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New potential inhibitors of cyclin-dependent kinase 4: Design and synthesis of pyrido[2,3-*d*]pyrimidine derivatives under microwave irradiation

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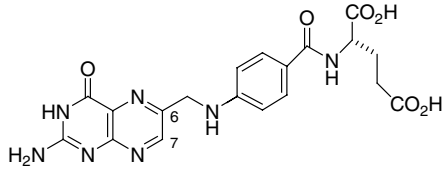
Abstract—A simple and efficient synthesis of 2-amino pyrido[2,3-*d*]pyrimidine derivatives was accomplished via a three-component reaction under microwave irradiation without catalyst. This method had many dramatic advantages such as the short reaction time, high yield, and broad substrate scope, as well as convenient operation. We provide new series of potential biologically active compounds as inhibitors of Cdk4.

Since the isolation and characterization of wing pigments of European butterflies at the end of the nineteenth century, the pterins have distinguished themselves as heterocycles of profound chemical and biological significance.[1] The discovery that the pyrazino[2,3-*d*]pyrimidine core of the pterin pigments was shared by the vitamin folic acid (**I**)[2] caused a dramatic increase in interest in this heterocycle in an effort to understand its role in the prevention of disease.[3] Structurally related folate antagonists[4] have been shown to possess a diverse range of biological properties and they elicit highly species-specific responses as antitumor,[5] antibacterial,[6] anti-inflammatory,[7] and antifungal agents.[8] For the preparation of these complex molecules large efforts have been directed toward the synthetic manipulation of uracil derivatives. As a result, a number of reports have appeared in the literature[9] which usually require long reaction times and complex synthetic pathways. Thus, new routes for the synthesis of these molecules have attracted considerable attention in search for a rapid entry to these heterocycles.



I

Inhibition of the cell cycle kinase, cyclin-dependent kinase-4 (Cdk4), is expected to provide an effective method for the treatment of proliferative diseases such as cancer.[10] The pyrido[2,3-*d*]pyrimidin-7-one template has been identified previously as a privileged structure for the inhibition of ATP-dependent kinases, and good potency against Cdks has been reported for representative examples.[11–13] Obtaining selectivity for individual Cdk enzymes, particularly Cdk4, has been challenging. A lot of extensive investigations of the structure–activity relationships for pyrido[2,3-*d*]pyrimidin-7-one inhibition of Cdk4 were initiated. Currently, Vander Wel et al.[10] found that remarkable levels of selectivity for Cdk4 versus other kinases have been achieved by appropriate substitution at C-5 and C-6 positions of **II**. Therefore, to obtain the new potential inhibitors of Cdk4, further modifications at C-5 and C-6 positions of the scaffold of pyrido[2,3-*d*]pyrimidin-7-one should be of great significance.

Keywords: Pyrido[2,3-*d*]pyrimidine; Microwave irradiation; Cdk4.
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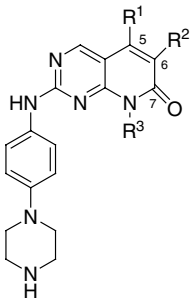


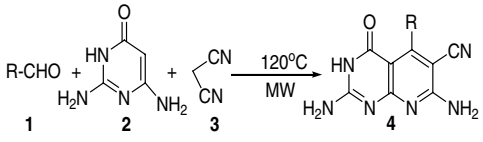
II

The diversity generating potential of multicomponent reactions (MCRs) has been recognized and their utility in preparing libraries to screen for functional molecules is well appreciated.[14–16] Microwave irradiation of organic reactions has rapidly gained in popularity as it accelerates a variety of synthetic transformations.[17] The microwave-enhanced procedures without the use of catalyst are particularly eco-friendly and the protocol has the advantages of short reaction time and high yield.[18]

In our continued interest[19] in the development of highly expedient methods for the synthesis of biologically active compound libraries, we report in this paper a highly efficient method for the synthesis of a series of pyrido[2,3-*d*]pyrimidine derivatives under microwave irradiation without catalyst.

When the reaction of aldehyde **1**, 2,6-diaminopyrimidin-4-one **2**, and malononitrile **3** was performed in the presence of glycol under microwave irradiation, 2,7-diamino-4-oxo-5-aryl-3,4-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives **4** were obtained in excellent yields (Scheme 1).[20] The results are summarized in Table 1.

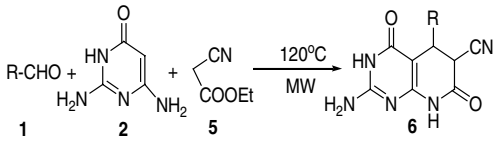
Under identical conditions, we performed the reactions of aldehyde **1**, 2,6-diaminopyrimidin-4-one **2**, and ethyl cyanoacetate **5** (Scheme 2).[21] As expected, a series of pyrido[2,3-*d*]pyrimidine-7-ones **6** were obtained in high



Scheme 1.

Table 1. Synthesis of **4** under microwave irradiation

Entry	R	Time (min)	Products	Yield (%)	Mp (°C)
1	C_6H_5	8	**4a**	92	>300
2	4-$CH_3OC_6H_4$	8	**4b**	93	>300
3	4-$NO_2C_6H_4$	6	**4c**	95	>300
4	4-ClC_6H_4	8	**4d**	96	>300
5	4-FC_6H_4	8	**4e**	99	>300
6	3,4-$OCH_2OC_6H_3$	7	**4f**	88	>300
7	CH_3CH_2	8	**4g**	74	>300
8	2-C_4H_3S	7	**4h**	94	>300

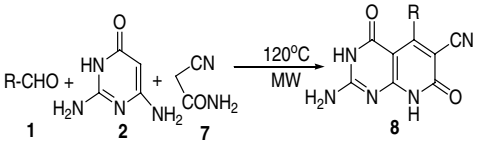


Scheme 2.

yields. Furthermore, when ethyl cyanoacetate **5** was replaced by 2-cyanoacetamide **7** (Scheme 3)[21] another series of pyrido[2,3-*d*]pyrimidine-7-ones **8** were obtained and the dehydrogenation of **6** was realized. The results are summarized in Table 2.

In order to make the compound libraries more diverse, **1**, **2**, and Meldrum's acid **9** were used as starting material under microwave irradiation, which gave the desired products **10** in good yields (Scheme 4).[22] The results are summarized in Table 3.

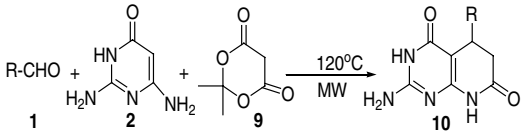
As shown in Table 1, we can see that a series of aldehydes bearing either electron-withdrawing or electron-donating groups perform equally well in the reaction. Additionally, aliphatic and heterocyclic aldehydes deliver the corresponding pyrido[2,3-*d*]pyrimidine derivatives in good yields. In order to search for the optimized condition for its reaction, we tested various temperatures. We found the reaction performed at 120 °C furnished the best result. For comparison, we performed the reaction for synthesizing **4a**, **6c**, **8a**, and **10f** under both MWI (120 °C) and classical heating mode (120 °C). As



Scheme 3.

Table 2. Synthesis of **6** and **8** under microwave irradiation

Entry	R	Time (min)	Products	Yield (%)	Mp (°C)
1	4-FC_6H_4	8	**6a**	88	>300
2	4-ClC_6H_4	8	**6b**	92	>300
3	4-BrC_6H_4	6	**6c**	94	>300
4	CH_3CH_2	8	**6d**	73	>300
5	4-FC_6H_4	8	**8a**	88	>300
6	4-ClC_6H_4	7	**8b**	93	>300
7	4-BrC_6H_4	8	**8c**	94	>300
8	4-$CH_3OC_6H_4$	7	**8d**	85	>300



Scheme 4.

Table 3. Synthesis of **10** under microwave irradiation

Entry	R	Time (min)	Products	Yield (%)	Mp (°C)
1	C_6H_5	8	**10a**	93	>300
2	3-CH_3O-4–OH–C_6H_3	8	**10b**	89	>300
3	4-$NO_2C_6H_4$	7	**10c**	92	>300
4	3,4-$Cl_2C_6H_3$	8	**10d**	92	>300
5	4-FC_6H_4	8	**10e**	93	>300
6	3,4-$OCH_2OC_6H_3$	9	**10f**	89	>300
7	$CH_3CH_2CH_2CH_2$	10	**10g**	78	>300
8	2-C_4H_3S	10	**10h**	88	>300

a result, we found that the reactions were efficiently promoted by MWI and the reaction times were strikingly shortened and the yields were increased. The reaction time of **4a** was shortened to 8 min from 3 h and the yield was remarkably increased to 92% from 72%. The reaction time of **6c** was shortened to 6 min from 5 h and the yield was remarkably increased to 94% from 70%. The reaction time of **8a** was shortened to 8 min from 4.5 h and the yield was remarkably increased to 88% from 72%. The reaction time of **10f** was shortened to 9 min from 3 h and the yield was remarkably increased to 89% from 73%. The mechanism is similar to that reported earlier.[23]

In Summary, we have demonstrated a rapid and direct method that offers a simple and efficient route for the synthesis of highly functionalized pyrido[2,3-*d*]pyrimidines of potential biological importance in excellent yields. Particularly valuable features of this method included the short reaction time, high yield, and broad substrate scope, as well as convenient operation. Most importantly, the series of pyrido[2,3-*d*]pyrimidine derivatives may be interesting new lead compounds for biological activity evaluation. Great efforts are underway to clarify their bioactivity and the results will be reported in due course.

Acknowledgments

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20. The general procedure for **4** was as follows: A mixture of aldehyde **1** (2 mmol), 2,6-diaminopyrimidin-4-one **2** (2 mmol), malononitrile **3** (2 mmol), and glycol (0.5 mL) was added to the reaction vessel of the monomodal Emrys™ Creator microwave synthesizer and allowed to

react under microwave irradiation at 200 W power and 120 °C for several minutes. The automatic mode stirred helps in mixing and the uniform heating of the reactants. The reaction vessel was cooled to room temperature. The solid compound was collected by filtration, washed with water, and recrystallized from DMF and ethanol mixture to give pure pyrido[2,3-*d*]pyrimidine derivatives **4**. Compound **4h**: mp >300 °C; ^{1}H NMR: δ 10.78 (s, 1H, NH), 7.67 (dd, 1H, J = 1.2 Hz, 5.2 Hz, thiophenyl-H), 7.28 (s, 2H, NH_2), 7.15 (dd, 1H, J = 1.2 Hz, 3.6 Hz, thiophenyl-H), 7.06 (dd, 1H, J = 3.6 Hz, 5.2 Hz, thiophenyl-H), 6.82 (s, 2H, NH_2). IR: (KBr, v, cm^{-1}): 3501, 3401, 3144, 2210, 1696. Anal. Calcd for $C_{12}H_8N_6OS$: C, 50.70; H, 2.84; N, 29.56. Found: C, 50.84; H, 2.68; N, 29.78.

21. The general procedure for **6** and **8** was as follows: A mixture of aldehyde **1** (2 mmol), 2,6-diaminopyrimidin-4-one **2** (2 mmol), ethylcyanoacetate **5** or 2-cyanoacetamide **7** (2 mmol), and glycol (0.5 mL) was added to the reaction vessel of the monomodal Emrys™ Creator microwave synthesizer and allowed to react under microwave irradiation at 200 W power and 120 °C for several minutes. The automatic mode stirred helps in mixing and the uniform heating of the reactants. The reaction vessel was cooled to room temperature. The solid compound was collected by filtration, washed with water, and recrystallized from DMF and ethanol mixture to give pure pyrido[2,3-*d*]pyrimidine-7-one derivatives **6** and **8**, respectively. Compound **6b**: mp >300 °C; ^{1}H NMR: δ 10.83 (s, 1H, NH), 10.78 (s, 1H, NH), 7.41 (d, 2H, J = 8.4 Hz, ArH), 7.29 (d, 2H, J = 8.4 Hz, ArH), 6.78 (s, 2H, NH_2), 4.98 (d, 1H, J = 7.2 Hz, CH), 4.37 (d, 1H, J = 7.2 Hz, CH). IR: (KBr, v, cm^{-1}): 3424, 3338, 3214, 2227, 1702, 1665. Anal. Calcd for $C_{14}H_{10}ClN_5O_2$: C, 53.26; H, 3.19; N, 22.18. Found: C, 53.05; H, 3.32; N, 22.31.
Compound **8d**: mp >300 °C; ^{1}H NMR: δ 12.31 (s, 1H, NH), 10.89 (s, 1H, NH), 7.19 (d, 2H, J = 8.8 Hz, ArH), 6.94 (d, 2H, J = 8.8 Hz, ArH), 6.78 (s, 2H, NH_2), 3.81 (s, 3H, OCH_3). IR: (KBr, v, cm^{-1}): 3349, 3140, 2227, 1715, 1671. Anal. Calcd for $C_{15}H_{11}N_5O_3$: C, 58.25; H, 3.58; N, 22.64. Found: C, 58.40; H, 3.64; N, 22.51.

22. The general procedure for **10** was as follows: A mixture of aldehyde **1** (2 mmol), 2,6-diaminopyrimidin-4-one **2** (2 mmol), Meldrum's acid **9** (2 mmol), and glycol (0.5 mL) was added to the reaction vessel of the monomodal Emrys™ Creator microwave synthesizer and allowed to react under microwave irradiation at 200 W power and 120 °C for several minutes. The automatic mode stirred helps in mixing and the uniform heating of the reactants. The reaction vessel was cooled to room temperature. The solid compound was collected by filtration, washed with water, and recrystallized from DMF and ethanol mixture to give pure pyrido[2,3-*d*]pyrimidine derivatives **10**. Compound **10a**: mp >300 °C; ^{1}H NMR: δ 10.63 (s, 1H, NH), 10.11 (s, 1H, NH), 7.31–7.04 (m, 5H, ArH), 6.57 (s, 2H, NH_2), 4.11 (m, 1H, CH), 2.97–2.44 (m, 2H, CH_2). IR: (KBr, v, cm^{-1}): 3440, 3335, 3158, 1683, 1645. Anal. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.86. Found: C, 61.05; H, 4.71; N, 21.78.

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