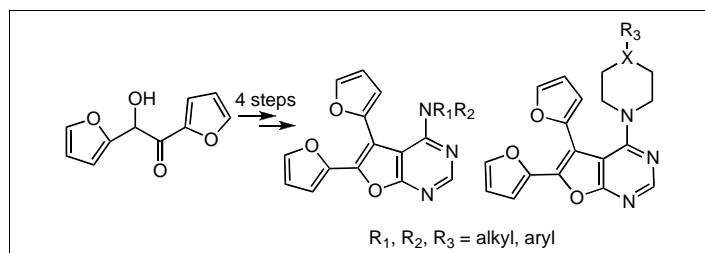


Jung In Pyo, So Ha Lee and Chan Seong Cheong\*

Life Science Division, Korea Institute of Science and Technology, P. O. Box 131,  
Cheongryang, Seoul 130-650, Korea  
Received February 17, 2004  
Received Revised October 18, 2005



Some substituted furopyrimidine derivatives are prepared in high yield in 4 steps, starting from the reaction of furoin (1,2-di(furan-2-yl)-2-hydroxyethanone) and malonitrile.

*J. Heterocyclic Chem.*, **43**, 1129 (2006).

Derivatives of furopyrimidines [1-9] and thienopyrimidines moieties are known to possess antitumor [10], analgesic [11], antihypertensive [12], and anti-inflammatory activity [13]. The thienopyrimidine-based analogues were reported to inhibit the Src family of tyrosine kinases [14]. Recently, furopyrimidines were also known to inhibit adenosine kinase in very low concentration [15]. Therefore, we synthesized new furopyrimidine derivatives to evaluate their potential as protein kinase inhibitors which in mammals comprises three highly homologous members known as PKB $\alpha$ , PKB $\beta$  and PKB $\gamma$ . PKB is activated in cells exposed to diverse stimuli such as hormones, growth factors, and extracellular matrix components [16].

Furoin reacts with malonitrile in the presence of diethyl amine to give 2-amino-4,5-di-(2-furanyl)-furan-3-carbonitrile (**1**) over 90% yield [5]. The nitrile **1** was stirred for 3 hours with formic acid in the presence of acetic anhydride at 0 °C and refluxed for 24 hours to afford pyrimidine-4-one **2** in 72% yield. Formation of compound **2** is thought to proceed *via* formylation of the amino group and transformation of the cyano group to the amide group, followed by attack of the amino group to the carbonyl group as showed in Scheme 1 [15]. Furopyrimidines (**4a-4z**) were obtained in high yield from the reaction of the chloride compound **3** with some amines. Here, the compound **3** was obtained *via* the reaction of pyrimidin-4-one **2** with phosphorus oxychloride under reflux. Structural assignments of all compounds were confirmed on the basis of nmr, infrared and elemental analysis.

At present, we are evaluating the synthesized furopyrimidines (**4a-4z**) as an inhibitor of protein kinase.

## EXPERIMENTAL

<sup>1</sup>H NMR (300 MHz) was recorded on a Varian Gemini 300 MHz spectrometer with TMS as an internal reference. IR spectra were recorded on a MIDAC 101025 FT-IR Spectrometer. Melting points were acquired using a Thomas-Hoover capillary melting apparatus and are uncorrected. Chemical analyses were carried out by EA 1108 CHNS-O of Fisons Instruments. Column chromatography was performed on Merck silica gel 60 (230 - 400 mesh). TLC was carried out using glass sheets pre-coated with silica gel 60 F<sub>254</sub> prepared by E. Merck. All the commercially available reagents were obtained from Aldrich and Tokyo Kasei Chemical and generally used without further purification.

### 5,6-Di-(2-furyl)-furo[2,3-d]pyrimidin-4(1H)-one (**2**).

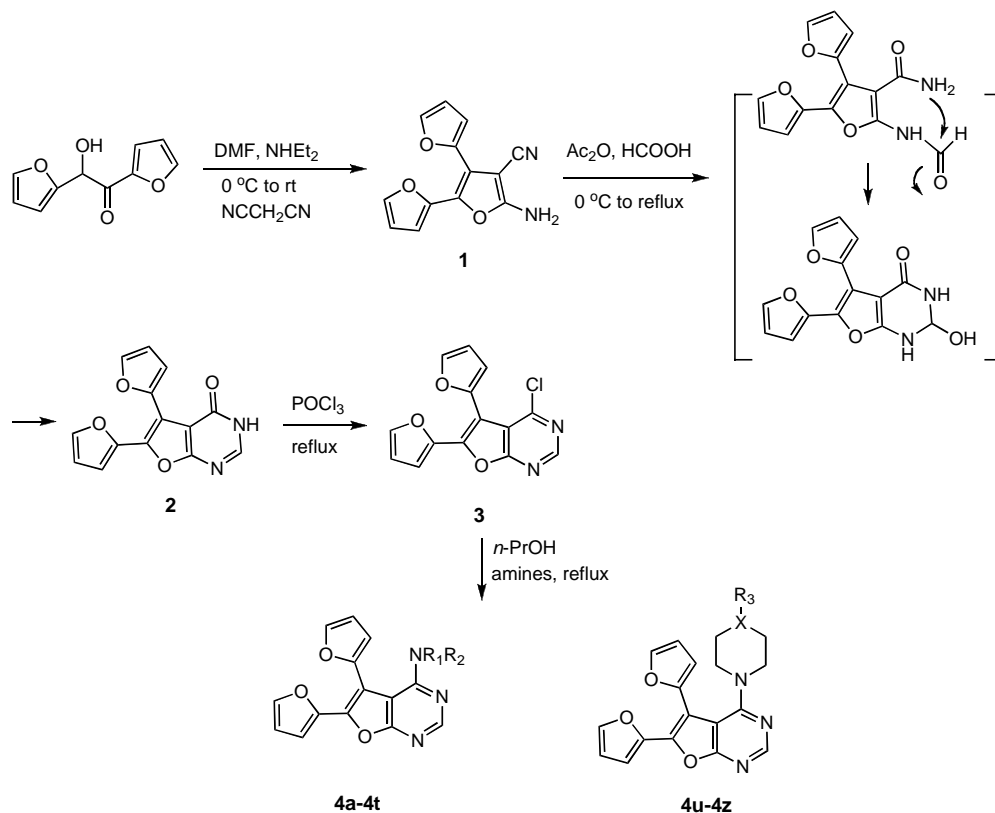
Formic acid 85% (46.0 ml, 1.22 mol) was added to acetic anhydride (93.0 ml, 0.98 mol) while cooling at 0 °C. 2-Amino-4,5-di-(2-furanyl)-furan-3-carbonitrile (**1**) (10.0 g, 0.049 mol) was added to the cold solution and stirred for 3 h, and the resulting solution was refluxed for 24 hours and evaporated *in vacuo*. The residue was recrystallized with the mixed solvent of *n*-hexane and ethyl acetate to give the black brown crystal in 72% yield; mp 248-249 °; ir (KBr):  $\nu$  3152, 2888, 1702, 1584, 1558, 1394, 1360, 1190, 1138, 1014, 984, 872, 748, 592 cm<sup>-1</sup>; <sup>1</sup>H NMR (dimethyl-d<sub>6</sub>-sulfoxide):  $\delta$  6.65 (d, *J* = 3.3 Hz, 1H), 6.71 (d, *J* = 1.8 Hz, 1H), 7.13 (d, *J* = 2.1 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.81 (s, 1H), 7.90 (s, 1H), 8.22 (s, 1H).

*Anal.* Calcd. for C<sub>14</sub>H<sub>8</sub>N<sub>2</sub>O<sub>4</sub>: C, 61.69; H, 3.01; N, 10.44. Found: C, 61.50; H, 3.00; N, 10.01.

### 4-Chloro-5,6-di-(2-furyl)-furo[2,3-d]pyrimidine (**3**).

A mixture of 5,6-di-(2-furyl)-furo[2,3-d]pyrimidin-4(1H)-one (**2**) (5.0 g, 18.0 mmol), POCl<sub>3</sub> (52.0 ml, 53.6 mmol) was refluxed for 2 hours and evaporated *in vacuo*. The residue was purified by chromatography on silicagel with *n*-hexane and ethyl acetate (3:1,v/v) as eluent to give a solid in 69% yield; mp 135-136 °; ir (KBr):  $\nu$  3132, 1586, 1552, 1376, 1244, 1150, 1020, 982, 888, 766 cm<sup>-1</sup>; <sup>1</sup>H NMR (deuteriochloroform):  $\delta$  6.47-6.85 (m, 4H), 7.48 (s, 1H), 7.57 (s, 1H), 8.67 (s, 1H).

Scheme 1



- 4a-4t**
- 4a, R<sub>1</sub> = -(CH<sub>2</sub>)<sub>2</sub>OH, R<sub>2</sub> = H
  - 4b, R<sub>1</sub> = -(CH<sub>2</sub>)<sub>4</sub>OH, R<sub>2</sub> = H
  - 4c, R<sub>1</sub> = -CH<sub>2</sub>CH(OH)CH<sub>3</sub>, R<sub>2</sub> = H
  - 4d, R<sub>1</sub> = -CH(CH<sub>2</sub>OH)CH<sub>2</sub>CH<sub>3</sub>, R<sub>2</sub> = H
  - 4e, R<sub>1</sub> = -CH<sub>2</sub>CH(OH)CH<sub>2</sub>CH<sub>3</sub>, R<sub>2</sub> = H
  - 4f, R<sub>1</sub> = -(CH<sub>2</sub>)<sub>2</sub>O(CH<sub>2</sub>)<sub>2</sub>OH, R<sub>2</sub> = H
  - 4g, R<sub>1</sub> = -(CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, R<sub>2</sub> = H
  - 4h, R<sub>1</sub> = -(CH<sub>2</sub>)<sub>3</sub>OH, R<sub>2</sub> = H
  - 4i, R<sub>1</sub> = -CH<sub>2</sub>CH<sub>3</sub>, R<sub>2</sub> = -CH<sub>2</sub>CH<sub>3</sub>
  - 4j, R<sub>1</sub> = -CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>3</sub>, R<sub>2</sub> = H
  - 4k, R<sub>1</sub> = -cycloheptyl, R<sub>2</sub> = H
  - 4l, R<sub>1</sub> = -(CH<sub>2</sub>)<sub>2</sub>Ph, R<sub>2</sub> = H
  - 4m, R<sub>1</sub> = -CH<sub>3</sub>, R<sub>2</sub> = H
  - 4n, R<sub>1</sub> = 2-hydroxycyclohexyl, R<sub>2</sub> = H
  - 4o, R<sub>1</sub> = 4-aminophenyl, R<sub>2</sub> = H
  - 4p, R<sub>1</sub> = 3,5-dimethoxyphenyl, R<sub>2</sub> = H
  - 4q, R<sub>1</sub> = 3,4-dimethylphenyl, R<sub>2</sub> = H
  - 4r, R<sub>1</sub> = 3,5-dimethylphenyl, R<sub>2</sub> = H
  - 4s, R<sub>1</sub> = 3,4-dichlorophenyl, R<sub>2</sub> = H
  - 4t, R<sub>1</sub> = 3-trifluoromethylphenyl, R<sub>2</sub> = H

- 4u-4z**
- 4u, X = O, R<sub>3</sub> = H
  - 4v, X = C, R<sub>3</sub> = H
  - 4w, X = N, R<sub>3</sub> = CH<sub>3</sub>
  - 4x, X = S, R<sub>3</sub> = H
  - 4y, X = C, R<sub>3</sub> = OH
  - 4z, X = C, R<sub>3</sub> = CH<sub>3</sub>

*Anal.* Calcd. for C<sub>14</sub>H<sub>9</sub>ClN<sub>2</sub>O<sub>5</sub>: C, 58.66; H, 2.46; N, 9.77.  
Found: C, 57.99; H, 3.11; N, 9.80.

#### General Procedure for the Preparations of 4a-4z.

4-Chloro-5,6-di-(2-furyl)-furo[2,3-*d*]pyrimidine (3) (30 mg, 0.11 mmol) was dissolved in 1-propanol (3 mL), followed by the substituted amines (over 0.11 mmol) and the mixture was refluxed for 24 hours. After the completion of reaction, the mixture was evaporated *in vacuo* and poured into a 2% HCl solution at which time a solid forms. The mixture containing the solid was poured into a saturated NaHCO<sub>3</sub> solution and then was filtered

and recrystallized in the mixed solvent of diethylether and methylene chloride to give the pure product.

#### 2-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]ethanol (4a).

Yield 73%; mp 163-164 °C; ir (KBr): ν 3390, 3266, 1600, 1498, 1332, 1146, 1072, 1010, 742, 594 cm<sup>-1</sup>; <sup>1</sup>H NMR (deuteriochloroform): δ 3.79 (t, J = 5.1 Hz, 2H), 3.92 (t, J = 5.1 Hz, 2H), 6.60-7.00 (m, 4H), 7.54 (s, 1H), 7.65 (s, 1H), 8.40 (s, 1H).

*Anal.* Calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>: C, 61.73; H, 4.21; N, 13.50.  
Found: C, 60.98; H, 4.08; N, 13.09.

4-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]butan-1-ol (**4b**).

Yield 99%; mp 103-104 °C; ir (KBr):  $\nu$  3414, 3266, 2936, 1608, 1490, 1451, 1138, 1012, 890, 746, 594  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  1.83-1.69 (m, 4H), 3.64-3.68 (m, 2H), 3.77 (t,  $J = 8.0$  Hz, 2H), 6.47 (s, 1H), 6.57-6.96 (m, 4H), 7.55 (s, 1H), 7.66 (s, 1H), 8.42 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_4$ : C, 63.71; H, 5.05; N, 12.38. Found: C, 63.90; H, 5.04; N, 12.50.

1-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]propan-2-ol (**4c**).

Yield 71%; mp 157-158 °; ir (KBr):  $\nu$  3396, 1604, 1506, 1312, 1156, 742, 594  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform)  $\delta$  1.31 (d,  $J = 6.3$  Hz, 3H), 3.48-3.53 (m, 1H), 3.79-3.86 (m, 2H), 4.12 (s, 1H), 6.58 (s, 1H), 6.64 (s, 1H), 6.97-7.05 (m, 2H), 7.56 (s, 1H), 7.64 (s, 1H), 8.39 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_4$ : C, 62.76; H, 4.65; N, 12.92. Found: C, 62.60; H, 4.60; N, 12.90.

2-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]butan-1-ol (**4d**).

Yield 50%; mp 135-136 °C; ir (KBr):  $\nu$  3380, 2930, 1604, 1496, 1314, 1146, 1016, 894, 740, 592  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  1.04 (t,  $J = 7.8$  Hz, 3H), 1.64-1.77 (m, 2H), 3.71-3.91 (m, 2H), 4.21-4.23 (m, 1H), 6.58-7.00 (m, 5H), 7.55 (s, 1H), 7.61 (s, 1H), 8.37 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_4$ : C, 63.71; H, 5.05; N, 12.38. Found: C, 63.90; H, 5.04; N, 12.00.

4-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]butan-2-ol (**4e**).

Yield 8%; mp 109-110 °C; ir (KBr):  $\nu$  3398, 2924, 1610, 1500, 1458, 1300, 1150, 1018, 744, 592  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.43 (t,  $J = 7.8$  Hz, 3H), 1.56-1.66 (m, 2H), 3.48-3.54 (m, 1H), 3.80-3.90 (m, 2H), 6.55-7.10 (m, 5H), 7.54 (s, 1H), 7.63 (s, 1H), 8.37 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_4$ : C, 63.71; H, 5.05; N, 12.38. Found: C, 63.90; H, 5.00; N, 12.00.

2-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]ethoxy-ethanol (**4f**).

Yield 90%; mp 128-129 °C; ir (KBr):  $\nu$  3406, 2872, 1608, 1502, 1338, 1230, 1120, 1068, 888, 744  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  3.64-3.88 (m, 8H), 6.55-6.93 (m, 4H), 7.53 (s, 1H), 7.69 (s, 1H), 8.04 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_5$ : C, 60.84; H, 4.82; N, 11.83. Found: C, 60.70; H, 4.50; N, 11.90.

1-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]-2-methoxyethane (**4g**).

Yield 43%; mp 80-82 °C; ir (KBr):  $\nu$  3406, 2924, 1604, 1500, 1448, 1336, 1114, 1018, 886, 794, 740  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  3.46 (s, 3H), 3.47-3.71 (m, 2H), 3.96-3.98 (m, 2H), 6.60-7.05 (m, 4H), 7.60 (s, 1H), 7.65 (s, 1H), 8.50 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_4$ : C, 62.76; H, 4.65; N, 12.92. Found: C, 62.80; H, 4.60; N, 12.80.

3-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]propan-1-ol (**4h**).

Yield 38%; mp 105-106 °C; ir (KBr):  $\nu$  3416, 2930, 1606, 1504, 1442, 1138, 1018, 890, 742  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  1.84-1.88 (m, 2H), 3.70 (t,  $J = 6$  Hz, 2H), 3.82 (t,  $J = 6$  Hz, 2H), 6.58-6.90 (m, 4H), 7.56 (s, 1H), 7.65 (s, 1H), 8.50 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_4$ : C, 62.76; H, 4.65; N, 12.92. Found: C, 62.80; H, 4.60; N, 12.91.

*N*-[5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl]diethylamine (**4i**).

Yield 77%; mp 108-109 °C; ir (KBr):  $\nu$  2974, 1584, 1542, 1466, 1360, 1280, 1078, 1018, 742, 599  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  1.07 (t,  $J = 6.6$  Hz, 6H), 3.41 (q,  $J = 6.6$  Hz, 4H), 6.48-6.60 (m, 4H), 7.48 (s, 1H), 7.62 (s, 1H), 8.41 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_4$ : C, 66.86; H, 5.30; N, 13.00. Found: C, 6.87; H, 5.29; N, 12.99.

1-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]isobutane (**4j**).

Yield 94%; mp 105-106 °C; ir (KBr):  $\nu$  3418, 2956, 1602, 1498, 1302, 1152, 1018, 888, 730, 599  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  1.03 (d,  $J = 6.6$  Hz, 6H), 1.91-2.00 (m, 1H), 3.47 (t,  $J = 5.4$  Hz, 2H), 6.43 (s, 1H), 6.57-6.96 (m, 4H), 7.54 (s, 1H), 7.62 (d,  $J = 2.7$  Hz, 1H), 8.42 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_3$ : C, 66.86; H, 5.30; N, 13.00. Found: C, 66.80; H, 5.35; N, 12.99.

1-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]cycloheptane (**4k**).

Yield 89%; mp 126-127 °C; ir (KBr):  $\nu$  3414, 2926, 1602, 1492, 1370, 1296, 1138, 1016, 888, 754, 592, 494  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  1.59-1.63 (m, 10H), 2.05-2.10 (m, 2H), 6.40 (d,  $J = 7.2$  Hz, 1H), 6.57-6.95 (m, 4H), 7.54 (s, 1H), 7.64 (s, 1H), 8.42 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_4$ : C, 69.41; H, 5.82; N, 11.56. Found: C, 69.40; H, 5.80; N, 11.55.

1-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]-2-phenylethane (**4l**).

Yield 83%; mp 120-121 °C; ir (KBr):  $\nu$  3418, 3126, 2872, 1600, 1492, 1452, 1340, 1298, 1122, 1010, 884, 744, 700  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  2.98 (t,  $J = 6.6$  Hz, 2H), 3.93-3.99 (m, 2H), 6.40-7.50 (m, 12H), 8.40 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}_4$ : C, 71.15; H, 4.61; N, 11.31. Found: C, 71.10; H, 4.65; N, 11.30.

1-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]methane (**4m**).

Yield 53%; mp 116-117 °C; ir (KBr):  $\nu$  3436, 3104, 2918, 1606, 1504, 1412, 1300, 1144, 1020, 886, 792, 732, 588  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  3.18 (d,  $J = 4.5$  Hz, 3H), 6.40 (s, 1H), 6.56-6.90 (m, 4H), 7.51 (s, 1H), 7.62 (s, 1H), 8.44 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_3$ : C, 64.05; H, 3.94; N, 14.94. Found: C, 64.04; H, 3.88; N, 14.90.

2-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]cyclohexanol (**4n**).

Yield 81%; mp 204-205 °C; ir (KBr):  $\nu$  3382, 2927, 1610, 1501, 1152, 1087, 1023, 746  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  1.28-1.49 (m, 4H), 1.78-1.84 (m, 2H), 2.10-2.20 (m, 2H), 3.48-3.49 (m, 2H), 3.98-4.05 (m, 2H), 6.50-7.00 (m, 5H), 7.56 (s, 1H), 7.62 (s, 1H), 8.36 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_4$ : C, 65.74; H, 5.24; N, 11.50. Found: C, 65.70; H, 5.23; N, 11.49.

*N*-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]-4-amino-benzene (**4o**).

Yield 71%; mp 192-193 °C; ir (KBr):  $\nu$  3390, 1592, 1514, 1458, 1292, 1152, 1082, 818, 742, 599, 534  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  6.59-7.44 (m, 7H), 7.57 (d,  $J = 1.8$  Hz, 1H), 7.71 (s, 1H), 8.10 (s, 1H), 8.48 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{14}\text{N}_4\text{O}_3$ : C, 67.03; H, 3.94; N, 15.63. Found: C, 67.02; H, 3.93; N, 15.67.

*N*-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]-3,5-dimethoxybenzene (**4p**).

Yield 69%; mp 166-167 °C; ir (KBr):  $\nu$  3392, 3134, 2936, 1584, 1484, 1200, 1154, 1066, 1020, 888, 790, 754, 678, 592  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  3.86 (s, 6H), 6.28-7.58 (m 8H), 8.34 (s, 1H), 8.57 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}_5$ : C, 65.50; H, 4.25; N, 10.42. Found: C, 65.60; H, 4.23; N, 10.32.

*N*-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]-3,4-dimethylbenzene (**4q**).

Yield 57%; mp 139-140 °C; ir (KBr):  $\nu$  3394, 3116, 2927, 1590, 1504, 1454, 1312, 1150, 1018, 888, 734, 594  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  2.23 (s, 3H), 2.33 (s, 3H), 6.60-7.58 (m, 8H), 8.21 (s, 1H), 8.53 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}_3$ : C, 71.15; H, 4.61; N, 11.31. Found: C, 71.14; H, 4.65; N, 11.30.

*N*-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]-3,5-dimethylbenzene (**4r**).

Yield 84%; mp 179-180 °C; ir (KBr):  $\nu$  3400, 1634, 1584, 1480, 1158, 1092, 1018, 888, 746, 594  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  2.39 (s, 6H), 6.60-7.02 (m, 6H), 7.57 (s, 1H), 7.75 (s, 1H), 8.23 (s, 1H), 8.55 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}_3$ : C, 71.15; H, 4.61; N, 11.31. Found: C, 71.13; H, 4.63; N, 11.29.

*N*-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidine-4-yl)amino]-3,4-dichlorobenzene (**4s**).

Yield 33%; mp 214-215 °C; ir (KBr):  $\nu$  3396, 1636, 1588, 1470, 1478, 1327, 1020, 888, 803, 734  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  6.62-7.06 (m, 4H), 7.41-7.60 (m 3H), 8.05 (d,  $J = 2.1$  Hz, 1H), 8.43 (s, 1H), 8.59 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{11}\text{N}_3\text{O}_3\text{Cl}_2$ : C, 58.27; H, 2.69; N, 10.19. Found: C, 58.20; H, 2.68; N, 10.15.

*N*-[(5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl)amino]-3-trifluoromethylbenzene (**4t**).

Yield 66%; mp 174-175 °C; ir (KBr):  $\nu$  3388, 2920, 1632, 1588, 1496, 1340, 1154, 1114, 1018, 870, 792, 736, 696, 592  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  6.62-8.10 (m, 10H), 8.57 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{12}\text{F}_3\text{N}_3\text{O}_3$ : C, 61.32; H, 2.94; N, 10.22. Found: C, 61.20; H, 2.92; N, 10.11.

*N*-[5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidine-4-yl]morpholine (**4u**).

Yield 99%; mp 170-171 °C; ir (KBr):  $\nu$  3098, 2856, 1588, 1546, 1444, 1362, 1254, 1112, 930, 884, 750, 596  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  3.40 (t,  $J = 4.5$  Hz, 4H), 3.62 (t,  $J = 4.5$  Hz, 4H), 6.51-6.82 (m, 4H), 7.51 (d,  $J = 2.7$  Hz, 1H), 7.64 (d,  $J = 2.7$  Hz, 1H), 8.47 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_4$ : C, 64.09; H, 4.48; N, 12.46. Found: C, 64.07; H, 4.46; N, 12.44.

*N*-[5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidine-4-yl]piperidine (**4v**).

Yield 60%; mp 155-156 °C; ir (KBr):  $\nu$  3156, 2930, 1586, 1538, 1458, 1368, 1254, 1152, 1094, 1010, 913, 752  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  1.28-1.62 (m, 6H), 3.38-3.42 (m, 4H), 6.49-6.76 (m, 4H), 7.50 (s, 1H), 7.62 (d,  $J = 3.0$  Hz, 1H), 8.44 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_3$ : C, 68.05; H, 5.11; N, 12.53. Found: C, 68.09; H, 5.11; N, 12.40.

*N*-[5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidine-4-yl]-*N'*-methylpiperazine (**4w**).

Yield 29%; mp 260< ; ir (KBr):  $\nu$  2930, 1586, 1548, 1446, 1369, 1263, 1148, 1019, 752  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  2.30 (s, 3H), 2.36 (t,  $J = 4.8$  Hz, 4H), 3.49 (t,  $J = 4.8$  Hz, 4H), 6.52-6.81 (m, 4H), 7.52 (d,  $J = 1.5$  Hz, 1H), 7.64 (d,  $J = 2.1$  Hz, 1H), 8.46 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_3$ : C, 65.13; H, 5.18; N, 15.99. Found: C, 65.13; H, 5.17; N, 15.89.

*N*-[5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidine-4-yl]thiomorpholine (**4x**).

Yield 84%; mp 161-162 °C; ir (KBr):  $\nu$  3118, 2918, 2846, 1584, 1544, 1446, 1368, 1284, 1244, 1146, 1098, 1018, 960, 894, 742  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  2.55 (t,  $J = 2.7$  Hz, 4H), 3.75 (t,  $J = 2.7$  Hz, 4H), 6.51-6.78 (m, 4H), 7.51 (s, 1H), 7.65 (s, 1H), 8.47 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_3\text{S}$ : C, 61.18; H, 4.28; N, 11.89. Found: C, 61.10; H, 4.28; N, 11.87.

1-[5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidin-4-yl]-4-hydroxypiperidine (**4y**).

Yield 57%; mp 140-141 °C; ir (KBr):  $\nu$  3318, 2926, 1592, 1548, 1496, 1450, 1366, 1230, 1148, 1068, 1014, 746  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  1.44-1.50 (m, 2H), 1.80-1.85 (m, 2H), 3.08-3.16 (m, 2H), 3.79-3.89 (m, 2H), 6.51-6.79 (m, 4H), 7.51 (s, 1H), 7.63 (s, 1H), 8.44 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_4$ : C, 64.95; H, 4.88; N, 11.96. Found: C, 64.95; H, 4.77; N, 11.90.

*N*-[5,6-Di-(2-furyl)-furo[2,3-*d*]pyrimidine-4-yl]-4-methylpiperidine (**4z**).

Yield 86%; mp 164-165 °C; ir (KBr):  $\nu$  3136, 2926, 1584, 1534, 1454, 1368, 1250, 1152, 1084, 1020, 976, 888, 750  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (deuteriochloroform):  $\delta$  0.91 (d,  $J = 6.0$  Hz, 3H), 1.07-1.12 (m, 1H), 1.54-1.57 (m, 4H), 2.76-2.85 (m, 2H), 4.00-4.09 (m, 2H), 6.50-6.83 (m, 4H), 7.48 (s, 1H), 7.60 (s, 1H), 8.42 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_3$ : C, 68.75; H, 5.48; N, 12.03. Found: C, 68.77; H, 5.47; N, 12.11.

Acknowledgements.

Financial support from Ministry of Science and Technology is gratefully acknowledged.

## REFERENCES

- [1] C. C. Lockhart and J. W. Sowell, *J. Heterocyclic Chem.*, **33**, 659 (1996).
- [2] S. Demirayak and A. Mohsen, *J. Heterocyclic Chem.*, **38**, 507 (2001).
- [3] C. J. Shishoo, M. B. Devani, V. S. Bhadti, K. S. Jain and S. Ananthan, *J. Heterocyclic Chem.*, **27**, 119 (1990).
- [4] K. G. Dave, C. J. Shishoo, M. B. Devani, R. Kalyanaraman, S. Ananthan, G. V. Ullas and V. S. Bhadti, *J. Heterocyclic Chem.*, **17**, 1497 (1980).
- [5] J. Prousek, A. Jurasek and J. Kovac, *Collection Czechoslov. Chem. Commun.*, **40**, 1581 (1980).
- [6] N. A. Hassan, *Molecules* **5**, 826 (2000).
- [7] M. M. Ali, M. A. Zahran, Y. A. Ammar, Y. A. Mohamed and A. T. Seleim, *Indian J. Heterocyclic Chem.*, **4**, 191 (1995).
- [8] S. A. Swelam, *Indian J. Heterocyclic Chem.*, **8**, 147 (1998).
- [9] S. Cheng, D. M. Goldstein, T. A. T. Martin and E. B. Sjogren, U. S. Patent 6,479,507 B2 (2002); *Chem. Abstr.*, **135**, 357921 (2001).
- [10] E. S. Hand and D. C. Baker, *Can. J. Chem.*, **62**, 2570 (1984).
- [11] K. Noda, A. Nakagawa, Y. Nakajima and Hi. Ide, Japanese Patent 85, 194 (1997); *Chem. Abstr.*, **88**, 50908q (1978).
- [12] A. Cannitro, M. Pemmsin, C. Lnu-Due, F. Hogue, C. Gaultier and J. Narcisse, *Eur. J. Chem.*, **25**, 635 (1990).
- [13] S. Nega, J. Aionso, A. Diazj and F. Junquere, *J. Heterocyclic Chem.*, **27**, 269 (1990).
- [14] M. A. Benish, M. L. St, Charles and R. J. A. Budde, U. S. Patent 6,503,914 B1 (2003); *Chem. Abstr.*, **137**, 109291 (2002).
- [15] E. Bischoff, M. Hauswald, P. Nell, S. Rohrig, K.-H. Schlemmer, H. Steinhagen, J. Stoltefub and S. Weigand, DE 10141212 A1 (2003); *Chem. Abstr.*, **138**, 221596 (2003).
- [16] K. M. Nicholson and N. G. Anderson, *Cellular Signalling* **14**, 381 (2002).