Green Microwave-assisted Multicomponent Route to the Formation of 5,8-Dihydropyrido[2,3-*d*]pyrimidine Skeleton in Aqueous Media

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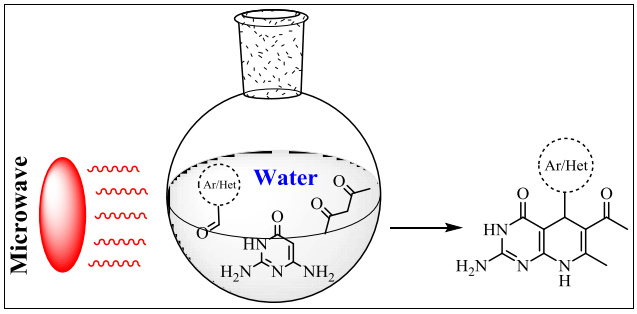


Three-component synthesis of 5-substituted 6-acetyl-2-amino-7-methyl-5,8-dihydropyrido[2,3-*d*]pyrimidines was brought to facile energy-efficient and environmental-friendly conditions using multicomponent reaction, microwave field as an activation method and hot water as a solvent. A series of the target compounds was synthesized using the developed procedure.

INTRODUCTION

The search and efficient synthesis of bioactive organic compounds is now one of the major priorities in modern medicinal-orientated chemistry because it may help with the treatment of diseases like tuberculosis, diabetes, cancer, AIDS, and other disastrous illnesses. However, one of the most serious problems of the synthesis of pharmaceuticals is its controversy with the principles of green chemistry, which makes pharmacological industry a top waster [1].

The problem of reducing of waste amount is widely discussed in many branches of modern science. Green chemistry, being one of these branches, is known not for methods of utilization of wastes but, first of all, for its benefits in preventing of waste generation and energy economy. The principles of green chemistry [2] lead us to several important ways of industry development, such as using of minimum amount of solvents and auxiliary substances (except for biosolvents, easily utilized by living organisms – water, ethanol, acetic acid, and so on), discovering new ways of syntheses (optimization of amounts of process steps, using alternative methods of reaction activation), and involving of renewable reagents (biomass recycling, development of bioengineering).

Multicomponent reactions have many benefits, such as step [3] and atom economy [4,5], low E-factor [6], high diversity and combinatorial capacity [6], and so on; therefore, they have become widely used in the latest few decades in the field of organic synthesis [7] and in many cases have already proven their advantage over sequential reactions. On the other hand, along with the common-used thermal heating non-classical methods of activation, such as microwave irradiation or ultrasonication, become popular that may also be used in the synthesis of various nitrogen-containing heterocycles [8–11].

In general, synthesis of nitrogen-containing heterocycles has gained much interest because the first methods had been discovered. One of the reasons of such level of interest is highly possible biological activity of this type of compounds. Pyrido[2,3-*d*]pyrimidines, being one of the classes of bioactive heterocycles, are in the field of attention as well. These fused heterocycles are known to show positive biological activity against various types of disease agents, that is bacteria [12,13] and fungi [13,14]. Derivatives of pyrido[2,3-*d*]pyrimidines can be used for inhibition of HIF prolyl hydroxylase [15] and as for treating cancer [16,17], leishmaniasis [18], can be effective antagonists of calcium channel [19] and CCR4 [20], tyrosine kinase inhibitors [21]. Due to all these indisputably important qualities, there are many synthetic methods to obtain these heterocyclic compounds using different reagents [15,20,22–28].

One of the most popular methods of synthesis of pyrido [2,3-*d*]pyrimidine is base on three-component reaction involving non-cyclic carbonyl-containing CH-acids, derivatives of 6-aminouracile and different aldehydes [27,28]. Nevertheless, there is no procedure for obtaining compounds of this class in high yields under green conditions because the known methods involve hazardous or poisonous solvents, require high temperatures or long time ranges or both. Moreover, some of the procedures published earlier turned up to be irreproducible. At the same time, similar products are obtained in "green" conditions using cyclic CH-acids like derivatives of cyclohexan-1,3-dione in high yields [26,29].

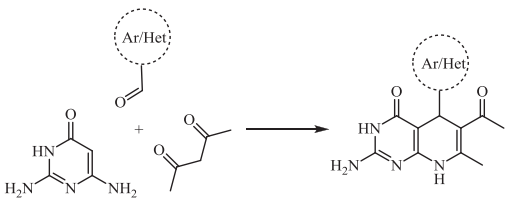
The main goal of our work was to elaborate efficient green conditions for the three-component reaction of 2,6-diaminopyrimido-2,4(1H,3H)-dione, acetylacetone, and substituted aromatic aldehydes to obtain 5-substituted-6-acetyl-2-amino-5,8-dihydro-7-methylpyrido[2,3-*d*]-4(3H)-ones (Scheme 1).

RESULTS AND DISCUSSIONS

Initially, the three-component treatment between 2,6-diaminouracil **1**, 4-methoxybenzaldehyde **2a,** and acetylacetone **3** was selected as model one to find and optimize the most suitable reaction conditions (Table 1). Firstly, to reduce the reaction time, we followed Van't Hoff's rule and chose high-boiling solvents, such as dimethyl sulfoxide (DMSO), *N*-methyl-2-pyrrolidone, polyethylene glycol (PEG-300), dimethylformamide, and so on.

Entries 1 and 2 show that an excess of volatile reagents is needed because their vaporization during the process. Increasing the temperature with application of microwave irradiation ended with no positive result at any process time even after consequent heating (Entries 3–11). Only prolonged heating of initial mixture of the reagents in dimethylformamide resulted in 43% yield of **4a** (Entry 12). The probable reasons of such results are degradation of DMSO at high temperatures, interactions of solvent's molecules with reagents, and non-compatible physical parameters of the media with the reaction flow. However, most of the solvents used in Entries 1–12 do not obtain along with the principles of green chemistry, because they are hazardous, carcinogenic and can hardly be utilized. To satisfy these principles, we proceeded to carry out the reaction studied in such solvents as alcohols and water with the use of catalysts.

Scheme 1. The reaction studied.



Rare-earth metals(III) salts proved their efficiency in multicomponent reactions in non-aqueous media [30], while cetyltrimethylammonium bromide (CTAB) – vitamin B_1 (VB_1) couple was used in water [31]. Nevertheless, application of $Sc(OTf)_3$ (10 mol%) in 1-butanol (BuOH) showed poor results using both conventional and microwave irradiation heating (Entries 13 and 14). Finally, the moderate yield of **4a** was observed after 8-hours heating in boiling water (Entry 15) with additives of CTAB and VB_1 (10 mol% of both).

Then, it was found (Entries 16–22) that the maximum yield of the target heterocycle was observed after 4 hours heating (68%, Entry 16). The ratio of reagents sometimes neglected the principle of atom economy for multicomponent reactions and, therefore, experiments to minimize consumption of substances were carried out as well. The most preferable combination of yield and reagents expense took place when the ratio of reagents **1**:**2a**:**3** equaled to 1:1:2 (mol.). The excess of reagents in different entries can be explained by the evaporation of the liquid initial substances used.

In order to check whether catalysts are surely essential for the efficient proceeding the process, a series of experiments was carried out that showed, surprisingly, that, indeed, in contrast to earlier described data for similar reactions [31,32], the presence of B_1 decreases product yield (Entry 23), while CTAB does not affect it at all (Entry 24).

Further, in chase of reducing process time, microwave irradiation as a source of energy was used instead of the conventional heating. Temperature, time, and ratio of the reagents were the optimized parameters (Entries 25–33). As it was noted, the excess of reagents was added because their evaporation; therefore, the microwave-assisted syntheses firstly were carried out with equimolar ratio of reagents (Entries 25–30). But after doubling the acetylacetone **3** quantity, higher yields were observed.

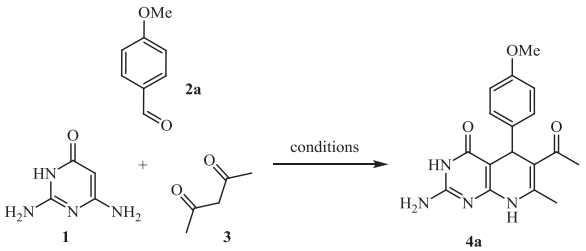
Finally, the experiments showed that the best conditions of the multicomponent reaction studied were heating of the starting materials **1**, **2a,** and **3** in 1:1:2 ratios in microwave field in water without any catalyst for 10 min at 180°C. However, the ^{1}H NMR spectra in all cases contains signals of impurities (up to ~5 mol%) caused by the presence of initial benzaldehyde and 2,6-diaminouracil that were removed by the use of saturated $NaHSO_3$ solution as a purifying agent (Entry 34).

Having optimized reaction conditions on the asset side, a series of experiments was carried out to estimate the scope and limitations of this multicomponent reaction with different aryl and hetaryl aldehydes (Table 2).

It can be seen that higher yields are observed in the cases of aldehydes containing electron-withdrawing substituents (–M and –I effects, compounds **4c**,**d**,**l**, and so on). On the other hand, surprisingly, the presence of *o*-substituents in

Table 1

Optimization of the reaction conditions.



Entry	Ratio **1**:**2a**:**3**	Conditions	Solvent	Catalyst	Yield
1	1:1:1	8 h 110°C	DMSO	None	Trace
2	1:2:2	8 h 110°C	DMSO	None	80%
3	1:2:2	1 h MW 150°C	DMSO	None	None
4	1:2:2	2 h MW 150°C	DMSO	None	Trace
5	1:2:2	(2 h MW + 8 h heating) 140°C	DMSO	None	Trace
6	1:2:2	8 h 140°C	NMP	None	None
7	1:2:2	10 h 140°C	$MeNO_2$	None	None
8	1:2:15	10 h 140°C	Acetylacetone	None	Trace
10	1:2:3	8 h 200°C	PEG-300	None	None
11	1:2:2	8 h 140°C	DMF	None	Trace
12	1:2:2	10 h 140°C	DMF	None	43%
13	1:2:3	1 h MW 200°C	BuOH	$Sc(OTf)_3$	None
14	1:2:3	8 h 120°C	BuOH	$Sc(OTf)_3$	None
15	1:2:3	8 h 100°C	Water	CTAB, VB_1	41%
16	1:2:3	4 h 100°C	Water	CTAB, VB_1	68%
17	1:2:3	2 h 100°C	Water	CTAB, VB_1	39%
18	1:2:3	1 h 100°C	Water	CTAB, VB_1	33%
19	1:2:3	0.5 h 100°C	Water	CTAB, VB_1	21%
20	1:2:2	4 h 100°C	Water	CTAB, VB_1	Trace
21	1:1:3	4 h 100°C	Water	CTAB, VB_1	48%
22	1:1:2	4 h 100°C	Water	CTAB, VB_1	55%
23	1:1:2	4 h 100°C	Water	CTAB	68%
24	1:1:2	4 h 100°C	Water	None	69%
25	1:1:1	1 h MW 150°C	Water	None	67%
26	1:1:1	30 min MW 180°C	Water	None	53%
27	1:1:1	15 min MW 180°C	Water	None	56%
28	1:1:1	10 min MW 180°C	Water	None	63%
29	1:1:1	5 min MW 180°C	Water	None	38%
30	1:1:1	5 min MW 200°C	Water	None	56%
31	1:1:2	2 h MW 150°C	Water	CTAB, VB_1	57%
32	1:1:2	1 h MW 180°C	Water	CTAB, VB_1	62%
33	1:1:2	10 min MW 180°C	Water	None	71%
34	1:1:2	10 min MW 180°C	Water[a]	None	66%

[a]purification by $NaHSO_3$ solution.

initial benzaldehydes **2a-s** increases yield as well (comparing yields of **4f** and **4 l**, also **4a**, **4 m,** and **4o**). The reaction of 2,6-diamonouracil **1** (2 eq.), acetylacetone **3** (2 eq.) and teraphtalaldehyde **2p** (1 eq.) resulted in a mixture of mono-(**4p'**) and bis-(6-acetyl-2-amino-7-methyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-4(*3H*)-one-5-yl) (**4p**) products with molar ratio 1:1.

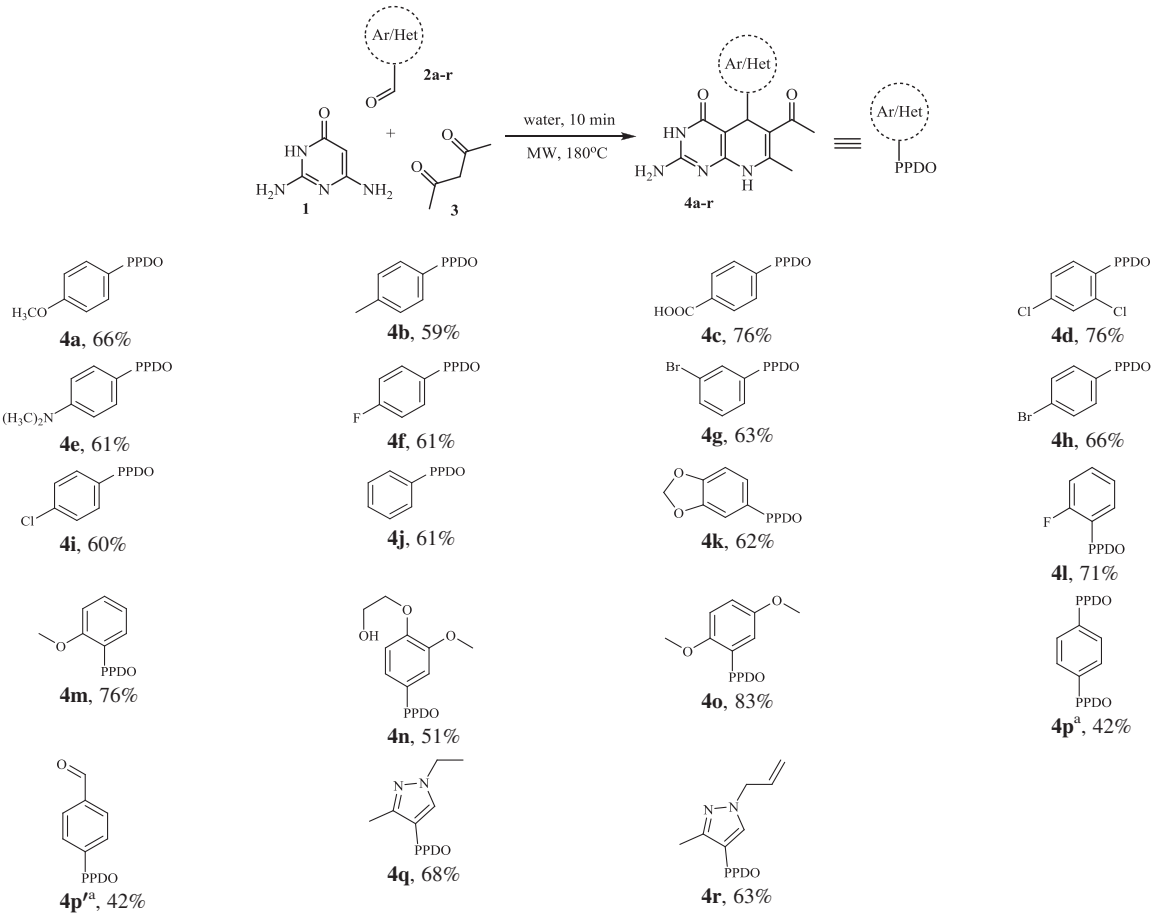
We also managed to repeat the experiment of Tu *et al.* [25] but, unfortunately, under the same conditions as stated in their study, we did not observe the results of claimed effectiveness. The most probable reason is instrumental: it gives us the right to presume that the reaction carried out by our method using other equipment could lead to even higher results that the authors of the article [25] report (Table 3).

CONCLUSION

In summary, we have developed a microwave-assisted method for one-pot synthesis of pyrido[2,3-*d*]pyrimidine derivatives using multicomponent reaction between 2,6-

Table 2

Microwave irradiation synthesis of 5-substituted-6-acetyl-2-amino-5,8-dihydro-7-methylpyrido[2,3-*d*]pyrimidin-4(*3H*)-ones **4**.



[a]compounds **4p** and **4p′** were obtained in a single experiment.

diaminouracil, acetylacetone, and various aromatic and heteroaromatic aldehydes. The procedure elaborated is reproducible with application of wide range of the starting materials and allows moderate-to-good yields of final heterocyclic compounds with a profit in atom economy, small waste amount, short reaction time and minimum use of water as a green solvent. Microwaves assisting also gives an advantage in energy consumption towards common heating [33,34]. All these aspects can be the reasons for further development of this method due to its friendliness to the environment. A huge variety of similar compounds can be also synthesized by this very method using other derivatives of uracil and different CH-acids, for instance, barbituric acid, cyclic 1,3-diketones, malonic dinitrile and so on, and possibly other heterocycles.

Table 3

Comparison of the developed and existing methods.

Entry	Aldehyde	Stated yield (%) [25]	Reproduced yield (%)	Our method yield (%)
1	**2a**	92	55	66
2	**2i**	95	45	60
3	**2d**	90	58	76

EXPERIMENTAL

General information. 2,6-Diaminouracil was synthesized from guanidinium chloride and ethyl cyanoacetate using procedure shown later. Guanidinium chloride, ethyl cyanoacetate, aromatic aldehydes and acetylacetone, solvents, catalysts, and inorganic compounds were obtained from commercial suppliers and were used without further purification. ^{1}H NMR spectra were recorded at 200 MHz on a Varian Mercury VX-200 instrument, ^{13}C NMR – at 126 MHz on a Bruker Avance spectrometer. Mass spectra were recorded on Varian 1200 L Mass Spectrometer (direct input, EI, 70 eV). LC-MS analysis

data were obtained with the use of Agilent 1100 instrument (ES-API). Microwave experiments were performed using the EmrysTM Creator EXP from Biotage AB (Uppsala, Sweden) possessing a single-mode microwave cavity (2.45 GHz). Elemental analysis was realized on EuroVector EA-3000 (samples for elemental analysis were additionally dried in vacuo).

Typical procedure for synthesis of 2,6-diaminouracil (1). Guanidinium chloride (4.5 g, 47 m*M*) and ethyl cyanoacetate (5 mL, 5.3 g, 47 m*M*) were added to a solution of sodium methylate in methanol obtained by adding of solid sodium (2.4 g, 104 m*M*) to 50 mL of methanol. The mixture was refluxed for 4 h, and then 50 mL of warm water were added to solve the precipitate. Methanol was removed in vacuo and after cooling to room temperature 6 mL of glacial acetic acid were added. The gold-yellow substance precipitated was filtered off and dried in the air. The method stated is modified comparing to the method of VanAllan *et al.* [35].

General procedure for the synthesis of 6-acetyl-2-amino-5-aryl-5,8-dihydro-7-methylpyrido[2,3-*d*]pyrimidin-4(*3H*)-ones (4). In a microwave reaction vial (maximum reaction volume 5 mL) 2,6-diaminouracil **1** (0.200 g, 1.59 m*M*), acetylacetone **3** (0.34 mL, 0.318 g, 3.18 m*M*) and corresponding aldehyde **2** (1.59 m*M*) were mixed in 3 mL of H_2O. The vial was capped, and the reaction mixture was irradiated at 180°C for 10 min (with fixed hold time option). Then, 1 mL of saturated $NaHSO_3$ solution was added to the vial (without isolation of the product), and the mixture was irradiated by microwaves at 95°C for additional 5 min. The precipitate formed was filtered off, washed with 10 mL of hot water, and dried in the air.

2,6-Diaminouracil (1). Yield 5.28 g (83%); mp: 262°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 4.43 (s, 1H, CH), 5.93 (s, 2H, 6-NH_2), 6.18 (s, 2H, 2-NH_2), 9.77 (s, 1H, 3-NH).

6-Acetyl-2-amino-5-(4′-methoxyphenyl)-7-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one (4a). Yield 66% as pale yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 1.99 (s, 3H, CH_3), 2.29 (s, 3H, CH_3CO), 3.65 (s, 3H, OCH_3), 4.81 (s, 1H, CH), 6.23 (s, 2H, NH_2), 6.75 (d, J = 8.4 Hz, 2H, ArH), 7.11 (d, J = 8.4 Hz, 2H, ArH), 9.02 (s, 1H, 8-NH), 10.33 (s, 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 19.35, 29.82, 36.32, 54.96, 92.17, 110.51, 113.44 (2C), 128.26 (2C), 139.74, 146.64, 153.30, 154.00, 157.50, 161.60, 196.78. MS for $C_{17}H_{18}N_4O_3$, *m/z*: 326 (M^+). LC-MS analysis data: max peak 93.46% at 0.885 min. *Anal.* Calcd for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.88; H, 5.64; N, 17.12.

6-Acetyl-2-amino-7-methyl-5-(p-tolyl)-5,8-dihydro-pyrido[2,3-d]pyrimidin-4(3H)-one (4b). Yield 59% as pale yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 1.99 (s, 3H, CH_3), 2.18 (s, 3H, CH_3CO), 2.29 (s, 3H, Ar-CH_3), 4.83 (s, 1H, CH), 6.23 (s, 2H, NH_2), 6.96 (d, J = 7.9 Hz, 2H, ArH), 7.11 (d, J = 7.8 Hz, 2H, ArH), 9.02 (s, 1H, 8-NH), 10.32 (s, 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 19.27, 20.57, 29.79, 36.68, 91.90, 110.28, 127.12, 128.54, 134.72, 141.97, 144.47, 146.68, 153.27, 153.93, 161.41, 196.59. MS for $C_{17}H_{18}N_4O_2$, *m/z*: 310 (M^+). *Anal.* Calcd for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.52; H, 5.78; N, 17.91.

6-Acetyl-2-amino-5-(4′-carboxyphenyl)-7-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one (4c). Yield 76% as red solid; mp: over 300 °C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 2.02 (s, 3H, CH_3), 2.32 (s, 3H, CH_3CO), 4.95 (s, 1H, CH), 6.37 (s, 2H, NH_2), 7.31 (d, J = 8.3 Hz, 2H, ArH), 7.78 (d, J = 8.2 Hz, 2H, ArH), 9.14 (s, 1H, 8-NH), 10.53 (br.s, 1H, COOH and 1H, 3-NH),. ^{13}C NMR (126 MHz, DMSO) δ (ppm): 19.47, 30.16, 37.30, 91.11, 110.17, 127.43 (2C), 128.59, 129.30 (2C), 147.43, 152.23, 153.66, 154.24, 161.52, 167.41, 196.26. MS for $C_{17}H_{16}N_4O_4$, *m/z*: 340 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_4O_4$: C, 60.00; H, 4.74; N, 16.46. Found: C, 60.25; H, 4.79; N, 16.62.

6-Acetyl-2-amino-5-(2′,4′-dichlorophenyl)-7-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one (4d). Yield 76% as orange solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 2.05 (s, 3H, CH_3), 2.21 (s, 3H, CH_3CO), 5.20 (s, 1H, CH), 6.33 (s, 2H, NH_2), 7.26 (s, 2H, ArH), 7.33 (s, 1-H, ArH), 9.10 (s, 1H, 8-NH), 10.32 (s, 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 19.38, 30.29, 35.90, 90.74, 110.79, 127.23, 128.36, 130.91, 132.49, 132.95, 144.23, 146.26, 153.78, 154.30, 161.25, 196.71. MS for $C_{16}H_{14}Cl_2N_4O_2$, *m/z*: 364, 366, 365 (M^+). *Anal.* Calcd for $C_{16}H_{14}Cl_2N_4O_2$: C, 52.62; H, 3.86; N, 15.34. Found: C, 52.21; H, 3.78; N, 14.99.

6-Acetyl-2-amino-5-(4′-(N,N-dimethylamino)phenyl)-7-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one (4e). Yield 61% as pale orange solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 1.99 (s, 3H, CH_3), 2.28 (s, 3H, CH_3CO), 2.78 (s, 6H, N-CH_3), 4.74 (s, 1H, CH), 6.22 (s, 2H, NH_2), 6.56 (d, J = 8.7 Hz, 2H, Ar-H), 7.02 (d, J = 8.6 Hz, 2H, ArH), 8.97 (s, 1H, 8-NH), 10.35 (s, 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 19.29, 29.68, 36.16, 40.40 (2C), 110.48, 112.40 (2C), 127.82 (2C), 131.59, 135.76, 146.23, 148.91, 153.07, 153.86, 161.54. MS for $C_{18}H_{21}N_5O_2$, *m/z*: 339 (M^+). *Anal.* Calcd for $C_{18}H_{21}N_5O_2$: C, 63.70; H, 6.24; N, 20.64. Found: C, 64.01; H, 6.27; N, 20.82.

6-Acetyl-2-amino-5-(4′-fluorophenyl)-7-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one (4f). Yield 61% as pale yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 2.02 (s, 3H, CH_3), 2.31 (s, 3H, CH_3CO), 4.91 (s, 1H, CH), 6.26 (s, 2H, NH_2), 6.99 (t, J = 8.9 Hz, 2H, ArH), 7.23 (t, J = 8.8 Hz, 2H, ArH), 9.02 (s, 1H, 8-NH), 10.39 (br.s, 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 19.40, 30.03, 36.43, 91.70, 110.38, 114.57, 114.73, 128.94, 129.00, 143.62, 147.11, 153.42, 154.11, 159.62, 161.48, 196.40. MS for $C_{16}H_{15}FN_4O_2$,

m/z: 314 (M^+). *Anal.* Calcd for $C_{16}H_{15}FN_4O_2$: C, 61.14; H, 4.81; N, 17.83. Found: C, 61.33; H, 4.75; N, 17.65.

6-Acetyl-2-amino-5-(3′-bromophenyl)-7-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one (4g). Yield 63% as pale yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 2.05 (s, 3H, CH_3), 2.32 (s, 3H, CH_3CO), 4.90 (s, 1H, CH), 6.30 (s, 2H, NH_2), 7.27 (m, 4H, ArH), 9.10 (s, 1H, 8-NH) 10.36 (s, 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 19.46, 30.25, 36.95, 91.16, 110.12, 121.40, 126.28, 128.76, 129.92, 130.38, 147.52, 150.14, 153.59, 154.22, 161.43, 196.12. MS for $C_{16}H_{15}BrN_4O_2$, *m/z*: 374, 376 (M^+). *Anal.* Calcd for $C_{16}H_{15}BrN_4O_2$: C, 51.22; H, 4.03; N, 14.93. Found: C, 51.01; H, 4.07; N, 15.02.

6-Acetyl-2-amino-5-(4′-bromophenyl)-7-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one (4h). Yield 66% as pale yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 2.02 (s, 3H, CH_3), 2.30 (s, 3H, CH_3CO), 4.88 (s, 1H, CH), 6.30 (s, 2H, NH_2), 7.16 (d, $J = 8.3$ Hz, 2H, ArH), 7.38 (d, $J = 8.3$ Hz, 2H, ArH), 9.11 (s, 1H, 8-NH), 10.41 (s, 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 19.44, 30.11, 36.73, 91.30, 110.16, 118.89, 129.54 (2C), 130.90 (2C), 146.76, 147.30, 153.52, 154.17, 161.50, 196.27. MS for $C_{16}H_{15}BrN_4O_2$, *m/z*: 374, 376 (M^+). *Anal.* Calcd for $C_{16}H_{15}BrN_4O_2$: C, 51.22; H, 4.03; N, 14.93. Found: C, 51.50; H, 4.09; N, 15.08.

6-Acetyl-2-amino-5-(4′-chlorophenyl)-7-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one (4i). Yield 60% as pale yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 2.02 (s, 3H, CH_3), 2.31 (s, 3H, CH_3CO), 4.90 (s, 1H, CH), 6.25 (s, 2H, NH_2), 7.23 (s, 4H, ArH), 9.07 (s, 1H, 8-NH), 10.34 (s, 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 19.44, 30.09, 36.65, 91.38, 110.20, 127.98 (2C), 129.11 (2C), 130.39, 146.35, 147.30, 153.51, 154.17, 161.48, 196.28. MS for $C_{16}H_{15}ClN_4O_2$, *m/z*: 330, 332 (M^+). *Anal.* Calcd for $C_{16}H_{15}ClN_4O_2$: C, 58.10; H, 4.57; N, 16.94. Found: C, 58.16; H, 4.70; N, 17.00.

6-Acetyl-2-amino-7-methyl-5-phenyl-5,8-dihydro-pyrido[2,3-d]pyrimidin-4(3H)-one (4j). Yield 61% as pale yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 2.01 (s, 3H, CH_3), 2.31 (s, 3H, CH_3CO), 4.89 (s, 1H, CH), 6.27 (s, 2H, NH_2), 7.21 (m, 5H, ArH), 9.06 (s, 1H, 8-NH), 10.36 (br.s., 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 19.36, 29.96, 37.14, 91.80, 110.34, 125.87, 127.29 (2C), 128.05 (2C), 146.96, 147.46, 153.44, 154.06, 161.47, 196.53. MS for $C_{16}H_{16}N_4O_2$, *m/z*: 296 (M^+). *Anal.* Calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.40; H, 5.40; N, 19.08.

6-Acetyl-2-amino-7-methyl-5-(benzo[d][1,3]dioxol-5-yl)-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one (4k). Yield 62% as pale yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 2.02 (s, 3H, CH_3), 2.30 (s, 3H, CH_3CO), 4.83 (s, 1H, CH), 5.90 (s, 2H, CH_2), 6.28 (s, 2H, NH_2), 6.71 (m, 3H, ArH), 9.05 (s, 1H, 8-NH), 10.37 (s, 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 19.34, 29.88, 36.78, 91.93, 100.65, 107.80, 107.84, 110.27, 119.94, 141.60, 145.34, 146.86, 146.96, 153.31, 154.01, 161.53, 196.64. MS for $C_{17}H_{16}N_4O_4$, *m/z*: 340 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_4O_4$: C, 60.00; H, 4.74; N, 16.46. Found: C, 59.59; H, 4.64; N, 16.76.

6-Acetyl-2-amino-5-(2′-fluorophenyl)-7-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one (4l). Yield 71% as pale yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 2.05 (s, 3H, CH_3), 2.23 (s, 3H, CH_3CO), 5.10 (s, 1H, CH), 6.30 (s, 2H, NH_2), 7.06 (m, 4H, ArH), 9.07 (s, 1H, 8-NH), 10.35 (s, 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 19.36, 29.69, 32.04, 90.67, 110.32, 114.99, 115.17, 124.21, 127.75, 130.79, 134.55, 146.32, 153.77, 154.24, 161.30, 196.61. MS for $C_{16}H_{15}FN_4O_2$, *m/z*: 314 (M^+). *Anal.* Calcd for $C_{16}H_{15}FN_4O_2$: C, 61.14; H, 4.81; N, 17.83. Found: C, 61.01; H, 4.74; N, 18.02.

6-Acetyl-2-amino-7-methyl-5-(2′-methoxyphenyl)-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one (4m). Yield 76% as pale yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 2.08 (s, 3H, CH_3), 2.10 (s, 3H, CH_3CO), 3.71 (s, 3H, OCH_3), 5.15 (s, 1H, CH), 6.22 (m, 2H, NH_2), 6.95 (m, 4H, ArH), 8.90 (s, 1H, 8-NH), 10.21 (s, 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 18.74, 29.17, 32.23, 55.59, 90.71, 111.31, 111.60, 120.49, 127.15, 129.47, 135.92, 143.76, 154.01, 154.38, 155.92, 161.31, 198.13. MS for $C_{17}H_{18}N_4O_3$, *m/z*: 326 (M^+). *Anal.* Calcd for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.42; H, 5.66; N, 17.02.

6-Acetyl-2-amino-7-methyl-5-(4′-(2-hydroxyethyl)-3′-methoxyphenyl)-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one (4n). Yield 51% as pale yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 2.02 (s, 3H, CH_3), 2.31 (s, 3H, CH_3CO), 3.66 (s, 3H, OCH_3), 3.86 (t, $J = 5.1$ Hz, 2H, CH_2), 4.79 (t, $J = 5.5$ Hz, 2H, $ArOCH_2$), 4.84 (s, 1H, CH), 6.32 (s, 2H, NH_2), 6.62 (dd, $J = 8.4$ Hz, $J = 1.9$ Hz, 1H, ArH), 6.78 (d, $J = 8.4$ Hz, 1H, ArH), 6.93 (d, $J = 1.9$ Hz, 1H, ArH), 9.04 (s, 1H, 8-NH), 10.48 (s, 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 19.31, 29.83, 36.56, 55.42, 59.69, 70.28, 92.07, 110.13, 111.86, 113.19, 118.99, 140.36, 146.48, 146.77, 148.54, 153.31, 153.96, 161.66, 196.79. MS for $C_{19}H_{22}N_4O_5$, *m/z*: 386 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_4O_5$: C, 59.06; H, 5.74; N, 14.50. Found: C, 59.00; H, 5.70; N, 14.44.

6-Acetyl-2-amino-5-(2′,5′-dimethoxyphenyl)-7-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one (4o). Yield 66% as pale yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 2.09 (s, 3H, CH_3), 2.10 (s, 3H, CH_3CO), 3.59 (s, 3H, 5′-OCH_3), 3.67 (s, 3H, 2′-OCH_3), 5.11 (s, 1H, CH), 6.25 (s, 2H, NH_2), 6.54 (d, $J = 4.8$ Hz, 1H, ArH), 6.66 (dd, $J = 8.7$ Hz, $J = 4.8$ Hz, 1H, ArH), 6.80 (d, $J = 8.6$ Hz, 1H, ArH), 8.93 (s, 1H, 8-NH), 10.30 (br.s, 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 18.73, 29.20, 32.35,

55.13, 56.39, 90.67, 110.68, 111.31, 112.81, 116.14, 137.35, 143.80, 150.25, 153.26, 154.04, 154.36, 161.28, 198.10. MS for $C_{18}H_{20}N_4O_4$, *m/z*: 356 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; N, 15.72. Found: C, 61.02; H, 5.73; N, 15.92.

5,5′-(1,4-Phenylene)bis(6-acetyl-2-amino-7-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one) (4p). Yield 42% as brownish yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 1.99 (s, 6H, CH_3), 2.27 (s, 6H, CH_3CO), 4.80 (s, 2H, CH), 6.25 (s, 4H, NH_2), 7.02 (s, 4H, ArH), 9.-02 (s, 2H, 3-NH), 10.38 (m, 2H, 8-NH). ^{13}C NMR spectrum is not obtained because of extremely low solubility. MS for $C_{26}H_{26}N_8O_4$, *m/z*: 514 (M^+).

4-(6-acetyl-2-amino-7-methyl-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidin-5-yl)benzaldehyde (4p′). Yield 42% as brownish yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 2.04 (s, 3H, CH_3), 2.33 (s, 3H, CH_3CO), 4.99 (s, 1H, CH), 6.34 (s, 2H, NH_2), 7.43 (d, J = 8.1 Hz, 1H, ArH), 7.75 (d, J = 8.4 Hz, 1H, ArH), 9.18 (s, 1H, 3-NH), 9.88 (s, 1H, CHO), 10.27 (br.s., 1H, 8-NH). ^{13}C NMR spectrum is not obtained because of extremely low solubility. MS for $C_{17}H_{16}N_4O_3$, *m/z*: 324 (M^+).

6-Acetyl-2-amino-5-(1-ethyl-3-methyl-1H-pyrazol-4-yl)-7-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one (4q). Yield 68% as pale yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 1.23 (t, J = 7.2 Hz, 3H, $\underline{CH_3}CH_2$), 2.03 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.23 (s, 3H, CH_3CO), 3.87 (q, J = 7.2 Hz, 2H, $CH_3\underline{CH_2}$), 4.69 (s, 1H, CH), 6.22 (s, 2H, NH_2), 7.17 (s, 1H, HetCH), 8.98 (s, 1H, 8-NH), 10.29 (br.s, 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 12.07, 15.46, 19.21, 27.47, 29.47, 45.54, 91.88, 110.72, 125.04, 128.17, 144.18, 145.36, 153.16, 153.80, 161.46, 196.83. MS for $C_{16}H_{20}N_6O_2$, *m/z*: 328 (M^+). *Anal.* Calcd for $C_{16}H_{20}N_6O_2$: C, 58.52; H, 6.14; N, 25.59. Found: C, 58.90; H, 6.25; N, 25.85.

6-Acetyl-5-(1-allyl-3-methyl-1H-pyrazol-4-yl)-2-amino-7-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one (4r). Yield 63% as pale yellow solid; mp: over 300°C. ^{1}H NMR (200 MHz, DMSO) δ (ppm): 2.02 (s, 2H, CH_3), 2.12 (s, 3H, CH_3CO), 2.22 (s, 3H, 3′-CH_3), 4.69 (s, 1H, 5-CH), 4.52 (m, 2H, N-CH_2), 5.07 (m, 2H, terminal CH_2), 5.86 (m, 1H, allyl-CH), 6.21 (s, 2H, NH_2), 7.15 (s, 1H, HetCH), 8.99 (s, 1H, 8-NH), 10.26 (br.s., 1H, 3-NH). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 12.02, 19.21, 27.50, 29.45, 53.36, 91.82, 110.69, 117.50, 125.53, 128.72, 134.50, 144.59, 145.40, 153.14, 153.82, 161.43, 196.78. MS for $C_{17}H_{20}N_6O_2$, *m/z*: 340 (M^+). *Anal.* Calcd for $C_{17}H_{20}N_6O_2$: C, 59.99; H, 5.92; N, 24.69. Found: C, 59.93; H, 5.98; N, 24.60.

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