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Synthesis of novel 5,6-substituted furo[2,3-*d*]pyrimidines via Pd-catalyzed cyclization of alkynylpyrimidinols with aryl iodides

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Abstract—A flexible method for the synthesis of 5,6-disubstituted furo[2,3-*d*]pyrimidine derivatives is described. The key step is a palladium-catalyzed arylative cyclization of alkynylpyrimidinols with various aryl iodides, which gave the title compounds in 36–75% yield.

1. Introduction

Furo[2,3-*d*]pyrimidines exhibit valuable biological activities such as antifolate,[1] anticancer,[2] antiviral,[3] and inhibitions of glycogen synthase kinase-3 (GSK-3)[4] and Chk1 kinase.[5] Generally, these compounds were synthesized by the conversion of 2-amino-3-cyano-5-substituted furans to 4-amino-furopyrimidines in several steps.[2,4–6] Various benzofurans have been obtained by palladium-catalyzed cyclization,[7–12] but the preparation of heterocycle-fused furan by this method is rare. In 1981, Robins and Barr reported the first nucleoside analogues with furopyrimidine ring system, as by-products in Pd/Cu-catalyzed Sonogashira coupling reactions[13] of terminal alkynes with 5-iodouracil nucleosides.[14] Others reported few examples to synthesize 2,4,6-substituted furo-[2,3-*d*]pyrimidine analogues by Sonogashira coupling reaction and direct cyclization from 5-iodopyrimidinones with acetylene.[3,15] So far, the known methods could not be used to generate diversified multi-substituted furo[2,3-*d*]-pyrimidines' derivatives, which are important for library generation.

Considering the potent bioactivities of the compounds with the furo[2,3-*d*]pyrimidine core, developing new strategy to efficiently synthesize the novel multi-substituted furo-[2,3-*d*]pyrimidine derivatives has attracted our attention. To introduce diversified four substituents of furo[2,3-*d*]pyrimidine derivatives, our retrosynthetic analysis implicated the use of amidines, β-keto esters, alkynes, and aryl halides as the starting materials and palladium-catalyzed cascade cross coupling-cyclization as the key step (Fig. 1).

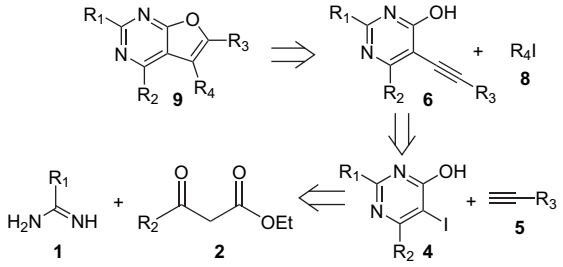

Figure 1. Retrosynthetic analysis of diversified furo[2,3-*d*]pyrimidines.

2. Results and discussion

To test the feasibility of our method, we first prepared 2-substituted iodopyrimidinols **4** as important intermediates by the condensation of ethyl 3-oxobutanoate **2** with methyl or phenyl amidine **1**[16] followed by iodination of the resulting pyrimidinols **3**.[17] The products **4a** (R_1=Me) and **4b** (R_1=Ph) were obtained in 49% and 90% yields, respectively (Fig. 2).

According to the general Sonogashira reaction condition, iodopyrimidinol **4a** was treated with various phenyl acetylenes **5** in the presence of an excess of *i*-Pr_2NEt, catalyzed by $PdCl_2(PPh_3)_2$ and CuI in CH_3CN at room temperature overnight to afford the desired arylethynylpyrimidinols **6** in low yields with the direct cyclized by-products in high yield. To avoid the

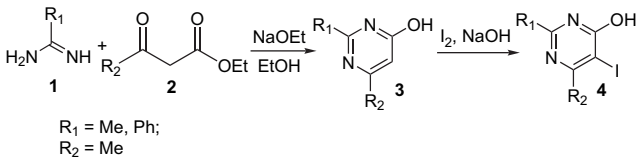

Figure 2. Preparation of iodopyrimidinols **4**.

Keywords: Furo[2,3-*d*]pyrimidines; Sonogashira coupling reaction; Palladium-catalyzed cyclization.
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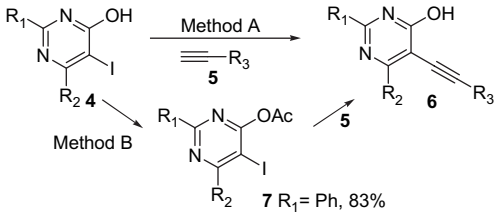
direct cyclized by-products, by decreasing the amount of the base (*i*-Pr_2NEt) to 1.0 equivalence the coupling of iodopyrimidinols **4a–b** with a series of substituted phenyl acetylenes **5** gave the products **6a–g** in good yields (Table 1, Method A).

Unfortunately, the reaction of iodopyrimidinol **4b** with alkyl acetylene **5e** did not proceed to give the corresponding **6h** under the same conditions. By raising reaction temperature to 60 °C, only the direct cyclized product was obtained. After the hydroxyl group of iodopyrimidinol **4b** was protected by acetyl bromide, Sonogashira couplings of compound **7a** with alkyl acetylenes proceeded smoothly to furnish a mixture of compounds **6h–i** and the hydroxyl protected coupling products, which could be transferred to the products **6h–i** by removal of acetyl group using hydrazine at 0 °C in THF (Table 1, Method B).

Alkynylpyrimidinol **6a** and iodobenzene (**8a**) were annulated by palladium-catalyzed cyclization under the reported conditions.[9] The desired product **9a** was obtained in 33%

Table 1. Preparation of alkynylpyrimidinols **6** by Sonogashira coupling



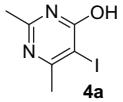
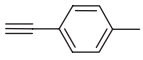
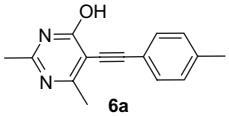
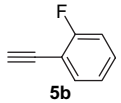
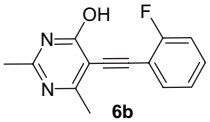
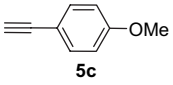
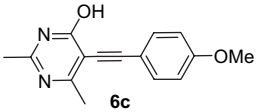
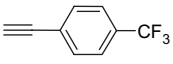
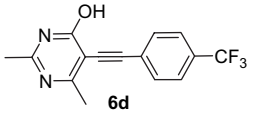
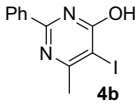
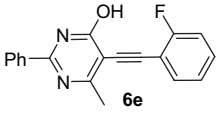
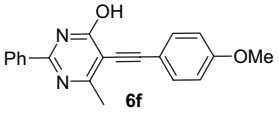
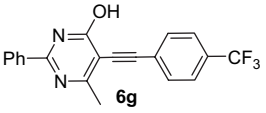
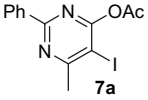
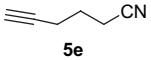
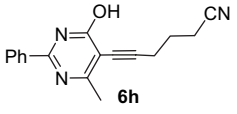
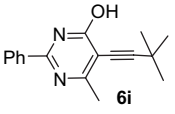
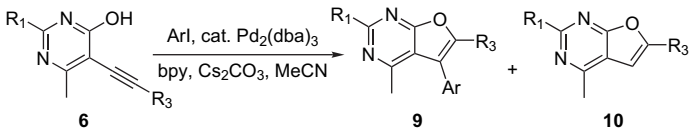
Entry	Iodopyrimidinol	Alkyne	Method	Product	Yield (%)
1	 **4a**	 **5a**	A	 **6a**	86
2	**4a**	 **5b**	A	 **6b**	83
3	**4a**	 **5c**	A	 **6c**	92
4	**4a**	 **5d**	A	 **6d**	89
5	 **4b**	**5b**	A	 **6e**	53
6	**4b**	**5c**	A	 **6f**	92
7	**4b**	**5d**	A	 **6g**	60
8	 **7a**	 **5e**	B	 **6h**	35
9	**7a**	 **5f**	B	 **6i**	65

Table 2. Synthesis of multi-substituted furo[2,3-*d*]pyrimidines **9**



6 **9** **10**

Entry	R_1	R_3	Ar	Yield of **9** (%)
1	Me	*p*-Tolyl	Phenyl	**9a** (57)
2	Me	*p*-Tolyl	4-Methoxyphenyl	**9b** (70)
3	Me	*p*-Tolyl	Thiophen-2-yl	**9c** (55)
4	Me	*p*-Tolyl	4-Methoxycarbonylphenyl	**9d** (36)
5	Me	2-Fluorophenyl	4-Methoxyphenyl	**9e** (75)
6	Me	4-Methoxyphenyl	4-Methoxyphenyl	**9f** (43)
7	Me	4-(Trifluoromethyl)phenyl	4-Methoxyphenyl	**9g** (48)
8	Ph	2-Fluorophenyl	4-Methoxyphenyl	**9h** (75)
9	Ph	4-Methoxyphenyl	4-Methoxyphenyl	**9i** (49)
10	Ph	4-(Trifluoromethyl)phenyl	4-Methoxyphenyl	**9j** (68)
11	Ph	3-Cyanopropyl	4-Methoxyphenyl	**9k** (38)

yield accompanied with the directly cyclized by-product **10a** (R_1=Me, R_3=*p*-tolyl). When Cs_2CO_3 was used as a soft base, the cyclization yield of **6a** with **8a** was increased to 57% to give **9a** as the major product (Table 2, Entry 1).

Subsequently, various aryl iodides were subjected to the cyclization under the improved reaction conditions as shown in Table 2. It was found that the aryl iodide (1-iodo-4-methoxybenzene, **8b**) with electron-donating group gave the best result of 70% yield (Table 2, Entry 2), presumably due to the favorable stabilization of ligation to palladium(0) complex with triple bond. On the contrary, the methyl 4-iodobenzoate (**8d**) with electron-withdrawing group reacted with arylethynylpyrimidinol **6a** to afford product **9d** in low yield (Entry 4). Cyclization of compound **6a** with iodothiophene (**8c**) furnished the product **9c** in 55% yield. Compound **6a** with the sterically hindered 2-iodotoluene and 2-iodonaphene, only produced the direct cyclized product **10a** and recovered the starting material.

Substitution on aryl group of arylethynylpyrimidinols **6** didn't show significant effects on the cyclization. Most of the corresponding products **9** were obtained in moderate yields. Compound **6h** was cyclized with 4-methoxyl iodobenzene to give the product **9k** in low yield. Sterically hindered **6i** gave complicated products.

3. Conclusion

In summary, we have developed an efficient method via palladium-catalyzed cyclization to synthesize novel 2,4,5,6-tetrasubstituted furo[2,3-*d*]pyrimidines. The method allows for the generation of libraries of such compounds.

4. Experimental

4.1. General methods

Reaction solvents were purchased from Sinopharm Chemical Reagent Co. Ltd. and were dried, distilled before use. Ethanol was distilled over sodium and acetonitrile was distilled over CaH_2. Reaction was monitored by thin layer chromatography (TLC) on 0.15–0.20 mm precoated Merck Silica Gel 60 F_{254}, visualizing with ultraviolet light. Flash column chromatography was performed on silica ZCX-II (Qingdao Haiyang Chemical Co. Ltd., 200–300 mesh) using reagent grade petroleum ether, dichloromethane, ethyl acetate, and methanol. Ethyl acetoacetate, potassium carbonate, and cesium carbonate were purchased from Sinopharm Chemical Reagent Co. Ltd. Acetamidine hydrochloride, benzamidine hydrochloride hydrate, copper(I) iodide, and alkynes were purchased from Alfa Aesar GmbH & Co. KG. Bis(triphenylphosphine) palladium(II) dichloride, tris(dibenzylideneacetone) dipalladium(0), and aryl iodides were purchased from Sigma–Aldrich Inc. 2,2′-Bipyridine was purchased from Tokyo Kasei Kogyo Co. Ltd. All other commercial reagents were used without further purification, unless otherwise indicated.

Melting points were determined in a capillary tube and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with Gemini-300 or Bruker AMX-400 spectrometers using chloroform-*d*, DMSO-d_6 or CF_3COOD as solvents. Chemical shifts (δ) reported in parts per million relative to chloroform-*d* (7.26 ppm ^{1}H, 77.07 ppm ^{13}C), DMSO-d_6 (2.50 ppm ^{1}H, 39.52 ppm ^{13}C), and CF_3COOD (11.50 ppm ^{1}H, 116.6 and 164.2 ppm ^{13}C). Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet). Coupling constants (*J*) are reported in hertz. Mass spectra were recorded with Varian MAT-711 and MAT-95 spectrometers.

4.2. General procedure of the preparation of pyrimidinols 3

To a solution of sodium (2.3 g, 0.1 mol) in EtOH (60 mL) were added ethyl acetoacetate **2** (6.38 mL, 0.05 mol) and amidine **1** (0.05 mol). The reaction mixture was refluxed for 18 h and then cooled to room temperature. The resulting mixture was adjusted to pH=5.5 using concentrated HCl and concentrated. The residue was directly purified by flash column chromatography to afford the product **3**.

4.2.1. 2,6-Dimethylpyrimidin-4-ol (3a, R_1=R_2=Me). Yield: 85%; white solid; mp 194–195.5 °C (lit.[16b] 194.5–

195 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.14 (br s, 1H), 6.17 (s, 1H), 2.46 (s, 3H), 2.29 (s, 3H).

4.2.2. 6-Methyl-2-phenylpyrimidin-4-ol (3b, R_1=Ph; R_2=Me). Yield: 98%; yellow solid; mp 217–218 °C (lit.[16d] 218–219 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.75 (br s, 1H), 8.18–8.15 (m, 2H), 7.57–7.50 (m, 3H), 6.30 (s, 1H), 2.40 (s, 3H).

4.3. General procedure for the preparation of iodopyrimidinols 4

To a well-stirred solution of **3** (10 mmol) in 1.25 N NaOH (18 mL) was added iodine (2.80 g, 11 mmol). The reaction mixture was refluxed for 2 h and then cooled to room temperature. The mixture was extracted with $CHCl_3$ for three times. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography to afford the product **4**.

4.3.1. 5-Iodo-2,6-dimethylpyrimidin-4-ol (4a). Yield: 49%; white solid; mp 196–199 °C (lit.[17b] 198–203 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.59 (s, 3H), 2.47 (s, 3H); LRMS (EI) *m*/*z* 250 (100, M^+).

4.3.2. 5-Iodo-6-methyl-2-phenylpyrimidin-4-ol (4b). Yield: 90%; white solid; mp 239–240 °C (lit.[17b] 249–251 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.26 (br s, 1H), 8.25–8.22 (m, 2H), 7.60–7.53 (m, 3H), 2.70 (s, 3H); LRMS (EI) *m*/*z* 313 ([M+1]$^+$), 312 (100, M^+), 209, 104; HRMS (EI) calcd for $C_{11}H_9IN_2O$ (M^+): 311.9760, found 311.9757.

4.4. General procedure for the preparation of alkynylpyrimidinols 6 by Sonogashira reaction

A mixture of iodopyrimidinol (1.00 mmol), alkyne (1.20 mmol), copper(I) iodide (0.05 mmol), dichlorobis(triphenylphosphine)-palladium (0.05 mmol), and diisopropylethylamine (1.00 mmol) in dry acetonitrile (10 mL) or DMF (5 mL) was stirred at 25–40 °C for 24 h under N_2 protection. The reaction mixture was filtered and the solid phase was washed with methanol (10 mL). The filtrate was concentrated, and the residue was purified by flash column chromatography to afford the coupling products **6a**–**g** (Method A). For compounds **6h** and **6i**, the reactant was changed into the corresponding hydroxyl protected iodopyrimidinol (Method B).

4.4.1. 2,6-Dimethyl-5-(2-*p*-tolylethynyl)pyrimidin-4-ol (6a). Yield: 86%; white solid; mp 151–153 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.73 (br s, 1H), 7.45 (d, J=8.4 Hz, 2H), 7.15 (d, J=8.4 Hz, 2H), 2.56 (s, 3H), 2.54 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.9, 161.0, 157.6, 138.4, 131.0, 129.4, 119.7, 106.5, 97.8, 82.9, 23.1, 21.2, 21.0; LRMS (EI) *m*/*z* 239 ([M+1]$^+$), 238 (100, M^+), 197; HRMS (EI) calcd for $C_{15}H_{14}N_2O$ (M^+): 238.1106, found 238.1115.

4.4.2. 5-(2-(2-Fluorophenyl)ethynyl)-2,6-dimethylpyrimidin-4-ol (6b). Yield: 83%; white solid; mp 117–119 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57–7.52 (m, 1H), 7.37–7.29 (m, 1H), 7.16–7.07 (m, 2H), 2.58 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.7, 161.6 (d, $^1J_{C-F}$=247.7 Hz), 160.9, 158.2, 133.0, 130.8 (d, $^3J_{C-F}$=8.7 Hz), 124.8 (d, $^4J_{C-F}$=3.2 Hz), 115.7 (d, $^2J_{C-F}$=20.4 Hz), 111.1 (d, $^3J_{C-F}$=15.5 Hz), 106.0, 90.7, 88.7, 22.9, 21.2; LRMS (EI) *m*/*z* 243 ([M+1]$^+$), 242 (100, M^+), 201; HRMS (EI) calcd for $C_{14}H_{11}FN_2O$ (M^+): 242.0855, found 242.0856.

4.4.3. 5-(2-(4-Methoxyphenyl)ethynyl)-2,6-dimethylpyrimidin-4-ol (6c). Yield: 92%; yellow solid; mp 158–159 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, J=8.7 Hz, 2H), 6.88 (d, J=8.7 Hz, 2H), 3.83 (s, 3H), 2.56 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.6, 161.0, 159.4, 157.3, 132.6, 114.6, 114.4, 107.0, 97.7, 82.0, 55.3, 23.0, 21.2; LRMS (EI) *m*/*z* 255 ([M+1]$^+$), 254 (21, M^+), 239, 84 (100); HRMS (EI) calcd for $C_{15}H_{14}N_2O_2$ (M^+): 254.1055, found 254.1065.

4.4.4. 5-(2-(4-(Trifluoromethyl)phenyl)ethynyl)-2,6-dimethylpyrimidin-4-ol (6d). Yield: 89%; white solid; mp 194–196 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66–7.59 (m, 4H), 2.57 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.1, 160.8, 158.4, 131.7, 128.6 (q, $^2J_{C-F}$=31.9 Hz), 126.9, 125.6, 124.0 (d, $^1J_{C-F=}$270.6 Hz), 105.7, 96.1, 86.3, 23.1, 21.2; LRMS (EI) *m*/*z* 293 ([M+1]$^+$), 292 (M^+), 251, 149 (100); HRMS (EI) calcd for $C_{15}H_{11}F_3N_2O$ (M^+): 292.0823, found 292.0830.

4.4.5. 5-(2-(2-Fluorophenyl)ethynyl)-6-methyl-2-phenylpyrimidin-4-ol (6e). Yield: 53%; yellow solid; mp 205–206 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.83 (br s, 1H), 8.21–8.18 (m, 2H), 7.60–7.53 (m, 4H), 7.39–7.31 (m, 1H), 7.18–7.11 (m, 2H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.7, 161.7 (d, $^1J_{C-F}$=248.1 Hz), 155.2, 133.1, 132.1, 131.9, 131.1 (d, $^3J_{C-F}$=8.2 Hz), 128.8, 128.1, 124.9 (d, $^4J_{C-F}$=3.2 Hz), 115.8 (d, $^2J_{C-F}$=20.5 Hz), 111.0 (d, $^3J_{C-F}$=15.4 Hz), 91.7, 88.9, 23.3; LRMS (EI) *m*/*z* 305 ([M+1]$^+$), 304 (M^+), 277, 201, 149 (100); HRMS (EI) calcd for $C_{19}H_{13}FN_2O$ (M^+): 304.1012, found 304.1019.

4.4.6. 5-(2-(4-Methoxyphenyl)ethynyl)-6-methyl-2-phenylpyrimidin-4-ol (6f). Yield: 92%; yellow solid; mp 157–160 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23–8.20 (m, 2H), 7.56–7.51 (m, 5H), 6.91 (d, J=8.7 Hz, 2H), 3.86 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.4, 159.6, 154.5, 132.7, 131.9, 128.7, 127.9, 114.6, 114.4, 98.9, 82.3, 55.3, 23.3; LRMS (EI) *m*/*z* 317 ([M+1]$^+$), 316 (100, M^+), 301, 277, 149; HRMS (EI) calcd for $C_{20}H_{16}N_2O_2$ (M^+): 316.1212, found 316.1212.

4.4.7. 5-(2-(4-(Trifluoromethyl)phenyl)ethynyl)-6-methyl-2-phenylpyrimidin-4-ol (6g). Yield: 60%; yellow solid; mp 204–207 °C; ^{1}H NMR (300 MHz, CF_3COOD): δ 7.91 (d, J=8.1 Hz, 2H), 7.81 (t, J=7.5 Hz, 1H), 7.65–7.53 (m, 6H), 2.77 (s, 3H); ^{13}C NMR (75 MHz, CF_3COOD): δ 160.9, 159.9, 139.8, 134.88 (q, $^2J_{C-F}$=32.2 Hz), 134.3, 132.8, 130.6, 127.6, 127.5, 126.4, 124.9, 124.1, 113.6, 106.5, 79.4, 19.9; LRMS (EI) *m*/*z* 354 (M^+), 277 (100); HRMS (EI) calcd for $C_{20}H_{13}F_3N_2O$ (M^+): 354.0980, found 354.0976.

4.4.8. 6-(4-Hydroxy-6-methyl-2-phenylpyrimidin-5-yl)-hex-5-ynonitrile (6h). Yield: 35%; white solid; mp 145–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.95 (br s, 1H),

8.14–8.12 (m, 2H), 7.56–7.53 (m, 3H), 2.74 (t, J=6.9 Hz, 2H), 2.57 (t, J=7.2 Hz, 2H), 2.56 (s, 3H), 2.05–1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 164.4, 154.1, 132.2, 131.6, 128.8, 128.0, 119.1, 108.1, 97.9, 75.3, 24.7, 23.7, 19.0, 16.2; LRMS (EI) m/z 278 ([M+1]$^+$), 277 (100, M$^+$), 223; HRMS (EI) calcd for $C_{17}H_{15}N_3O$ (M$^+$): 277.1215, found 277.1211.

4.4.9. 6-Methyl-5-(3,3-dimethylbut-1-ynyl)-2-phenylpyrimidin-4-ol (6i). Yield: 65%; white solid; mp 199–201 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27–8.24 (m, 2H), 7.55–7.52 (m, 3H), 2.56 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 164.5, 153.7, 131.8, 128.7, 128.0, 109.5, 108.7, 71.9, 31.1, 28.6, 23.6; LRMS (EI) m/z 266 (50, M$^+$), 251 (100); HRMS (EI) calcd for $C_{17}H_{18}N_2O$ (M$^+$): 266.1419, found 266.1423.

4.5. General procedure for the synthesis of furo[2,3-*d*]-pyrimidines 9

To a solution of alkynylpyrimidinol (0.500 mmol), ArI (1.00 mmol), bpy (0.100 mmol), Cs_2CO_3 (1.00 mmol), and acetonitrile (20 mL) was added $Pd_2(dba)_3$ (0.025 mmol) under N_2 atmosphere. The reaction was stirred at 50 °C for 24 h. The mixture was filtered and the solid phase was washed with methanol (10 mL). The filtrate was concentrated and the residue was purified by flash column chromatography to afford the corresponding product.

4.5.1. 2,4-Dimethyl-5-phenyl-6-*p*-tolylfuro[2,3-*d*]pyrimidine (9a). Yield: 57%; white solid; mp 103–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51–7.48 (m, 3H), 7.45–7.40 (m, 4H), 7.09 (d, J=8.4 Hz, 2H), 2.79 (s, 3H), 2.32 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 162.6, 160.9, 149.3, 139.0, 132.6, 130.3, 129.2, 129.1, 128.4, 126.6, 126.4, 116.4, 114.8, 25.8, 21.7, 21.3; LRMS (EI) m/z 315 ([M+1]$^+$), 314 (100, M$^+$), 173; HRMS (EI) calcd for $C_{21}H_{18}N_2O$ (M$^+$): 314.1419, found 314.1423.

4.5.2. 5-(4-Methoxyphenyl)-2,4-dimethyl-6-*p*-tolylfuro[2,3-*d*]pyrimidine (9b). Yield: 70%; white solid; mp 133–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, J=8.1 Hz, 2H), 7.32 (d, J=6.6 Hz, 2H), 7.09 (d, J=8.1 Hz, 2H), 7.02 (d, J=6.6 Hz, 2H), 3.90 (s, 3H), 2.79 (s, 3H), 2.32 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 162.6, 161.0, 159.7, 158.4, 149.5, 139.0, 131.4, 129.2, 126.6, 124.4, 116.7, 114.5, 55.3, 25.7, 21.6, 21.3; LRMS (EI) m/z 345 ([M+1]$^+$), 344 (100, M$^+$), 119; HRMS (EI) calcd for $C_{22}H_{20}N_2O_2$ (M$^+$): 344.1525, found 344.1531.

4.5.3. 2,4-Dimethyl-5-(thiophen-2-yl)-6-*p*-tolylfuro[2,3-*d*]-pyrimidine (9c). Yield: 55%; white solid; mp 126–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55–7.52 (m, 3H), 7.21–7.18 (m, 1H), 7.16–7.14 (m, 2H), 7.13–7.12 (m, 1H), 2.80 (s, 3H), 2.37 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 163.2, 161.4, 151.6, 139.8, 132.6, 129.5, 129.4, 128.0, 127.9, 126.9, 126.1, 116.8, 107.3, 25.6, 21.2, 21.0; LRMS (EI) m/z 321 ([M+1]$^+$), 320 (100, M$^+$), 119, 91; HRMS (EI) calcd for $C_{19}H_{16}N_2OS$ (M$^+$): 320.0983, found 320.0990.

4.5.4. Methyl 4-(2,4-dimethyl-6-*p*-tolylfuro[2,3-*d*]pyrimidin-5-yl)benzoate (9d). Yield: 36%; white solid; mp 184–186 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, J=8.4 Hz, 2H), 7.52 (d, J=8.4 Hz, 2H), 7.39 (d, J=8.4 Hz, 2H), 7.09 (d, J=8.4 Hz, 2H), 3.97 (s, 3H), 2.81 (s, 3H), 2.32 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 165.6, 163.0, 160.8, 149.7, 139.5, 137.7, 130.5, 130.3, 129.3, 126.8, 126.0, 116.1, 113.9, 52.3, 25.7, 21.8, 21.3; LRMS (EI) m/z 373 ([M+1]$^+$), 372 (100, M$^+$), 238, 119; HRMS (EI) calcd for $C_{23}H_{20}N_2O_3$ (M$^+$): 372.1474, found 372.1475.

4.5.5. 6-(2-Fluorophenyl)-5-(4-methoxyphenyl)-2,4-dimethylfuro[2,3-*d*]pyrimidine (9e). Yield: 75%; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51–7.45 (m, 1H), 7.41–7.33 (m, 1H), 7.29–7.27 (m, 2H), 7.17–7.08 (m, 2H), 6.95 (d, J=6.9 Hz, 2H), 3.88 (s, 3H), 2.83 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 163.1, 161.6, 159.7 (d, $^1J_{C-F}$=252.8 Hz), 159.5, 145.4, 131.2, 131.1 (d, $^4J_{C-F}$=3.6 Hz), 131.0, 124.0, 123.8, 118.4, 117.5 (d, $^3J_{C-F}$= 16.6 Hz), 116.3 (d, $^2J_{C-F}$=21.4 Hz), 115.5, 114.0, 55.2, 25.8, 22.1; LRMS (EI) m/z 348 (14, M$^+$), 156, 86, 84 (100); HRMS (EI) calcd for $C_{21}H_{17}FN_2O_2$ (M$^+$): 348.1274, found 348.1269.

4.5.6. 5,6-Bis(4-methoxyphenyl)-2,4-dimethylfuro-[2,3-*d*]pyrimidine (9f). Yield: 43%; white solid; mp 138–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, J=9.0 Hz, 2H), 7.32 (d, J=9.0 Hz, 2H), 7.02 (d, J=9.0 Hz, 2H), 6.81 (d, J=9.0 Hz, 2H), 3.89 (s, 3H), 3.79 (s, 3H), 2.78 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 162.3, 160.6, 160.0, 159.6, 149.4, 131.5, 128.2, 124.5, 122.0, 116.7, 114.5, 114.0, 113.5, 55.3, 55.2, 25.7, 21.6; LRMS (EI) m/z 360 (40, M$^+$), 254 (100), 239, 156, 84; HRMS (EI) calcd for $C_{22}H_{20}N_2O_3$ (M$^+$): 360.1474, found 360.1467.

4.5.7. 6-(4-(Trifluoromethyl)phenyl)-5-(4-methoxyphenyl)-2,4-dimethylfuro[2,3-*d*]pyrimidine (9g). Yield: 48%; white solid; mp 47–49 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J=8.4 Hz, 2H), 7.54 (d, J=8.7 Hz, 2H), 7.34 (d, J=8.4 Hz, 2H), 7.05 (d, J=8.7 Hz, 2H), 3.91 (s, 3H), 2.80 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 164.0, 162.4, 160.4, 147.9, 133.1, 131.5, 130.6 (q, $^2J_{C-F}$=32.8 Hz), 127.0, 125.8, 124.1 (q, $^1J_{C-F}$= 270.5 Hz), 123.9, 117.8, 116.7, 115.2, 55.6, 26.2, 22.0; LRMS (EI) m/z 399 ([M+1]$^+$), 398 (100, M$^+$), 173; HRMS (EI) calcd for $C_{22}H_{17}F_3N_2O_2$ (M$^+$): 398.1242, found 398.1243.

4.5.8. 6-(2-Fluorophenyl)-5-(4-methoxyphenyl)-4-methyl-2-phenylfuro[2,3-*d*]pyrimidine (9h). Yield: 75%; white solid; mp 130–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57–8.54 (m, 2H), 7.52–7.48 (m, 3H), 7.39–7.26 (m, 4H), 7.15–7.03 (m, 2H), 6.95 (d, J=8.7 Hz, 2H), 3.86 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 161.9, 159.9, 159.8 (d, $^1J_{C-F}$=253.2 Hz), 159.5, 146.2, 137.6, 131.2, 131.1, 131.0, 130.3, 128.5, 128.3, 124.0, 123.9, 118.8, 117.6 (d, $^3J_{C-F}$=13.6 Hz), 116.44, 116.39 (d, $^2J_{C-F}$=21.4 Hz), 114.0, 55.2, 22.5; LRMS (EI) m/z 411 ([M+1]$^+$), 410 (100, M$^+$), 233, 123; HRMS (EI) calcd for $C_{26}H_{19}FN_2O_2$ (M$^+$): 410.1431, found 410.1388.

4.5.9. 5,6-Bis(4-methoxyphenyl)-4-methyl-2-phenylfuro[2,3-*d*]pyrimidine (9i). Yield: 49%; yellow solid; mp 145–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55–8.51 (m, 2H), 7.55 (d, J=8.7 Hz, 2H), 7.50–7.48 (m, 3H), 7.37

(d, J=8.4 Hz, 2H), 7.05 (d, J=8.4 Hz, 2H), 6.83 (d, J=8.7 Hz, 2H), 3.91 (s, 3H), 3.80 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 160.9, 160.1, 159.7, 159.3, 150.2, 137.8, 131.5, 130.1, 128.5, 128.3, 128.2, 124.6, 122.1, 117.7, 114.6, 114.0, 113.9, 55.30, 55.27, 22.03; LRMS (EI) m/z 423 ([M+1]$^+$), 422 (100, M$^+$), 407, 316, 149; HRMS (EI) calcd for $C_{27}H_{22}N_2O_3$ (M$^+$): 422.1630, found 422.1615.

4.5.10. 6-(4-(Trifluoromethyl)phenyl)-5-(4-methoxyphenyl)-4-methyl-2-phenylfuro[2,3-*d*]pyrimidine (9j). Yield: 68%; yellow solid; mp 188–192 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55–8.52 (m, 2H), 7.71 (d, J=8.4 Hz, 2H), 7.55 (d, J=9.0 Hz, 2H), 7.50–7.48 (m, 3H), 7.36 (d, J=8.4 Hz, 2H), 7.07 (d, J=8.4 Hz, 2H), 3.91 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 162.3, 160.5, 160.1, 148.2, 137.5, 132.8, 131.2, 130.5, 128.6, 128.4, 126.8, 125.5, 123.8, 117.9 117.2, 114.9, 55.4, 22.1; LRMS (EI) m/z 461 ([M+1]$^+$), 460 (100, M$^+$), 173; HRMS (EI) calcd for $C_{27}H_{19}F_3N_2O_2$ (M$^+$): 460.1399, found 460.1398.

4.5.11. 4-(5-(4-Methoxyphenyl)-4-methyl-2-phenylfuro[2,3-*d*]pyrimidin-6-yl)butanonitrile (9k). Yield: 38%; white solid; mp 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.54–8.50 (m, 2H), 7.51–7.48 (m, 3H), 7.30 (d, J=8.7 Hz, 2H), 7.05 (d, J=8.7 Hz, 2H), 3.90 (s, 3H), 2.92 (t, J=7.5 Hz, 2H), 2.46 (s, 3H), 2.42 (t, J=6.9 Hz, 2H), 2.19–2.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 161.0, 159.7, 159.5, 151.9, 137.6, 131.2, 130.3, 128.5, 128.2, 123.0, 118.8, 117.2, 115.9, 114.2, 55.3, 25.1, 23.7, 22.2, 16.6; LRMS (EI) m/z 384 ([M+1]$^+$), 383 (70, M$^+$), 329, 277, 223 (100); HRMS (EI) calcd for $C_{24}H_{21}N_3O_2$ (M$^+$): 383.1634, found 383.1639.

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