Synthesis of New Furo[2,3-d]pyrimidines and Pyrimido[4′,5′:4,5]furo[2,3-d]pyrimidines

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Sodium salt of 4-hydroxy-6-methyl-2-phenylpyrimidine-5-carbonitrile (**3**) was subjected to alkylation with different α-halo compounds, where the corresponding O-alkylated products $\mathbf{4_{a-g}}$ were obtained. Ring closure of the O-alkylated product $\mathbf{4_{a-c}}$ performed using sodium ethoxide in refluxing ethanol afforded furo[2,3-d]pyrimidines $\mathbf{5_{a-c}}$. The latter compounds on reaction with a variety of reagents gave other new furopyrimidines as well as a number of furodipyrimidines.

Keywords: Furopyrimidines; Pyrimidofuropyrimidines; Synthesis; Biological activity.

INTRODUCTION

Pyrimidine derivatives play important roles as analgesic,[1] antihypertensive,[2] antipyretic,[3] antiviral,[4] and anti-inflammatory drugs.[5] Also they are used in agriculture as pesticides[6] and plant growth regulators.[7] In addition, the furo-[2,3-d]pyrimidine ring system is of biological interest; thus furo[2,3-d]pyrimidine derivatives were reported as inhibitors of dihydrofolate reductase, thymidyates synthase, antitumor agents antibacterial and antiprotozoan agents.[7-10]

Because the chemistry of furopyrimidines has been little explored and in view of the above observation, we report herein the synthesis of new furopyrimidines and pyrimidofuropyrimidines hoping to get compounds with enhanced biological activity and medicinal applications.

RESULTS AND DISCUSSION

The target compound **3** was synthesized through hydrolysis of S-ethylthio derivative **2** in alcoholic sodium hydroxide to give the corresponding sodium salt. The reason for using sodium salt rather than the hydroxyl derivative is to force the reaction towards the formation of O-alkylated products instead of the expected N-alkylated products.[11]

Compound **3** was subjected to react with different halo compounds, namely chloroacetone, phenacyl bromide, diethyl bromolmalonate, ethyl chloroacetate, methyl 2-bromopropionate, ethyl bromoacetoacetate and chloroacetonitrile in refluxing acetone yielded O-alkylated products $\mathbf{4_{a-g}}$ in good yield. Some of the O-alkylated derivatives $\mathbf{4_{a-c}}$ were chosen and subjected to additional reactions to build up new furo[2,3-d]pyrimidines, e.g. compounds $\mathbf{4_{a-c}}$ underwent ring closure by refluxing in ethanol containing sod. ethoxide to give furo[2,3-d]pyrimidine derivatives $\mathbf{5_{a-c}}$. Furthermore, the compounds $\mathbf{5_{a,b}}$ may also be synthesized in one step by direct interaction of **3** with respective halo compounds in acetone containing anhydrous pot. carbonate (Scheme I). It is important to note that the reason for using compound $\mathbf{4_c}$ as intermediate to obtain the o-amino ester instead of cyclisation of compound $\mathbf{4_d}$ directly is that attempts to cyclize compound $\mathbf{4_d}$ failed. So we use compound $\mathbf{4_c}$ in which cyclisation was found more easily due to the high activation of the methine proton with two ester groups followed by loss of an ester group to give the desired compound. Compound $\mathbf{5_b}$ was reacted with chloroacetyl chloride in dioxane to yield N-(6-benzoyl-4-methyl-2-phenylfuro[2,3-d]pyrimidine-5-yl)-2-chloroacetamide (**6**), which underwent nucleophilic displacement when treated with piperidine to give piperidine-1-yl-acetamide derivative **7**.

Saponification of O-amino ester $\mathbf{5_c}$ with an ethanolic sodium hydroxide solution resulted in formation of sodium salt **8**, which in turn was treated with orthophosphoric acid at room temperature and underwent smooth decarboxylation followed by hydrolysis of the imino group to give 4-methyl-2-phenylfuro[2,3-d]pyridin-5(6H)-one (**9**).[12] Condensation of **9** with aromatic aldehydes in ethanol in the presence of a catalytic amount of piperidine furnished the arylidene derivatives $\mathbf{10_{a,b}}$ (Scheme II). Refluxing of compound **8** with an excess amount of acetic anhydride didn't give the expected ox-

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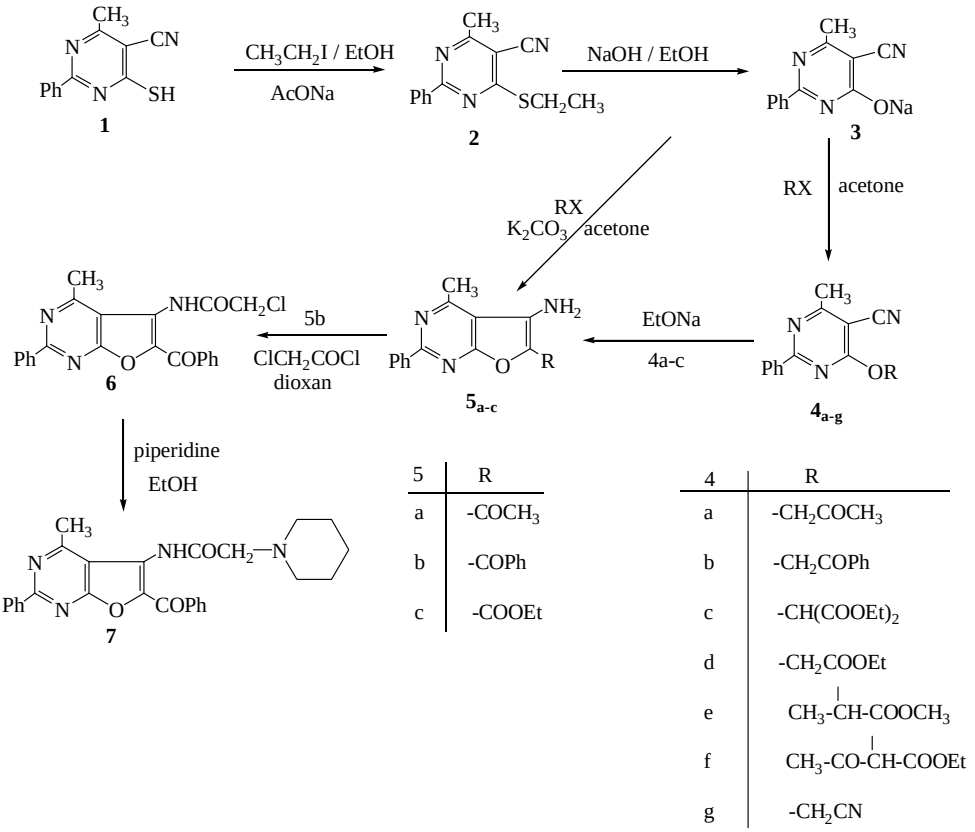
Scheme I



5	R
a	-$COCH_3$
b	-COPh
c	-COOEt

4	R
a	-CH_2COCH_3
b	-CH_2COPh
c	-$CH(COOEt)_2$
d	-CH_2COOEt
e	CH_3-CH(-)-$COOCH_3$
f	CH_3-CO-CH(-)-COOEt
g	-CH_2CN

azine derivative **11** and instead 5-(N,N-diacetylamino)-4-methyl-2-phenylfuro[2,3-d]pyrimidine (**12**) was produced. Hydrazonolysis of **12** failed to give the corresponding amino derivative; instead N-acetylamino derivative **13** was obtained.

Refluxing $\mathbf{5_c}$ with hydrazine hydrate in ethanol afforded carbohydrazide derivative **14** (Scheme III). Treatment of compound **14** with nitrous acid yielded the corresponding carboazide **15**, which upon boiling in dry xylene underwent *Curtius rearrangement* to give 4-methyl-2-phenylimidazo-[4′,5′:4,5]furo[2,3-d]pyrimidin-6(5H,7H)-one (**16**).

Furthermore, heating of carbohydrazide **14** with formic acid and/or acetic anhydride led to the formation of 7-N-formylamino-4-methyl-2-phenyl pyrimido[4′,5′:4,5]furo[2,3-d]pyrimidine (**17**) and 7-N-diacetylamino-4,6-dimethyl-2-phenylpyrimido[4′,5′:4,5]furo[2,3-d]pyrimidin-8(7H)-one (**18**), respectively. Condensation of the carbohydrazide **14** with different aromatic aldehydes in ethanol in the presence of a catalytic amount of piperidine furnished arylidene derivatives $\mathbf{19_{a\text{-}c}}$ in high yield. New 3,5-dimethylpyrazolyl compound **20** was prepared by the condensation of **14** with acetyl acetone in refluxing ethanol.

Some new pyrido[2′,3′:4,5]furo[2,3-d]pyrimidines **21**, **22** (Scheme IV) may be obtained by the reaction of $\mathbf{5_{a,b}}$ with an equimolar amount of ethyl cyanoacetate in the presence of an excess amount of ammonium acetate.[13]

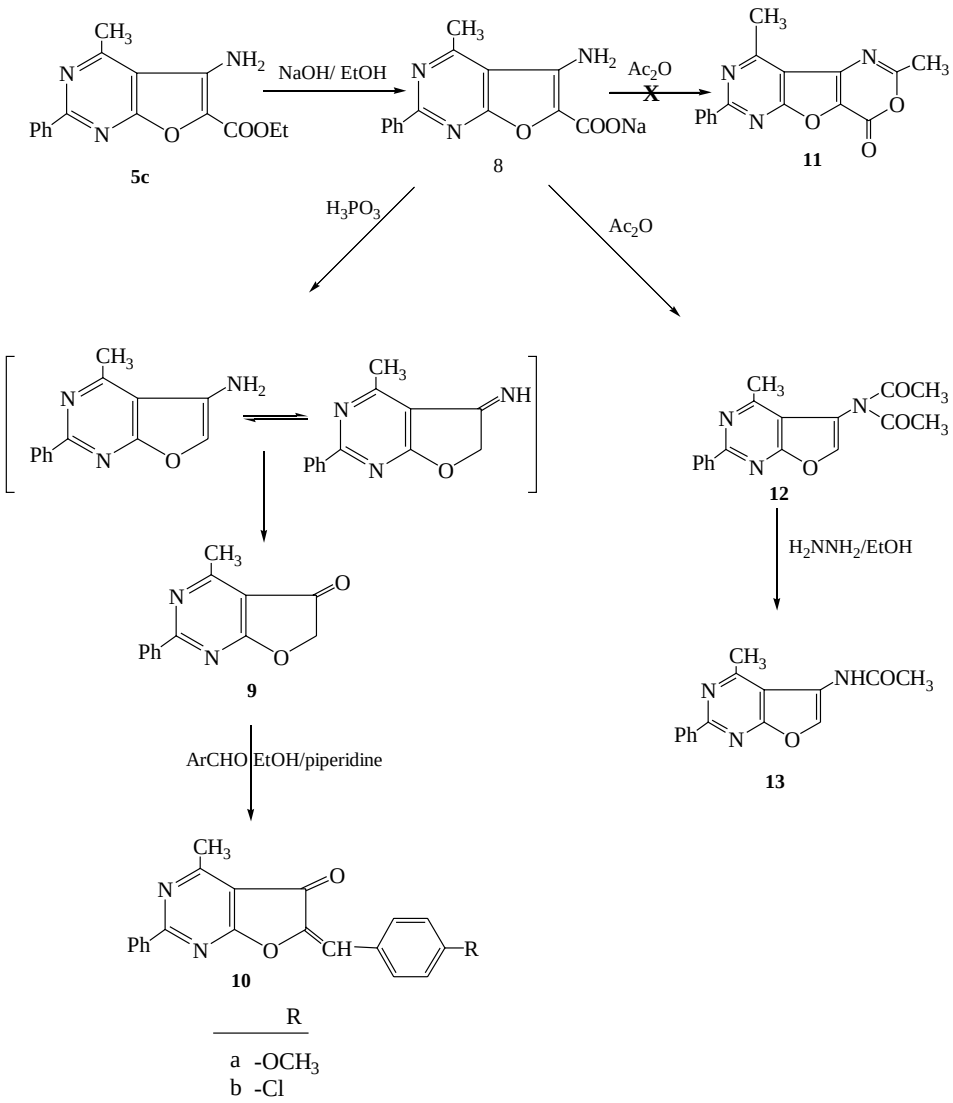
Ethyl 5-amino-4-methyl-2-phenylfuro[2,3-d]pyrimidine-6-carboxylate ($\mathbf{5_c}$) proved also to be a versatile synthon for some new pyrimido[4′,5′:4,5]furo[2,3-d]pyrimidines. Thus, the reaction of $\mathbf{5_c}$ with an equimolar quantity of phenylisothiocyanate in pyridine gave 4-methyl-8-oxo-5,6,7,8-tetrahydro-2,7-diphenyl[4′,5′:4,5]pyrimidofuro[2,3-d]pyrimidin-6-thione (**23**). Heating $\mathbf{5_c}$ in formamide lead to the formation of pyrimido[4′,5′:4,5]furo[2,3-d]pyrimidine derivative **24** in moderate yield.

Chlorination of **24** an with excess amount of phosphoryl chloride gave 8-chloro-4-methyl-2-phenylpyrimido-[4′,5′:4,5]furo[2,3-d]pyrimidine (**25**). Treatment of the latter compound with hydrazine hydrate 99% in ethanol gave the corresponding hydrazino compound **26**.

Biological Activity

Thirteen compounds were selected and screened in vitro for their antimicrobial activity against two strains of bac-

Scheme II



teria (*Escherichia coli* and *Bacillus cereus*) and six fungal species (*Aspergillus terreus, Penicillium chrysogenum, Fusarium solani, Paecilomyces variotii, Alternaria alternata* and *Scopulariopsis brumptii*) using the filter paper disc method.[14] The biological activity, as expressed by the growth of the inhibition zones of the tested microorganism are summarized in Table 1. From Table 1, it is obvious that, as bactericides there is no activity for the tested compounds against *Bacillus cereus* except for compound **13**, while *Escherichia coli* showed a moderate sensitivity against most of the newly synthesized compounds. As for fungicides, high activity was shown against *Aspergillus terreus, Paecilomyces variotii, Alternaria alternata* and *Scopulariopsis brumptii* while *Penicillium chrysogenum* and *Fusarium solani* showed no sensitivity against the tested compounds.

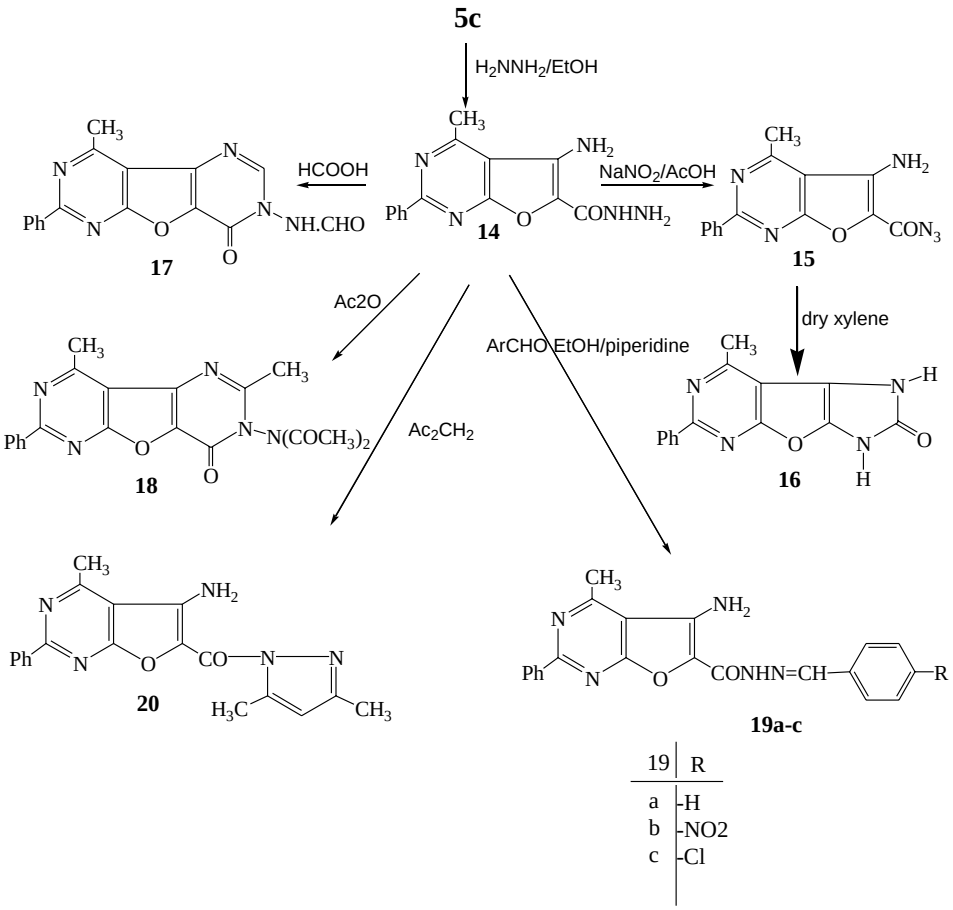
EXPERIMENTAL

Melting points were recorded on a Gallen-Kamp apparatus and are uncorrected. (IR) spectra were recorded on a Shimadzu-470 IR-Spectrophotometer (KBr; ν_{max} in cm^{-1}), ^1H NMR Spectra on a Varian EM-390, 90 MHz spectrometer with TMS as internal standard or on a Jeol LA 400 MHz FT. NMR spectrometer (δ in ppm), and MS on a Jeol JMS-600 mass spectrometer. Elemental analyses were recorded on a Perkin Elmer 240C elemental analyzer.

4-Methyl-6-mercapto-2-phenylpyrimidine-5-carbonitrile (1)

This compound was prepared according to a literature procedure.[15]

Scheme III



6-Ethylthio-4-methyl-2-phenylpyrimidine-5-carbonitrile (2)

A mixture of **1** (2.27 gm, 0.01 mol), ethyl bromide (0.015 mol) and anhydrous potassium carbonate (0.015 mol) in ethanol (30 mL) was refluxed for 3 hours. The solid product separated from the hot mixture was filtered off, washed with water and recrystallized from ethanol as pale yellow crystals in 85% yield, mp 118-120 °C. Anal. Calcd. for $C_{14}H_{13}N_3S$ (255.34): C, 65.58; H, 5.13; N, 16.46; S, 12.56. Found: C, 65.60; H, 5.10; N, 16.50; S, 12.52. IR: ν 2200 (C≡N) cm^{-1}. ^1H NMR in (DMSO-d_6): δ 1.3-1.5 (t, 3H, CH_3); 2.7 (s, 3H, CH_3), 3.3-3.6 (q, 2H, CH_2), 7.6-7.7(m, 3H, Ar-H), 8.4-8.6 (m, 2H, Ar-H).

Sodium-5-cyano-4-methyl-2-phenyl-6-pyrimidinate (3)

A mixture of **2** (2.55 gm; 0.01 mol) and sodium hydroxide (0.02 mol) in ethanol (20 mL) and water (3 mL) was refluxed for 4 hours then allowed to cool. The solid product was filtered off as white crystals in 60% yield. Compound **3** was subjected to the next step without further purification.

General procedure for the synthesis of 4_{a-g}

A mixture of **3** (2.33 gm; 0.01 mol) and respective halo compounds (0.01 mol) in acetone (20 mL) was refluxed for 4 hours then allowed to cool and poured on cold water with stirring. The solid product was collected and recrystallized from ethanol as white crystals.

5-Cyano-4-methyl-2-phenylpyrimidin-6-yloxy)acetone (4_a)

Produced in 76% yield; mp 179-181 °C. Anal. Calcd. for $C_{15}H_{13}N_3O_2$ (267.28): C, 67.40; H, 4.90; N, 15.72. Found: C, 67.35; H, 4.80; N, 15.63. IR: ν 2200 (C≡N), 1720 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.3 (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 5.0 (s, 2H, CH_2), 7.2-7.4 (m, 3H, Ar-H), 8.2-8.4 (m, 2H, Ar-H).

6-Benzoylmethoxy-4-methyl-2-phenylpyrimidine-5-carbonitrile (4_b)

Produced in 73% yield; mp 163-165 °C. Anal. Calcd. for $C_{20}H_{15}N_3O_2$ (329.35): C, 72.94; H, 4.59; N, 12.76. Found: C, 72.90 H, 4.60; N, 12.73. IR: ν 2200 (C≡N), 1690 (C=O),

Scheme IV

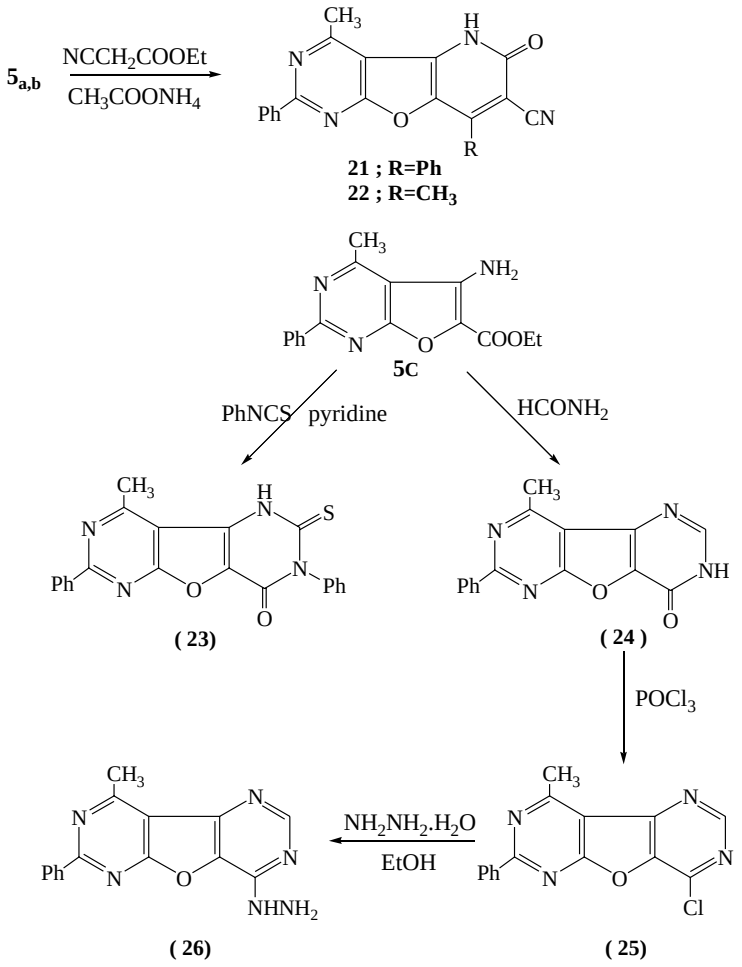


Table 1. The antimicrobial activity of selected compounds

No	Bacteria Inhibition zone (mm)		Fungi Inhibition zone (mm)					
	E. coli	*B. cereus*	*A. terreus*	*P. chrysogenum*	*F. solani*	*P. variotti*	*A. alternata*	*S. brumptii*
4a	-	-	13	-	-	-	-	12
4b	-	-	-	-	-	-	12	12
5b	15	-	15	-	-	-	-	-
5c	-	-	-	-	-	-	-	-
9	12	-	14	-	-	14	15	-
10a	15	-	-	-	-	-	14	-
13	-	13	-	-	-	13	12	14
17	14	-	12	-	-	-	14	-
18	14	-	14	-	12	14	15	-
19b	-	-	12	-	-	14	13	-
20	-	-	-	-	-	-	-	-
25	-	-	-	-	-	-	12	12
26	-	14	-	-	-	13	12	-

1580 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.7 (s, 3H, CH_3), 6.0 (s, 2H, CH_2), 7.2-8.8 (m, 10H, Ar-H).

Diethyl 2-(5-cyano-4-methyl-2-phenylpyrimidin-6-yloxy)-malonate (4_c)

Produced in 74% yield; mp 98-100 °C. Anal. Calcd. for $C_{19}H_{19}N_3O_5$ (369.13): C, 61.78; H, 5.18; N, 11.38. Found; C, 61.80; H, 5.16; N, 11.41. IR: ν 2900 (CH, aliphatic), 2200 (C≡N), 1760, 1750 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.08-1.12 (m, *J* = 7 Hz, 6H, $2CH_3$), 2.55 (s, 3H, $-CH_3$), 4.11-4.13 (m, *J* = 7 Hz, 4H, $2CH_2$), 5.7 (s, 1H, CH), 7.26-7.32 (m, 3H, Ar-H), 8.14-8.16 (m, 2H, Ar-H).

Ethyl (5-cyano-4-methyl-2-phenylpyrimidin-6-yloxy)acetate (4_d)

Produced in 73% yield; mp 118-119 °C. Anal. Calcd. for $C_{16}H_{15}N_3O_3$ (297.31); C, 64.64; H, 5.09; N, 14.13. Found: C, 64.62; H, 5.14; N, 14.01. IR: ν 2960 (CH, aliphatic), 2200 (C≡N), 1740 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.15-1.30 (t, 3H, CH_3), 2.7 (s, 3H, $-CH_3$), 4.05-4.30 (q, 2H, CH_2), 5.0 (s, 2H, CH_2), 7.2-7.5 (m, 3H, Ar-H), 8.2, 8.4 (m, 2H, Ar-H).

Methyl 2-(5-cyano-4-methyl-2-phenyl-pyridin-6-yloxy)-propanoate (4_e)

Produced in 75% yield; mp 138-140 °C. Anal. Calcd for $C_{16}H_{15}N_3O_3$ (297.31); C, 64.64; H, 5.09; N, 14.13. Found: C, 64.61; H, 5.31; N, 14.11. IR: ν 2950 (CH, aliphatic), 2200 (C≡N), 1750 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.8-1.9 (d, 3H, CH_3), 2.8 (s, 3H, CH_3), 4.2 (s, 3H, OCH_3), 5.4-5.7 (q, 1H, CH), 7.4-7.6 (m, 3H, Ar-H), 8.3-8.5 (m, 2H, Ar-H).

Ethyl 3-oxo-2-(5-cyano-4-methyl-2-phenylpyrimidin-6-yloxy)butanoate (4_f)

Produced in 78% yield, mp 119-121 °C. Anal Calcd. for $C_{18}H_{17}N_3O_4$ (339.35): C, 63.71; H, 5.05; N, 12.38, Found: C, 63.65; H, 5.0; N, 12.32. IR: ν 2960 (CH, aliphatic), 2200 (C≡N), 1750, 1730 (2C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.2-1.4 (t, 3H, CH_3), 2.7 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 4.0-4.3 (q, 2H, CH_2), 5.2 (s, H, CH), 7.3-7.5 (m, 3H, Ar-H), 8.2-8.4, (m, 2H, Ar-H).

6-Cyanomethoxy-4-methyl-2-phenylpyrimidine-5-carbonitrile (4_g)

Produced in 76% yield; mp 173-175 °C. Anal. Calcd. for $C_{14}H_{10}N_4O$ (250.26); C, 67.19; H, 4.03; N, 22.39. Found: C, 67.23; H, 4.14; N, 22.34. IR: ν 2200 (C≡N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.8 (s, 3H, CH_3), 5.2 (s, 2H, CH_2), 7.4-7.6 (m, 3H, Ar-H), 8.4-8.5 (m, 2H, Ar-H).

General procedure for the synthesis of 5_{a-c}

A mixture of compound 4_{a-c} (0.05 mol) in absolute ethanol (50 mL) containing sodium (0.5 gm) was refluxed for 1 hour. The solid product was collected, washed with water and recrystallized from suitable solvent.

5-Amino-6-acetyl-4-methyl-2-phenylfuro[2,3-d]pyrimidine (5_a)

Produced in 90% yield, yellow crystals from ethanol; mp 208-210 °C. Anal. Calcd. for $C_{15}H_{13}N_3O_2$ (267.28); C, 67.40; H, 4,90; N, 15.72. Found: C, 67.35; H, 4.92; N, 15.64. IR: ν 3400, 3300 (NH_2); 1630 (C=O); ^1H NMR (DMSO-d_6): δ 2.5 (s, 3H, CH_3), 2.9 (s, 3H, CH_3), 6.9 (s, 2H, NH_2), 7.4-7.6 (m, 3H, Ar-H), 8.3-8.5 (m, 2H, Ar-H).

5-Amino-6-benzoyl-4-methyl-2-phenylfuro[2,3-d]pyrimidine (5_b)

Produced in 76% yield, yellow crystals from ethanol mp 218-220 °C. Anal. Calcd. for $C_{20}H_{15}N_3O_2$ (329.35): C, 72.94; H, 4.59; N, 12.76. Found: C, 72.92; H, 4.60; N, 12.80. IR: ν = 3350, 3450 (NH_2), 1610 (C=O), 1560 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.9 (s, 3H, CH_3), 6.3 (s, 2H, NH_2), 7.4-8.7 (m, 10H, Ar-H).

5-Amino-4-methyl-2-phenylfuro[2,3-d]pyrimidine-6-carboxylate (5_c)

Produced in 83% yield, yellow crystals from ethanol, mp 178-180 °C. Anal. Calcd. for $C_{16}H_{15}N_3O_3$ (297.11): C, 64.64; H, 5.09; N, 14.13. Found: C, 64.64; H, 5.13; N, 14.16. IR: ν 3480, 3380 (NH_2); 1680 (C=O); 1600 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.4-1.5 (t, 3H, CH_3), 2.8 (s, 3H, CH_3), 4.3-4.6 (q, 2H, CH_2), 5.2 (s, 2H, NH_2), 7.2-7.4 (m, 3H, Ar-H), 8.4-8.6 (m, 2H, Ar-H).

N-(6-Benzoyl-4-methyl-2-phenylfuro[2,3-d]pyrimidin-5-yl)-2-chloroacetamide (6)

A mixture of 5_b (1.65 g; 0.005 mol), chloroacetyl chloride (0.005 mol) in dioxane (20 mL) was refluxed for 2 hours; after cooling the reaction mixture was poured into cold water. The solid product was collected and recrystallized from ethanol as pale yellow crystals, yield 81%, mp 248-250 °C. Anal. Calcd. for $C_{22}H_{16}ClN_3O_3$ (405.8): C, 65.11; H, 3.97; Cl, 8.74; N, 10.35. Found: C, 65.15; H, 3.86; Cl, 8.80; N, 10.46. IR: ν 3250 (NH), 1680, 1630 (2C=O), 1570 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.8 (s, 3H, CH_3), 4.3 (s, 2H, CH_2), 7.5-8.5 (m,

10H, Ar-H), 10.6 (s, H, NH).

N-(6-Benzoyl-4-methyl-2-phenylfuro[2,3-d]pyrimidin-5-yl)-2-piperidin-1-yl)acetamide (7)

A mixture of **6** (2 gm; 0.05 mol), piperidine (0.005 mol) in ethanol (20 mL) was refluxed for 4 hours then allowed to cool. The solid product was collected and recrystallized from a mixture of benzene: pet. ether (2:1) as pale yellow crystals. Yield 75%, mp 228-230 °C. Anal. Calcd. for $C_{27}H_{26}N_4O_3$ (454.52): C, 71.35; H, 5.77; N, 12.33. Found: C, 71.28; H, 5.78; N, 12.35. IR: ν 3200 (NH), 1700, 1682 (2C=O), 1580 (C=N) cm^{-1}; Ms: *m/z* 454 (M^+).

Sodium 5-amino-4-methyl-2-phenylfuro[2,3-d]pyrimidine-6-carboxylate (8)

A mixture of $\mathbf{5_c}$ (1.5 gm; 0.005 mol), sodium hydroxide (0.2 gm; 0.005 mol) in ethanol (20 mL) was refluxed for 5 hours then allowed to cool. The solid product was filtered off, washed with ethanol and air dried to give a yellowish white solid in 80% yield. Compound **8** was subjected to the next step without further purification.

4-Methyl-2-phenylfuro[2,3-d]pyrimidin-5(6H)-one (9)

A sample of compound **8** (2 g) was stirred for 2 hours in orthophosphoric acid (10 mL), then neutralized by ammonium hydroxide. The solid product was filtered off and recrystallized from ethanol as white crystals in 72% yield, mp 148-150 °C. Anal. Calcd. for $C_{13}H_{10}N_2O_2$ (226.23): C, 69.02; H, 4.46; N, 12.38. Found: C, 69.00; H, 4.43; N, 12.35. IR: ν 1710 (C=O); 1580 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.8 (s, 3H, CH_3), 4.8 (s, 2H, CH_2), 7.4-7.6 (m, 3H, Ar-H), 8.4-8.6 (m, 2H, Ar-H). ^{13}C NMR 15.6, 77.8, 118.8, 126.9, 127.0, 128.7, 129.0, 129.2, 135.4, 166.3, 172.2, 172.6, 192.4; Ms: *m/z* 226 (M^+).

General procedure for the synthesis of $\mathbf{10_{a,b}}$

A mixture of **9** (2.269; 0.01 mol) and the respective aromatic aldehyde (0.01 mol) in ethanol (50 mL) containing a catalytic amount of piperidine was refluxed for 2 hours. The solid product which formed after cooling was filtered off and recrystallized from a suitable solvent.

6-(p-Methoxybenzyledine)-4-methyl-2-phenylfuro[2,3-d]-pyrimidin-5-one ($\mathbf{10_a}$)

Produced in 78% yield, mp 230-232 °C, yellow crystals from ethanol. Anal. Calcd. for $C_{21}H_{16}N_2O_3$ (344.36): C, 73.24; H, 4.68; N, 8.13. Found: C, 73.18; H, 4.71; N, 8.07. IR: ν 1690 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.8 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 7.3 (s, 1H, CH), 6.9-7.1 (m, 2H, Ar-H), 7.45-7.65 (m, 3H, Ar-H), 7.94, 7.96 (d, 2H, Ar-H), 8.58-8.60 (d, 2H, Ar-H).

6-(p-Chlorobenzylidene)-4-methyl-2-phenylfuro[2,3-d]-pyrimidin-5-one ($\mathbf{10_b}$)

Produced in 76% yield; mp 174-176 °C; yellow crystals from ethanol Anal. Calcd. for $C_{20}H_{13}N_2O_2Cl$ (348.78): C, 68.87; H, 3.76; N, 8.03; Cl, 10.16. Found: C, 68.84; H, 3.77; N, 8.00; Cl, 10.12. IR: ν 1700 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.8 (s, 3H, CH_3), 6.7-8.7 (m, 10H, Ar-H and CH).

5-N,N-Diacetylamino-4-methyl-2-phenylfuro[2,3-d]pyrimidine (12)

A sample of **8** (1.45 g, 0.005 mol) was refluxed in (30 mL) acetic anhydride for 4 hours, then allowed to cool and poured into a ice/water mixture. The solid product was filtered off and recrystallized from ethanol as pale yellow crystals in 74% yield, mp 138-140 °C. Anal. Calcd. for $C_{17}H_{15}N_3O_3$ (309.32): C, 66.01; H, 4.89; N, 13.58. Found: C, 66.03; H, 4.90; N, 13.56. IR: ν 1720, 1700 (2C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.5 (s, 6H, $2COCH_3$), 2.8 (s, 3H, CH_3), 7.7 (s, 1H, CH), 7.4-7.6 (m, 3H, Ar-H), 8.4-8.6 (m, 2H, Ar-H).

N-(4-Methyl-2-phenylfuro[2,3-d]pyrimidin-5-yl)acetamide (13)

A mixture of **12** (1.55 gm; 0.05 mol), hydrazine hydrate (3 mL) in ethanol (30 mL) was refluxed for 4 hours then allowed to cool. The solid product which formed after cooling was filtered off and recrystallized from ethanol as yellowish white crystals in 70% yield, mp 208-210 °C. Anal. Calcd. for $C_{15}H_{13}N_3O_2$ (267.28): C, 67.40; H, 4.90; N, 15.72. Found: C, 67.38; H, 4.87; N, 15.74. ^{1}H NMR ($CDCl_3$): δ 2.3 (s, 3H, $COCH_3$), 2.9 (s, 2H, CH_3), 7.4-7.6 (m, 3H, Ar-H), 8.1 (s, 1H, CH), 8.3-8.5 (m, 2H, Ar-H); Ms: *m/z* 267 (M^+).

5-Amino-4-methyl-2-phenylfuro[2,3-d]pyrimidine-6-carbohydrazide (14)

A mixture of $\mathbf{5_c}$ (2.97; 0.01 mol) and hydrazine hydrate (3 mL) in ethanol (20 mL) were refluxed for 3 hours. The solid product which formed during reflux was filtered off and recrystallized from dioxane as pale yellow crystals in 73% yield, mp 263-265 °C. Anal. Calcd. for $C_{14}H_{13}N_5O_2$ (283.29): C, 59.36; H, 4.63; N, 24.72. Found: C, 59.2; H, 4.62; N, 24.75. IR: ν 4500, 3350, 3250 (NH, NH_2), 1620 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.9 (s, 3H, CH_3), 4.5 (s, 2H, NH_2), 6.0 (s, 2H, NH_2), 7.4-7.6 (m, 3H, Ar-H), 8.3-8.5 (m, 2H, Ar-H), 9.0 (s, 1H, NH).

5-Amino-4-methyl-2-phenylfuro[2,3-d]pyrimidine-6-carboazide (15)

To a cooled solution of compound **14** (1.4 gm; 0.005 mol) in glacial acetic acid (20 mL), sodium nitrite solution (0.69 gm in 5 mL H_2O) was added dropwise with stirring. The stirring was continued for an additional 2 hours, then the reaction mixture was allowed to stand 5 hours. The solid product was filtered off, washed several times with water and air dried to give pale yellow crystals without purification in 84% yield, mp 179-180 °C. Anal. Calcd. for $C_{14}H_{10}N_6O_2$ (294.27): C, 57.14; H, 3.43; N, 28.56. Found: C, 57.24; H, 3.84; N, 28.39. IR: ν 3450, 3350 (NH_2), 3130 (N_3), 1650 (C=O) cm^{-1}.

4-Methyl-2-phenylimidazo[4′,5′:4,5]furo[2,3-d]pyrimidin-6-(5H,7H)-one (16)

A sample of compound **15** (0.5 gm) in dry xylene (10 mL) was heated under reflux for 3 hours then allowed to cool to room temperature. The solid product which separated from the hot mixture was filtered off and recrystallized from dioxane as brownish red crystals in 73% yield, mp > 300 °C. Anal. Calcd. for $C_{14}H_{10}N_4O_2$ (266.25): C, 63.15; H, 3.79; N, 21.04. Found: C, 63.26; H, 3.71; N, 21.00. IR: ν 3200 (NH), 1710 (C=O) cm^{-1}, Ms: *m/z* 266 (M^+).

7-N-Formylamino-4-methyl-2-phenylpyrimido[4′,5′:4,5]-furo[2,3-d]pyrimidin-8-(7H)-one (17)

A sample of compound **14** (0.5 g) in formic acid (10 mL) was refluxed for 5 hours then allowed to cool to the room temperature. The solid product was collected and recrystallized from dioxane as pale yellow crystals in 80% yield, mp 290-292 °C. Anal. Calcd. for $C_{16}H_{11}N_5O_3$ (321.29): C, 59.81; H, 3.45; N, 21.80. Found: C, 59.72; H, 3.50; N, 21.74. IR: ν 3170 (NH); 1720, 1680 (2C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.9 (s, 3H, CH_3) 7.4-7.6 (m, 3H, Ar-H), 8.4-8.5 (m, 2H, Ar-H and 1H, pyrimidine), 8.5 (s, 1H, CHO), 9.4 (s, 1H, NH).

7-N,N-Diacetylamino-4,6-dimethyl-2-phenylpyrimido-[4′,5′:4,5]furo[2,3-d]pyrimidin-8-(7H)-one (18)

A sample of compound **14** (0.5 gm) in acetic anhydride (10 mL) was refluxed for 2 hours then allowed to cool and poured into cold water. The solid product was collected and recrystallized from dioxane as pale yellow crystals in 82% yield, mp 220-221 °C. Anal. Calcd. for $C_{20}H_{17}N_5O_4$ (391.38): C, 61.38; H, 4.38; N, 17.89. Found: C, 61.29; H, 4.48; N, 17.90. IR: ν 1730, 1620 (C=O), 1560 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.46 (s, 6H, $2COCH_3$), 2.52 (s, 3H, CH_3), 3.0 (s, 3H, CH_3), 7.8-8.6 (2m, 5H, Ar-H).

General procedure for the synthesis of (19_{a-c})

A mixture of furopyrimidine carbohydrazide **14** (2.83 gm; 0.01 mole) and an appropriate aromatic aldehyde (0.01 mol) in ethanol : acetic acid mixture (30 mL) was refluxed for 4 hours then allowed to cool at room temperature. The solid product was collected and recrystallized from a suitable solvent.

Benzylidene 5-amino-4-methyl-2-phenylfuro[2,3-d]pyrimidine-6-carbohydrazone (19_a)

Produced in 86% yield, mp 256-258 °C, yellow crystals from acetic acid. Anal. Calcd. for $C_{21}H_{17}N_5O_2$ (371.39): C, 67.91; H, 4.61; N, 18.86. Found: C, 67.83; H, 4.51; N, 18.93. IR: ν 3450, 3350 (NH, NH_2), 1640 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.9 (s, 3H, CH_3), 6.2 (s, 2H, NH_2), 7.3-7.8, 8.3-8.5 (2m, 10H, Ar-H), 8.6 (s, 1H, CH), 12.2 (s, 1H, NH).

5-Amino-6-(p-nitrobenzylidene)-4-methyl-2-phenylfuro-[2,3-d]pyrimidine-6-carbohydrazone (19_b)

Produced in 81% yield, mp 308-310 °C, reddish yellow crystals from acetic acid. Anal. Calcd. for $C_{21}H_{16}N_6O_4$ (416.39): C, 60.57; H, 3.87; N, 20.18. Found: C, 60.65; H, 4.00; N, 20.03. IR: ν 3450, 3300 (NH, NH_2), 1640 (C=O) cm^{-1}. ^{1}H NMR (T.F.A): δ 3.3 (s, 3H, CH_3), 7.6-8.5 (m, 10H, Ar-H and -N=CH).

5-Amino-6-(p-chorobenzylidene)-4-methyl-2-phenylfuro-[2,3-d]pyrimidine-6-carbohydrazone (19_c)

Produced in 78% yield, mp 268-270 °C, yellow crystals from acetic acid. Anal. Calcd. for $C_{21}H_{16}ClN_5O_2$ (405.84): C, 62.15; H, 3.97; Cl, 8.74; N, 17.26. Found: C, 62.23; H, 4.01; Cl, 8.62; N, 17.08. IR: ν 3450, 3300 (NH, NH_2), 1670 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): 2.8 (s, 3H, CH_3), 6.9 (s, 2H, NH_2), 7.3, 7.32 (d, 2H, Ar-H), 7.65, 7.67 (d, 2H, Ar-H), 7.4-7.6 (m, 3H, Ar-H), 8.4-8.6 (m, 2H, Ar-H), 8.0 (s, 1H, CH), 9.6 (s, 1H, NH).

5-Amino-4-methyl-2-phenyl-6-[3′,5′-dimethylpyrazol-1-ylcarbonyl]furo[2,3-d]pyrimidine (20)

A mixture of carbohydrazide **14** (2.83 gm; 0.01 mol) and acetyl acetone (0.021 mol) in ethanol (40 mL) was refluxed for 2 hours then allowed to cool at room temperature. The solid product was collected and recrystallized from ethanol as yellow needles in 69% yield, mp 200-202 °C. Anal. Calcd. for $C_{19}H_{17}N_5O_2$ (347.37): C, 65.69; H, 4.93; N, 20.16. Found: C, 65.61; H, 4.83; N, 20.26. IR: ν 3450, 3350 (NH_2); 1630 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.3, 2.5

(2S, 6H, $2CH_3$), 2.9 (s, 3H, CH_3), 6.2 (s, 1H, CH), 7.3 (s, 2H, NH_2), 7.4-7.6 (m, 3H, Ar-H), 8.4-8.6 (m, 2H, Ar-H).

General procedure for the synthesis of 21, 22

A mixture of **5a** or **5b** (0.01 mol), ethyl cyanoacetate (1.13 gm; 0.01 mol) and ammonium acetate (3 gm) was refluxed for 3 hours. The solid product was collected and recrystallized from dioxane as yellow crystals.

7-Cyano-4-methyl-2,8-diphenylpyrido[2′,3′:4,5]furo[2,3-d]-pyrimidin-6-(5H)-one (21)

Produced in 61% yield, mp > 350 °C. Anal. Calcd. for $C_{23}H_{14}N_4O_2$ (378.38): C, 73.01; H, 3.73; N, 14.81. Found: C, 72.86; H, 3.70; N, 14.80. IR: ν 3150 (NH); 2200 (C=N); 1620 (C=O); 1580 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): 2.9 (s, 3H, CH_3), 7.6-7.8, 8.4-8.5 (2m, 11H, NH and Ar-H).

7-Cyano-4,8-dimethyl-2-phenylpyrido[4′,5′:4,5]furo[2,3-d]-pyrimidin-6(5H)-one (22)

Produced in 60% yield, mp > 350 °C. Anal. Calcd. for $C_{18}H_{12}N_4O_2$ (316.70): C, 68.35; H, 3.82; N, 17.71. Found: C, 68.31; H, 3.85; N, 17.74. IR: ν 3150 (NH); 2200 (C=N); 1630 (C=O); 1580 (C=N); Ms: *m/z* 316 (M^+).

4-Methyl-8-oxo-5,6,7,8-tetrahydro-2,7-diphenylpyrimido-[4′,5′:4,5]furo[2,3-d]pyrimidin-6-thione (23)

A mixture of **5c** (1.5 gm; 0.005 mol), phenyl isothiocyanate (0.67 gm; 0.005 mol) in pyridine (30 mL) was refluxed for 10 hours then allowed to cool at room temperature. The solid product was filtered off and recrystallized from DMF as yellow crystal in 56% yield, mp > 350 °C. Anal. Calcd. for $C_{21}H_{14}N_4O_2S$ (386.43): C, 65.27; H, 3.65; N, 14.50; S, 8.30. Found: C, 65.24; H, 3.57; N, 14.45; S, 8.33. IR: ν 3300 (NH); 1700 (C=O), 1590 (C=N) cm^{-1}. ^1H NMR (T.F.A): δ 3.6 (s, 3H, CH_3), 7.4-8.5 (m, 10H, Ar-H).

4-Methyl-2-phenylpyrimido[4′,5′:4,5]furo[2,3-d]pyrimidin-8-(7H)-one (24)

A sample of compound **5c** (1 gm) in formamide (10 mL) was refluxed for 3 hours. The solid product which separated from the hot mixture was filtered off and recrystallized from acetic acid as yellowish brown crystals in 76% yield, mp > 310 °C. Anal. Calcd. for $C_{15}H_{10}N_4O_2$ (278.27): C, 64.74; H, 3.62; N, 20.13. Found: C, 64.63; H, 3.71; N, 20.10. IR: ν 3150 (NH), 1670 (C=O) cm^{-1}. ^1H NMR (T.F.A): δ 3.5 (s, 3H, CH_3), 7.6-7.9 (m, 3H, Ar-H), 8.4-8.6 (m, 2H, Ar-H), 8.9 (s, 1H, CH).

8-Chloro-4-methyl-2-phenylpyrimido[4′,5′:4,5]furo[2,3-d]-pyrimidine (25)

A sample of compound **24** (1 g) in phosphoryl chloride (15 mL) was heated under reflux for 3 hours, then allowed to cool and poured on ice-water mixture with stirring. The solid product was collected and recrystallized from ethanol as yellowish red crystals in 68% yield, mp 210-212 °C. Anal. Calcd. for $C_{15}H_9N_4Ocl$ (296.71): C, 60.72; H, 3.06; N, 18.88; Cl, 11.95. Found: C, 60.64; H, 2.97; N, 19.01; Cl, 11.78. IR: ν 1580 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.0 (s, 3H, CH_3), 7.2-7.4 (m, 3H, Ar-H), 8.51-8.63 (m, 2H, Ar-H), 8.9 (s, 1H, CH). Ms: *m/z* 296 (M^+).

8-Hydrazino-4-methyl-2-phenylpyrimido[4′,5′:4,5]furo-[2,3-d]pyrimidine (26)

A sample of **25** (1 gm), hydrazine hydrate (2 mL) in ethanol (15 mL) was refluxed for 4 hours then allowed to cool. The solid product was collected and recrystallized from ethanol as yellowish red crystals, in 71% yield, mp 218-220 °C. Anal. Calcd. for $C_{15}H_{12}N_6O$ (292.30): C, 61.64; H, 4.14; N, 28.75. Found: C, 61.57; H, 4.21; N, 28.85. IR: ν 3450, 3300, 3200 (NH, NH_2); 1590 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.0 (s, 3H, CH_3), 3.5 (s, 2H, NH_2), 7.56-7.57 (m, 3H, Ar-H), 8.47-8.50 (m, 2H, Ar-H), 8.57 (s, 1H, CH). ^{13}C NMR (DMSO-d_6) 17.9, 121.3, 127.4, 127.7, 128.5, 129.4, 129.6, 135.8, 155.5, 156.4, 165.6, 165.9, 165.3, 166.4, 168.6.

Received February 9, 2004.

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