Pot, Atom and Step Economic Synthesis of Fused Three Heterocyclic Ring Compounds under Microwave Irradiation in Water

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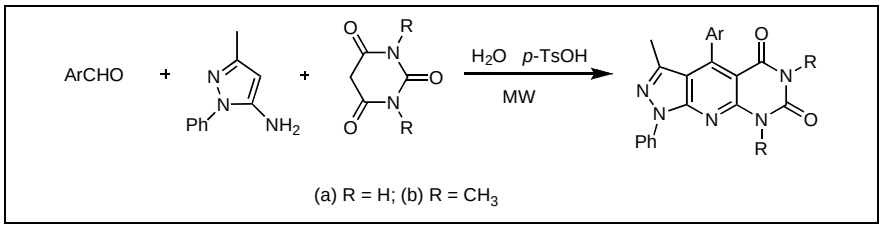

A new series of fused three heterocyclic ring compounds, consisting of a pyrazolo (ring A), a pyridine (ring B), and a pyrimidine (ring C) core, pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine derivatives were successfully synthesized by pot, atom and step economic (PASE) method under microwave irradiation in the presence of *p*-toluene sulphonic acid in water.

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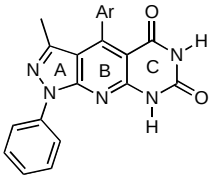
INTRODUCTION

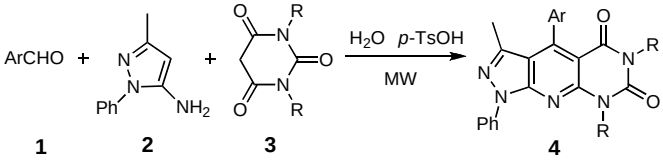
Pyrazolo-annelated heterocycles have demonstrated wide spectrum of agriculture and pharmacological activities [1,2], such as diagnosis of brain disorders [3], treatment of coronary heart disease [4], viral diseases [5], central nervous system diseases [6] and show pharmacological efficacy [7]. Pyrazolo[4',3':5,6]pyrido-[2,3-*d*]pyrimidines showed wide spectrum applications such as anticonvulsant agents [8], colorants [9], heat/moisture resistant agents and thermal transfer printing agent [10], photographic couplers [11]. However, to the best of our knowledge, there have only been a few reports of the synthesis of pyrazolopyridopyrimidine derivatives (Fig. 1) in the literature [12]. Recently, Hussein [13] *et al*. disclosed that the condensation of 5-amino-3-methyl-1-phenyl-pyrazole-4-carbaldehyde as precursors with cyanoacetamide in refluxing ethanolic piperidine yielded the intermediate compounds of aminocarboxamide derivatives in moderate yields, then reacted with urea derivatives to yield the pyrazolo-pyridopyrimidine derivatives. Jachak and co-workers [14] reported the synthesis of pyrazolopyrido-pyrimidine derivatives by multi-step reaction and using organic solvent.

In all these methods a multi-step reaction is needed. Furthermore, organic solvent is required and the procedure is not economic and environmentally friendly. Therefore, the development of a new, pot, atom [15] and step economic [16] (PASE) method for the synthesis of pyrazolopyridopyrimidine derivatives is of prime interest. Pot, atom and step economy aims to combine as many transformations as possible into a single reaction vessel, without the need for work-up and isolation of intermediate compounds. Ideally, all the reagents should also be incorporated into the final product.



We have recently become interested in the development of facile methods [17] for the synthesis of heterocyclic compounds. In this paper, we wish to report a simple, facile and one-pot method for the synthesis of fused three heterocyclic ring compound, consisting of a pyrazolo (ring A), a pyridine (ring B), and a pyrimidine (ring C) core, assisted by *p*-toluene sulphonic acid (*p*-TsOH) in water under microwave (MW) heating (Scheme 1).

Scheme 1

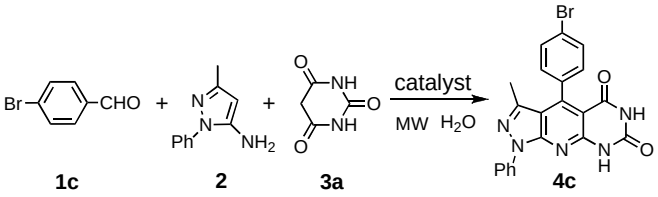


RESULTS AND DISCUSSION

We first chose barbituric acid **3a** (1.0 mmol) and searched for the optimized conditions for its reaction with 4-bromobenzaldehyde **1c** (1.0 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2** (1.0 mmol) affording

pyrazolopyridopyrimidines under microwave irradiation conditions (Scheme 2).

Scheme 2



Different acidic catalysts (1 mmol) were examined. The results of these comparative experiments are summarized in Table 1. From the results it is obvious that *p*-TsOH (entry 1) demonstrates superior catalytic activity and is the best catalyst among those examined.

Table 1

Optimization of the catalyst in the synthesis of product **4c** in water at 100 °C.

Entry	Catalyst	Time / min	Yield [a] / %
1	*p*-TsOH	10	80
2	NH_2SO_3H	10	56
3	H_2SO_4	10	35
4	$CuSO_4{\cdot}5H_2O$	10	47
5	$FeCl_3{\cdot}6H_2O$	10	65
6	KH_2PO_4	10	74
7	H_3PO_4	10	70

[a] Crude yields

In order to further evaluate the influence of *p*-TsOH concentration, this reaction was carried out using different amounts of *p*-TsOH under microwave irradiation at 100 °C. The results are listed in Table 2. From Table 2 it can be seen that the reaction proceeded in the presence of 0.1 equivalents of *p*-TsOH to give the product **4c** in 59% yield under microwave irradiation at 100 °C after 10 minutes of the reaction (entry 1). Increasing the amount of catalyst to 0.3, 0.6, 0.8 and 0.9 equivalents successively resulted in the increasing of the yield to 69%, 72%, 75% and 76%, respectively. Use of just 1.0 equivalent under microwave irradiation was sufficient to reach the highest yield (entry 6). Further increases in the amount of catalyst did not improve the yield (entries 7–8).

Moreover, to further optimize the reaction temperature, reactions using 4-bromobenzaldehyde (**1c**, 1.0 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**2**, 1.0 mmol) and barbituric acid (**3a**, 1.0 mmol) were carried out in the range of 90 to 160 °C in increments of 10 °C each time. The results are shown in Table 3. When the temperature was increased from 90 °C to 140 °C, the yield of product **4c** was improved. However, no significant increase in the yield of product **4c** was observed as the reaction temperature was raised from 150 °C to 160 °C. Therefore, the temperature of 140 °C was chosen for all further MW-assisted reactions.

Table 2

Optimization of the amount of *p*-TsOH in the synthesis of product **4c** in water at 100°C.

Entry	*p*-TsOH/ eq.	Time / min	Yield [a] / %
1	0.1	10	59
2	0.3	10	69
3	0.6	10	72
4	0.8	10	75
5	0.9	10	76
6	1.0	10	80
7	1.2	10	78
8	1.4	10	77

[a] Crude yields

Table 3

Temperature optimization for the synthesis of product **4c**.

Entry	T / °C	Time / min	Yield / %
1	90	13	76
2	100	10	80
3	110	9	82
4	120	9	83
5	130	8	86
6	140	6	90
7	150	6	88
8	160	6	88

We therefore selected 1.0 equivalent of *p*-TsOH as the catalyst, 140 °C for further study. At the beginning of the search for the aldehyde substrate scope, barbituric acid **3a** and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine were used as model substrates (Table 4, entries 1–11), and the results indicated that aromatic aldehydes bearing either electron-donating (such as alkoxyl groups) or electron-withdrawing (such as nitro or halide groups) functional groups were all suitable to the reaction. Moreover, a heterocyclic aldehyde, thiophene-2-carbaldehyde (Table 4, entry 12), still showed high reactivity and clean reaction under these standard conditions. The mechanisms are similar to that reported in earlier work [18].

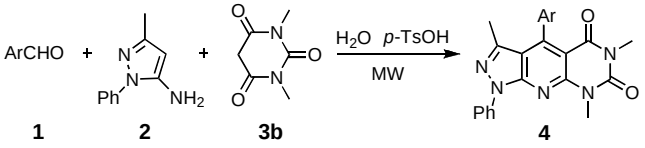
In order to expand the scope of the present method, we used different aldehydes and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine as model substrates, the replacement of barbituric acid with 1,3-dimethyl barbituric acid (1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) was also examined (Scheme 3). In all these cases, the reactions proceeded smoothly to give the corresponding pyrazolopyridopyrimidines in good yields. All the products in this study were characterized by IR and ^{1}H NMR spectroscopy, as well as by elemental analyses, some products were characterized by ^{13}C NMR spectroscopy.

Table 4

Synthesis of compounds **4** in water under microwave irradiation at 140 °C.

Entry	Ar	**3**	R	Product	Time / min	Yield / %	Mp / °C
1	4-FC_6H_4	**3a**	H	**4a**	7	88	>300
2	4-ClC_6H_4	**3a**	H	**4b**	7	86	>300
3	4-BrC_6H_4	**3a**	H	**4c**	6	90	>300
4	4-$NO_2C_6H_4$	**3a**	H	**4d**	8	85	>300
5	4-$CH_3OC_6H_4$	**3a**	H	**4e**	9	84	>300
6	4-$CH_3C_6H_4$	**3a**	H	**4f**	9	82	>300
7	3-$NO_2C_6H_4$	**3a**	H	**4g**	6	92	>300
8	C_6H_5	**3a**	H	**4h**	7	86	>300
9	2,4-$Cl_2C_6H_3$	**3a**	H	**4i**	7	87	>300
10	3,4-$(CH_3O)_2C_6H_3$	**3a**	H	**4j**	9	88	>300
11	4-OH-3-$NO_2C_6H_3$	**3a**	H	**4k**	7	90	>300
12	thiophen-2-yl	**3a**	H	**4l**	7	91	>300
13	4-FC_6H_4	**3b**	CH_3	**4m**	8	87	>300
14	4-ClC_6H_4	**3b**	CH_3	**4n**	7	85	>300
15	4-BrC_6H_4	**3b**	CH_3	**4o**	7	86	>300
16	4-$CH_3C_6H_4$	**3b**	CH_3	**4p**	6	89	>300
17	3-$NO_2C_6H_4$	**3b**	CH_3	**4q**	7	88	>300
18	3-BrC_6H_4	**3b**	CH_3	**4r**	6	88	>300
19	2-ClC_6H_4	**3b**	CH_3	**4s**	9	86	>300
20	C_6H_5	**3b**	CH_3	**4t**	7	88	>300
21	2,4-$Cl_2C_6H_3$	**3b**	CH_3	**4u**	9	84	>300
22	3,4-$OCH_2OC_6H_3$	**3b**	CH_3	**4v**	9	85	>300
23	4-OH-3-$NO_2C_6H_3$	**3b**	CH_3	**4w**	7	87	>300
24	thiophen-2-yl	**3b**	CH_3	**4x**	8	85	>300

Scheme 3



1 **2** **3b** **4**

In conclusion, a pot, atom, and step economic (PASE) method for the synthesis of pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine derivatives, important classes of building blocks in natural products and pharmaceuticals, was accomplished *via* a three-component reaction in water under microwave heating. Obtaining good to excellent product yields, avoiding multi-step reactions to construct useful heterocycles, and eliminating the use of organic solvent are some of the salient features of this approach.

EXPERIMENTAL

Microwave irradiation was carried out with an Emrys™ Creator microwave oven from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken with a FT-IR-Tensor 27 spectrometer in KBr pellets and are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were measured with a Bruker DPX 400 MHz spectrometer in DMSO-d_6 with chemical shifts (δ) given in ppm relative to TMS as internal standard. Elemental analysis was determined with a Perkin-Elmer 240c elemental analysis instrument.

General procedure for the one-pot synthesis of compounds derivatives 4 in water under microwave irradiation condition. Typically, in a 10-mL Emrys™ reaction vial, an aldehyde **1** (1 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2** (1 mmol), and barbituric acids **3** (1 mmol), water (1 mL), *p*-TsOH (1 mmol) were mixed and then capped. The mixture was irradiated for a given time at 140 °C under microwave irradiation (initial power 100 W and maximum power 250 W). Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and then poured into cold water. The solid product was collected by Büchner filtration, which was further purified by recrystallization from EtOH (95%) to give the pure product.

4-(4-Fluorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4a). ir (KBr): 3185 (NH), 1720 (C=O), 1695 (C=O) cm^{-1}; ^1H nmr: δ 11.81 (s, 1H, NH), 11.21 (s, 1H, NH), 8.26 (d, 2H, J = 8.0 Hz, ArH), 7.56 (t, 2H, J = 8.0 Hz, ArH), 7.42-7.30 (m, 5H, ArH), 1.81 (s, 3H, CH_3). ^{13}C nmr: δ 161.7, 153.0, 150.4, 150.0, 149.9, 145.1, 138.7, 132.4, 130.0, 129.3, 126.2, 120.6, 114.8, 114.6, 113.9, 104.1, 14.5. *Anal*. calcd for $C_{21}H_{14}FN_5O_2$: C, 65.11; H, 3.64; N, 18.08. Found: C, 65.18; H, 3.60; N, 18.14.

4-(4-Chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4b). ir (KBr): 3185 (NH), 1716 (C=O), 1701 (C=O) cm^{-1}; ^1H nmr: δ 11.82 (s, 1H, NH), 11.22 (s, 1H, NH), 8.25 (d, 2H, J = 7.6 Hz, ArH), 7.58-7.54 (m, 4H, ArH), 7.40-7.36 (m, 3H, ArH), 1.82 (s, 3H, CH_3). ^{13}C nmr: δ 161.7, 152.9, 150.4, 150.0, 149.4, 145.0,

138.7, 135.1, 132.9, 129.7, 129.4, 127.8, 126.2, 120.6, 113.6, 104.0, 14.3. *Anal*. calcd for $C_{21}H_{14}ClN_5O_2$: C, 62.46; H, 3.49; N, 17.34. Found: C, 62.39; H, 3.45; N, 17.39.

4-(4-Bromophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4c). ir (KBr): 3186 (NH), 1713 (C=O), 1699 (C=O) cm^{-1}; ^1H nmr: δ 11.82 (s, 1H, NH), 11.22 (s, 1H, NH), 8.25 (d, 2H, J = 8.4 Hz, ArH), 7.69 (d, 2H, J = 8.0 Hz, ArH), 7.56 (t, 2H, J = 8.0 Hz, ArH), 7.38-7.32 (m, 3H, ArH), 1.82 (s, 3H, CH_3). ^{13}C nmr: δ 161.7, 152.9, 150.3, 150.0, 149.4, 145.0, 138.7, 135.5, 130.7, 130.0, 129.3, 126.2, 121.4, 120.6, 113.5, 103.9, 14.4. *Anal*. calcd for $C_{21}H_{14}BrN_5O_2$: C, 56.27; H, 3.15; N, 15.62. Found: C, 56.20; H, 3.18; N, 15.69.

3-Methyl-4-(4-nitrophenyl)-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4d). ir (KBr): 3195 (NH), 1729 (C=O), 1686 (C=O) cm^{-1}; ^1H nmr: δ 11.91 (s, 1H, NH), 11.31 (s, 1H, NH), 8.36 (d, 2H, J = 8.8 Hz, ArH), 8.25 (d, 2H, J = 8.0 Hz, ArH), 7.68 (d, 2H, J = 8.4 Hz, ArH), 7.57 (t, 2H, J = 8.0 Hz, ArH), 7.38 (t, 1H, J = 7.6 Hz, ArH), 1.79 (s, 3H, CH_3). ^{13}C nmr: δ 161.8, 152.9, 150.4, 150.1, 148.1, 147.4, 144.8, 143.6, 138.6, 129.4, 126.3, 122.9, 120.7, 113.1, 104.5, 103.9, 14.7. *Anal*. calcd for $C_{21}H_{14}N_6O_4$: C, 60.87; H, 3.41; N, 20.28. Found: C, 60.80; H, 3.38; N, 20.22.

4-(4-Methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4e). ir (KBr): 3190 (NH), 1722 (C=O), 1703 (C=O) cm^{-1}; ^1H nmr: δ 11.77 (s, 1H, NH), 11.16 (s, 1H, NH), 8.25 (d, 2H, J = 8.0 Hz, ArH), 7.55 (t, 2H, J = 7.6 Hz, ArH), 7.34 (t, 1H, J = 7.6 Hz, ArH), 7.26 (d, 2H, J = 8.0 Hz, ArH), 7.03 (d, 2H, J = 8.0 Hz, ArH,), 3.85 (s, 3H, OCH_3), 1.81 (s, 3H, CH_3). ^{13}C nmr: δ 161.6, 159.2, 153.0, 151.1, 150.4, 150.0, 145.3, 138.8, 129.3, 129.2, 128.0, 126.1, 120.6, 114.2, 113.1, 104.1, 55.3, 14.4. *Anal*. calcd for $C_{22}H_{17}N_5O_3$: C, 66.16; H, 4.29; N, 17.53. Found: C, 66.10; H, 4.24; N, 17.47.

3-Methyl-4-(4-methylphenyl)-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4f). ir (KBr): 3185 (NH), 1723 (C=O), 1708 (C=O) cm^{-1}; ^1H nmr: δ 11.77 (s, 1H, NH), 11.16 (s, 1H, NH), 8.25 (d, 2H, J = 8.0 Hz, ArH), 7.55 (t, 2H, J = 8.0 Hz, ArH), 7.34 (t, 1H, J = 7.6 Hz, ArH), 7.29 (d, 2H, J = 8.0 Hz, ArH), 7.21 (d, 2H, J = 8.0 Hz, ArH), 2.42 (s, 3H, CH_3), 1.76 (s, 3H, CH_3). ^{13}C nmr: δ 161.6, 152.9, 151.2, 150.4, 150.0, 145.2, 138.8, 137.2, 133.2, 129.3, 128.2, 127.6, 126.0, 120.5, 113.9, 104.0, 21.2, 18.7. *Anal*. calcd for $C_{22}H_{17}N_5O_2$: C, 68.92; H, 4.47; N, 18.27. Found: C, 68.98; H, 4.44; N, 18.20.

3-Methyl-4-(3-nitrophenyl)-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4g). ir (KBr): 3184 (NH), 1710 (C=O), 1695 (C=O) cm^{-1}; ^1H nmr: δ 11.89 (s, 1H, NH), 11.29 (s, 1H, NH), 8.37 (d, 1H, J = 7.6 Hz, ArH), 8.26 (t, 3H, J = 8.0 Hz, ArH), 7.88 (d, 1H, J = 7.2 Hz, ArH), 7.80 (t, 1H, J = 8.0 Hz, ArH), 7.57 (t, 2H, J = 7.6 Hz, ArH), 7.36 (t, 1H, J = 7.6 Hz, ArH), 1.79 (s, 3H, CH_3). ^{13}C nmr: δ 162.2, 153.2, 150.7, 150.4, 147.9, 147.7, 145.1, 138.9, 138.2, 134.9, 129.7, 129.6, 126.5, 123.4, 123.2, 120.9, 113.8, 104.4, 14.7. *Anal*. calcd for $C_{21}H_{14}N_6O_4$: C, 60.87; H, 3.41; N, 20.28. Found: C, 60.94; H, 3.44; N, 20.19.

3-Methyl-1,4-diphenyl-1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]-pyrimidine-5,7(6*H*,8*H*)-dione (4h). ir (KBr): 3183 (NH), 1712 (C=O), 1697 (C=O) cm^{-1}; ^1H nmr: δ 11.80 (s, 1H, NH), 11.18 (s, 1H, NH), 8.26 (d, 2H, J = 8.0 Hz, ArH), 7.56 (t, 2H, J = 8.0 Hz, ArH), 7.49-7.48 (m, 3H, ArH), 7.37-7.33 (m, 3H, ArH), 1.75 (s, 3H, CH_3). ^{13}C nmr: δ 161.9, 153.3, 150.7, 145.5, 139.0, 136.5, 129.6, 128.0, 127.9, 126.5, 126.4, 125.3, 123.7, 120.9, 114.1, 104.2, 14.3. *Anal*. calcd for $C_{21}H_{15}N_5O_2$: C, 68.28; H, 4.09; N, 18.96. Found: C, 68.22; H, 4.13; N, 18.88.

4-(2,4-Dichlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4i). ir (KBr): 3178 (NH), 1716 (C=O), 1701 (C=O) cm^{-1}; ^1H nmr: δ 11.95 (s, 1H, NH), 11.36 (s, 1H, NH), 8.24 (d, 2H, J = 8.0 Hz, ArH), 7.83-7.82 (m, 1H, ArH), 7.57 (t, 3H, J = 8.0 Hz, ArH), 7.45 (d, 1H, J = 8.4 Hz, ArH), 7.37 (t, 1H, J = 7.6 Hz, ArH), 1.85 (s, 3H, CH_3). ^{13}C nmr: δ 161.5, 153.0, 150.4, 150.3, 145.8, 144.6, 138.6, 134.3, 133.8, 132.1, 130.8, 129.4, 128.5, 127.3, 126.3, 120.7, 113.0, 104.2, 15.1. *Anal*. calcd for $C_{21}H_{13}Cl_2N_5O_2$: C, 57.55; H, 2.99; N, 15.98. Found: C, 57.46; H, 2.95; N, 15.90.

4-(3,4-Dimethoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4j). ir (KBr): 3200 (NH), 1719(C=O), 1704(C=O) cm^{-1}; ^1H nmr: δ 11.76 (s, 1H, NH), 11.16 (s, 1H, NH), 8.25 (d, 2H, J = 8.0 Hz, ArH), 7.56 (t, 2H, J = 8.0. Hz, ArH), 7.35 (t, 1H, J = 7.6 Hz, ArH), 7.05 (d, 1H, J = 8.4 Hz, ArH), 6.96-6.95 (m, 1H, ArH), 6.85 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.6 Hz, ArH), 3.85 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 1.86 (s, 3H, CH_3). ^{13}C nmr: δ 161.8, 153.3, 151.3, 150.7, 150.3, 149.0, 148.5, 145.7, 139.1, 129.6, 128.6, 126.4, 120.8, 120.5, 114.4, 112.4, 111.3, 104.4, 56.1, 56.0, 14.5. *Anal*. calcd for $C_{23}H_{19}N_5O_4$: C, 64.33; H, 4.46; N, 16.31. Found: C, 64.26; H, 4.44; N, 16.24.

4-(4-Hydroxy-3-nitrophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4k). ir (KBr): 3209 (NH), 1721 (C=O), 1706 (C=O) cm^{-1}; ^1H nmr: δ 11.84 (s, 1H, NH), 11.29 (s, 1H, OH), 11.26 (s, 1H, NH), 8.25 (d, 2H, J = 8.0 Hz, ArH), 7.92-7.91 (m, 1H, ArH), 7.58-7.54 (m, 3H, ArH), 7.36 (t, 1H, J = 7.6 Hz, ArH), 7.24 (d, 1H, J = 8.8 Hz, ArH), 1.92 (s, 3H, CH_3). ^{13}C nmr: δ 162.1, 153.3, 152.3, 150.6, 150.4, 148.5, 145.3, 139.0, 136.7, 135.3, 129.7, 127.1, 126.5, 125.0, 120.9, 118.8, 114.2, 104.5, 15.0. *Anal*. calcd for $C_{21}H_{14}N_6O_5$: C, 58.61; H, 3.28; N, 19.53. Found: C, 58.52; H, 3.24; N, 19.59.

3-Methyl-1-phenyl-4-thien-2-yl-1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4l). ir (KBr): 3183 (NH), 1715 (C=O), 1698 (C=O) cm^{-1}; ^1H nmr: δ 11.82 (s, 1H, NH), 11.25 (s, 1H, NH), 8.24 (d, 2H, J = 8.0 Hz, ArH), 7.80-7.79 (m, 1H, ArH), 7.56 (t, 2H, J = 8.0 Hz, ArH), 7.36 (t, 1H, J = 7.6 Hz, ArH), 7.21-7.19 (m, 1H, ArH), 7.13-7.12 (m, 1H, ArH), 1.92 (s, 3H, CH_3). ^{13}C nmr: δ 161.2, 152.9, 150.3, 149.8, 145.1, 143.7, 138.6, 135.0, 129.3, 127.6, 127.4, 126.8, 126.2, 120.6, 114.8, 105.3, 18.7. *Anal*. calcd for $C_{19}H_{13}N_5O_2S$: C, 60.79; H, 3.49; N, 18.66; S, 8.54. Found: C, 60.71; H, 3.44; N, 18.59; S, 8.62.

4-(4-Fluorophenyl)-3,6,8-trimethyl-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4m). ir (KBr): 1712 (C=O), 1667 (C=O) cm^{-1}; ^1H nmr: δ 8.25 (d, 2H, J = 8.0 Hz, ArH), 7.60 (t, 2H, J = 8.0 Hz, ArH), 7.41-7.32 (m, 5H, ArH), 3.71 (s, 3H, NCH_3), 3.19 (s, 3H, NCH_3), 1.82 (s, 3H, CH_3). ^{13}C nmr: δ 161.2, 151.1, 151.0, 150.5, 149.3, 145.3, 138.5, 132.0, 128.8, 128.6, 125.8, 120.3, 115.2, 114.9, 114.0, 103.7, 30.4, 28.2, 14.1. *Anal*. calcd for $C_{23}H_{18}FN_5O_2$: C, 66.50; H, 4.37; N, 16.86. Found: C, 66.44; H, 4.35; N, 16.74.

4-(4-Chlorophenyl)-3,6,8-trimethyl-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4n). ir (KBr): 1708 (C=O), 1664 (C=O) cm^{-1}; ^1H nmr: δ 8.25 (d, 2H, J = 8.4 Hz, ArH), 7.63-7.57 (m, 5H, ArH), 7.39-7.37 (m, 2H, ArH), 3.72 (s, 3H, NCH_3), 3.19 (s, 3H, NCH_3), 1.85 (s, 3H, CH_3). *Anal*. calcd for $C_{23}H_{18}ClN_5O_2$: C, 63.96; H, 4.20; N, 16.22. Found: C, 63.90; H, 4.23; N, 16.29.

4-(4-Bromophenyl)-3,6,8-trimethyl-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4o). ir (KBr): 1709 (C=O), 1664 (C=O) cm^{-1}; ^1H nmr: δ 8.25 (d, 2H, J = 8.0 Hz, ArH), 7.71 (d, 2H, J = 8.0 Hz, ArH), 7.61 (t, 2H, J = 8.0 Hz, ArH), 7.38 (t, 1H, J = 7.6 Hz, ArH), 7.31 (d, 2H, J = 8.4 Hz, ArH), 3.72 (s, 3H, NCH_3), 3.19 (s, 3H, NCH_3), 1.85 (s, 3H, CH_3). *Anal*. calcd for $C_{23}H_{18}BrN_5O_2$: C, 58.00; H, 3.81; N, 14.70. Found: C, 58.08; H, 3.85; N, 14.64.

3,6,8-Trimethyl-4-(4-methylphenyl)-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4p). ir (KBr): 1709 (C=O), 1665 (C=O) cm^{-1}; ^1H nmr: δ 8.25 (d, 2H, J = 8.4 Hz, ArH), 7.60 (t, 2H, J = 8.0 Hz, ArH), 7.37 (t, 1H, J = 7.6 Hz, ArH), 7.31 (d, 2H, J = 8.0 Hz, ArH), 7.21 (d, 2H, J = 8.0 Hz, ArH), 3.71 (s, 3H, NCH_3), 3.18 (s, 3H, NCH_3), 2.44 (s, 3H, CH_3), 1.80 (s, 3H, CH_3). ^{13}C nmr: δ 160.6, 152.0, 151.2, 151.0, 149.3, 145.7, 138.6, 137.7, 133.2, 128.8, 128.5, 126.5, 125.7, 120.3, 114.1, 103.7, 30.3, 28.2, 21.3, 14.0. *Anal*. calcd for $C_{24}H_{21}N_5O_2$: C, 70.06; H, 5.14; N, 17.02. Found: C, 70.00; H, 5.16; N, 17.09.

3,6,8-Trimethyl-4-(3-nitrophenyl)-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4q). ir (KBr): 1716 (C=O), 1667 (C=O) cm^{-1}; ^1H nmr: δ 8.39 (d, 1H, J = 7.2 Hz, ArH), 8.26 (d, 3H, J = 8.0 Hz, ArH), 7.87-7.81 (m, 2H, ArH), 7.62 (t, 2H, J = 8.0 Hz, ArH), 7.39 (t, 1H, J = 7.2 Hz, ArH), 3.74 (s, 3H, NCH_3), 3.19 (s, 3H, NCH_3), 1.82 (s, 3H, CH_3). ^{13}C nmr: δ 160.5, 151.6, 150.9, 149.4, 148.0, 147.6, 144.5, 138.3, 137.9, 133.0, 128.9, 126.0, 125.3, 123.0, 122.1, 120.4, 113.4, 103.4, 30.4, 28.2, 14.3. *Anal*. calcd for $C_{23}H_{18}N_6O_4$: C, 62.44; H, 4.10; N, 19.00. Found: C, 62.49; H, 4.13; N, 19.06.

4-(3-Bromophenyl)-3,6,8-trimethyl-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4r). ir (KBr): 1713 (C=O), 1667 (C=O) cm^{-1}; ^1H nmr: δ 8.26-8.24 (m, 2H, ArH), 7.73-7.70 (m, 1H, ArH), 7.63-7.59 (m, 3H, ArH), 7.50-7.46 (m, 1H, ArH), 7.40-7.35 (m, 2H, ArH), 3.72 (s, 3H, NCH_3), 3.20 (s, 3H, NCH_3), 1.84 (s, 3H, CH_3). *Anal*. calcd for $C_{23}H_{18}BrN_5O_2$: C, 58.00; H, 3.81; N, 14.70. Found: C, 58.11; H, 3.84; N, 14.59.

4-(2-Chlorophenyl)-3,6,8-trimethyl-1-phenyl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4s). ir (KBr): 1713 (C=O), 1666 (C=O) cm^{-1}; ^1H nmr: δ 8.25 (d, 2H, J = 8.4 Hz, ArH), 7.65-7.59 (m, 3H, ArH), 7.51-7.48 (m, 2H, ArH), 7.40-7.36 (m, 2H, ArH), 3.73 (s, 3H, NCH_3), 3.21 (s, 3H, NCH_3), 1.82 (s, 3H, CH_3). *Anal*. calcd for $C_{23}H_{18}ClN_5O_2$: C, 63.96; H, 4.20; N, 16.22. Found: C, 63.84; H, 4.26; N, 16.15.

3,6,8-Trimethyl-1,4-diphenyl-1*H*-pyrazolo[4',3':5,6]pyrido-[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4t). ir (KBr): 1715 (C=O), 1670 (C=O) cm^{-1}; ^1H nmr: δ 8.21 (d, 2H, J = 7.6 Hz, ArH), 7.56 (t, 2H, J = 8.0 Hz, ArH), 7.46-7.45 (m, 3H, ArH), 7.34-7.27 (m, 3H, ArH), 3.67 (s, 3H, NCH_3), 3.14 (s, 3H, NCH_3), 1.72 (s, 3H, CH_3). ^{13}C nmr: δ 160.5, 151.6, 151.2, 151.0, 149.3, 145.5, 138.6, 136.3, 128.8, 128.0, 127.8, 126.6, 125.7, 120.3, 113.9, 103.6, 30.3, 28.2, 13.8. *Anal*. calcd for $C_{23}H_{19}N_5O_2$: C, 69.51; H, 4.82; N, 17.62. Found: C, 69.59; H, 4.80; N, 17.73.

4-(2,4-Dichlorophenyl)-3,6,8-trimethyl-1-phenyl-1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4u). ir (KBr): 1710 (C=O), 1663 (C=O) cm^{-1}; ^1H nmr: δ 8.25 (d, 2H, J = 8.0 Hz, ArH), 7.85-7.84 (m, 1H, ArH), 7.61 (t, 3H, J = 8.0 Hz, ArH), 7.43-7.38 (m, 2H, ArH), 3.72 (s, 3H, NCH_3), 3.21 (s, 3H, NCH_3), 1.89 (s, 3H, CH_3). ^{13}C nmr: δ 160.1, 151.4, 150.9, 149.5, 146.3, 144.7, 138.5, 134.7, 133.9, 132.1, 130.6, 128.6, 127.4, 126.4, 120.5, 114.7, 112.6, 104.5, 30.5, 28.2, 13.5. *Anal*. calcd for $C_{23}H_{17}Cl_2N_5O_2$: C, 59.24; H, 3.67; N, 15.02. Found: C, 59.18; H, 3.63; N, 15.10.

4-(1,3-Benzodioxol-5-yl)-3,6,8-trimethyl-1-phenyl-1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4v). ir (KBr): 1711 (C=O), 1668 (C=O) cm^{-1}; ^1H nmr: δ 8.25 (d, 2H, J = 8.4 Hz, ArH), 7.60 (t, 2H, J = 8.0 Hz, ArH), 7.36 (t, 1H, J = 7.6 Hz, ArH), 7.04 (d, 1H, J = 8.0 Hz, ArH), 6.92 (s, 1H, ArH), 6.77 (d, 1H, J = 8.0 Hz, ArH), 6.15-6.14 (m, 2H, CH_2), 3.70 (s, 3H, NCH_3), 3.20 (s, 3H, NCH_3), 1.93 (s, 3H, CH_3). ^{13}C nmr: δ 160.4, 151.2, 151.1, 150.9, 149.3, 147.4, 147.3, 145.5, 138.6, 129.5, 128.8, 125.7, 120.2, 120.1, 114.2, 107.9, 107.8, 103.8, 101.1, 30.3, 28.2, 14.1. *Anal*. calcd for $C_{24}H_{19}N_5O_4$: C, 65.30; H, 4.34; N, 15.86. Found: C, 65.23; H, 4.38; N, 15.78.

4-(4-Hydroxy-3-nitrophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4w). ir (KBr): 1714 (C=O), 1667 (C=O) cm^{-1}; ^1H nmr: δ 11.29 (s, 1H, OH), 8.22 (d, 2H, J = 8.0 Hz, ArH), 7.91-7.90 (m, 1H, ArH), 7.59-7.51 (m, 3H, ArH), 7.34 (t, 1H, J = 7.6. Hz, ArH), 7.26 (d, 1H, J = 8.4 Hz, ArH), 3.69 (s, 3H, NCH_3), 3.18 (s, 3H, NCH_3), 1.90 (s, 3H, CH_3). ^{13}C nmr: δ 160.3, 152.0, 151.3, 150.9, 149.2, 148.5, 145.0, 138.5, 136.5, 134.7, 129.5, 127.2, 126.1, 124.3, 120.1, 118.7, 113.5, 104.5, 30.5, 28.2, 14.6. *Anal*. calcd for $C_{23}H_{18}N_6O_5$: C, 60.26; H, 3.96; N, 18.33. Found: C, 60.33; H, 3.98; N, 18.39.

3,6,8-Trimethyl-1-phenyl-4-thien-2-yl-1*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4x). ir (KBr): 1710 (C=O), 1660 (C=O) cm^{-1}; ^1H nmr: δ 8.28-8.27 (m, 2H, ArH), 7.58-7.56 (m, 3H, ArH), 7.35-7.33 (m, 3H, ArH), 3.66 (s, 3H, NCH_3), 3.20 (s, 3H, NCH_3), 1.91 (s, 3H, CH_3). *Anal*. calcd for $C_{21}H_{17}N_5O_4S$: C, 62.52; H, 4.25; N, 17.36; S, 7.95. Found: C, 62.45; H, 4.28; N, 17.43; S, 7.85.

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