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Focused microwave-assisted efficient and convenient synthesis of new pyrido[2,3-*d*] pyrimidinone derivatives

Abstract: A rapid and efficient method for the preparation of new pyrido[2,3-*d*]pyrimidinone derivatives by the condensation of 2-amino-4-aryl-6-arylnicotinamides with carbon disulfide or cycloalkanones under focused microwave irradiation is described.

Keywords: cyclization; microwave; pyrido[2,3-*d*]pyrimidinone; synthesis.

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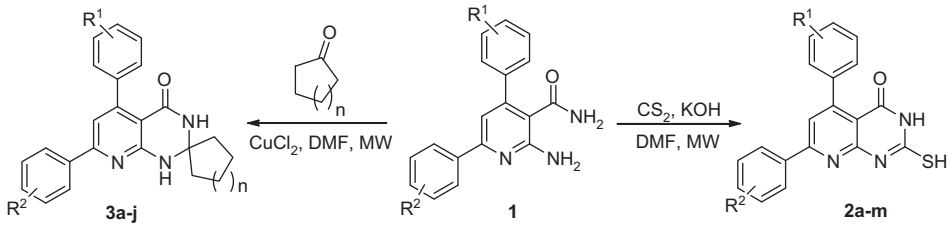
Introduction

Microwave irradiation (MWI) has been utilized extensively as a clean source of energy for the synthesis of organic compounds (Galema, 1997; Van Eldik and Hubbard, 1997; Varma, 1999). Some important reviews have been published in recent years, covering a large number of microwave induced reactions (Dallinger and Kappe, 2007; Polshettiwar and Varma, 2008). We have reported the PS-supported, Pd(II)-catalyzed coupling reaction which was performed in a focused microwave synthesis system so that it is possible to control the temperature, pressure, microwave power, and reaction time very easily and with a high degree of reproducibility (Bai et al., 2004; Bai and Wang, 2008).

Heterocyclic systems are common structural elements in many natural products and pharmacologically active substances. Accordingly, the development of efficient methods for the synthesis of heterocyclic compounds has been posing a real challenge to organic chemists for over a century. For example, the 4(3*H*)-quinazolinone moiety has been found in several bioactive natural products (Welch et al., 2001; Saleh et al., 2004). Many different classes of ligands have been designed, synthesized, and tested at the A1 receptor as antagonists, and these encompass all kinds of different mono-, bi-, tri-, and even quadricyclic mostly nitrogen-containing aromatic compounds (Chang et al., 2004). In addition, 2-spiroquinazolinones are an important class of fused heterocycles that have attracted significant interest in medicinal chemistry, in view of their great variety of biological and pharmaceutical activities (Hirose et al., 1973; Tinker et al., 2003; Birch et al., 2005; Mustazza et al., 2006). Quinazolinones are also useful synthetic materials in heterocyclic chemistry (Hsu et al., 2008). There are a number of synthetic methods available for the preparation of quinazolinones using *N*-(2-cyanoaryl)amides (Kim et al., 2010), 2-aminobenzonitrile (Kabri et al., 2009), 2-aminobenzamide (Bakavoli et al., 2007a), and isatoic anhydride (Bakavoli et al., 2007b) as common starting materials. New synthesis of pyrazolo[3,4-*d*]pyrimidine derivatives by the reaction of 5-amino-1-(2,4-dinitrophenyl)-1*H*-4-pyrazolcarboxamides with aromatic aldehydes has been described (Bakavoli et al., 2010). The preparation of spiro[cyclohexane-1,2′(1′*H*)-quinazolin]-4′(3′*H*)-one has also been reported (Miklós and Fülöp, 2010). However, the preparation of pyrido[2,3-*d*]pyrimidinone derivatives by using the MWI method has not been reported previously. Herein, we report a rapid and efficient procedure to synthesize pyrido[2,3-*d*]pyrimidinone derivatives by condensation of 2-amino-4-aryl-6-arylnicotinamides with carbon disulfide or cycloalkanones using a focused MWI method (Scheme 1).

Results and discussion

To synthesize pyrido[2,3-*d*]pyrimidinone derivatives **2** and **3**, various 2-amino-4-aryl-6-arylnicotinamides **1**



2a: $R^1 = R^2 = H$; **2b**: R^1 = 4-Cl, $R^2 = H$; **2c**: R^1 = 4-Me, $R^2 = H$; **2d**: R^1 = 4-MeO, $R^2 = H$; **2e**: R^1 = 4-F, $R^2 = H$
2f: R^1 = 2-MeO, $R^2 = H$; **2g**: R^1 = 4-Br, $R^2 = H$; **2h**: $R^1 = H$, R^2 = 4-Br; **2i**: R^1 = 4-Me, R^2 = 4-Br
2j: R^1 = 4-Cl, R^2 = 4-Br; **2k**: R^1 = 4-F, R^2 = 4-Br; **2l**: R^1 = 4-Br, R^2 = 4-Br; **2m**: R^1 = 4-MeO, R^2 = 4-Br;
3a: $R^1 = R^2 = H$, n = 1; **3b**: $R^1 = R^2 = H$, n = 2; **3c**: R^1 = 4-Cl, $R^2 = H$, n = 1; **3d**: R^1 = 4-Cl, $R^1 = H$, n = 2
3e: R^1 = 4-Me, $R^2 = H$, n = 1; **3f**: R^1 = 4-Me, $R^2 = H$, n = 2; **3g**: R^1 = 4-F, $R^2 = H$, n = 1; **3h**: R^1 = 4-F, $R^2 = H$, n = 2
3i: R^1 = 4-Br, R^2 = 4-Br, n = 2; **3j**: R^1 = 4-Me, R^2 = 4-Br, n = 1;

Scheme 1 Synthesis of pyrido[2,3-*d*]pyrimidinone derivatives.

were employed as starting materials to develop a cluster of new compounds and corresponding key intermediates according to a known procedure (Kambe et al., 1980; Chang et al., 2007). Initially, our study was performed by the focused microwave-promoted model reaction of **1a** with carbon disulfide which furnished the expected compound **2a** (Scheme 1). The best yield (81%) of **2a** was obtained by carrying out the reaction in DMF at 155°C, with MW energy of 10 W for 15 min using substrate **1a** (1 mmol), CS_2 (2 mmol), and KOH (3 mmol). Other bases including K_2CO_3, NaOH or K_3PO_4 could also be used, although the yields of **2a** were lower. The use of NaOH was especially disadvantageous to give product **2a** in a low yield of 40%. Product **2a** could not be obtained in the absence of base. After experimenting with various bases, base quantity, reaction time, and reaction temperature, the optimized conditions for the preparation of **2a** are as follows: **1a** (1 mmol), CS_2 (2 mmol), KOH (3 mmol), and DMF (2 mL), focused MWI at 10 W. Under these optimal conditions, we used various 2-amino-4-aryl-6-arylnicotinamides **1** to test the reaction scope. A wide array of substrates **1** containing an electron-withdrawing group and/or an electron-donating group were efficiently reacted with CS_2 giving the corresponding pyrido[2,3-*d*] pyrimidinones **2a–m** in good to excellent isolated yields (74–95%).

After successful preparation of compounds **2a–m**, another synthetic method was examined by the cyclization of 2-amino-4-aryl-6-arylnicotinamides **1** with cycloalkanones, including cyclopentanone and cyclohexanone, in the presence of $CuCl_2$ and using DMF as the solvent under focused MWI at 200°C, 10 W (Scheme 1). The corresponding products spiro[cycloalkane-1,2′-(1′*H*)-5-aryl-7-arylpyrido[2,3-*d*]pyrimidin]-4′(3′*H*)-ones **3a–j** were obtained in moderate to good yields (70–95%) within 8 min. The yields are good for the reactions of **1** bearing electron-donating, electron-neutral, and electron-withdrawing substituents on the benzene ring. The formation of six-membered spiro products (n=2) is more efficient (Scheme 1).

In the absence of focused MWI the reaction times are long and the yields are quite low. The results of many experiments under different conditions show that the synthesis of compounds **2** and **3** under focused MWI is 24–45 times faster in comparison to the classical heating method and the yields (>80%) are higher than in the conventional heating method (<30%). Although the beneficial MWI in organic synthesis has been in use in varied research fields for many years, the mode of action is not yet fully understood (Herrero et al., 2008; Kappe, 2008).

Conclusions

A simple and efficient practical method for heterocyclization of 2-amino-4-aryl-6-arylnicotinamides **1** to products **2a–m** and **3a–j** has been developed. The salient features include high yields and ease of work-up.

Experimental

IR spectra were measured using KBr pellets on a Digilab Merlin FT-IR spectrophotometer. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded on a Mercury plus 400 MHz spectrometer in DMSO-d_6 with TMS as an internal standard. Melting points were determined on an XT-4 electrothermal micromelting point apparatus and are uncorrected. Mass spectra were obtained on a Bruker Daltonics APEXII 47e FT-ICR spectrometer. Elemental analyses were performed on a Carlo-Erba 1106 Elemental Analysis instrument. Microwave reactions were conducted using a CEM Focused Microwave™ Synthesis System (CEM Corp., Matthews, NC, USA). All experiments

were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon coated magnetic stir bar in the vessel.

General procedure for the synthesis of 5-aryl-2-mercapto-7-arylpyrido[2,3-*d*]-pyrimidin-4(3*H*)-ones 2a–m

In a 10-mL glass tube were placed 2-amino-4-aryl-6-arylnicotinamide **1** (1 mmol), CS_2 (2 mmol), KOH (3 mmol), DMF (2 mL), and a magnetic stir bar. The vessel was sealed with a septum and placed in the microwave cavity. Microwave irradiation of 10 W was used; the temperature ramped from room temperature to 155°C. Once 155°C was reached, the reaction mixture was held at this temperature for 15 min. After cooling, the tube was opened and the contents poured into a flask. Then water was added and the resultant precipitate was filtered and crystallized from DMF/ethanol.

2-Mercapto-5,7-diphenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (2) Mp > 250°C; yield 81%; IR: 3107, 3051, 2892, 1682, 1597, 1555, 1496, 1406, 1177, 766 cm^{-1}; ^1H NMR: δ 13.20 (br, 1H), 12.40 (br, 1H), 8.24 (d, *J* = 6.4 Hz, 2H), 7.65–7.43 (m, 9H); ^{13}C NMR: δ 175.5, 159.3, 159.1, 154.1, 153.5, 138.7, 136.8, 130.8, 129.0, 128.7, 128.1, 127.6, 127.5, 118.7, 108.2; MS (EI) m/z 331 (M^+). Anal. Calcd for $C_{19}H_{13}N_3OS$: C, 68.86; H, 3.95; N, 12.68. Found: C, 68.98; H, 4.08; N, 12.60.

5-(4-Chlorophenyl)-2-mercapto-7-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (2b) Mp > 250°C; yield 88%; IR: 3125, 3047, 2899, 2539, 1676, 1597, 1555, 1494, 1176, 772 cm^{-1}; ^1H NMR: δ 13.14 (br, 1H), 12.43 (br, 1H), 8.24 (m, 2H), 7.66–7.49 (m, 8H); ^{13}C NMR: δ 175.3, 159.5, 158.8, 152.7, 152.3, 137.2, 136.5, 133.2, 131.0, 130.7, 129.0, 127.7, 127.5, 119.0, 108.1; MS (EI) m/z 365 (M^+). Anal. Calcd for $C_{19}H_{12}ClN_3OS$: C, 62.38; H, 3.31; N, 11.49. Found: C, 62.12; H, 3.37; N, 11.40.

2-Mercapto-7-phenyl-5-(p-tolyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (2c) Mp > 250°C; yield 93%; IR: 3055, 2910, 1701, 1601, 1555, 1170, 776 cm^{-1}; ^1H NMR: δ 13.09 (br, 1H), 12.38 (br, 1H), 8.23 (m, 2H), 7.61–7.23 (m, 8H), 2.38 (s, 3H); ^{13}C NMR: δ 175.2, 159.3, 158.7, 153.9, 152.7, 137.8, 136.6, 135.4, 130.9, 129.0, 128.9, 128.2, 127.7, 119.3, 108.0, 21.0; MS (EI) m/z 345 (M^+). Anal. Calcd for $C_{20}H_{15}N_3OS$: C, 69.54; H, 4.38; N, 12.17. Found: C, 69.67; H, 4.51; N, 12.10.

2-Mercapto-5-(4-methoxyphenyl)-7-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (2d) Mp > 250°C; yield 80%; IR: 3120, 3050, 2900, 2538, 1676, 1600, 1492, 1495, 1176, 778 cm^{-1}; ^1H NMR: δ 14.49 (br, 1H), 13.32 (br, 1H), 8.29 (m, 2H), 7.80–6.91 (m, 8H), 3.81 (s, 3H); ^{13}C NMR: δ 175.4, 159.5, 158.6, 152.6, 151.4, 137.6, 135.5, 133.0, 130.0, 129.5, 128.1, 127.7, 127.9, 119.2, 108.0, 58.9; MS (EI) m/z 361 (M^+). Anal. Calcd for $C_{20}H_{15}N_3O_2S$: C, 66.46; H, 4.18; N, 11.63. Found: C, 66.65; H, 4.27; N, 11.52.

5-(4-Fluorophenyl)-2-mercapto-7-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (2e) Mp > 250°C; yield 74%; IR: 3067, 2917, 1701, 1668, 1603, 1557, 1508, 1410, 1173, 774 cm^{-1}; ^1H NMR: δ 12.89 (br, 1H), 12.28 (br, 1H), 8.09 (m, 2H), 7.51–7.40 (m, 8H); ^{13}C NMR: δ 172.8, 157.0, 156.3, 150.2, 149.8, 134.7, 134.0, 130.0, 128.5, 128.2, 126.5, 125.0, 125.0, 116.5, 105.6; MS (EI) m/z 349 (M^+). Anal. Calcd for $C_{19}H_{12}FN_3OS$: C, 65.32; H, 3.46; N, 12.03. Found: C, 65.44; H, 3.59; N, 11.95.

2-Mercapto-5-(2-methoxyphenyl)-7-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (2f) Mp > 250°C; yield; 83%; IR: 3163, 3061, 2930, 2860, 1669, 1588, 1548, 1496, 1364, 1173, 753 cm^{-1}; ^1H NMR: δ 13.16 (br, 1H), 12.38 (br, 1H), 8.24 (m, 2H), 7.70–6.81 (m, 8H), 3.82 (s, 3H); ^{13}C NMR: δ 174.3, 160.5, 148.8, 142.7, 142.0, 127.2, 126.5, 123.2, 121.0, 120.7, 119.0, 117.7, 117.5, 109.0, 100.1, 57.7; MS (EI) m/z 361 (M^+). Anal. Calcd for $C_{20}H_{15}N_3O_2S$: C, 66.46; H, 4.18; N, 11.63. Found: C, 66.23; H, 4.42; N, 11.67.

5-(4-Bromophenyl)-2-mercapto-7-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (2g) Mp > 250°C; yield 78%; IR: 3128, 3063, 2903, 2541, 1677, 1595, 1553, 1492, 1406, 1176, 772 cm^{-1}; ^1H NMR: δ 13.27 (br, 1H), 12.56 (br, 1H), 8.25 (m, 2H), 7.68–7.42 (m, 8H); ^{13}C NMR: δ 175.3, 159.6, 158.8, 152.6, 152.4, 137.6, 136.5, 133.2, 131.0, 130.5, 129.1, 127.7, 121.9, 119.0, 108.0; MS (EI) m/z 409 (M^+). Anal. Calcd for $C_{19}H_{12}BrN_3OS$: C, 55.62; H, 2.95; N, 10.24. Found: C, 55.46; H, 3.20; N, 10.27.

7-(4-Bromophenyl)-2-mercapto-5-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (2h) Mp > 250°C; yield 83%; IR: 3092, 3058, 2868, 2541, 1705, 1647, 1595, 1566, 1402, 1185, 765 cm^{-1}; ^1H NMR: δ 13.15 (br, 1H), 12.46 (br, 1H), 8.22 (d, *J* = 8.4 Hz, 2H), 7.95–7.44 (m, 8H); ^{13}C NMR: δ 175.2, 158.6, 158.2, 154.0, 152.6, 138.3, 135.7, 132.0, 129.7, 128.8, 128.3, 127.6, 124.8, 119.2, 108.3; MS (EI) m/z 409 (M^+). Anal. Calcd for $C_{19}H_{12}BrN_3OS$: C, 55.62; H, 2.95; N, 10.24. Found: C, 55.77; H, 3.07; N, 10.17.

7-(4-Bromophenyl)-2-mercapto-5-(p-tolyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (2i) Mp > 250°C; yield 95%; IR: 3042, 2911, 2482, 1590, 1553, 1510, 1493, 1152, 812, 712 cm^{-1}; ^1H NMR: δ 13.18 (br, 1H), 12.47 (br, 1H), 8.24 (m, 2H), 7.65–7.33 (m, 7H), 2.40 (s, 3H); ^{13}C NMR: δ 174.1, 158.5, 157.7, 152.8, 151.7, 136.8, 135.6, 134.5, 129.9, 128.0, 127.9, 126.4, 125.7, 118.3, 108.0, 19.7; MS (EI) m/z 423 (M^+). Anal. Calcd for $C_{20}H_{14}BrN_3OS$: C, 56.61; H, 3.33; N, 9.90. Found: C, 56.81; H, 3.41; N, 9.87.

7-(4-Bromophenyl)-5-(4-chlorophenyl)-2-mercaptopyrido[2,3-*d*]pyrimidin-4(3*H*)-one (2j) Mp > 250°C; yield 90%; IR: 3125, 3047, 2899, 2539, 1631, 1597, 1574, 1491, 1012, 824, 667 cm^{-1}; ^1H NMR: δ 13.13 (br, 1H), 12.45 (br, 1H), 8.23 (d, *J* = 7.0 Hz, 2H), 7.81–7.47 (m, 7H); ^{13}C NMR: δ 173.4, 157.4, 156.8, 150.7, 150.3, 135.2, 134.5, 131.2, 129.0, 128.7, 127.0, 125.7, 125.5, 117.0, 106.1; MS (EI) m/z 443 (M^+). Anal. Calcd for $C_{19}H_{11}BrClN_3OS$: C, 51.31; H, 2.49; N, 9.45. Found: C, 51.26; H, 2.56; N, 9.33.

7-(4-Bromophenyl)-5-(4-fluorophenyl)-2-mercaptopyrido[2,3-*d*]pyrimidin-4(3*H*)-one (2k) Mp > 250°C; yield 80%; IR: 3067, 2928, 1701, 1668, 1634, 1557, 1509, 1452, 1173, 774 cm^{-1}; ^1H NMR: δ 13.02 (br, 1H), 12.37 (br, 1H), 8.16 (d, *J* = 7.0 Hz, 2H), 7.73–7.43 (m, 7H); ^{13}C NMR: δ 169.5, 153.0, 152.0, 147.2, 146.8, 131.7, 131.0, 127.0, 125.5, 125.2, 123.5, 122.0, 121.0, 113.5, 102.6; MS (EI) m/z 427 (M^+). Anal. Calcd for $C_{19}H_{11}BrFN_3OS$: C, 53.28; H, 2.59; N, 9.81. Found: C, 53.01; H, 2.66; N, 9.72.

5,7-Bis(4-bromophenyl)-2-mercaptopyrido[2,3-*d*]pyrimidin-4(3*H*)-one (2l) Mp > 250°C; yield 92%; IR: 3128, 3060, 2903, 2545, 1678, 1595, 1553, 1492, 1406, 1176, 778 cm^{-1}; ^1H NMR: δ 13.21 (br, 1H), 12.51 (br, 1H), 8.24 (d, *J* = 7.0 Hz, 2H), 7.82–7.43 (m, 7H); ^{13}C NMR: δ 173.1, 158.5, 157.6, 151.6, 151.3, 136.2, 135.5, 132.0, 130.0, 129.4, 128.1, 126.3,

120.9, 118.4, 107.2; MS (EI) *m/z* 489 (M^+). Anal. Calcd for $C_{19}H_{11}Br_2N_3OS$: C, 46.65; H, 2.27; N, 8.59. Found: C, 46.29; H, 2.38; N, 8.65.

7-(4-Bromophenyl)-2-mercapto-5-(4-methoxyphenyl) pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (2m) Mp > 250°C; yield 86%; IR: 3165, 3055, 2948, 2838, 1701, 1591, 1555, 1512, 1169, 829 cm^{-1}; ^1H NMR: δ 13.82 (br, 1H), 12.89 (br, 1H), 8.26 (d, *J* = 7.0 Hz, 2H), 7.88–7.18 (m, 7H), 3.79 (s, 3H); ^{13}C NMR: δ 171.4, 155.5, 154.6, 148.6, 147.4, 133.6, 131.5, 129.0, 126.0, 125.5, 124.1, 123.7, 122.9, 115.2, 104.0, 54.5; MS (EI) m/z 439 (M^+). Anal. Calcd for $C_{20}H_{14}BrN_3O_2S$: C, 54.56; H, 3.20; N, 9.54. Found: C, 54.75; H, 3.26; N, 9.45.

General procedure for the synthesis of spiro[cycloalkane-1,2′-(1′*H*)-5-aryl-7-arylpyrido[2,3-*d*]pyrimidin]-4′(3′*H*)-ones 3a–j

In a 10-mL glass tube were placed 2-amino-4-aryl-6-arylnicotinamide **1** (1 mmol), cycloalkanones (1 mmol), $CuCl_2$ (0.1 mmol), DMF (2 mL), and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity. MWI of 10 W was used, the temperature being increased from room temperature to 200°C. Once 200°C was reached, the mixture was held at this temperature for 8 min. After cooling the tube was opened and the contents poured into a flask. Then water was added and the resultant precipitate was filtered and crystallized from DMF/ethanol.

5′,7′-Diphenyl-1′H-spiro[cyclopentane-1,2′-pyrido[2,3-*d*] pyrimidin]-4′(3′*H*)-one (3a) Mp > 250°C; yield; 84%; IR: 3254, 3193, 3057, 2960, 2868, 1669, 1562, 1496, 1232, 761, 701 cm^{-1}; ^1H NMR: δ 8.27 (d, *J* = 6.4 Hz, 2H), 8.23 (br, 1H), 7.89 (br, 1H), 7.68–7.46 (m, 9H), 1.92 (m, 4H), 1.71 (m, 4H); ^{13}C NMR: δ 159.3, 159.2, 157.8, 156.0, 154.8, 148.8, 135.0, 133.5, 127.7, 127.6, 126.7, 125.7, 124.0, 111.5, 111.3, 110.0, 102.7, 72.5, 19.2; MS (EI) m/z 355 (M^+). Anal. Calcd for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82. Found: C, 77.68; H, 6.03; N, 11.93.

5′,7′-Diphenyl-1′H-spiro[cyclohexane-1,2′-pyrido[2,3-*d*] pyrimidin]-4′(3′*H*)-one (3b) Mp > 250°C; yield; 85%; IR: 3254, 3107, 3051, 2950, 2930, 2801, 1682, 1597, 1555, 1496, 1406, 1177, 704 cm^{-1}; ^1H NMR: δ 8.25 (m, 2H), 7.66–7.44 (m, 9H), 1.83 (m, 4H), 1.61 (m, 4H), 1.39 (m, 2H); ^{13}C NMR: δ 159.9, 159.1, 156.7, 154.1, 153.3, 147.6, 133.9, 132.4, 126.6, 126.5, 125.6, 124.6, 123.0, 110.5, 110.3, 109.0, 101.5, 62.3, 32.4, 20.6, 17.0; MS (EI) m/z 369 (M^+). Anal. Calcd for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.27; N, 11.37. Found: C, 77.78; H, 6.33; N, 11.28.

5′-(4-Chlorophenyl)-7′-phenyl-1′H-spiro[cyclopentane-1,2′-pyrido[2,3-*d*]pyrimidin]-4′(3′*H*)-one (3c) Mp > 250°C; yield; 80%; IR: 3226, 3125, 3047, 2920, 2899, 2539, 1676, 1598, 1573, 1493, 1176, 773 cm^{-1}; ^1H NMR: δ 8.17 (m, 2H), 8.13 (br, 1H), 7.79 (br, 1H), 7.56–7.15 (m, 8H), 1.96 (m, 4H), 1.72 (m, 4H); ^{13}C NMR: δ 162.2, 161.3, 159.8, 158.0, 156.8, 150.8, 137.0, 135.5, 129.7, 129.6, 128.7, 127.7, 126.0, 113.5, 113.3, 112.0, 104.7, 74.5, 21.2; MS (EI) m/z 389 (M^+). Anal. Calcd for $C_{23}H_{20}ClN_3O$: C, 70.85; H, 5.17; N, 10.78. Found: C, 70.50; H, 5.27; N, 10.83.

5′-(4-Chlorophenyl)-7′-phenyl-1′H-spiro[cyclohexane-1,2′-pyrido[2,3-*d*]pyrimidin]-4′(3′*H*)-one (3d) Mp > 250°C; yield 95%; IR: 3292, 3190, 2932, 2899, 2539, 1623, 1601, 1573, 1492, 1089, 772 cm^{-1}; ^1H NMR: δ 8.07 (m, 2H), 7.44–7.02 (m, 8H), 1.80 (m, 4H), 1.60 (m, 4H), 1.37 (m, 2H); ^{13}C NMR: δ 162.8, 161.5, 159.7, 157.4, 156.7, 150.3, 136.1, 135.4, 129.2, 129.0, 128.7, 127.6, 126.0, 113.5, 113.3, 112.5, 104.5, 65.6, 35.7, 23.6, 20.0; MS (EI) m/z 403 (M^+). Anal. Calcd for $C_{24}H_{22}ClN_3O$: C, 71.37; H, 5.49; N, 10.40. Found: C, 71.11; H, 5.56; N, 10.49.

7′-Phenyl-5′-(p-tolyl)-1′H-spiro[cyclopentane-1,2′-pyrido[2,3-*d*] pyrimidin]-4′(3′*H*)-one (3e) Mp > 250°C; yield; 70%; IR: 3259, 3155, 2910, 2810, 1701, 1653, 1541, 1170, 796 cm^{-1}; ^1H NMR: δ 8.21 (br, 1H), 8.19 (m, 2H), 7.87 (br, 1H), 7.57–7.19 (m, 8H), 2.40 (s, 3H), 1.97 (m, 4H), 1.74 (m, 4H); ^{13}C NMR: δ 159.2, 158.3, 156.8, 155.0, 153.8, 147.8, 134.0, 132.5, 126.7, 126.6, 125.7, 124.7, 123.0, 110.5, 110.3, 109.0, 101.7, 73.5, 21.2, 20.0; MS (EI) m/z 369 (M^+). Anal. Calcd for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.27; N, 11.37. Found: C, 77.68; H, 6.39; N, 11.44.

7′-Phenyl-5′-(p-tolyl)-1′H-spiro[cyclohexane-1,2′-pyrido[2,3-*d*] pyrimidin]-4′(3′*H*)-one (3f) Mp > 250°C; yield 90%; IR: 3229, 3155, 2925, 2832, 1660, 1581, 1533, 1059, 773 cm^{-1}; ^1H NMR: δ = 8.22 (m, 2H), 7.59–7.21 (m, 8H), 1.80 (m, 4H), 1.61 (m, 4H), 1.36 (m, 2H), 2.36 (s, 3H); ^{13}C NMR: δ 160.0, 159.1, 157.7, 155.2, 154.9, 147.6, 134.9, 133.4, 127.6, 127.4, 126.7, 125.6, 124.0, 111.5, 111.3, 110.0, 102.5, 63.5, 33.8, 21.6, 21.0, 18.0; MS (EI) m/z 383 (M^+). Anal. Calcd for $C_{25}H_{25}N_3O$: C, 78.30; H, 6.57; N, 10.96. Found: C, 78.43; H, 6.70; N, 10.88.

5′-(4-Fluorophenyl)-7′-phenyl-1′H-spiro[cyclopentane-1,2′-pyrido[2,3-*d*]pyrimidin]-4′(3′*H*)-one (3g) Mp > 250°C; yield 90%; IR: 3426, 3174, 3058, 2962, 2931, 1668, 1599, 1561, 1508, 1442, 1214, 774 cm^{-1}; ^1H NMR: δ 8.12 (br, 1H), 8.07 (m, 2H), 7.78 (br, 1H), 7.46–7.05 (m, 8H), 1.94 (m, 4H), 1.70 (m, 4H); ^{13}C NMR: δ 163.2, 162.3, 160.8, 159.0, 157.8, 151.8, 138.0, 136.5, 130.7, 130.6, 129.7, 128.7, 127.0, 114.5, 114.3, 113.0, 105.7, 75.5, 22.2; MS (EI) m/z 373 (M^+). Anal. Calcd for $C_{23}H_{20}FN_3O$: C, 73.98; H, 5.40; N, 11.25. Found: C, 74.16; H, 5.49; N, 11.27.

5′-(4-Fluorophenyl)-7′-phenyl-1′H-spiro[cyclohexane-1,2′-pyrido[2,3-*d*]pyrimidin]-4′(3′*H*)-one (3h) Mp >250°C; yield 95%; IR: 3267, 3194, 3066, 2931, 2857, 1672, 1564, 1510, 1452, 1223, 697 cm^{-1}; ^1H NMR: δ 8.08 (m, 2H), 7.47–7.05 (m, 8H), 1.82 (m, 4H), 1.62 (m, 4H), 1.38 (m, 2H); ^{13}C NMR: δ 163.1, 162.1, 160.7, 158.2, 157.9, 151.6, 137.9, 136.4, 130.6, 130.5, 129.7, 128.6, 127.0, 114.5, 114.3, 113.0, 105.5, 66.5, 36.8, 24.6, 21.0; MS (EI) m/z 387 (M^+). Anal. Calcd for $C_{24}H_{22}FN_3O$: C, 74.40; H, 5.72; N, 10.85. Found: C, 74.68; H, 5.80; N, 10.94.

5′,7′-Bis(4-bromophenyl)-1′H-spiro[cyclohexane-1,2′-pyrido[2,3-*d*]pyrimidin]-4′(3′*H*)-one (3i) Mp > 250°C; yield 85%; IR: 3383, 3164, 2933, 2811, 1678, 1589, 1527, 1487, 1404, 1009, 719 cm^{-1}; ^1H NMR: δ 8.23 (m, 2H), 7.81–7.42 (m, 7H), 1.81 (m, 4H), 1.61 (m, 4H), 1.37 (m, 2H); ^{13}C NMR: δ 161.2, 160.1, 158.7, 156.2, 155.9, 149.6, 135.9, 134.4, 128.6, 128.5, 127.7, 126.6, 125.0, 112.5, 112.3, 111.0, 103.5, 64.5, 34.8, 22.6, 19.0; MS (EI) m/z 527 (M^+). Anal. Calcd for $C_{24}H_{21}Br_2N_3O$: C, 54.67; H, 4.01; N, 7.97. Found: C, 54.82; H, 4.15; N, 7.86.

7′-(4-Bromophenyl)-5′-(p-tolyl)-1′H-spiro[cyclopentane-1,2′-pyrido[2,3-*d*]pyrimidin]-4′(3′*H*)-one (3j) Mp > 250°C; yield 80%; IR: 3385, 3188, 2920, 2809, 1610, 1584, 1544, 1490, 1008, 816, 775 cm^{-1}; ^1H NMR: δ 8.26 (m, 2H), 8.24 (br, 1H), 7.80 (br, 1H), 7.67–7.35 (m, 7H), 2.41 (s, 3H), 1.95 (m, 4H), 1.72 (m, 4H); ^{13}C NMR: δ = 158.2, 157.3, 155.8, 154.0, 152.8, 146.8, 133.0, 131.5, 125.7, 125.6, 124.7, 123.7, 122.0, 109.5, 109.3, 108.0, 100.7, 75.0, 21.2, 19.5; MS (EI) m/z 447 (M^+). Anal. Calcd for $C_{24}H_{22}BrN_3O$: C, 64.29; H, 4.95; N, 9.37. Found: C, 64.11; H, 4.87; N, 9.29.

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