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SYNTHESIS AND REACTION OF FUSED POLYNUCLEAR HETEROCYCLES

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ABSTRACT

Reaction of furo [2,3-b] pyridine **1** with malononitrile, ethyl cyanoacetate, formic acid/sodium acetate mixture and formamide afforded the corresponding 2,4-daimino-3-cyano-furo [2',3': 6,5] pyrido [2,3-b] pyridine **4**, 4-amino-3-cyano-furo [2',3': 6,5] pyrido [2,3-b] pyridine-2(IH)-on **5**, furo [2',3': 6,5] pyrido [2,3-d] pyrimidine-4(3H)-on **6** and 4-aminofuro [2',3': 6,5] pyrido [2,3-d]-pyrimidine **7**. Treatment of furo [2,3-d] pyrimidine-6 thione 2 with benzoyl hydrazine and ethyl chloroacetate afforded the corresponding furo [3,2-e] [1,2,4] triazolo [4,3-a]-pyridimidine **8** and 6-(carbethoxymethylthio) furo [2,3-d] pyridimidine **9** Condenstation of furo [2,3-b] pyrane 3 with acetic anhydride, acetic antydride pyridine mixture and p-chlorocinnamonitrile afforded the corresponding 6-acetamide-4H-furo [2,3-b] pyrane **10**, 2-methyl-4-oxo-3,4-dihydro-5H-furo [2',3': 6,5] pyrano [2,3-d] pyrimidine **11** and 4-amino-3-cyano-5H-furo [2',3': 6,5] pyrano [2,3-b] pyridine **12**. The structure of new compounds were established by analytical and spectroscopic measurements.

INTRODUCTION

The chemistry of condensed heterocyclic system especially containing furane moiety acquired much attention owing to its pharmacological activities[1,2]. In this work a series of unreported fused polynuclear heterocycles were prepared from furo $[2,3-b]$ pyridine[3], furo $[2,3-d]$ pyrimidine[4] and furo $[2,3-b]$ pyrane[5].

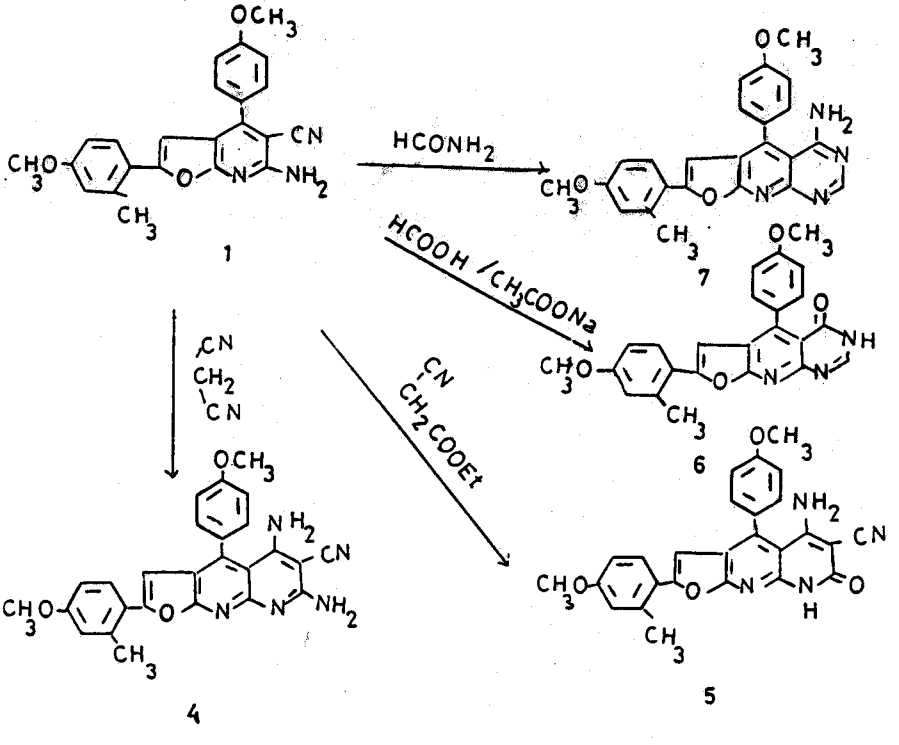
RESULTS

Reaction of furo $[2,3-b]$ pyridine derivative **1** with malonitile in thanol/piperidine solution[6] yielded the 2,4-diamino-3-cyano-furo $[2',3': 6,5]$ pyrido $[2,3-b]$pyridine **4** Structure of **4** was established for the reaction product based on its analytical and spectral data (see Experimental and Table 1).

Table 1: Spectral date of prepared compounds (4-12).

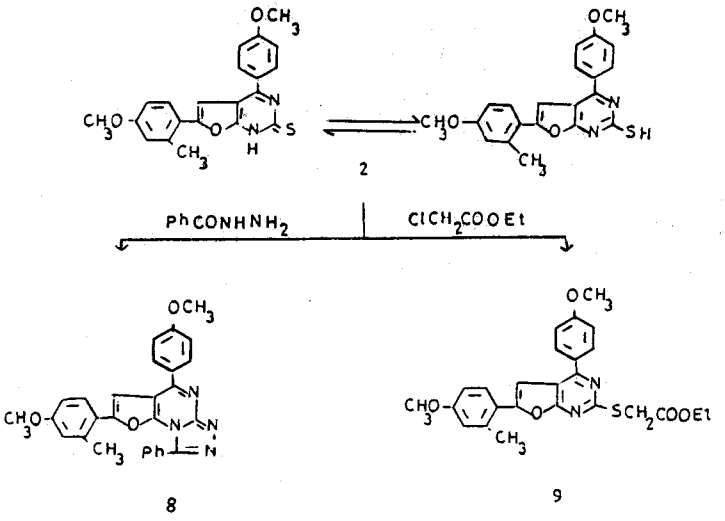
Compoud No	IR (cm^{-1})	^{1}H-NMR (δ ppm)
4	2207 (CN), 1644 (C=N), 3330-3200 (NH_2)	6.1 (s, 1H, furan), 3.2 (s, 3H, CH_3), 3.4 (s, 6H, 2 OCH_3) , 7.3 - 8.1 (m, 11H, Ar-H and $2NH_2$).
5	2216 (CN), 3307-3211 (NH, NH_2), 1643 (C=N), 1675 (C=0).	6.3 (s, 1H, furan, 3.1 (s, 3H, CH_3), 3.5 (s, 6H, $2OCH_3$), 7.1-8.0(m, 9H, Ar-H and NH_2), 10.1 (bs, 1H, NH).
6	1675 (C=0), 1606 (C=N), 3205 (NH).	6.1 (s, 1H, furan), 3.1(s, 3H,CH_3), 3.5 (s, 6H, $2OCH_3$), 6.9-7.3 (m,8H, Ar-H and heterocyclic H), 10.2(bs, 1H, NH).
7	3363-3290 (NH_2), 1601 (C=N)	6.8-7.4(m, 8H, Ar-H and heterocyclic H), 6.1(bs, 2H,NH_2), 6.1(s,1H, furan), 3.1 (s, 3H, CH_3), 3.5 (s, 6H, 2 OCH_3).
8	1577 (C=N), 2847 (CH), 1509 (C=C)	6.2 (s, 1H, furan), 3.0 (s,3H,CH_3), 3.4 (s, 6H, 2 OCH_3), 7.1-7.6 (m, 12 H, Ar-H).
9	1738 (C=O), 1606 (C=N), 2930 (CH)	6.2 (s, 1H, furan), 3.1 (s, 3H, CH_3), 3.5 (s, 6H, 2 OCH_3),7.1-7.4 (m,7H, Ar-H), 4.1 (q, 2H, CH_3-CH_2),3.0 (t 3H, CH_3-CH_2), 4.4 (s, 2H, S-CH_2-CO).
10	2210 (CN), 1605 (C=N), 3206 (NH), 1650 (C=O)	4.0(s, 3H, CH_3), 10.1(bs,1H, NH), 6.1(s, 1H, furan), 3.1(s, 3H, CH_3-Ar), 3.6 (s, 6H, 2 OCH_3), 7.2-7.6 (m, 7H, Ar-H).
11	3210 (NH), 1631 (C=N), 1670 (C=O)	7.2-8.1(m, 7H, Ar-H), 10.3(bs, 1H, NH), 3.2 (s, 3H, CH_3), 3.5 (s, 6H, 2 OCH_3), 6.0 (s, 1H, furan), 3.9 (s, 3H, CH_3).
12	2208 (CN), 3447-3350 (NH_2), 2926 (CH), 1610 (C=N)	7.3-8.5 (m, 13H, Ar-H and NH_2), 3.1(s, 3H, CH_3),3.5(s,6H,2 OCH_3), 6.1 (s, 1H, furan).

Also, furo [2',3':6,5] pyrido [2,3-b] pyridine-2 1H-on **5** was prepared via condensation on **1** with ethyl eyanoacetate in basic medium. Moreover, interaction of **1** with formic acid/sodium acetate mixture[7] afforded the corresponding furo [2',3':6,5] pyrido [2,3-d] pyrimidine-4 (3H)-on **6**, while the reaction of **1** with formamide afforded the corresponding 4-Amino-furo [2',3':6,5] pyrido [2,3-d] pyrimidine **7** (Scheme 1).



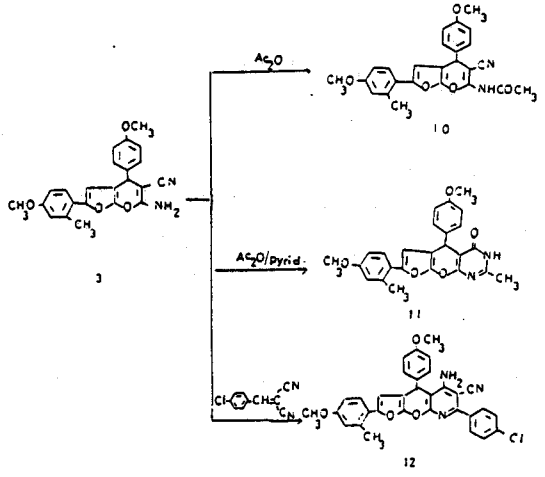
Scheme 1

Treatment of furo [2,3-d] pyrimidine-6thione **2** with benzoyl hydrazine[8]afforded the corresponding furo [3,2-e][1,2,4] triazolo [4,3-a] pyrimidine **8** Condensation of **2** with ethyl chloroacetate[9] in boiling dry acetone containing anhydrous potassium carbonate resulting in alkylation on S atom to give the corresponding **6**(carbethoxymethylthio) furo [2,3-d] pyrimidine **9**. The structure of **9** was confirmed by analytical data. The IR absorption on spectra of **9** showed the disappearance of absorption band at 2800 cm^{-1} (SH) confirming S alkylation.



Scheme 2

Treatment or furo [2,3-b] pyran **3** with acetic anhdride[10] yielded the 6-acetamido-4H-furo [2,3-b] pyrane **10**. Also, compound **3** reaction with acetic anhydride/pyridine mixture afforded the corresponding 2-methyl-4-oxo-3,4-dihydro-5H-furo [2',3': 6,5] pyrano [2,3-d] pyrimidine **11** (Scheme 3). The analytical and spectral data of **10** and **11** were in accordance with the proposed structures.



Scheme 3

Treatment of **3** with p-chlorocinnamonitrile to yield 5H-furo [2',3': 6,5] pyrano [2,3 – b] pyridine **12**. The formation of **12** is assumed to proceed by addition of the amino function in **3** to the double bond in p-chlorocinnamonitrile, this is followed by cyclization and hydrogen cyanide elimination, the structure of **12** was confirmed based on analytical and spectral data (see Experimental and Table 1).

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Pyeunican spectrophotometer type 1200 using KBr Wafer technique. The ^{1}H-NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer using TMS as internal standard and DMSO-d_6 as solvent. Chemical shifts were expressed in δ (ppm) values. Elemental analyses were determined using Perkin-Elmer 340^{0}C Microanalyser.

Starting compounds 1,2 and 3 has been synthesized by the method reported earlier[3-5]

2,4-Diamino-3-cyano-5-(4-methoxyphenyl)-7-((2-methyl-4-methoxy)phenyl)furo [2,3:6,5] pyrido [2.3-b] pyridine 4.

A suspension of equimolar amounts (3.82 g, 0.01 mol) of **1** and malonotrile in ethanol (50 ml) and a catalytic amount of piperidine was reflexud for 5 h. The solid product was collected by filtration, and crystallized from ethanol, mp. 164-167^0, yield 3.8 g (85%) (Found: C, 69.15; H, 4.61; N, 15.49. $C_{26}H_{12}N_5O_3$ required C,69.17; H, 4.65; N, 15.52%).

4-Amino-3-cyano-5-(4-methoxypenyl)-7-((2-methyl-4-methoxy)phenyl))-2-oxofuro [2',3': 6,5] pyrido [2,3-b] pyridine-2- (1H)-on 5

A mixture of **1** (3.82, 0.01 mol) in ethanol (50 mol) containing a few drops of piperidine was heated under ruflux for 5 h. The solvent was then evaporated under reduced pressure and the solid was collected and cyrstallized from acetone, mp. 145-147^0, yield 2.7 (60%). (Found: C, 69.00; H, 4.40; N, 12.33. C_{26} $H_{20}N_4O_4$ required C, 69.02;H,4.42; N,12.38%).

5-(4-Methoxyphenyl)-7-(2-methyl-4-methoxy) phenyl furo [2',3': 6,5] pyrido [2,3-d] pyrimidine-4(3H)-on 6

A mixture of **1** (3.82 g, 0.01 mol), formic acid (40 ml) and 1.5 g (0.18 mol) of sodium acetate was refluxed for 4 h. After cooling the reaction mixture and the preciptated was filtered off and crystallized from ethanol, mp. 180-183^0, yield, 2.6 g

(65%). (Found: C,69.70; H, 4.57;N, 10.14. $C_{24}H_{19}N_3O_4$ required C, 69.73; H, 4.60;N, 10.16%).

4-Amino-5-(4-methoxyphenyl)-7-((2-methyl-4-methoxy) phenyl) phenyl) furo [2' ,3' : 6,5] pyrido-[2,3-d] pyrimidine 7

A mixture of **1** (3.82 g, 0.01 mol) and formamide (20 ml) was heated under refluxed for 4 h. After cooling, the prepitated product was filtered off and washed several times with cold ethanol, crystallized from acetone; mp. 172-175^0, yield 2.8 g (70%). (Found:C, 69.87; H, 4.83; N, 13.57, $C_{24}H_{20}N_4O_3$required C, 69.90; H, 4.85; N, 13.59%).

7-((2-Methyl-4-methoxy) phenyl) – 5 - (4-methoxypenyl)-1-phenyl-furo[3,2-e] [1,2,4] - triazolo [4,3-a] pyrimidine 8

A mixture of **2** (4.78 g, 0.01 mol) and benzoyl hydrazine (1.36 g, 0.01 mol) in n-butanol (30 ml) was refluxed for 48 h. The reaction mixture was cooled and excess of solvent was removed under reduced pressure. Residue was crystallized from ethanol, mp. 120-122°; yiel 2.7 g (60%) (Found: C, 72.70; H, 4.73; N, 12.10 $C_{28}H_{22}N_4O_3$ required C, 72.72; H, 4.76: N, 12.12%).

6-(Carbethoxymethylthio)-4-(4-methoxyphenyl)-2((methyl-4-methoxy)phenyl) furo [2,3-d] pyrimidine 9

A mixture of **2** (4.78 g, 0.01 mol) ethyl chloroacetate (1.22 ml, 0.01 mol) and anydrous K_2CO_3 (5.52 g, 0.04 mol) in dry acetone (50 ml) was refluxed for 24 h. Then it was cooled, poured into cold water (50 ml) the separated solid filtered off and crystallized from ethanol, mp. 110-113^0, yield 2.3 g (50%) (Found: C, 64.62; H 5.15; N, 6.00; S, 6.86 $C_{25}H_{24}N_2SO_5$ required: C, 64; H, 5.17; N, 6.03; S, 6.89%).

6-Acetamido-5-cyano-4-(4-methoxypenyl)-4H-furo [2,3-b] pyrane 10

A mixture of **3** (3.87 g, 0.01 mol); acetic anhydride (20 ml) and acetic acid (10 ml) was refluxed for 4h. Then cooled and poured into an ice/water mixture. The product was filtered off and washed several times with water and crystallized from ethanol, mp. 170-172^0, yield 3 g (70%). (Found: C, 69.90; H, 4.85; N, 6.50 C, 69.93; H, 4.89; N, 6.52%).

7-((2-methyl-4-methoxy)-5-(4-methoxypenyl)-2-methyl-4-oxo-3,4- dihydro-5H-furo [2' ,3' : 6,5] pyrano [2,3-d] pyrimidine 11

A mixture of **3** (3.87g, 0.01 mol) Ac_2O pyridine mixture (20 ml, 2:1 v/v) was heated on a steam bath for 10 h. Then cooled, and poured into ice/water mixture. The solid product formed was filtered off and washed several times with water and crystallized from acetone, mp 100-102^0, yield 2.5 g (60%). (Found: C, 69.90; H, 4.91; N, 6.55. $C_{25}H_{21}N_2O_5$ required: C, 69.93; H, 4.89; N, 6.52%).

4-Amino-3-cyano-2-(4-chlorophenyl)-5-(4-methoxyphenyl)-7-((2-methyl-4-methoxy) phenyl-5H-furo [2',3' : 6,5] pyrano [2,3-b] pyridine 12

A mixture of **3** (3.87 g, 0.01 mol) and p-chlorocinnamonitrile (1.88 g, 0.01 mol) in ethanol (50 ml) containing a catalytic amount of piperidine was heated under reflux for 5h. The solvent was then evaporated under reduced pressure and the solid was collected by filtration and crystallized from ethanol, mp. 140-143^0, yield 3.8 g (70%). Found: C, 70.03; H, 4.16; CI, 6.44; N, 7.60.$C_{32}H_{23}CIN_3O_4$ required: C, 70.01; H, 4.19; CI, 6.47; N, 7.65%).

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