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ORIGINAL ARTICLE

Facile access to new pyrido[2,3-*d*]pyrimidine derivatives

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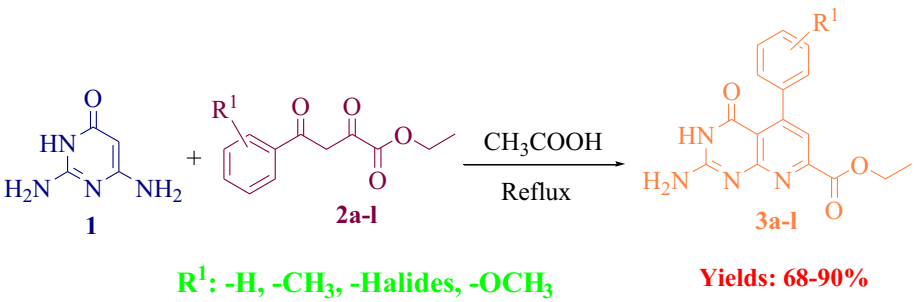
Abstract

In this report, a facile, operationally, simple and highly efficient one-pot coupling of 2,6-diaminopyrimidin-4(3H)-one and ethyl-2,4-dioxo-4-phenylbutanoate derivatives is reported. This method afforded a novel series of ethyl-2-amino-3,4-dihydro-4-oxo-5-phenyl pyrido[2,3-*d*] pyrimidine-7-carboxylate heterocycle derivatives in high yields under refluxing AcOH.

Graphical abstract



Keywords Pyrido[2,3-*d*]pyrimidine heterocycles · One-pot coupling · Ethyl-2,4-dioxo-4-phenylbutanoate

Introduction

Pyrimidines are an important class of nitrogen heterocyclic compounds with a wide range of applications, and these compounds have proven to be convenient building blocks for the synthesis of various fused heterocycles [1–4]. One of the most important fused heterocycles is pyrido[2,3-*d*]pyrimidines. These compounds exhibit a wide range of biological properties such as antiviral [5], anti-inflammatory [6], antimicrobial [7], antifungal [8] and anticancer activity [9]. For example, compounds such as 2,4-diamino-6-(thioarylmethyl)pyrido[2,3-*d*]pyrimidines were shown as inhibitors of dihydrofolate reductases (Fig. 1) [10]. Therefore, the synthesis of diverse structures belonging to this class of compounds is very important. Also, these compounds exist in purine bases of DNA and RNA [11]. There are several synthetic procedures for the preparation of fused pyrimidine systems under different conditions which have opened new horizons in the synthesis of pyridopyrimidines. For example,

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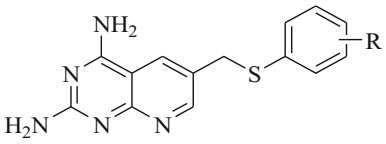


Fig. 1 Bioactive compound on pyrido[2,3-*d*]pyrimidine derivative as inhibitor of dihydrofolate reductases

they can be made with 3-cyano-2-aminopyridines via formamidine formation followed by selective nucleophilic addition with different primary amines [12]. Cyclocondensation of 4,6-dichloro-2-methylsulfanylpyrimidine-5-carbaldehyde with beta-alkyl and beta-aryl-beta-aminoacrylic esters is another route for their preparation [13]. The Michael addition and subsequent cyclodehydration of 2,6-diaminopyrimidin-4-one and butynones provided another method for the synthesis of pyrido [2,3-*d*]pyrimidines [14]. The three-component reaction of aldehydes, alkyl nitriles and aminopyrimidines in water and in the presence of KF-Al_2O_3 as catalyst provided the aforementioned compounds in reasonable yields [15]. Some of the reported methods suffer from one or more disadvantages such as multi-step synthesis, use of toxic chemicals, low yields and tedious workup. In addition, these approaches only afford series of anticipated N-fused heterocycle structures. The biological and medicinal character of these compounds inspires us to examine a different and effective method for their preparation. Furthermore, in this paper, we plan to present new pyrido[2,3-*d*]pyrimidines structures which aims to synthesize tricyclic heterocycles and easily methodologies for the preparation of compounds. Following up on our interest in the synthesis of N-fused heterocycles [16–22], herein we describe a novel and highly efficient technique for the preparation of new derivatives of pyrido[2,3-*d*]pyrimidines from 2,6-diaminopyrimidin-4(3H)-one **1** and ethyl-2,4-dioxo-4-phenylbutanoate derivatives **2** (Scheme 1).

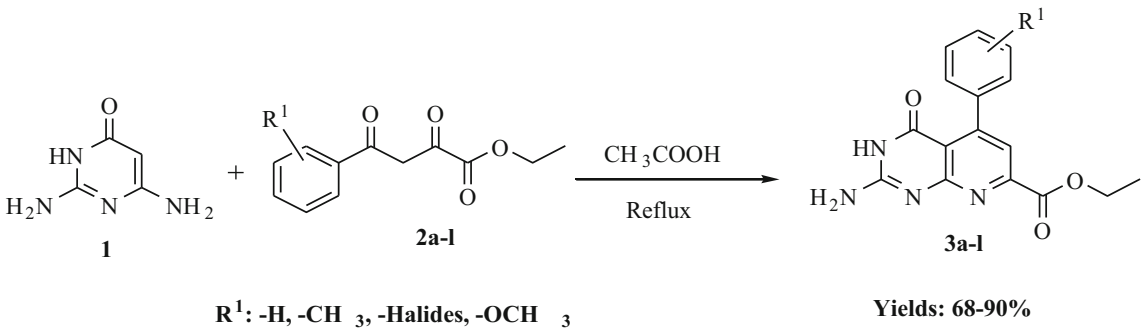
Results and discussion

First, the desired starting materials, including 2,6-diaminopyrimidin-4(3H)-one **1** and ethyl-2,4-dioxo-4-phenylbutanoate derivatives **2** (prepared from acetophenones **4** and diethyl oxalate **5**), were synthesized by conventional methods according to the literature (Scheme 2) [23, 24].

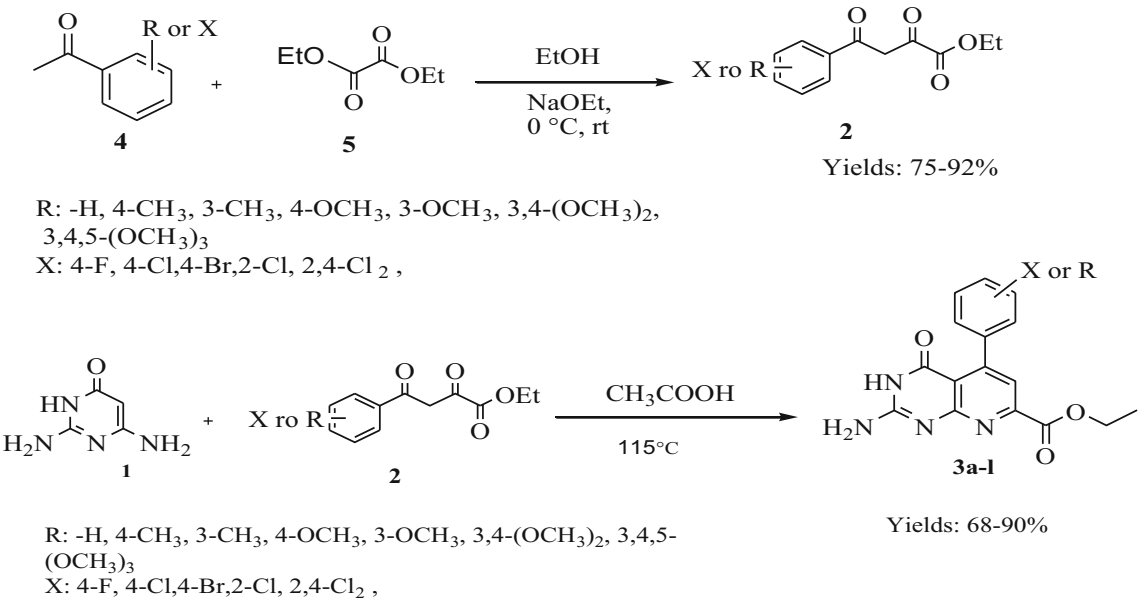
At first, we tested the reaction of starting materials (**1** and **2a**) in the presence of different solvents to optimize the reaction conditions (Table 1). As shown in Table 1, the best result (based on the yield of the reaction) was obtained in refluxing AcOH (Table 1, entry 7).

With these results in hand, different ethyl-2-amino-3,4-dihydro-4-oxo-5-phenyl pyrido[2,3-*d*] pyrimidine-7-carboxylate derivatives **3a–l** were prepared using various ethyl-2,4-dioxo-4-arylbutanoates **2** (Table 2, entries 1–12). For all substrates, the reaction could be completed in 5–6 h in high yields.

It was observed that the desired products were obtained in good to excellent yields in almost all cases and their structures were verified by IR, ^{1}H NMR and ^{13}C NMR spectroscopy as well as mass spectrometry. A proposed mechanism for the synthesis of phenylpyrido[2,3-*d*] pyrimidine-7-carboxylate derivative **3a** is shown in Scheme 3. Initially, the acid-catalyzed condensation of amine group from 2,6-diaminopyrimidin-4(3H)-one **1** with the more active carbonyl group of ethyl-2,4-dioxo-4-phenylbutanoates **2a** in the presence of acetic acid as solvent gave intermediate **6**. In the end, compound **3a** can be attained after tautomerization, cyclization and water elimination sequences on intermediate **6** can lead to compound **3a** (Scheme 3). We have used acetic acid (50%, solution in water) in the reaction. The acid catalyzes the condensation of an amino group in 2,6-diaminopyrimidin-4(3H)-one **1** with the more active carbonyl group of ethyl-2,4-dioxo-4-phenylbutanoates **2a** by donating H^+ to the more activated carbonyl group for obtaining intermediate **6**. pK_a of acetic acid is 4.75 (at 25 °C) and



Scheme 1 General route for the synthesis of novel pyrido[2,3-*d*]pyrimidines **3**



Scheme 2 Synthesis of starting materials **2** needed for the synthesis of pyrido[2,3-*d*]pyrimidine derivatives **3**

Table 1 Solvent screening for the synthesis of compound **3a**

Entry	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	THF	68	10	35
2	MeOH	65	15	25
3	H_2O	100	13	25
4	H_2O, $CH_3C_6H_4SO_3H$[b]	100	13	15
5	H_2O, HCl[b]	100	15	40
6	H_2O, AcOH[b]	100	17	45
7	AcOH	115	7	90
8	HCl	100	10	5
9	DMF	130	12	25

[a]Isolated yield
[b]Catalytic amount (1×10^{-4} mol%)
[c]Reaction conditions: **1** (1 mmol), **2a** (1 mmol), solvent (10 mL)

can give a positive proton to lone pair of oxygen atoms of carbonyl compounds to activate them for nucleophilic attack. Furthermore, acetic acid-catalyzed tautomerization, cyclization and water elimination sequences on intermediates **6** and **7** for converting them to target molecule **3a** (Scheme 3). Although the glacial acetic acid can be used in this reaction, as it is toxic, we used just acetic acid (50%, solution in water). Furthermore, the acetic acid has higher boiling point than water and can provide higher activation energy for reaction. The temperature is important for providing the activation energy for different steps (especially rate-determining step) of the reaction. However, acetic acid can act as an efficient catalyst and appropriate solvent for the synthesis of entitled fused pyrido[2,3-*d*]pyrimidine structures.

The nature of the substituents on aromatic ring of compound **2** has a significant effect on the yield of the reaction (Table 2). Aromatic rings of compound **2** bearing electron-withdrawing groups have less electron density than unsubstituted rings or rings containing electron-donating substituents. This electron deficiency renders carbonyl group more susceptible toward nucleophilic attack in the cyclization step, resulting in the desired products in higher yields (Table 2, entries 2–6). From this point of view, one can conclude that the cyclization step (conversion of compound **6** to **7**) in Scheme 3 is rate-determining step.

Table 2 Synthesis of pyrido[2,3-*d*]pyrimidine derivatives **3**

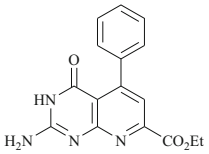
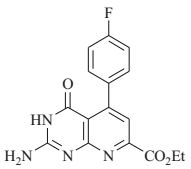
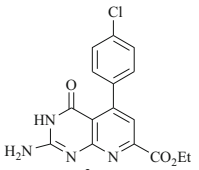
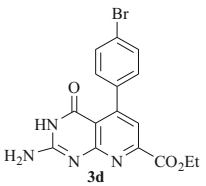
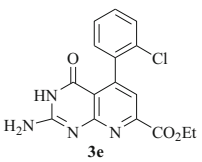
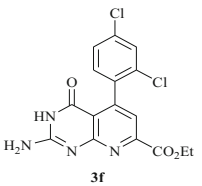
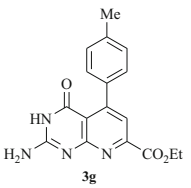
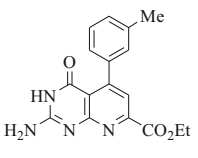
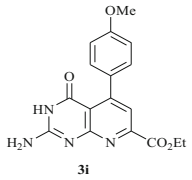
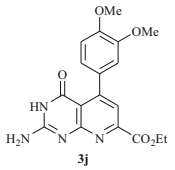
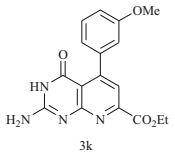
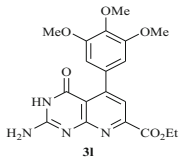
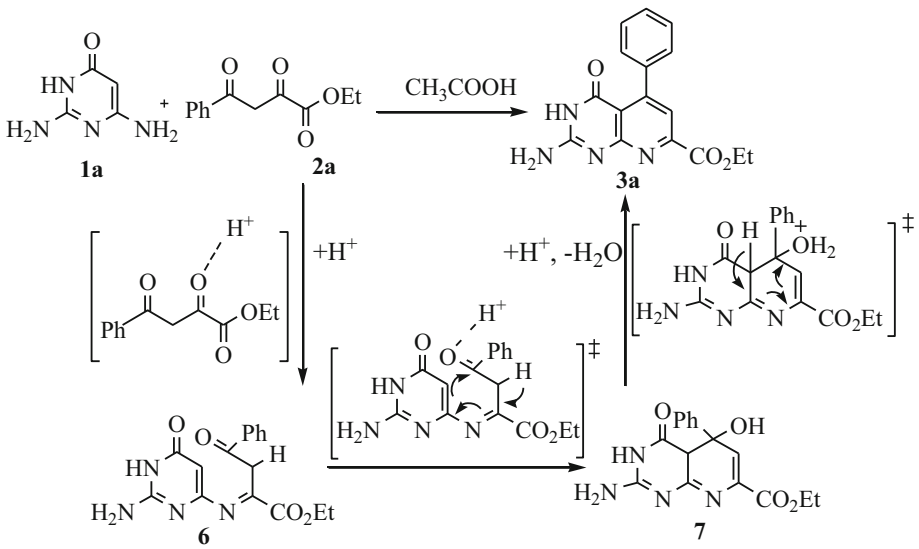
Entry	Ar- R_1 on **2 a–l**	Product **3 a–l**	Yield[b] (%)
1	Ph	 **3a**	90
2	4-F–C_6H_4	 **3b**	88
3	4-Cl–C_6H_4	 **3c**	85
4	4-Br–C_6H_4	 **3d**	86
5	2-Cl–C_6H_4	 **3e**	84
6	2,4-Cl_2–C_6H_3	 **3f**	81
7	4Me–C_6H_4	 **3g**	80
8	3-Me–C_6H_4	 **3h**	75

Table 2 continued

Entry	Ar- R_1 on **2 a–l**	Product **3 a–l**	Yield[b] (%)
9	4-OMe–C_6H_4	 **3i**	71
10	3,4-$(OMe)_2$–C_6H_3	 **3j**	69
11	3-OMe–C_6H_4	 **3k**	68
12	3,4,5-$(OMe)_3$–C_6H_2	 **3l**	trace

[a]The reaction time was prolonged to 7 h
[b]Isolated yield
[c]Reaction conditions: **1** (1 mmol), **2a–l** (1 mmol), solvent (10 mL)

Scheme 3 Plausible mechanism for the formation of pyrido[2,3-*d*]pyrimidine derivative **3a** in AcOH



Conclusion

In conclusion, we developed an efficient process for the synthesis of pyrido[2,3-*d*]pyrimidine-fused heterocycles in good yields (68–90%) in AcOH medium. Prominent among the advantages of this new method are novelty, an easy workup, the absence of a catalyst and operational simplicity.

Experimental

General remarks

All commercially available chemicals and reagents were purchased from Merck and Fluka Chemical Company and were used without further purification. Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker FT-500, using TMS as an internal standard. The abbreviations used are as follows: s, singlet; d, doublet; and m, multiplet. IR spectra were recorded on a Nicolet Magna FTIR 550 spectrophotometer (KBr disks). MS were recorded with an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis was Elemental Analysensystem GmbH VarioEL.

General procedure for the synthesis of oxopyrido[2,3-*d*]pyrimidine derivatives 3

A mixture of 6-diaminopyrimidin-4(3H)-one **1** (1 mmol), ethyl 2,4-dioxo-4-arylbutanoates **2** (1 mmol) in refluxing AcOH (10 mL) was stirred at 115 °C for 7 h. The progress of the reaction was monitored by TLC (ethyl acetate/n-hexane: 1/2). After the completion of the reaction, the mixture was cooled to room temperature, and the precipitate was filtered, washed with ethanol (20 mL) and purified by crystallization or column chromatography to afford pure products **3a–l**.

Ethyl-2-amino-3,4-dihydro-4-oxo-5-phenylpyrido[2,3-*d*] pyrimidine-7-carboxylate (3a) Yield: 90%; yellow crystals; mp 119–121 °C; IR (KBr): 1685, 1725, 2990, 3019, 3127, 3389 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ_H = 1.3 (t, J = 7 Hz, 3H, CH_3), 4.26 (q, J = 7 Hz, 2H, OCH_2), 6.850 (s, 2H, NH_2), 7.51–7.53 (m, 3H, Ar), 7.67 (s, 1H, pyridine), 8.17–8.19 (m, 2H, Ar). ^{13}C NMR (125 MHz, DMSO): 13.7, 61.3, 106.0, 115.4, 127.3, 129.9, 130.6, 130.9, 131.3, 137.9, 142.4, 154.9, 161.2, 167.0. Anal. Calcd for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06. Found: C, 61.63; H, 4.25; N, 17.76.

Ethyl-2-amino-5-(4-fluorophenyl)-3,4-dihydro-4-oxopyrido [2,3-*d*]pyrimidine-7-carboxylate (3b) Yield: 88%; yellow crystals; mp 210–212 °C; IR (KBr): 1668, 1737, 3227, 3253, 3347 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ_H = 1.33 (t, J=7 Hz, 3H, CH_3), 4.24 (q, J = 7 Hz, 2H, OCH_2), 6.84 (s, 2H, NH_2), 7.33 (t, J = 8.5 Hz, 2H, Ar), 7.68 (s, 1H, pyridine), 8.24 (t, J=8.5 Hz, 2H, Ar). ^{13}C NMR (125 MHz, DMSO): 13.7, 61.3, 105.8, 111.3, 115.4, 115.8 (d, $J_{C–F}$ = 22 Hz), 129.6 (d, $J_{C–F}$ = 8.7 Hz), 133.7, 135.1, 143.4, 154.8, 159.6, 163.6 (d, $J_{C–F}$ = 247 Hz), 167.2. Anal. Calcd for $C_{16}H_{13}FN_4O_3$: C, 58.5; H, 3.99; N, 17.7. Found: C, 58.2; H, 3.49; N, 17.4.

Ethyl-2-amino-5-(4-chlorophenyl)-3,4-dihydro-4-oxopyrido [2,3-*d*]pyrimidine-7-carboxylate (3c) Yield: 85%; yellow crystals; mp 215–217 °C; IR (KBr): 1679, 1731, 2994, 3278, 3358 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ_H = 1.32 (t, J = 7 Hz, 3H, CH_3), 4.36 (q, J = 7 Hz, 2H, OCH_2), 6.95 (s, 2H, NH_2), 7.57 (d, J = 8.5 Hz, 2H, Ar), 7.72 (s, 1H, pyridine), 8.21 (d, J = 8.5 Hz, 2H, Ar). ^{13}C NMR (125 MHz, DMSO): 13.7, 61.2, 105.4, 106.1, 111.6, 128.8, 1128.9, 135.3, 136.0, 143.4, 154.7, 159.4, 161.8, 167.1. Anal. Calcd for $C_{16}H_{13}ClN_4O_3$: C, 55.7; H, 3.8; N, 16.2. Found: C, 55.4; H, 3.5; N, 15.9.

Ethyl-2-amino-5-(4-bromophenyl)-3,4-dihydro-4-oxopyrido [2,3-*d*] pyrimidine-7-carboxylate (3d) Yield: 86%; yellow crystals; mp: 218–220 °C; IR (KBr): 1693, 1780, 3210, 3245, 3375 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ_H = 1.32 (t, J=7 Hz, 3H, CH_3), 4.34 (q, J = 7 Hz, 2H, OCH_2), 6.83 (S, 2H, NH_2), 7.13 (s, 1 H, Pyridine), 7.68 (t, J=8 Hz, 2H, Ar), 8.13 (d, J=8 Hz, 2H, Ar).^{13}C NMR (125 MHz, DMSO): 13.7, 61.2, 95.37, 106.01, 111.9, 112.05, 115.2, 121.3, 129.2, 131.7, 132.3, 143.8, 162.6, 167.5. m/z (%) = 389 [M$^+$] (100), 318.0 (50), 237 (30), 165 (20). Anal. Calcd for $C_{16}H_{13}BrN_4O_3$: C, 42.38; H, 3.37, N; 14.4. Found: C, 42.33; H, 3.41; N; 13.9.

Ethyl-2-amino-5-(2-chlorophenyl)-3,4-dihydro-4-oxopyrido [2,3-*d*]pyrimidine-7-carboxylate (3e) Yield: 84%; yellow crystals; mp: 215–217 °C; IR (KBr): 1680, 1752, 2983, 3333, 3326 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ_H = 1.30 (t, J = 7 Hz, 3H, CH_3), 4.34 (q, J = 7 Hz, 2H, OCH_2), 6.97 (S, 2H, NH_2), 7.28 (S, 1H, Pyridine), 7.47–7.55 (m, 2H, Ar), 7.57–7.63 (m, 2H, Ar), 11.4 (s, NH). ^{13}C NMR (125 MHz, DMSO): 13.7, 61.2, 105.1, 106.04, 127.2, 127.4, 129.9, 130.6, 130.7, 130.9, 131.3, 137.9, 142.4, 154.8, 161.4, 167.0. Anal. Calcd for $C_{16}H_{13}ClN_4O_3$: C, 55.7; H, 3.80; N, 16.25; Found: C, 55.2; H, 3.30; N, 15.95.

Ethyl-2-amino-5-(2,4-dichlorophenyl)-3,4-dihydro-4-oxopyrido [2,3-*d*]pyrimidine-7-carboxylate (3f) Yield: 81%; yellow crystals; mp: 210–212 °C; IR (KBr): 1679, 1756, 3143, 3292 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ_H = 1.30 (t, J = 7 Hz, 3H, CH_3), 4.34 (q, J = 7 Hz, 2H, OCH_2), 7.04 (s, 2H, NH_2), 7.31 (S, 1H, Pyridine), 7.56 (d, J = 8 Hz, Ar, 1H), 7.64 (d, J = 8 Hz, Ar, 1H), 7.75 (s, 1H, Ar). ^{13}C NMR (125 MHz, DMSO): 13.8, 61.52, 106.35, 115.75, 130.3, 132.17, 132.75, 134.6, 142.6, 155.01, 159.4, 160.4, 167.0, 172. Anal. Calcd for $C_{16}H_{12}Cl_2N_4O_3$: C, 50.6; H, 3.19; N, 14.78. Found: C, 50.1; H, 2.79; N; 14.26.

Ethyl-2-amino-3,4-dihydro-4-oxo-5-*p*-tolylpyrido[2,3-*d*] pyrimidine-7-carboxylate (3g) Yield: 80%; yellow crystals; mp: 214–217 °C; IR (KBr): 1698, 1738, 3040, 3230, 3330 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ_H = 1.32 (t, J = 7 Hz, 3H, CH_3), 1.3 (S, 3H, CH_3), 4.3 (q, J = 7 Hz, 2H,

OCH_2), 6.89 (s, 2H, NH_2), 7.52 (d, J = 6 Hz, 2H, Ar), 7.69 (s, 1H, Pyridine), 8.18 (d, J = 6 Hz, 2H, Ar). ^{13}C NMR (125 MHz, DMSO): 14.30, 16.30, 62.01, 114.3, 114.6, 121.3, 125.6, 128.9, 130.9, 134.2, 139.5, 142.5, 152.2, 156.3, 165.7. Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 62.65; H, 4.77; N, 16.77.

Ethyl-2-amino-3,4-dihydro-4-oxo-5-m-tolylpyrido[2,3-*d*] pyrimidine-7-carboxylate (3h) Yield: 75%; yellow crystals; mp: 218–220 °C; IR (KBr): 1676, 1727, 3277, 3376, 3346 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ_H = 1.32 (t, J = 7 Hz, 3H, CH_3), 2.5 (S, 3H, CH_3), 4.35 (q, J = 7 Hz, 2H, OCH_2), 6.83 (s, 2H, NH_2), 7.32 (d, J = 7 Hz, 2H, Ar), 7.40 (t, J = 7 Hz, 1H, Ar), 7.66 (S, 1H, Pyridine), 7.98 d, J = 7 Hz, 1H, Ar), 8.02 (1H, NH). ^{13}C NMR (125 MHz, DMSO): 14.3, 16.2, 62.0, 115.2, 121.3, 124.7, 125.6, 128.1, 128.8, 128.9, 130.6, 138.4, 138.5, 139.4, 142.5, 156.8, 165.7. Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 62.45; H, 4.67; N, 16. 77.

Ethyl-2-amino-3,4-dihydro-5-(4-methoxyphenyl)-4-oxopyrido[2,3-*d*]pyrimidine-7-carboxylate (3i) Yield: 71%; yellow crystals; mp: 214–16 °C; IR (KBr): 1682, 1738, 2984, 3270, 3335, 3417 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ_H = 1.32 (t, J=7 Hz, 3H, CH_3), 3.4 (s, 3H, OCH_3), 4.35 (q, J=7 Hz, 2H, OCH_2), 6.89 (s, 2H, NH_2), 7.5 (d, J=6 Hz, 2H, Ar), 7.6 (s, 1H, Pyridine), 8.1 (d, J=6 Hz, 2H, Ar), 11.3 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO): 13.7, 60.0, 61.2, 111.6, 127.1, 127.2, 128.7, 128.8, 129.6, 130.5, 137.2, 143.3, 154.8, 160.7, 167.3. Anal. Calcd for: $C_{17}H_{16}N_4O_4$: C, 59.99; H, 4.74; N, 16.46. Found: C, 59.69; H, 4.44; N, 16.16.

Ethyl-2-amino-3,4-dihydro-5-(3,4-dimethoxyphenyl)-4-oxopyrido[2,3-*d*]pyrimidine-7-carboxylate (3j) Yield: 69%; yellow crystals; mp: 217–219 °C; IR (KBr): 1667, 1734, 2887, 2915, 3253, 3360 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ_H = 1.32 (t, J=7 Hz, 3H, CH_3), 3.84 (s, OCH_3), 3.87 (OCH_3), 4.35 (q, J=7 Hz, 2H, OCH_2), 7.07 (d, J=8 Hz, 1H, Ar), 7.68 (s, 1H, Pyridine), 7.79 (d, J=8 Hz, 2H, Ar), 7.80 (s,1H, NH). ^{13}C NMR (125 MHz, DMSO): 13.7, 51.6, 55.56, 61.2, 105.2, 110.3, 111.1, 111.54, 111.7, 120.5, 129.8, 143.1, 148.9, 151.0, 154.8, 160.4, 167.4, 171.8. Anal. Calcd for: $C_{18}H_{18}N_4O_5$: C, 58.37; H, 4.90; N, 15.13. Found: C, 58.07; H, 4.70; N, 14.93.

Ethyl-2-amino-3,4-dihydro-5-(3-methoxyphenyl)-4-oxopyrido[2,3-*d*]pyrimidine-7-carboxylate (3k) Yield: 68%; yellow crystals; mp: 220–222 °C; IR (KBr):1689, 1735, 2995, 3220, 3295 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ_H = 1.3 (t, J=7 Hz, 3H, CH_3), 2.4 (s, 3H, OMe), 4.3 (q, J=7 Hz, 2H, OCH_2), 6.8 (s, 1H, Pyridine), 7.32 (d, J=7.5 Hz, 1H, Ar), 7.4 (t, J=7.5 Hz, 1H, Ar), 7.66 (s, 1H, NH) 7.97 (d, J=7.5 Hz, 1H, Ar), 8.02 (s, 1H, Ar). ^{13}C NMR (125 MHz, DMSO): 13.7, 55.5, 61.2, 105.2, 106.1, 111.9, 112.5, 119.5, 120.5, 129.7, 138.7, 143.2, 154.8, 159.6, 160.4, 167.2, 171.8. Anal. Calcd for: $C_{17}H_{16}N_4O_4$: C, 59.99; H, 4.74; N, 16.46; Found: C, 59.69; H, 4.44; N, 16.26.

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