One-pot Synthesis of Pyrido[2,3-*d*]pyrimidines via Efficient Three-component Reaction in Aqueous Media

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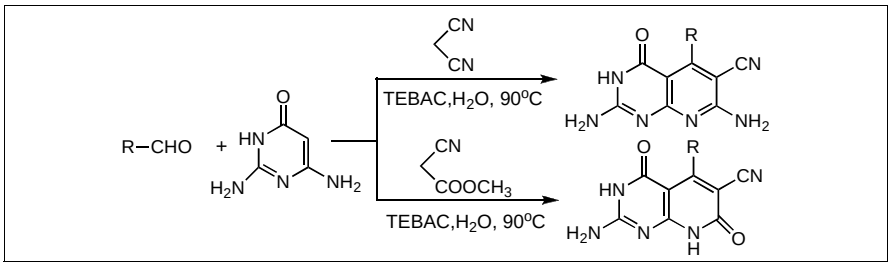

A short and facile synthesis of pyrido[2,3-*d*]pyrimidine derivatives was accomplished in good yields *via* the three-component reaction of aldehydes, alkyl nitriles and aminopyrimidines in water in the presence of triethylbenzylammonium chloride (TEBAC). The structures of these compounds were characterized by elemental analysis, IR and ^{1}H NMR spectra and further confirmed by single crystal X-ray diffraction analysis.

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INTRODUCTION

The importance of uracil and its annulated derivatives is well recognized by synthetic [1] as well as biological [2] chemists. With the development of clinically useful anticancer and antiviral drugs [3], there has recently been remarkable interest in the synthetic manipulations of uracils [4]. Pyrido[2,3-*d*]pyrimidines represent a heterocyclic ring system of considerable interest because of several biological activities associated with this scaffold. Some analogues have been found to act as anticancer agents inhibiting dihydrofolate reductases or tyrosine kinases [5], while others are known antiviral agents [6]. Therefore, for the preparation of these complex molecules large efforts have been directed towards the synthetic manipulation of uracils. As a result, a number of reports have appeared in the literature. Broom *et al.* [7] synthesized pyrido[2,3-*d*]pyrimidines from the reaction of DMAD and 6-aminouracil in protic solvent but obtained uncyclized condensed acetylenic adduct [8] when the reaction was carried in dimethylformamide. Bhuyan *et al.* [9] reported the synthesis of pyrido[2,3-*d*]pyrimidines from the reaction of arylidenemalononitrile with 6-aminouracil in refluxing 1-propanol, but in this reaction, benzylmalononitrile was obtained as by-product and the amount of arylidenemalononitrile needed was in excess. Recently Devi *et al.* [10] reported a novel three-component one-pot synthesis of pyrido[2,3-*d*]pyrimidines using microwave heating. These methods usually require forcing conditions, using organic solvents, long reaction times and complex synthetic pathways. Thus new routes for the synthesis of these molecules have attracted considerable attention in search for a rapid entry to these heterocycles.

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry. The first MCR was described by Strecker in 1850 for the synthesis of amino acids [11]. However, in the past decade there have been tremendous developments in three- and four-component reactions and great efforts continue to be made to develop new MCRs [12]. The need to reduce the amount of toxic waste and by-product arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods. One of the most promising approaches is using water as the reaction media. Breslow [13], who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic chemistry in the 1980's. There has been growing recognition that water is an attractive medium for many organic reactions [14] and many MCRs in aqueous medium have been reported [15]. As part of our current studies on the development of new routes to heterocyclic systems [16], we now report an efficient and clean synthetic route to pyrido[2,3-*d*]pyrimidine derivatives in aqueous media catalyzed by TEBAC.

RESULTS AND DISCUSSION

When the reaction of 4-chlorobenzaldeyhde **1a**, malononitrile **2** and 1,3-dimethyl-6-aminouracile **3a** was

performed in water in the presence of TEBAC at 90 °C, in a 96% yield of 2-amino-6,8-dimethyl-5,7-dioxo-4-(4-chlorophenyl)pyrido[2,3-*d*]pyrimidine-3-carbonitrile (**4a**) was obtained (Scheme 1). We tested this reaction in different organic solvents and the yields were lower (Table 1). When substituted aldehydes **1b**-**z** and 6-aminouraciles **3b**-**z** were employed, the same products **4b-z** were obtained (Table 2).

Scheme 1

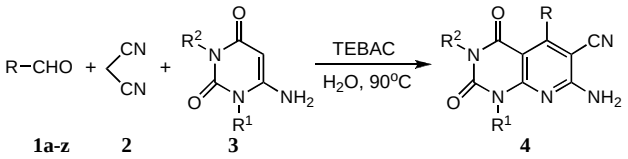


Table 1

Synthesis of 7-amino-1,3-dimethyl-2,4-dioxo-5-(4-chlorophenyl)-pyrido[2,3-*d*]pyrimidine-6-carbonitrile (**4a**) in different solvents

Entry	Solvent	Time (h)	Temperature (°C)	Yield (%)
4a	water	12	90	96
4a	ethanol	18	78	55
4a	acetone	24	55	42
4a	1,2-dichloroethane	17	80	38
4a	dichloromethane	19	40	60
4a	DMF	24	90	20

Table 2

Synthesis of pyrido[2,3-*d*]pyrimidine derivatives **4** in aqueous medium

Entry	R	R^1	R^2	Time (h)	Yield (%)
4a	4-ClC_6H_4	CH_3	CH_3	12	96
4b	2-$NO_2C_6H_4$	CH_3	CH_3	12	71
4c	4-$CH_3C_6H_4$	CH_3	CH_3	13	90
4d	3-$NO_2C_6H_4$	CH_3	CH_3	14	89
4e	3-ClC_6H_4	CH_3	CH_3	10	76
4f	4-HOC_6H_4	CH_3	CH_3	8	86
4g	4-$NO_2C_6H_4$	CH_3	CH_3	12	89
4h	4-$CH_3OC_6H_4$	CH_3	CH_3	20	91
4i	4-BrC_6H_4	CH_3	CH_3	8	74
4j	3-ClC_6H_4	CH_3	H	12	95
4k	4-BrC_6H_4	CH_3	H	18	86
4l	3-$NO_2C_6H_4$	CH_3	H	16	97
4m	4-$CH_3OC_6H_4$	CH_3	H	20	95
4n	4-HOC_6H_4	CH_3	H	20	96
4o	4-$NO_2C_6H_4$	CH_3	H	20	92
4p	3-Pyridyl	CH_3	H	14	86
4q	4-Pyridyl	CH_3	H	12	88
4r	n-C_4H_9	H	H	15	82
4s	2,4-$Cl_2C_6H_3$	H	H	10	90
4t	4-BrC_6H_4	H	H	9	96
4u	4-FC_6H_4	H	H	12	92
4v	3,4-$Cl_2C_6H_3$	H	H	8	77
4w	3-$NO_2C_6H_4$	H	H	10	97
4x	2-ClC_6H_4	H	H	10	80
4y	4-$NO_2C_6H_4$	H	H	4	94
4z	4-ClC_6H_4	H	H	16	80

Similarly, the reaction of aldehyde **1**, malononitrile **2** and 2,4-diamino-6-hydroxypyrimidine **5** in the same reaction conditions afforded 2,7-diamino-3,4-dihydro-4-oxo-5-arylpyrido[2,3-*d*]-pyrimidine-6-carbonitrile **6** (Scheme 2) and the results are summarized in Table 3.

Scheme 2

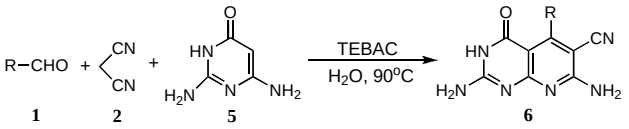


Table 3

Synthesis of pyrido[2,3-*d*]pyrimidine derivatives **6** in aqueous medium

Entry	R	Time (h)	Yield (%)
6a	4-$NO_2C_6H_4$	6	93
6b	4-HOC_6H_4	10	84
6c	2-ClC_6H_4	6	80
6d	2,4-$Cl_2C_6H_3$	5	76
6e	4-BrC_6H_4	8	78
6f	3,4-$(CH_3)_2C_6H_3$	7	81
6g	4-ClC_6H_4	6	86
6h	n-C_4H_9	10	77

However, the reaction of aldehyde **1**, methyl cyanoacetate **7** and 2,4-diamino-6-hydroxypyrimidine **5** in the same reaction conditions afforded 2-amino-3,4,7,8-tetrahydro-4,7-dioxo-5-arylpyrido[2,3-*d*]pyrimidine-6-carbonitrile **8**, which is different from the reaction reported by Bhuyan *et al.* [9]. The desired product methyl 2,7-diamino-3,4-dihydro-4-oxo-5-arylpyrido[2,3-*d*]pyrimidine-6-carboxy late **9** was not obtained (Scheme 3). The results are summarized in Table 4. Recently, Tu *et al.* [17] reported a three-component synthesis of compound **8** under microwave irradiation. The spectra data of **8g** are matching the literature data.

Scheme 3

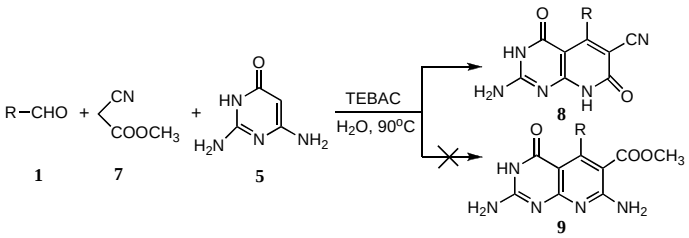


Table 4

Synthesis of pyrido[2,3-*d*]pyrimidine derivatives **8** in aqueous medium

Entry	R	Time (h)	Yield (%)
8a	4-$CH_3C_6H_4$	12	96
8b	3,4-$Cl_2C_6H_3$	12	91
8c	3-ClC_6H_4	16	92
8d	2,4-$Cl_2C_6H_3$	16	90
8e	4-BrC_6H_4	8	95
8f	C_6H_5	11	89
8g	4-$CH_3OC_6H_4$	8	89
8h	3,4-$(CH_3)_2C_6H_3$	9	87
8i	4-FC_6H_4	8	95
8j	3-Pyridyl	10	93

All the products **4**, **6** and **8** were characterized by IR, ^{1}H NMR and elemental analysis. The structure of **4g** was further confirmed by single crystal X-ray diffraction analysis. Figure 1 shows the molecular structure of **4g**. The crystallographic data of this compound is summarized in Table 5.

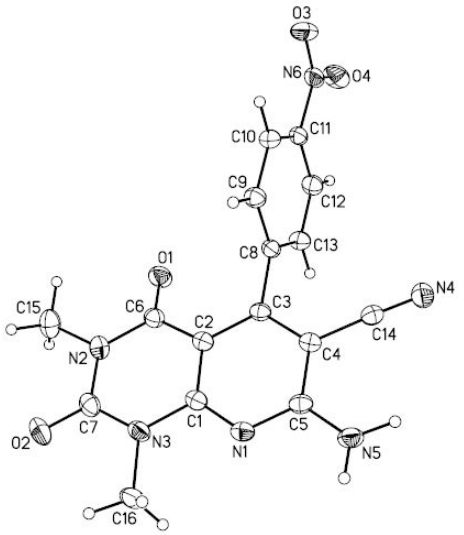


Figure 1. X-ray structure of **4g**.

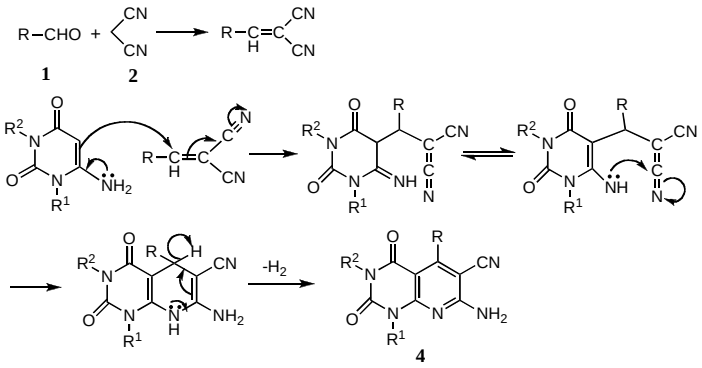
Table 5

Crystallographic Data for **4g**

Empirical formula	$C_{16}H_{12}N_6O_4$
Formula weight	352.32
Wave length (Å)	0.71070
Crystal system	Monoclinic
Space group	$P2_1/n$
a (Å)	9.6209(9)
b (Å)	11.7064(12)
c (Å)	14.5493(16)
α (°)	90
β (°)	106.939(3)
γ (°)	90
V (Å^3)	1567.5(3)
Z	4
Dcalc. (Mg/m^3)	1.493
Absorption coefficient(mm^{-1})	0.112
F(000)	728
Crystal size (mm)	0.60 × 0.40 × 0.32
θ Range (°)	3.41 to 27.48
Limiting indices	$-12 \le h \le 10$
	$-15 \le k \le 14$
	$-18 \le l \le 18$
Reflections collected	17123
Independent reflections	3595
Data/restraints/parameters	3595/0/246
Goodness-of-fit on F^2	1.107
Final R indices [$I>2\sigma(I)$]	$R_1 = 0.0458$
	w$R = 0.1177$
R indices (all data)	$R_1 = 0.0516$
	w$R = 0.1217$
Largest diff. Peak and hole (e·Å^{-3})	0.238 and -0.250

Though the detailed mechanism of these reactions has not been clarified yet, the formation of **4** can be explained by the possible mechanism presented in Scheme 4. The reaction occurs *via* an initial formation of the cyano-olefin, from the condensation of aldehyde and alkyl nitriles as shown in Scheme 4, which suffers nucleophilic attack to give the Michael adduct [A]. The intermediate [A] then cyclizes and subsequently losses a hydrogen molecule to afford the fully aromatized compound. This type of hydrogen loss is well documented [18].

Scheme 4



In conclusion, a series of pyrido[2,3-*d*]pyrimidine derivatives were synthesized *via* novel three-component reaction of aldehyde, alkyl nitrile and aminopyrimidine in water in the presence of TEBAC. Compared to other methods, this new method has the advantages of high yields, mild reaction conditions, easy work-up, inexpensive reagents and an environmentally friendly procedure.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were measured on a FTIR-8101 spectrometer. ^{1}H NMR spectra were measured on an Inova-400 MHz spectrometer using TMS as internal standard, DMSO-d_6 as solvent. Microanalyses were carried out on Perkin-Elmer 2400 II instruments. X-ray diffraction was recorded on a Rigaku Mercury diffractometer.

General Procedure for the Synthesis of pyrido[2,3-*d*]-pyrimidine derivatives 4. A suspension of a mixture of aldehyde **1** (2 mmol), malononitrile **2** (2 mmol), 6-aminouracile **3** (2 mmol) and TEBAC (0.15 g) was stirred in water (10 mL) at 90°C for several hours. After completion monitored by TLC, the reaction mixture was allowed to cool to room temperature. The crystalline powder formed recrystallized from DMF to give pure **4**.

7-Amino-1,3-dimethyl-2,4-dioxo-5-(4-chlorophenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (4a). This compound was obtained as solid with mp 280-281 °C; ir (potassium bromide): 3416, 3314, 3220, 2215, 1715, 1667, 1623, 1573, 1549, 1508, 1494, 1439, 1369, 1278, 1229, 1165, 1014, 974, 847, 831, 805, 753 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 3.09 (s, 3H, CH_3), 3.51 (s, 3H,

CH_3), 7.28 (d, J = 8.4 Hz, 2H, ArH), 7.51 (d, J = 8.4 Hz, 2H, ArH), 7.92 (s, 2H, NH_2). *Anal.* Calcd. for $C_{16}H_{12}ClN_5O_2$: C, 56.23; H, 3.54; N, 20.49. Found: C, 56.38; H, 3.41; N, 20.64.

7-Amino-1,3-dimethyl-2,4-dioxo-5-(2-nitrophenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (4b). This compound was obtained as solid with mp 290-291 °C; ir (potassium bromide): 3459, 3350, 3233, 2221, 1708, 1668, 1636, 1578, 1522, 1439, 1371, 1347, 1310, 1278, 1234, 1146, 1102, 1060, 973, 850, 804, 788, 769, 749, 735, 720 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.06 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 7.43 (d, J = 7.6 Hz, 1H, ArH), 7.74-7.78 (m, 1H, ArH), 7.87-7.91 (m, 1H, ArH), 8.03 (s, 2H, NH_2), 8.32 (d, J = 8.0 Hz, 1H, ArH). *Anal.* Calcd. for $C_{16}H_{12}N_6O_4$: C, 54.55; H, 3.43; N, 23.85. Found: C, 54.73; H, 3.26; N, 23.68.

7-Amino-1,3-dimethyl-2,4-dioxo-5-(4-methylphenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (4c). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3457, 3310, 3219, 2212, 1715, 1667, 1621, 1562, 1508, 1439, 1368, 1307, 1278, 1229, 1096, 960, 825, 805, 754 cm^{-1}; ^1H nmr (DMSO-d_6): 2.38 (s, 3H, CH_3), 3.08 (s, 3H, CH_3), 3.51 (s, 3H, CH_3), 7.11 (d, J = 8.0 Hz, 2H, ArH), 7.23 (d, J = 8.0 Hz, 2H, ArH), 7.83 (s, 2H, NH_2). *Anal.* Calcd. for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.71; N, 21.79. Found: C, 63.85; H, 4.61; N, 21.94.

7-Amino-1,3-dimethyl-2,4-dioxo-5-(3-nitrophenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (4d). This compound was obtained as solid with mp 298-299 °C; ir (potassium bromide): 3460, 3337, 3235, 3093, 2225, 1713, 1668, 1638, 1565, 1530, 1442, 1393, 1368, 1350, 1280, 1231, 1095, 1068, 981, 805, 752, 722, 698 cm^{-1}; ^1H nmr (DMSO-d_6): 3.09 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 7.76-7.80 (m, 2H, ArH), 7.96 (s, 2H, NH_2), 8.18 (s, 1H, ArH), 8.32-8.33 (m, 1H, ArH). *Anal.* Calcd. for $C_{16}H_{12}N_6O_4$: C, 54.55; H, 3.43; N, 23.85. Found: C, 54.81; H, 3.24; N, 23.97.

7-Amino-1,3-dimethyl-2,4-dioxo-5-(3-chlorophenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (4e). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3465, 3337, 3235, 3074, 2224, 1712, 1674, 1638, 1558, 1509, 1481, 1436, 1416, 1367, 1307, 1279, 1228, 1090, 980, 898, 808, 789, 753, 710 cm^{-1}; ^1H nmr (DMSO-d_6): 3.10 (s, 3H, CH_3), 3.52 (s, 3H, CH_3), 7.21-7.22 (m, 1H, ArH), 7.34 (s, 1H, ArH), 7.45-7.51 (m, 2H, ArH), 7.90 (s, 2H, NH_2). *Anal.* Calcd. for $C_{16}H_{12}ClN_5O_2$: C, 56.23; H, 3.54; N, 20.49. Found: C, 56.40; H, 3.32; N, 20.27.

7-Amino-1,3-dimethyl-2,4-dioxo-5-(4-hydroxyphenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (4f). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3465, 3309, 3140, 2958, 2217, 1710, 1654, 1612, 1574, 1514, 1436, 1372, 1269, 1226, 1172, 1098, 1066, 974, 839, 823, 806, 755 cm^{-1}; ^1H nmr (DMSO-d_6): 3.10 (s, 3H, CH_3), 3.50 (s, 3H, CH_3), 6.79 (d, J = 8.0 Hz, 2H, ArH), 7.05 (d, J = 8.0 Hz, 2H, ArH), 7.77 (s, 2H, NH_2), 7.96 (s, 1H, OH). *Anal.* Calcd. for $C_{16}H_{13}N_5O_3$: C, 59.44; H, 4.05; N, 21.66. Found: C, 59.68; H, 3.81; N, 21.74.

7-Amino-1,3-dimethyl-2,4-dioxo-5-(4-nitrophenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (4g). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3457, 3342, 3112, 2225, 1718, 1654, 1559, 1512, 1431, 1373, 1342, 1286, 1252, 1216, 1148, 1093, 1070, 1014, 975, 860, 847, 811, 785, 753, 728, 694 cm^{-1}; ^1H nmr (DMSO-d_6): 3.08 (s, 3H, CH_3), 3.51 (s, 3H, CH_3), 7.57 (d, J = 8.8 Hz, 2H, ArH), 8.02 (s, 2H, NH_2), 8.32 (d, J = 8.8 Hz, 2H, ArH). *Anal.* Calcd. for $C_{16}H_{12}N_6O_4$: C, 54.55; H, 3.43; N, 23.85. Found: C, 54.72; H, 3.29; N, 23.60.

7-Amino-1,3-dimethyl-2,4-dioxo-5-(4-methoxyphenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (4h). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3458, 3306, 3218, 2213, 1716, 1666, 1616, 1580, 1509, 1439, 1366, 1292, 1254, 1178, 1096, 1064, 1034, 973, 932, 838, 807, 770, 754, 725 cm^{-1}; ^1H nmr (DMSO-d_6): 3.09 (s, 3H, CH_3), 3.51 (s, 3H, CH_3), 3.83 (s, 3H, CH_3O), 6.98 (d, J = 8.4 Hz, 2H, ArH), 7.18 (d, J = 8.4 Hz, 2H, ArH), 7.79 (s, 2H, NH_2). *Anal.* Calcd. for $C_{17}H_{15}N_5O_3$: C, 60.53; H, 4.48; N, 20.76. Found: C, 60.75; H, 4.58; N, 20.57.

7-Amino-1,3-dimethyl-2,4-dioxo-5-(4-bromophenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (4i). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3460, 3313, 3220, 2960, 2215, 1714, 1660, 1623, 1568, 1547, 1509, 1492, 1438, 1369, 1278, 1229, 1164, 1096, 1011, 973, 830, 805, 753 cm^{-1}; ^1H nmr (DMSO-d_6): 3.09 (s, 3H, CH_3), 3.51 (s, 3H, CH_3), 7.21 (d, J = 8.0 Hz, 2H, ArH), 7.64 (d, J = 8.0 Hz, 2H, ArH), 7.90 (s, 2H, NH_2), *Anal.* Calcd. for $C_{16}H_{12}BrN_5O_2$: C, 49.76; H, 3.13; N, 18.13. Found: C, 49.51; H, 3.26; N, 18.37.

7-Amino-1-methyl-2,4-dioxo-5-(3-chlorophenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (4j). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3392, 3295, 3165, 3032, 2845, 2217, 1702, 1650, 1618, 1558, 1513, 1483, 1439, 1411, 1373, 1242, 1204, 1190, 1100, 1085, 1054, 868, 803, 784, 693 cm^{-1}; ^1H nmr (DMSO-d_6): 3.44 (s, 3H, CH_3), 7.20-7.22 (m, 1H, ArH), 7.35 (s, 1H, ArH), 7.44-7.50 (m, 2H, ArH), 7.87 (s, 2H, NH_2), 11.22 (s, 1H, NH). *Anal.* Calcd. for $C_{15}H_{10}ClN_5O_2$: C, 54.97; H, 3.08; N, 21.37. Found: C, 55.08; H, 3.12; N, 21.15.

7-Amino-1-methyl-2,4-dioxo-5-(4-bromophenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (4k). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3459, 3334, 3179, 3043, 2832, 2223, 1721, 1681, 1633, 1575, 1550, 1507, 1484, 1451, 1434, 1379, 1371, 1303, 1238, 1189, 1073, 1010, 990, 963, 877, 828, 806, 793, 774, 667 cm^{-1}; ^1H nmr (DMSO-d_6): 3.43 (s, 3H, CH_3), 7.22 (d, J = 8.4 Hz, 2H, ArH), 7.63 (d, J = 8.4 Hz, 2H, ArH), 7.90 (s, 2H, NH_2), 11.22 (s, 1H, NH). *Anal.* Calcd. for $C_{15}H_{10}BrN_5O_2$: C, 48.41; H, 2.71; N, 18.82. Found: C, 48.67; H, 2.50; N, 18.69.

7-Amino-1-methyl-2,4-dioxo-5-(3-nitrophenyl)pyrido[2,3-*d*]-pyrimidine-6-carbonitrile (4l). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3455, 3347, 3224, 3081, 2811, 2229, 1699, 1629, 1562, 1445, 1359, 1241, 1206, 1051, 848, 817, 800, 753, 736, 701, 686 cm^{-1}; ^1H nmr (DMSO-d_6): 3.45 (s, 3H, CH_3), 7.74-7.77 (m, 2H, ArH), 7.96 (s, 2H, NH_2), 8.19 (s, 1H, ArH), 8.31-8.33 (m, 1H, ArH), 11.28 (s, 1H, NH). *Anal.* Calcd. for $C_{15}H_{10}N_6O_4$: C, 53.26; H, 2.98; N, 24.84. Found: C, 53.52; H, 2.77; N, 24.68.

7-Amino-1-methyl-2,4-dioxo-5-(4-methoxyphenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (4m). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3482, 3351, 3189, 3064, 2835, 2214, 1709, 1671, 1613, 1575, 1557, 1512, 1459, 1427, 1368, 1309, 1292, 1254, 1231, 1201, 1175, 1114, 1077, 1049, 1025, 963, 837, 798, 779, 754, 705, 669 cm^{-1}; ^1H nmr (DMSO-d_6): 3.43 (s, 3H, CH_3), 3.82 (s, 3H, CH_3O), 6.97 (d, J = 8.4 Hz, 2H, ArH), 7.19 (d, J = 8.4 Hz, 2H, ArH), 7.80 (s, 2H, NH_2), 11.13 (s, 1H, NH). *Anal.* Calcd. for $C_{16}H_{13}N_5O_3$: C, 59.44; H, 4.05; N, 21.66. Found: C, 59.61; H, 3.94; N, 21.79.

7-Amino-1-methyl-2,4-dioxo-5-(4-hydroxyphenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (4n). This compound was

obtained as solid with mp > 300 °C; ir (potassium bromide): 3433, 3334, 3224, 3071, 2222, 1703, 1635, 1610, 1560, 1516, 1437, 1373, 1271, 1241, 1204, 1175, 1105, 882, 843, 805 cm^{-1}; ^1H nmr (DMSO-d_6): 3.43 (s, 3H, CH_3), 6.78 (d, J = 8.4 Hz, 2H, ArH), 7.06 (d, J = 8.4 Hz, 2H, ArH), 7.75 (s, 2H, NH_2), 9.60 (s, 1H, OH), 11.10 (s, 1H, NH). *Anal.* Calcd. for $C_{15}H_{11}N_5O_3$: C, 58.25; H, 3.58; N, 22.64. Found: C, 58.10; H, 3.74; N, 22.83.

7-Amino-1-methyl-2,4-dioxo-5-(4-nitrophenyl)pyrido[2,3-*d*]-pyrimidine-6-carbonitrile (4o). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3414, 3329, 3238, 3048, 2836, 2223, 1727, 1678, 1639, 1558, 1515, 1442, 1374, 1351, 1287, 1239, 1205, 1107, 1051, 1014, 967, 887, 859, 847, 806, 753, 719, 692 cm^{-1}; ^1H nmr (DMSO-d_6): 3.44 (s, 3H, CH_3), 7.58 (d, J = 8.4 Hz, 2H, ArH), 8.00 (s, 2H, NH_2), 8.30 (d, J = 8.4 Hz, 2H, ArH), 11.32 (s, 1H, NH). *Anal.* Calcd. for $C_{15}H_{10}N_6O_4$: C, 53.26; H, 2.98; N, 24.84. Found: C, 53.47; H, 2.76; N, 24.63.

7-Amino-1-methyl-2,4-dioxo-5-(3-pyridyl)pyrido[2,3-*d*]-pyrimidine-6-carbonitrile (4p). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3490, 3323, 3222, 3050, 2219, 1694, 1650, 1561, 1514, 1442, 1413, 1374, 1246, 1208, 1061, 1041, 960, 827, 806, 791, 754, 709 cm^{-1}; ^1H nmr (DMSO-d_6): 3.44 (s, 3H, CH_3), 7.74-7.77 (m, 2H, ArH), 7.96 (s, 2H, NH_2), 8.19 (s, 1H, ArH), 8.31 (d, J = 7.2 Hz, 1H, ArH), 11.27 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_{10}N_6O_2$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.29; H, 3.25; N, 28.63.

7-Amino-1-methyl-2,4-dioxo-5-(4-pyridyl)pyrido[2,3-*d*]-pyrimidine-6-carbonitrile (4q). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3384, 3318, 3166, 3052, 2219, 1703, 1667, 1567, 1530, 1509, 1437, 1369, 1310, 1243, 1220, 1205, 1182, 1073, 1055, 1004, 960, 889, 836, 806, 790, 757 cm^{-1}; ^1H nmr (DMSO-d_6): 3.44 (s, 3H, CH_3), 7.29 (d, J = 5.2 Hz, 2H, ArH), 7.95 (s, 2H, NH_2), 8.64 (d, J = 5.2 Hz, 2H, ArH), 11.28 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_{10}N_6O_2$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.24; H, 3.59; N, 28.36.

7-Amino-2,4-dioxo-5-butylpyrido[2,3-*d*]pyrimidine-6-carbonitrile (4r). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3384, 3329, 3170, 2954, 2810, 2229, 1697, 1654, 1606, 1556, 1448, 1436, 1376, 1259, 1187, 1156, 1023, 822, 800, 756, 720 cm^{-1}; ^1H nmr (DMSO-d_6): 0.93 (t, J = 7.2 Hz, 3H, CH_3), 1.38-1.54 (m, 4H, 2 x CH_2), 3.21 (t, J = 7.6 Hz, 2H, CH_2), 7.51 (s, 2H, NH_2), 11.04 (s, 1H, NH), 11.33 (s, 1H, NH). *Anal.* Calcd. for $C_{12}H_{13}N_5O_2$: C, 55.59; H, 5.05; N, 27.01. Found: C, 55.72; H, 4.95; N, 27.27.

7-Amino-2,4-dioxo-5-(2,4-dichlorophenyl)pyrido[2,3-*d*]-pyrimidine-6-carbonitrile (4s). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3385, 3334, 3156, 3081, 2924, 2820, 2223, 1717, 1651, 1636, 1598, 1560, 1485, 1440, 1383, 1306, 1257, 1205, 1145, 1100, 1056, 1026, 906, 877, 826, 802, 756, 711 cm^{-1}; ^1H nmr (DMSO-d_6): 7.36 (d, J = 8.4 Hz, 1H, ArH), 7.52 (d, J = 8.4 Hz, 2H, ArH), 7.74 (s, 1H, ArH), 7.81 (s, 2H, NH_2), 11.05 (s, 1H, NH), 11.60 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_7Cl_2N_5O_2$: C, 48.30; H, 2.03; N, 20.12. Found: C, 48.45; H, 2.09; N, 20.37.

7-Amino-2,4-dioxo-5-(4-bromophenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (4t). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3400, 3329, 3172, 3080, 2931, 2803, 2221, 1716, 1698, 1645, 1592, 1545, 1491, 1441, 1410, 1374, 1298, 1264, 1199, 1143, 1105, 1073, 1014, 876, 801, 768, 706 cm^{-1}; ^1H nmr (DMSO-d_6): 7.24 (d, J = 8.4 Hz, 2H, ArH), 7.62 (d, J = 8.4 Hz, 2H, ArH), 7.68 (s, 2H, NH_2), 10.95 (s, 1H, NH), 11.50 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_8BrN_5O_2$: C, 46.95; H, 2.25; N, 19.55. Found: C, 47.08; H, 2.11; N, 19.36.

7-Amino-2,4-dioxo-5-(4-fluorophenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (4u). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3362, 3334, 3147, 3015, 2802, 2229, 1734, 1703, 1674, 1646, 1606, 1566, 1512, 1440, 1387, 1302, 1224, 1160, 1097, 1028, 877, 832, 808, 756 cm^{-1}; ^1H nmr (DMSO-d_6): 7.24-7.27 (m, 2H, ArH), 7.30-7.35 (m, 2H, ArH), 7.66 (s, 2H, NH_2), 10.94 (s, 1H, NH), 11.48 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_8FN_5O_2$: C, 56.57; H, 2.71; N, 23.56. Found: C, 56.70; H, 2.52; N, 23.38.

7-Amino-2,4-dioxo-5-(3,4-dichlorophenyl)pyrido[2,3-*d*]-pyrimidine-6-carbonitrile (4v). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3396, 3328, 3187, 3090, 2818, 2223, 1715, 1699, 1645, 1592, 1560, 1478, 1440, 1372, 1302, 1261, 1203, 1138, 1103, 1033, 947, 899, 803, 733, 702, 685 cm^{-1}; ^1H nmr (DMSO-d_6): 7.30 (d, J = 8.0 Hz, 1H, ArH), 7.63 (s, 1H, ArH), 7.71 (d, J = 8.0 Hz, 2H, ArH), 7.74 (s, 2H, NH_2), 11.01 (s, 1H, NH), 11.54 (s, 1H, NH). *Anal*. Calcd. for $C_{14}H_7Cl_2N_5O_2$: C, 48.30; H, 2.03; N, 20.12. Found: C, 48.44; H, 2.17; N, 20.02.

7-Amino-2,4-dioxo-5-(3-nitrophenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (4w). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3401, 3326, 3188, 3090, 2803, 2227, 1724, 1702, 1646, 1598, 1560, 1532, 1485, 1447, 1370, 1340, 1304, 1205, 1099, 1030, 924, 847, 803, 737, 703, 682 cm^{-1}; ^1H nmr (DMSO-d_6): 7.74-7.81 (m, 4H, ArH and NH_2), 8.21-8.22 (m, 1H, ArH), 8.30-8.32 (m, 1H, ArH), 11.02 (s, 1H, NH), 11.56 (s, 1H, NH). *Anal*. Calcd. for $C_{14}H_8N_6O_4$: C, 51.86; H, 2.49; N, 25.92. Found: C, 51.95; H, 2.23; N, 25.78.

7-Amino-2,4-dioxo-5-(2-chlorophenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (4x). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3386, 3325, 3164, 2921, 2223, 1717, 1673, 1648, 1598, 1563, 1484, 1439, 1381, 1306, 1258, 1204, 1154, 1100, 1057, 1028, 808, 763, 707 cm^{-1}; ^1H nmr (DMSO-d_6): 7.28-7.31 (m, 1H, ArH), 7.39-7.46 (m, 2H, ArH), 7.52-7.54 (m, 1H, ArH), 7.76 (s, 2H, NH_2), 11.01 (s, 1H, NH), 11.55 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_8ClN_5O_2$: C, 53.60; H, 2.57; N, 22.33. Found: C, 53.52; H, 2.46; N, 22.57.

7-Amino-2,4-dioxo-5-(4-nitrophenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (4y). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3609, 3535, 3321, 3199, 3081, 2848, 2227, 1706, 1666, 1589, 1553, 1522, 1450, 1381, 1348, 1208, 1151, 1108, 1018, 926, 887, 852, 812, 770, 750, 696 cm^{-1}; ^1H nmr (DMSO-d_6): 7.59 (d, J = 6.8 Hz, 2H, ArH), 7.80 (s, 2H, NH_2), 8.29 (d, J = 6.8 Hz, 2H, ArH), 11.03 (s, 1H, NH), 11.56 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_8N_6O_4$: C, 51.86; H, 2.49; N, 25.92. Found: C, 51.98; H, 2.31; N, 26.02.

7-Amino-2,4-dioxo-5-(4-chlorophenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (4z). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3398, 3330, 3169, 3090, 2224, 1706, 1645, 1590, 1556, 1495, 1442, 1409, 1375, 1299, 1260, 1200, 1144, 1092, 1018, 877, 803, 771, 680 cm^{-1}; 7.30 (d, J = 8.4 Hz, 2H, ArH), 7.48 (d, J = 8.4 Hz, 2H, ArH), 7.66 (s, 2H, NH_2), 10.95 (s, 1H, NH), 11.47 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_8ClN_5O_2$: C, 53.60; H, 2.57; N, 22.33. Found: C, 53.47; H, 2.39; N, 22.46.

General Procedure for the Synthesis of pyrido[2,3-*d*]-pyrimidine derivatives 6. A suspension of a mixture of aldehyde **1** (2 mmol), malononitrile **2** (2 mmol), 2,4-diamino-6-

hydroxypyrimid-ine **5** (2 mmol) and TEBAC (0.15g) was stirred in water (10 mL) at 90°C for several hours. After completion monitored by TLC, the reaction mixture was allowed to cool to room temperature. The crystalline powder formed recrystallized from DMF to give pure **6**.

2,7-Diamino-3,4-dihydro-4-oxo-5-(4-nitrophenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (6a). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3446, 3343, 3187, 2170, 1670, 1550, 1515, 1472, 1439, 1385, 1346, 1301, 1216, 1106, 916, 885, 851, 816, 742 cm^{-1}; ^1H nmr (DMSO-d_6): 6.95 (s, 2H, NH_2), 7.35 (s, 2H, NH_2), 7.55 (d, J = 8.8 Hz, 2H, ArH), 8.26 (d, J = 8.8 Hz, 2H, ArH), 10.70 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_9N_7O_3$: C, 52.02; H, 2.81; N, 30.33. Found: C, 52.25; H, 2.67; N, 30.59.

2,7-Diamino-3,4-dihydro-4-oxo-5-(4-hydroxyphenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (6b). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3381, 3181, 3140, 2800, 2213, 1696, 1667, 1636, 1613, 1549, 1515, 1425, 1388, 1309, 1266, 1223, 1196, 1173, 1106, 917, 877, 835, 813 cm^{-1}; ^1H nmr (DMSO-d_6): 6.75 (d, J = 8.0 Hz, 2H, ArH), 6.91 (s, 2H, NH_2), 7.04 (d, J = 8.0 Hz, 2H, ArH), 7.08 (s, 2H, NH_2), 9.55 (s, 1H, OH), 10.58 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_{10}N_6O_2$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.36; H, 3.24; N, 28.70.

2,7-Diamino-3,4-dihydro-4-oxo-5-(2-chlorophenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (6c). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3463, 3333, 3177, 2189, 1661, 1556, 1458, 1389, 1300, 1205, 1135, 1035, 811, 786, 755 cm^{-1}; ^1H nmr (DMSO-d_6): 6.92 (s, 2H, NH_2), 7.25-7.28 (m, 1H, ArH), 7.33 (s, 2H, NH_2), 7.36-7.44 (m, 2H, ArH), 7.50-7.52 (m, 1H, ArH), 10.78 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_9ClN_6O$: C, 53.77; H, 2.90; N, 26.87. Found: C, 53.85; H, 2.73; N, 26.69.

2,7-Diamino-3,4-dihydro-4-oxo-5-(2,4-dichlorophenyl)-pyrido[2,3-*d*]pyrimidine-6-carbonitrile (6d). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3368, 3190, 3098, 2886, 2222, 1673, 1626, 1555, 1479, 1433, 1340, 1199, 1143, 1104, 1054, 921, 878, 816, 797 cm^{-1}; ^1H nmr (DMSO-d_6): 6.90 (s, 2H, NH_2), 7.33 (d, J = 8.4 Hz, 1H, ArH), 7.35 (s, 2H, NH_2), 7.49 (d, J = 8.4 Hz, 1H, ArH), 7.70 (s, 1H, ArH), 10.76 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_8Cl_2N_6O$: C, 48.44; H, 2.32; N, 24.21. Found: C, 48.61; H, 2.16; N, 24.42.

2,7-Diamino-3,4-dihydro-4-oxo-5-(4-bromophenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (6e). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3389, 3330, 3197, 3150, 3078, 2214, 1685, 1667, 1615, 1546, 1489, 1428, 1309, 1195, 1071, 1012, 916, 876, 810 cm^{-1}; ^1H nmr (DMSO-d_6): 6.62 (s, 2H, NH_2), 7.21 (d, J = 8.0 Hz, 2H, ArH), 7.28 (s, 2H, NH_2), 7.59 (d, J = 8.0 Hz, 2H, ArH), 10.70 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_9BrN_6O$: C, 47.08; H, 2.54; N, 23.53. Found: C, 47.23; H, 2.37; N, 23.66.

2,7-Diamino-3,4-dihydro-4-oxo-5-(3,4-dimethylphenyl)-pyrido[2,3-*d*]pyrimidine-6-carbonitrile (6f). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3510, 3407, 3195, 3031, 2878, 2206, 1694, 1665, 1612, 1547, 1500, 1472, 1423, 1306, 1188, 1099, 961, 878, 832, 811 cm^{-1}; ^1H nmr (DMSO-d_6): 2.24 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 6.78 (s, 2H, NH_2), 6.93 (d, J = 8.4 Hz, 1H, ArH), 6.98 (s, 1H, ArH), 7.11-7.17 (m, 3H, NH_2 and ArH), 10.56 (s, 1H, NH). *Anal.* Calcd. for $C_{16}H_{14}N_6O$: C, 62.74; H, 4.61; N, 27.44. Found: C, 62.91; H, 4.58; N, 27.64.

2,7-Diamino-3,4-dihydro-4-oxo-5-(4-chlorophenyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (6g). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3501, 3394, 3318, 3056, 2214, 1681, 1668, 1615, 1549, 1492, 1428, 1309, 1195, 1088, 1016, 916, 877, 812, 683 cm^{-1}; ^1H nmr (DMSO-d_6): 6.82 (s, 2H, NH_2), 7.22 (s, 2H, NH_2), 7.27 (d, J = 8.4 Hz, 2H, ArH), 7.45 (d, J = 8.4 Hz, 2H, ArH), 10.64 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_9ClN_6O$: C, 53.77; H, 2.90; N, 26.87. Found: C, 53.86; H, 2.73; N, 26.59.

2,7-Diamino-3,4-dihydro-4-oxo-5-butylpyrido[2,3-*d*]pyrimi-dine-6-carbonitrile (6h). This compound was obtained as solid with mp > 300 °C; 3401, 3341, 3118, 2959, 2215, 1697, 1665, 1617, 1556, 1467, 1429, 1397, 1367, 1258, 1205, 1193, 1128, 1054, 1028, 855, 815, 736 cm^{-1}; 0.94 (t, J = 7.6 Hz, 3H, CH_3), 1.37-1.55 (m, 4H, 2 x CH_2), 3.22 (t, J = 7.6 Hz, 2H, CH_2), 6.74 (s, 2H, NH_2), 7.06 (s, 2H, NH_2), 10.72 (s, 1H, NH). *Anal.* Calcd. for $C_{12}H_{14}N_6O$: C, 55.80; H, 5.46; N, 32.54. Found: C, 55.63; H, 5.38; N, 32.69.

General Procedure for the Synthesis of pyrido[2,3-*d*]-pyrimidine derivatives 8. A suspension of a mixture of aldehyde **1** (2 mmol), methyl cyanoacetate **7** (2 mmol), 2,4-diamino-6-hydroxypyrimidine **5** (2 mmol) and TEBAC (0.15 g) was stirred in water (10 mL) at 90°C for several hours. After completion monitored by TLC, the reaction mixture was allowed to cool to room temperature. The crystalline powder formed recrystallized from DMF to give pure **8**.

2-Amino-3,4,7,8-tetrahydro-4,7-dioxo-5-(4-methylphenyl)-pyrido[2,3-*d*]pyrimidine-6-carbonitrile (8a). This compound was obtained as solid with mp > 300 °C; 3348, 3130, 2225, 1714, 1671, 1617, 1575, 1545, 1471, 1368, 1255, 1165, 1059, 916, 880, 797, 729, 683 cm^{-1}; 2.36 (s, 3H, CH_3), 6.68 (s, 2H, NH_2), 7.13 (d, J = 7.6 Hz, 2H, ArH), 7.21 (d, J = 7.6 Hz, 2H, ArH), 10.90 (s, 1H, NH), 12.30 (s, 1H, NH). *Anal.* Calcd. for $C_{15}H_{11}N_5O_2$: C, 61.43; H, 3.78; N, 23.88. Found: C, 61.58; H, 3.61; N, 23.73.

2-Amino-3,4,7,8-tetrahydro-4,7-dioxo-5-(3,4-dichlorol-phenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (8b). This compound was obtained as solid with mp > 300 °C; 3326, 3129, 2226, 1715, 1668, 1573, 1561, 1467, 1382, 1250, 1200, 1172, 1132, 1104, 1032, 944, 878, 794, 718, 686 cm^{-1}; 6.72 (s, 2H, NH_2), 7.29 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H, ArH), 7.60 (d, J = 2.0 Hz, 1H, ArH), 7.69 (d, J = 8.4 Hz, 1H, ArH), 10.96 (s, 1H, NH), 12.41 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_7Cl_2N_5O_2$: C, 48.30; H, 2.03; N, 20.12. Found: C, 48.52; H, 1.96; N, 20.35.

2-Amino-3,4,7,8-tetrahydro-4,7-dioxo-5-(3-chlorolphenyl)-pyrido[2,3-*d*]pyrimidine-6-carbonitrile (8c). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3392, 3132, 2228, 1713, 1669, 1620, 1573, 1541, 1466, 1365, 1252, 1196, 1163, 1083, 938, 877, 803, 784, 728, 689 cm^{-1}; ^1H nmr (DMSO-d_6): 6.70 (s, 2H, NH_2), 7.22-7.24 (m, 1H, ArH), 7.35-7.36 (m, 1H, ArH), 7.42-7.48 (m, 2H, ArH), 10.91 (s, 1H, NH), 12.39 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_8ClN_5O_2$: C, 53.60; H, 2.57; N, 22.33. Found: C, 53.81; H, 2.44; N, 22.48.

2-Amino-3,4,7,8-tetrahydro-4,7-dioxo-5-(2,4-dichlorol-phenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (8d). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3333, 3103, 2227, 1712, 1682, 1636, 1583, 1559, 1470, 1384, 1247, 1201, 1173, 1102, 1055, 919, 877, 801, 754, 727 cm^{-1}; 6.81 (s, 2H, NH_2), 7.35 (d, J = 8.0 Hz, 1H, ArH), 7.50 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H, ArH), 7.71 (d, J = 2.0 Hz, 1H, ArH), 11.04 (s, 1H, NH), 12.45 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_7Cl_2N_5O_2$: C, 48.30; H, 2.03; N, 20.12. Found: C, 48.49; H, 2.15; N, 20.36.

2-Amino-3,4,7,8-tetrahydro-4,7-dioxo-5-(4-bromophenyl)-pyrido[2,3-*d*]pyrimidine-6-carbonitrile (8e). This compound was obtained as solid with mp > 300 °C (Lit. [17] mp > 300 °C); ir (potassium bromide): 3341, 3154, 3088 , 2225, 1717, 1676, 1617, 1561, 1473, 1369, 1257, 1166, 1073, 1012, 915, 897, 820, 798, 731, 684 cm^{-1}; ^1H nmr (DMSO-d_6): 6.72 (s, 2H, NH_2), 7.23 (d, J = 8.0 Hz, 2H, ArH), 7.61 (d, J = 8.0 Hz, 2H, ArH), 10.92 (s, 1H, NH), 12.35 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_8BrN_5O_2$: C, 46.95; H, 2.25; N, 19.55. Found: C, 47.10; H, 2.08; N, 19.72.

2-Amino-3,4,7,8-tetrahydro-4,7-dioxo-5-phenylpyrido[2,3-*d*]-pyrimidine-6-carbonitrile (8f). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3305, 3114, 2219, 1699, 1659, 1578, 1545, 1470, 1438, 1379, 1254, 1198, 1170, 1152, 1106, 913, 895, 804, 761, 736, 721, 701, 667 cm^{-1}; ^1H nmr (DMSO-d_6): 6.68 (s, 2H, NH_2), 7.23-7.25 (m, 2H, ArH), 7.38-7.40 (m, 3H, ArH), 10.89 (s, 1H, NH), 12.34 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_9N_5O_2$: C, 60.21; H, 3.25; N, 25.08. Found: C, 60.46; H, 3.21; N, 25.24.

2-Amino-3,4,7,8-tetrahydro-4,7-dioxo-5-(4-methoxyphenyl)-pyrido[2,3-*d*]pyrimidine-6-carbonitrile (8g). This compound was obtained as solid with mp > 300 °C (Lit. [17] mp > 300 °C); ir (potassium bromide): 3376, 3132, 2225, 1714, 1674, 1629, 1605, 1575, 1545, 1518, 1469, 1368, 1303, 1254, 1180, 1116, 1060, 1027, 915, 879, 800, 756, 733, 685 cm^{-1}; ^1H nmr (DMSO-d_6): 3.81 (s, 3H, CH_3O), 6.82 (s, 2H, NH_2), 6.94 (d, J = 8.4 Hz, 2H, ArH), 7.19 (d, J = 8.4 Hz, 2H, ArH), 10.91 (s, 1H, NH), 12.25 (s, 1H, NH). *Anal.* Calcd. for $C_{15}H_{11}N_5O_3$: C, 58.25; H, 3.58; N, 22.64. Found: C, 58.12; H, 3.68; N, 22.85.

2-Amino-3,4,7,8-tetrahydro-4,7-dioxo-5-(3,4dimethyl-phenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (8h). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3393, 3134, 2227, 1719, 1673, 1606, 1537, 1470, 1366, 1260, 1225, 1203, 1164, 1124, 1060, 960, 880, 800, 727, 681 cm^{-1}; ^1H nmr (DMSO-d_6): 2.23 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 6.65 (s, 2H, NH_2), 6.95 (d, J = 8.0 Hz, 1H, ArH), 7.00 (s, 1H, ArH), 7.15 (d, J = 8.0 Hz, 1H, ArH), 10.86 (s, 1H, NH), 12.30 (s, 1H, NH). *Anal.* Calcd. for $C_{16}H_{13}N_5O_2$: C, 62.53; H, 4.26; N, 22.79. Found: C, 62.67; H, 4.12; N, 22.90.

2-Amino-3,4,7,8-tetrahydro-4,7-dioxo-5-(4-fluorophenyl)-pyrido[2,3-*d*]pyrimidine-6-carbonitrile (8i). This compound was obtained as solid with mp > 300 °C (Lit. [17] mp > 300 °C); ir (potassium bromide): 3401, 3092, 2229, 1696, 1670, 1600, 1585, 1561, 1503, 1474, 1437, 1382, 1255, 1216, 1167, 1102, 1062, 1022, 917, 879, 838, 802, 760, 728, 691 cm^{-1}; ^1H nmr (DMSO-d_6): 6.72 (s, 2H, NH_2), 7.21-7.26 (m, 2H, ArH), 729-7.33 (m, 2H, ArH), 10.92 (s, 1H, NH), 12.35 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_8FN_5O_2$: C, 56.57; H, 2.71; N, 23.56. Found: C, 56.74; H, 2.45; N, 23.68.

2-Amino-3,4,7,8-tetrahydro-4,7-dioxo-5-(3-pyridyl)pyrido-[2,3-*d*]pyrimidine-6-carbonitrile (8j). This compound was obtained as solid with mp > 300 °C; ir (potassium bromide): 3338, 3132, 2223, 1712, 1667, 1636, 1581, 1553, 1469, 1416, 1375, 1260, 1197, 1106, 1056, 1028, 916, 876, 798, 771, 724, 675 cm^{-1}; ^1H nmr (DMSO-d_6): 6.81 (s, 2H, NH_2), 7.45 (dd, J_1 = 4.8 Hz, J_2 = 7.6 Hz, 1H, ArH), 7.73 (d, J = 7.6 Hz, 2H, ArH), 8.47 (s, 1H, ArH), 8.59 (d, J = 4.8 Hz, 2H, ArH), 10.96 (s, 1H, NH), 12.40 (s, 1H, NH). *Anal.* Calcd. for $C_{13}H_8N_6O_2$: C, 55.72; H, 2.88; N, 29.99. Found: C, 55.93; H, 2.72; N, 30.07.

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