/42

[a] Reaction conditions: The reaction was carried out in the presence of HMF (1 mmol), acetylacetone (1 mmol) and urea (1.5 mmol) under solvent (2.5 mL) or solvent-free conditions, stirred at the corresponding temperature. [b] Conversion and ratio of products were calculated on the basis of ^{1}H NMR analysis. [c] 1 mmol urea was used.

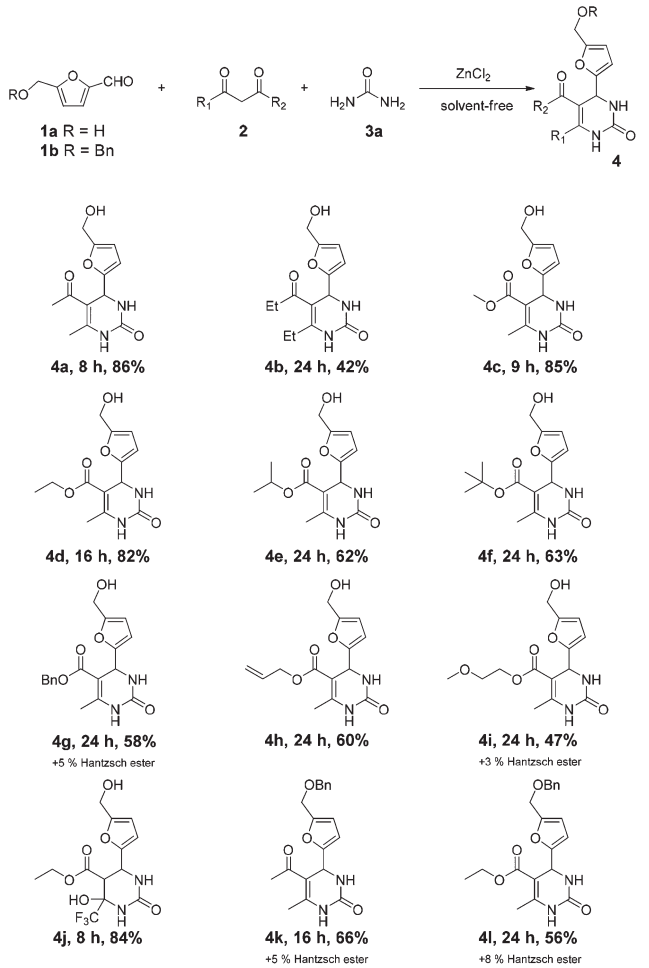
Initial studies focused on the Biginelli reaction of HMF with acetylacetone and urea as partners. Following the seminal work of Pietro Biginelli who used the mineral acid HCl in 1891, we conducted our first experiment by reacting HMF in refluxing ethanol, in the presence of concentrated HCl as a catalyst (two drops). Although HMF was consumed completely after 24 hours, a complex mixture was obtained with no trace of the expected product (Table 1, entry 1). The degradation could be explained by the sensitivity of the furan ring under acidic conditions. The same result was observed when the reaction was performed in the presence of organic trifluoroacetic acid (Table 1, entry 2). In the presence of Amberlyst®15 hydrogen form, a conversion of 86% was obtained by ^{1}H NMR. The Biginelli product was obtained in 59% selectivity along with 27% ratio of the Knoevenagel adduct **5a** between acetylacetone and HMF (Table 1, entry 3).

Doubling the weight of the Amberlyst®15 hydrogen form engaged in the reaction led to a conversion of 90% with a selectivity of 63% in favour of compound **4a** (results are not reported in Table 1 as they are similar to entry 3). The classical Lewis acid $ZnCl_2$ led to 94% conversion of HMF, but 29% of the Knoevenagel adduct was still formed (Table 1, entry 4).

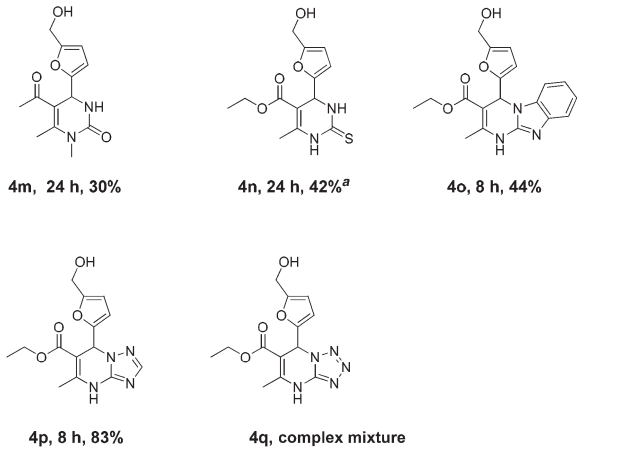
Switching ethanol to acetonitrile slightly improved the conversion of HMF as well as the selectivity in favour of the Biginelli product (Table 1, entry 5). When the reaction was conducted under solvent-free conditions at 80 °C, a complete conversion was observed after 4 hours with an excellent selectivity of 94% of dihydropyrimidinone **4a**. A stoichiometric ratio between the three partners (instead of 1.5 equiv. of urea) led to a modest decrease of the selectivity of product **4a** (Table 1, entry 7). Decreasing the loading of the catalyst (Table 1, entries 8 and 9) has a moderate but perceptible impact on the yield, which encouraged us to go on for the further experiments with a 20% loading of the catalyst. The screening of other zinc salts such as $ZnBr_2$ or $Zn(ClO_4)_2{\cdot}6H_2O$ was performed and they were at best as efficient as zinc chloride (Table 1, entries 10 and 11). It was notable that in the absence of any catalyst, the reaction occurred almost quantitatively (97% conversion), but with a poor selectivity of 55% for compound **4a**, which was not a satisfactory result to free the reaction from any use of an acidic catalyst (Table 1, entry 12).

The substrate scope was next examined under the optimized conditions [*i.e.*, 1 equiv. of HMF, 1 equiv. of dicarbonyl compound, 1.5 equiv. of urea, $ZnCl_2$ (20 mol%), 80 °C, neat]. Depending on the carbonyl substrate, the reaction time was extended to 24 hours to allow the complete conversion. Under the retained conditions, a large diversity of 1,3-diketones and β-keto esters was tolerated (Scheme 1). Acetylacetone afforded the Biginelli product **4a** in 78% yield by simple filtration and aqueous washing. The purification of the filtrate by column chromatography increased the yield to 86% and two other products were identified in negligible quantities: a Knoevenagel product (2%) and a Hantzsch ester (2%). The presence of a Hantzsch ester has already been reported in the literature arising from the dissociation of urea, generating *in situ* NH_3.[16]

Conducting the reaction with heptane-3,5-dione gave **4b** only in 42% yield (and 1% of the Hantzsch ester) after purification by column chromatography, despite 85% yield based on the crude sample by ^{1}H NMR. The drop in the yield could be probably explained by a less efficient reaction (crude NMR, less cleaner) associated with the solubility issues of the final compounds. The best yields were obtained for compounds iso-



Scheme 1 The Biginelli reaction of 5-HMF with 1,3-dicarbonyl compounds. Reaction conditions: The reactions were carried out with HMF or its derivatives (**1**, 2 mmol), 1,3-dicarbonyl compounds (**2**, 2 mmol), urea (**3a**, 3 mmol) and $ZnCl_2$ (20 mol%) under solvent-free conditions, stirred at 80 °C for an indicated time.



Scheme 2 The Biginelli reaction of 5-HMF with urea-like blocks. Reaction conditions: The reactions were carried out with HMF (**1a**, 2 mmol), 1,3-dicarbonyl compounds (**2**, 2 mmol), urea-like building blocks (**3**, 3 mmol) and $ZnCl_2$ (20 mol%) under solvent-free conditions, stirred at 80 °C for an indicated time. [a]At 100 °C.

lated by simple filtration (**4a**, **4c**, **4d**, **4j** and **4p**). All the other compounds required isolation by column chromatography to guarantee a satisfactory purity for all the compounds. Taking into account these parameters, a range of acetoacetates (methyl-, ethyl-, isopropyl-, ^{t}butyl-, benzyl-, allyl- and 2-methoxyethyl acetoacetate) reacted smoothly, yielding the corresponding DHPMs **4c–i** respectively in 85%, 82%, 62%, 63%, 58%, 60% and 47% yield.

In the case of ethyl trifluoroacetoacetate, the intermediate hexahydropyrimidine derivative **4j** was obtained with 84% yield, which was in accordance with the previous reports.[17] Probably, the strong electron-withdrawing group CF_3 inhibits the elimination of H_2O. When HMF was protected by a benzyl ether (**1b**), moderate yields were observed with the use of acetylacetone (66% for **4k**) and ethyl acetoacetate (56% for **4l**). Notably, for some 1,3-dicarbonyl compounds, a trace amount of Hantzsch dihydropyridines was observed after the reaction completion (respectively 5 and 8%), which could slow down the purification procedure and explain the slight decrease in the yield.

The generality of the Biginelli reactions of urea, thiourea and heterocyclic urea derivatives was established next (Scheme 2). *N*-Methylurea yielded N_1-substituted DHPM **4m** as the major product in poor 30% yield, along with a trace amount of N_3-substituted regioisomer. The same range of yields was obtained with thiourea (42% for **4n**) but the reaction required a higher temperature (100 °C instead of 80 °C), probably due to competitive nucleophilic sites. 2-Aminobenzimidazole was tested as an alternative partner, yielding a fused pyrimidine derivative **4o** in 44% yield. Furthermore, 3-amino-1,2,4-triazole afforded the corresponding product in 83% yield (Scheme 2, **4p**). In the case of 5-aminotetrazole, no desired product was obtained. Despite the use of the optimized conditions, the reactions with other ureas led to unsatisfactory results with a serious decrease of the yield of the DHPMs, except for compound **4p**.

As we were conscious of the purification issues, we tried to purify the di-acetylated compound (at OH and C-3 positions) produced for **4b** under standard conditions. The yield obtained for 2 steps was 27%, which was not satisfactory but was consistent with the limitations already observed for the first step.

The mechanism of the Biginelli reaction has been a subject of debate for a long time. In general, there are three major pathways accepted for this reaction, namely iminium,[18] enamine,[19] and Knoevenagel mechanisms.[20] In order to establish which mechanism is the most dominant route in our case, we used NMR spectroscopy to monitor the reaction (Fig. 1). We chose the protons of the furan ring to make a comparison. The protons of the starting material HMF appeared at 7.49 and 6.60 ppm, the signals of Knoevenagel compound **5a** were at 6.94 and 6.51 ppm, and the peaks of Biginelli product **4a** were at 6.17 and 6.03 ppm. It was noticeable that the reaction took place rapidly during the first 30 min, and then slowed down.

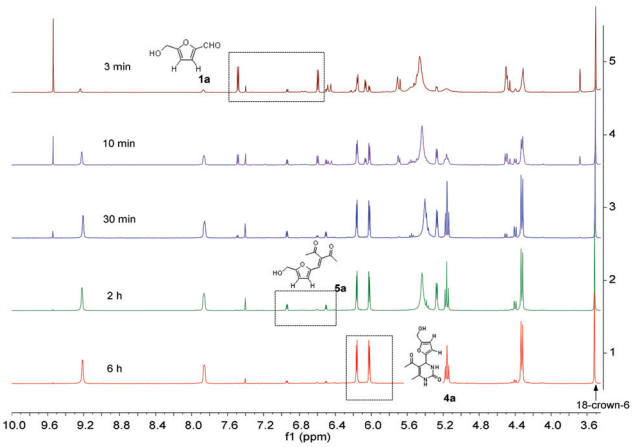
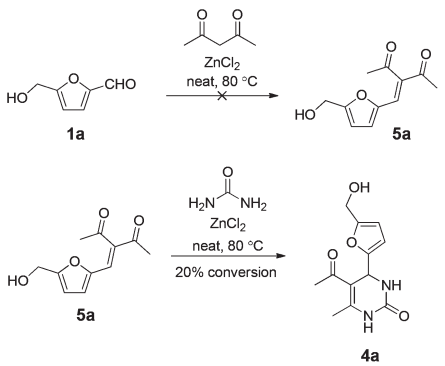


Fig. 1 ^{1}H NMR spectra of the Biginelli reaction of HMF, acetyl acetone and urea.



Scheme 3 Control experiments.

Knoevenagel compound **5a**, which was the sole by-product or intermediate detected by ^{1}H NMR in the reaction, appeared at first, then converted to Biginelli product **4a** slowly. No other intermediate was found in ^{1}H NMR through the reaction. Next, we carried out a couple of experiments, as shown in Scheme 3. When the mixture of HMF and acetyl acetone was subjected to the identified conditions, an unexpected messy result was obtained. In the second control experiment, only 20% prepared Knoevenagel compound **5a** was converted to Biginelli product **4a** in the presence of urea under the identified conditions after 4 h (Scheme 3). According to the experiment results and literature,[18–21] we supposed that the Knoevenagel route might not be the dominant mechanism even though **5a** was the sole intermediate observed during the reaction. Considering these preliminary experiments, we were much more in favour of mixed mechanisms that should require additional experiments.

Conclusions

In summary, we have reported our primary results about the first application of biomass-derived HMF in the multi-component Biginelli reaction. The solvent-free reaction conditions were simple, economical, and environmentally benign. The co-reagents, urea and acetylacetone, have a low environmental fingerprint after an overview of their industrial production.[22] All the DHPM products obtained here were new compounds, which undoubtedly extended the DHPM libraries. The hydroxymethylfuran moiety provides an interesting motif in target DPHMs, providing a much wider scope compared to simpler systems such as those obtained from furfural. Studies on the details of the reaction mechanism are ongoing in our laboratory.

Experimental section

Reagents and solvents were supplied by Aldrich, Acros, Lancaster, Alfa Aesar, Fluka or TCI and purchased at the highest commercial quality to be used without further purification, unless otherwise stated in the procedure. NMR spectra were recorded on a Bruker DRX-300 (^{1}H: 300 or 400 MHz; ^{13}C: 75 or 100 MHz) spectrometer using DMSO-d_6. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on a Bruker MicrOTOF-Q II XL spectrometer using ESI as the ionization source. Analytical thin-layer chromatography was carried out on silica gel Merck 60 D254 (0.25 mm). Flash chromatographies were performed on Merck Si 60 silica gel (40–63 μm).

General procedure

A mixture of HMF (2 mmol), 1,3-dicarbonyl compound (2 mmol), urea-type compound (3 mmol) and $ZnCl_2$ (20 mol%) was stirred at 80 °C in a sealed tube for 8 h to 24 h.

Depending on the substrates, two work-ups were performed after completing the reaction. For the preparation of products **4a**, **4c**, **4d**, **4j** and **4p**, after the addition of water (3 mL) to the reaction vessel, the mixture was stirred and cooled down to 0 °C. The expected product precipitated and was then filtered. The cake was rinsed with cold water (3 mL) and dried overnight giving the Biginelli product. After concentration, the filtrate was purified by column chromatography on silica gel with DCM/MeOH (50 : 1–15 : 1) as the eluent. For the preparation of products **4b**, **4e–4i** and **4k–4o**, the reaction mixture was transferred into a separating funnel with MeOH (3 mL). After the addition of water (50 mL), the mixture was extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with brine (15 mL), dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with DCM/MeOH (50 : 1–15 : 1).

5-Acetyl-4-[5′-(hydroxymethyl)furan-2′-yl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4a). Reaction time: 8 h; global yield: 86% (78% yield after simple filtration + additional 8%

yield after the purification of the filtrate by column chromatography).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (d, 1H, J = 1.2 Hz, H_1), 7.88 (dd, 1H, J = 3.4, 1.2 Hz, H_3), 6.16 (d, 1H, J = 3.1 Hz, $H_{4'}$), 6.03 (d, 1H, J = 3.1 Hz, $H_{3'}$), 5.27 (d, 1H, J = 3.4 Hz, H_4), 5.18 (t, 1H, J = 5.6 Hz, OH), 4.33 (d, 2H, J = 5.6 Hz, CH_2), 2.25 (s, 3H, CH_3-C_6), 2.17 (s, 3H, CH_3CO). ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.9 ($COCH_3$), 155.1, 154.9 ($C_{2'}$, $C_{5'}$), 152.4 (C_2), 149.0 (C_6), 107.7 ($C_{4'}$), 107.1 (C_5), 106.3 ($C_{3'}$), 55.7 (CH_2OH), 47.9 (C_4), 30.0 (CH_3CO), 19.0 (CH_3-C_6). HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{12}H_{14}N_2NaO_4$ 273.0846; found 273.0850.

6-Ethyl-4-[5′-(hydroxymethyl)furan-2′-yl]-5-propionyl-3,4-dihydropyrimidin-2(1*H*)-one (4b). Reaction time: 24 h; global yield: 42% after purification by column chromatography.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (d, 1H, J = 1.8 Hz, H_1), 7.84 (dd, 1H, J = 3.6, 1.8 Hz, H_3), 6.17 (d, 1H, J = 3.1 Hz, $H_{4'}$), 6.02 (d, 1H, J = 3.1 Hz, $H_{3'}$), 5.31 (d, 1H, J = 3.6 Hz, H_4), 5.19 (t, 1H, J = 5.6 Hz, OH), 4.34 (d, 2H, J = 5.5 Hz, CH_2OH), 2.79–2.50 (m, 3H, CH_2, CHCO), 2.31–2.25 (m, 1H, CHCO), 1.10 (t, 3H, J = 7.4 Hz, C_6-CH_2CH_3), 0.88 (t, 3H, J = 7.2 Hz, $COCH_2CH_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.8 ($COCH_2CH_3$), 155.2, 155.1 ($C_{2'}$, $C_{5'}$), 153.9 (C_6), 152.8 (C_2), 107.8 ($C_{4'}$), 106.6 ($C_{3'}$), 105.4 (C_5), 55.9 (CH_2OH), 48.0 (C_4), 33.1 ($COCH_2$), 24.6 (C_6-CH_2), 13.0 (C_6-CH_2CH_3), 8.4 ($COCH_2CH_3$). HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{14}H_{18}N_2NaO_4$ 301.1159; found 301.1164.

Methyl 4-[5′-(hydroxymethyl)furan-2′-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c). Reaction time: 9 h; global yield: 85% after filtration.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.23 (d, 1H, J = 1.3 Hz, H_1), 7.78 (dd, 1H, J = 3.6, 1.3 Hz, H_3), 6.16 (d, 1H, J = 3.1 Hz, $H_{4'}$), 6.00 (d, 1H, J = 3.1 Hz, $H_{3'}$), 5.18–5.13 (m, 2H, H_4 and OH), 4.32 (d, 2H, J = 5.6 Hz, CH_2), 3.57 (s, 3H, OCH_3), 2.24 (s, 3H, C_6-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.5 (CO_2), 155.0, 154.8 ($C_{2'}$, $C_{5'}$), 152.3 (C_2), 149.8 (C_6), 107.7 ($C_{4'}$), 106.0 ($C_{3'}$), 96.4 (C_5), 55.7 (CH_2OH), 50.9 (CO_2CH_3), 47.7 (C_4), 17.8 (C_6-CH_3). HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{12}H_{14}N_2NaO_5$ 289.0795; found 289.0791.

Ethyl 4-[5′-(hydroxymethyl)furan-2′-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d). Reaction time: 16 h; global yield: 82% after filtration.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.20 (s, 1H, H_1), 7.76 (d, 1H, J = 1.2 Hz, H_3), 6.16 (d, 1H, J = 3.1 Hz, $H_{4'}$), 6.00 (d, 1H, J = 3.1 Hz, $H_{3'}$), 5.20–5.12 (m, 2H, H_4 and OH), 4.32 (d, 2H, J = 5.6 Hz, CH_2OH), 4.04 (q, 2H, J = 7.1 Hz, CH_2CH_3), 2.23 (s, 3H, C_6-CH_3), 1.14 (t, 3H, J = 7.1 Hz, CH_2CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.1 (CO_2), 155.2, 154.7 ($C_{2'}$, $C_{5'}$), 152.4 (C_2), 149.4 (C_6), 107.7 ($C_{4'}$), 105.9 ($C_{3'}$), 96.7 (C_5), 59.3 (OCH_2CH_3), 55.7 (CH_2OH), 47.8 (C_4), 17.8 (C_6-CH_3), 14.2 (CH_2CH_3). HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{13}H_{16}N_2NaO_5$ 303.0951; found 303.0951.

Isopropyl 4-[5′-(hydroxymethyl)furan-2′-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e). Reaction time: 24 h; global yield: 62% after purification by column chromatography.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (d, 1H, J = 2.0 Hz, H_1), 7.75 (dd, J = 3.4, 1.8 Hz, 1H, H_3), 6.16 (d, 1H, J = 3.1 Hz, $H_{4'}$), 5.99 (d, 1H, J = 3.1 Hz, $H_{3'}$), 5.18–5.15 (m, 2H, H_4 and OH), 4.93–4.80 (m, 1H, $CH(CH_3)_2$), 4.31 (d, 2H, J = 5.6 Hz, CH_2OH), 2.22 (s, 3H, C_6-CH_3), 1.18 (d, 3H, J = 6.3 Hz, $CH(CH_3)_2$), 1.09 (d, 3H, J = 6.3 Hz, $CH(CH_3)_2$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.6 (CO_2), 155.3 ($C_{2'}$), 154.6 ($C_{5'}$), 152.4 (C_2), 149.1 (C_6), 107.6 ($C_{4'}$), 105.9 ($C_{3'}$), 97.0 (C_5), 66.4 ($CH(CH_3)_2$), 55.7 (CH_2OH), 47.9 (C_4), 21.8 ($CH(CH_3)_2$), 21.6 ($CH(CH_3)_2$), 17.8 (C_6-CH_3). HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{14}H_{18}N_2NaO_5$ 317.1108; found 317.1105.

***t*ert-Butyl 4-[5′-(hydroxymethyl)furan-2′-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f).** Reaction time: 24 h; global yield: 63% after purification by column chromatography.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (d, 1H, J = 1.6 Hz, H_1), 7.70 (dd, 1H, J = 3.3 Hz, 1.6 Hz, H_3), 6.17 (d, 1H, J = 3.1 Hz, $H_{4'}$), 5.98 (d, 1H, J = 3.1 Hz, $H_{3'}$), 5.17 (t, 1H, J = 5.4 Hz, OH), 5.12 (d, 1H, J = 3.3 Hz, H_4), 4.32 (d, 2H, J = 5.4 Hz, CH_2OH), 2.19 (s, 3H, C_6-CH_3), 1.36 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5 (CO_2), 155.5 ($C_{2'}$), 154.6 ($C_{5'}$), 152.4 (C_2), 148.3 (C_6), 107.6 ($C_{4'}$), 105.7 ($C_{3'}$), 98.1 (C_5), 79.2 ($C(CH_3)_3$), 55.8 (CH_2OH), 48.2 (C_4), 27.9 ($C(CH_3)_3$), 17.7 (C_6-CH_3). HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{15}H_{20}N_2NaO_5$ 331.1264; found 331.1274.

Benzyl 4-[5′-(hydroxymethyl)furan-2′-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g). Reaction time: 24 h; global yield: 58% after purification by column chromatography.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.30 (d, 1H, J = 1.2 Hz, H_1), 7.81 (dd, 1H, J = 3.4, 1.2 Hz, H_3), 7.40–7.20 (m, 5H, H_{Ar}), 6.17 (d, 1H, J = 3.1 Hz, $H_{4'}$), 5.98 (d, 1H, J = 3.1 Hz, $H_{3'}$), 5.23 (d, 1H, J = 3.4 Hz, H_4), 5.18 (t, 1H, J = 5.6 Hz, OH), 5.15–5.02 (AB, 2H, $PhCH_2$), 4.33 (d, 2H, J = 5.6 Hz, CH_2OH), 2.27 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.8 (CO_2), 155.1, 154.8 ($C_{2'}$, $C_{5'}$), 152.3 (C_2), 150.3 (C_6), 136.7 ($C_{q,Ar}$), 128.4 (2 CH_{Ar}), 127.7 (CH_{Ar}), 127.5 (2 CH_{Ar}), 107.7 ($C_{4'}$), 106.1 ($C_{3'}$), 96.3 (C_5), 64.9 (CH_2Ph), 55.8 (CH_2OH), 47.8 (C_4), 17.9 (CH_3). HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{18}H_{18}N_2NaO_5$ 365.1108; found 365.1115.

Dibenzyl 4-[5′-(hydroxymethyl)furan-2′-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4g′). 5% yield of Hantzsch product **4g′** was obtained along with Biginelli product **4g**.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.07 (s, 1H, H_1), 7.36–7.26 (m, 10H, H_{Ar}), 6.06 (d, 1H, J = 3.1 Hz, $H_{4'}$), 5.72 (dd, 1H, J = 3.1, 0.7 Hz, $H_{3'}$), 5.21–5.00 (m, 6H, H_4, $2CH_2Ph$ and OH), 4.26 (d, 2H, J = 5.5 Hz, CH_2OH), 2.27 (s, 6H, 2 CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.4 (2 CO_2), 158.0 ($C_{2'}$), 153.7 ($C_{5'}$), 147.1 (C_2, C_6), 136.9 (2 $C_{q,Ar}$), 128.3 (4 CH_{Ar}), 127.6 (2 CH_{Ar}), 127.4 (4 CH_{Ar}), 107.5 ($C_{4'}$), 104.9 ($C_{3'}$), 98.4 (C_3, C_5), 64.7 (2 CH_2Ph), 55.8 (CH_2OH), 32.7 (C_4), 18.3 (2 CH_3). HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{28}H_{27}NNaO_6$ 496.1731; found 496.1709.

Allyl 4-[5′-(hydroxymethyl)furan-2′-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h). Reaction time: 24 h; global yield: 60% after purification by column chromatography.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (d, 1H, J = 2.0 Hz, H_1), 7.82 (dd, 1H, J = 3.8, 2.0 Hz, H_3), 6.16 (d, 1H, J = 3.1 Hz, $H_{4'}$), 6.01 (d, 1H, J = 3.1 Hz, $H_{3'}$), 5.94–5.82 (m, 1H, C$\underline{H}$CH$_2$), 5.26–5.08 (m, 4H, OH, CHC$\underline{H}_2$ and H_4), 4.60–4.46 (m, 2H, OC$\underline{H}_2$CH=CH$_2$), 4.32 (d, 2H, J = 5.7 Hz, C$\underline{H}_2$OH), 2.26 (s, 3H, C_6-C$\underline{H}_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7 (CO_2), 155.1 ($C_{2'}$), 154.8 ($C_{5'}$), 152.3 (C_2), 150.2 (C_6), 133.1 (C$\underline{H}$=CH$_2$), 117.0 (CH=C$\underline{H}_2$), 107.7 ($C_{4'}$), 106.1 ($C_{3'}$), 96.4 (C_5), 63.8 (OC$\underline{H}_2$CH=CH$_2$), 55.8 (C$\underline{H}_2$OH), 47.7 (C_4), 17.9 (C_6-C$\underline{H}_3$). HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{14}H_{16}N_2NaO_5$ 315.0951; found 315.0945.

2-Methoxyethyl-4-[5′-(hydroxymethyl)furan-2′-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4i). Reaction time: 24 h; global yield: 47% after purification by column chromatography.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (d, 1H, J = 2.0 Hz, H_1), 7.79 (dd, 1H, J = 3.6, 2.0 Hz, H_3), 6.17 (d, 1H, J = 3.1 Hz, $H_{4'}$), 6.03 (dd, 1H, J = 3.1, 0.6 Hz, $H_{3'}$), 5.21 (d, 1H, J = 3.6 Hz, H_4), 4.34 (s, 2H, C$\underline{H}_2$OH), 4.14–4.10 (m, 2H, CH$_2$OCO), 3.72–3.39 (m, 2H, CH$_3$OC$\underline{H}_2$), 3.22 (s, 3H, OCH$_3$), 2.25 (s, 3H, C_6-C$\underline{H}_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.2 (CO_2), 155.2, 154.9 ($C_{2'}$ and $C_{5'}$), 152.6 (C_2), 149.9 (C_6), 107.8 ($C_{4'}$), 106.2 ($C_{3'}$), 96.8 (C_5), 70.1 (CH$_3$OC$\underline{H}_2$), 62.6 (C$\underline{H}_2$OCO), 58.2 (OC$\underline{H}_3$), 55.9 (C$\underline{H}_2$OH), 48.0 (C_4), 18.0 (C_6-C$\underline{H}_3$). HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{14}H_{18}N_2NaO_6$ 333.1057; found 333.1051.

Ethyl 4-hydroxy-6-[5′-(hydroxymethyl)furan-2′-yl]-2-oxo-4-(trifluoromethyl)hexahydro pyrimidine-5-carboxylate (4j). Reaction time: 8 h; global yield: 84%; (66% yield after simple filtration + additional 18% yield after the purification of the filtrate by column chromatography).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (s, 1H, H_3), 7.47 (s, 1H, C_4-OH), 7.32 (d, 1H, J = 1.2 Hz, H_1), 6.30 (d, J = 3.2 Hz, 1H, $H_{3'}$), 6.19 (d, J = 3.2 Hz, 1H, $H_{4'}$), 5.24 (t, 1H, J = 5.8 Hz, CH$_2$O$\underline{H}$), 4.86 (d, 1H, J = 11.7 Hz, H_6), 4.33 (d, 2H, J = 5.8 Hz, C$\underline{H}_2$OH), 3.96–3.88 (m, 2H, C$\underline{H}_2$CH$_3$), 3.08 (d, 1H, J = 11.7 Hz, H_5), 0.98 (t, 3H, J = 7.1 Hz, CH$_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.8 (CO_2), 155.6 ($C_{5'}$), 153.3 (C_2), 149.8 ($C_{2'}$), 133.1–116.2 (q, J = 286 Hz, CF_3), 109.3 ($C_{3'}$), 107.4 ($C_{4'}$), 80.3 (q, J = 31 Hz, C_4), 60.5 (C$\underline{H}_2$CH$_3$), 55.6 (C$\underline{H}_2$OH), 48.1 (C_5), 47.1 (C_6), 13.7 (CH$_3$). ^{19}F NMR (282 MHz, DMSO-d_6) δ −80.70. HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{13}H_{15}F_3N_2NaO_6$ 375.0774; found 375.0771.

5-Acetyl-4-[5′-((benzyloxy)methyl)furan-2′-yl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4k). Reaction time: 16 h; global yield: 66% after purification by column chromatography.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (d, 1H, J = 1.8 Hz, H_1), 7.93 (dd, 1H, J = 3.5, 1.8 Hz, H_3), 7.40–7.25 (m, 5H, H_{Ar}), 6.34 (d, 1H, J = 3.1 Hz, $H_{4'}$), 6.08 (d, 1H, J = 3.1 Hz, $H_{3'}$), 5.31 (d, 1H, J = 3.6 Hz, H_4), 4.48 (s, 2H, PhC$\underline{H}_2$), 4.39 (s, 2H, C$\underline{H}_2$OCH$_2$Ph), 2.26 (s, 3H, C_6-C$\underline{H}_3$), 2.18 (s, 3H, COC$\underline{H}_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.8 (C$\underline{O}$CH$_3$), 156.1 ($C_{2'}$), 152.4 (C_2), 151.1 ($C_{5'}$), 149.0 (C_6), 138.1 ($C_{q,Ar}$), 128.3 (2 CH_{Ar}), 127.7 (2 CH_{Ar}), 127.5 (CH_{Ar}), 110.3 ($C_{4'}$), 107.1 (C_5), 106.3 ($C_{3'}$), 71.0 (Ph$\underline{C}H_2$), 63.4 (C$\underline{H}_2$OCH$_2$Ph), 47.9 (C_4), 30.0 (CO$\underline{C}$H$_3$), 19.0 (C_6-C$\underline{H}_3$). HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{19}H_{20}N_2NaO_4$ 363.1315; found 363.1305.

Ethyl 4-[5′-((benzyloxy)methyl)furan-2′-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4l). Reaction time: 24 h; global yield: 56% after purification by column chromatography.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (d, 1H, J = 1.6 Hz, H_1), 7.83 (dd, 1H, J = 3.1 Hz, 1.6 Hz, H_3), 7.40–7.20 (m, 5H, H_{Ar}), 6.34 (d, 1H, J = 3.1 Hz, $H_{4'}$), 6.07 (d, 1H, J = 3.1 Hz, $H_{3'}$), 5.23 (d, 1H, J = 3.1 Hz, H_4), 4.47 (s, 2H, C$\underline{H}_2$Ph), 4.40 (s, 2H, $C_{5'}$-C$\underline{H}_2$), 4.11–3.95 (m, 2H, C$\underline{H}_2$CH$_3$), 2.26 (s, 3H, C_6-C$\underline{H}_3$), 1.13 (t, 3H, J = 7.1 Hz, CH$_2$C$\underline{H}_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1 (CO_2), 156.3 ($C_{2'}$), 152.4 (C_2), 150.9 ($C_{5'}$), 149.5 (C_6), 138.1 ($C_{q,Ar}$), 128.3 (2 CH_{Ar}), 127.7 (2 CH_{Ar}), 127.5 (CH_{Ar}), 110.3 ($C_{4'}$), 106.0 ($C_{3'}$), 96.7 (C_5), 71.0 (C$\underline{H}_2$Ph), 63.4 ($C_{5'}$-C$\underline{H}_2$), 59.3 (C$\underline{H}_2$CH$_3$), 47.9 (C_4), 17.8 (C_6-C$\underline{H}_3$), 14.2 (CH$_2$C$\underline{H}_3$). HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{20}H_{22}N_2NaO_5$ 393.1421; found 393.1435.

Diethyl 4-[5′-((benzyloxy)methyl)furan-2′-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4l′). 8% yield of Hantzsch product **4l′** was obtained along with Biginelli product **4l**.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H, H_1), 7.38–7.24 (m, 5H, H_{Ar}), 6.23 (d, 1H, J = 3.1 Hz, $H_{4'}$), 5.81 (d, 1H, J = 3.1, 1.0 Hz, $H_{3'}$), 5.06 (s, 1H, H_4), 4.43 (s, 2H, PhC$\underline{H}_2$), 4.32 (s, 2H, C$\underline{H}_2$OBn), 4.15–3.95 (m, 4H, OC$\underline{H}_2$CH$_3$), 2.26 (s, 6H, C_6-CH$_3$, C_2-CH$_3$), 1.16 (t, 6H, J = 7.1 Hz, OCH$_2$C$\underline{H}_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.7 (CO_2), 159.3 ($C_{2'}$), 149.8 ($C_{5'}$), 146.44 (C_2, C_6), 138.2 ($C_{q,Ar}$), 128.2 (2 CH_{Ar}), 127.6 (2 CH_{Ar}), 127.5 (CH_{Ar}), 110.2 ($C_{4'}$), 104.7 ($C_{3'}$), 98.5 (C_3, C_5), 70.8 (Ph$\underline{C}$H$_2$), 63.4 (C$\underline{H}_2$OBn), 59.1 (2 C$\underline{H}_2$CH$_3$), 33.0 (C_4), 18.2 (C_2-C$\underline{H}_3$, C_6-C$\underline{H}_3$), 14.3 (2 OCH$_2$C$\underline{H}_3$). HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{25}H_{29}NNaO_6$ 462.1887; found 462.1876.

5-Acetyl-4-[5′-(hydroxymethyl)furan-2′-yl]-1,6-dimethyl-3,4-dihydropyrimidin-2(1*H*)-one (4m). Reaction time: 24 h; global yield: 30% after purification by column chromatography.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.08 (d, 1H, J = 4.2 Hz, H_3), 6.17 (d, 1H, J = 3.1 Hz, $H_{4'}$), 6.05 (dd, 1H, J = 3.1, 0.5 Hz, $H_{3'}$), 5.22 (d, 1H, J = 4.1 Hz, H_4), 5.16 (t, 1H, J = 5.7 Hz, OH), 4.33 (d, 2H, J = 5.6 Hz, C$\underline{H}_2$OH), 3.07 (s, 3H, NCH$_3$), 2.42 (s, 3H, C_6-CH$_3$), 2.19 (s, 3H, COCH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 195.0 (C$\underline{O}$CH$_3$), 155.2, 154.5 ($C_{2'}$ and $C_{5'}$), 153.3 (C_2), 150.5 (C_6), 110.1 (C_5), 107.6 ($C_{4'}$), 106.4 ($C_{3'}$), 55.7 (C$\underline{H}_2$OH), 47.0 (C_4), 30.0 (CO$\underline{C}$H$_3$), 29.8 (NCH$_3$), 16.6 (C_6-C$\underline{H}_3$). HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{13}H_{16}N_2NaO_4$ 287.1002; found 287.0999.

Ethyl 4-[5′-(hydroxymethyl)furan-2′-yl]-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4n). Reaction time: 24 h; global yield: 42% after purification by column chromatography.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H, H_1), 9.65 (s, 1H, H_3), 6.18 (d, 1H, J = 3.0 Hz, $H_{4'}$), 6.05 (d, 1H, J = 3.1 Hz, $H_{3'}$), 5.24–5.17 (m, 2H, H_4 and OH), 4.33 (d, 2H, J = 5.5 Hz, C$\underline{H}_2$OH), 4.10–3.98 (m, 2H, C$\underline{H}_2$CH$_3$), 2.29 (s, 3H, C_6-C$\underline{H}_3$), 1.13 (t, 3H, J = 7.1 Hz, CH$_2$C$\underline{H}_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.9 (C_2), 164.9 (CO_2), 155.3 ($C_{5'}$), 153.9 ($C_{2'}$), 146.2 (C_6), 107.9 ($C_{4'}$), 107.1 ($C_{3'}$), 98.3 (C_5), 59.8 (C$\underline{H}_2$CH$_3$), 55.8 (C$\underline{H}_2$OH), 47.9 (C_4), 17.3 (C_6-C$\underline{H}_3$), 14.2 (CH$_2$C$\underline{H}_3$). HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{13}H_{16}N_2NaO_4S$ 319.0723; found 319.0729.

Ethyl 4-[5′-(hydroxymethyl)furan-2′-yl]-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (4o). Reaction time: 8 h; global yield: 44% after purification by column chromatography.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H, H_1), 7.46–7.42 (m, 1H, H_9), 7.39–7.34 (m, 1H, H_6), 7.11–7.00 (m, 2H, H_7, H_8), 6.53 (d, 1H, J = 0.8 Hz, H_4), 6.38 (d, 1H, J = 3.2 Hz, $H_{3'}$), 6.14 (d, 1H, J = 3.1 Hz, $H_{4'}$), 5.11 (t, 1H, J = 5.7 Hz, $CH_2O\underline{H}$), 4.20 (d, 2H, J = 5.7 Hz, $C\underline{H}_2OH$), 4.14–3.98 (m, 2H, $C\underline{H}_2CH_3$), 2.46 (s, 3H, C_2-$C\underline{H}_3$), 1.17 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1 (CO_2), 155.1 ($C_{5'}$), 151.9 ($C_{2'}$), 147.7 (C_2), 145.5 (C_{10a}), 142.2 (C_{9a}), 131.6 (C_{5a}), 121.9 (C_8), 120.2 (C_7), 116.8 (C_6), 109.8 (C_9), 108.4 ($C_{3'}$), 107.6 ($C_{4'}$), 94.3 (C_3), 59.4 ($\underline{C}H_2CH_3$), 55.6 ($\underline{C}H_2OH$), 49.4 (C_4), 18.8 (C_2-$\underline{C}H_3$), 14.1 ($CH_2\underline{C}H_3$). HRMS (ESI) *m*/*z*: calcd for $[M + H]^+$ $C_{19}H_{20}N_3O_4$ 354.1448; found 354.1445.

Ethyl 7-[5′-(hydroxymethyl)furan-2′-yl]-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (4p). Reaction time: 8 h; global yield: 83% after filtration.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.84 (s, 1H, H_4), 7.70 (s, 1H, H_2), 6.34 (s, 1H, H_7), 6.22 (d, 1H, J = 3.2 Hz, $H_{3'}$ or $H_{4'}$), 6.17 (d, 1H, J = 3.2 Hz, $H_{3'}$ or $H_{4'}$), 5.16 (t, 1H, J = 5.8 Hz, OH), 4.26 (d, 2H, J = 5.8 Hz, $C\underline{H}_2OH$), 4.10–3.92 (m, 2H, $C\underline{H}_2CH_3$), 2.40 (s, 3H, C_5-$C\underline{H}_3$), 1.11 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.0 (CO_2), 155.2 ($C_{5'}$), 152.6 ($C_{2'}$), 150.1 (C_2), 147.4 (C_5), 147.1 (C_{3a}), 108.1 ($C_{3'}$ or $C_{4'}$), 107.8 ($C_{3'}$ or $C_{4'}$), 94.6 (C_6), 59.5 ($\underline{C}H_2CH_3$), 55.6 ($\underline{C}H_2OH$), 53.1 (C_7), 18.5 (C_5-$\underline{C}H_3$), 14.0 ($CH_2\underline{C}H_3$). HRMS (ESI) *m*/*z*: calcd for $[M + H]^+$ $C_{14}H_{17}N_4O_4$ 305.1244; found 305.1244.

Conflicts of interest

There are no conflicts to declare.

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