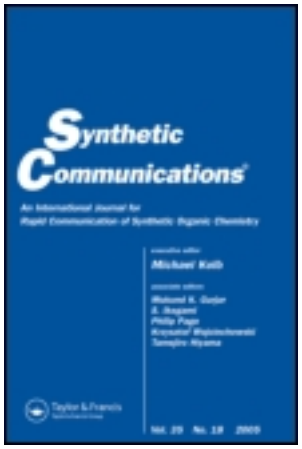

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Green Approach to the Synthesis of Polyfunctionalized Pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidines via Microwave-Assisted Multicomponent Reactions in Water Without Catalyst

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GREEN APPROACH TO THE SYNTHESIS OF POLYFUNCTIONALIZED PYRAZOLO[4′,3′:5,6] PYRIDO[2,3-*d*]PYRIMIDINES VIA MICROWAVE-ASSISTED MULTICOMPONENT REACTIONS IN WATER WITHOUT CATALYST

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A green approach to the synthesis of polyfunctionalized pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidines was successfully realized via multicomponent reactions of aldehydes, 3-methyl-1-phenyl-1H-pyrazol-5-amine, and 1-methylbarbituric acid in water under microwave irradiation without catalyst. This protocol has the prominent advantages of environmental friendliness, short reaction time, excellent yields, low cost, easy operation, and broad scope of applicability.

Keywords: Green synthesis; microwave irradiation; pyrazolopyridopyrimidine; water

INTRODUCTION

Pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines, which contain three fused heterocyclic skeletons in one molecule, have wide applications in medicinal and chemical industry, acting as anticonvulsant agents,[1] colorants,[2] heat/moisture-resistant and thermal transfer printing agents,[3] as well as photographic couplers.[4] Therefore, much attention has been paid to the synthesis of this class of polyfunctionalized compounds.[5] For example, Hussein and El-Emary[6] disclosed that the condensation of 5-amino-3-methyl-1-phenylpyrazole-4-carbaldehyde with cyanoacetamide in refluxing ethanol/piperidine yielded the intermediate compounds of aminocarboxamide derivatives in moderate yields, which then reacted with urea derivatives to yield the pyrazolopyridopyrimidine derivatives. Recently, Jachak and coworkers[7] reported the synthesis of pyrazolopyridopyrimidine derivatives by a three-step reaction in organic solvents from 5-aminopyrazole-4-carbaldehyde. However, these methods suffer from the disadvantage of complicated multistep reactions and are

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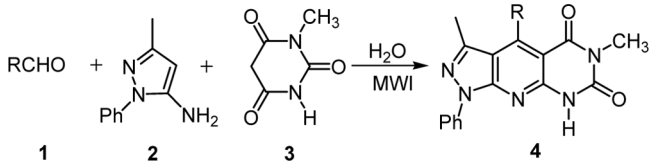


Scheme 1. The synthesis of pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidines.

environmentally unfriendly because volatile or toxic organic solvents are used. As a result, developing a green and facile approach to the synthesis of pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines is of great significance.

In recent years, microwave-assisted synthesis in water as solvent has become a hot spot of investigation because it combines the two prominent green chemistry principles of "safer solvents" and "energy efficiency."[8] Besides the general advantages of water and microwave irradiation (MWI),[9] several important benefits are expected when they are combined with each other.[10] On the other hand, multicomponent reactions (MCRs) occupy an outstanding position in organic and medicinal chemistry by virtue of the intrinsic atom economy and selectivity, simpler procedures and equipment, time and energy savings, as well as environmental friendliness.[11] Thus, it goes without saying that the use of water as a nontoxic reaction medium together with the employment of energy-efficient microwave heating and atom-economical MCRs must be considered to be a synergistic and effective green synthesis strategy in the sense that the combination in itself offers greater potential than the three parts in isolation.

Very recently, we have synthesized a series of pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine derivatives by a pot, atom, and step economical method under MWI in the presence of *p*-toluene sulfonic acid in water.[12] However, in this method, *p*-toluene sulfonic acid (a corrosive and irritant organic catalyst) was used, which is harmful to health and the environment. Hence, to some extent, this approach was still not a green one and should be improved toward the goal of environmental friendliness. Herein, we report an improved green and facile approach to the synthesis of another series of novel pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines **4** via microwave-assisted three-component reactions of aldehydes **1**, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2**, and 1-methylbarbituric acid **3** in water without catalyst (Scheme 1).

RESULTS AND DISCUSSION

Initially, we screened various conditions for the three-component reaction of 4-bromobenaldehyde **1e**, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2**, and 1-methylbarbituric acid **3** in different solvents at 100°C under MWI (Table 1, entries 1–5). Of the various polar solvents tested, water and glycol gave the great yields of the expected products within the shortest reaction time (Table 1, entries 4 and 5). Considering environmental friendliness and avoidance of organic solvents, water was preferred as solvent for all further microwave-assisted reactions.

Table 1. Reaction condition optimization for the synthesis of **4e**

Entry	Solvent	T (°C)	Time (min)	Yield (%)
1	EtOH	100	15	58
2	DMF	100	14	65
3	HOAc	100	15	72
4	Glycol	100	10	83
5	Water	100	8	81
6	Water	80	12	72
7	Water	90	10	78
8	Water	110	5	86
9	Water	120	6	85
10	Water	130	5	85

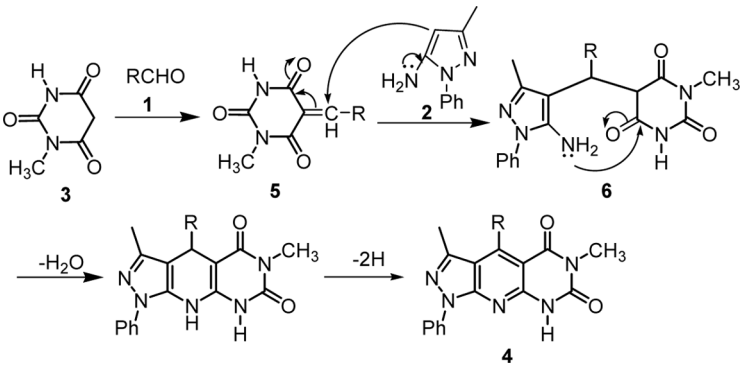
To further optimize the reaction conditions, the reaction was carried out under MWI using water as solvent at temperatures ranging from 80 to 130°C, with an increment of 10°C each time (Table 1, entries 5–10). The yield of product **4e** was improved and the reaction time was shortened as the temperature increased from 80°C to 110°C (Table 1, entries 5–8). However, the yield was decreased when temperature was further increased to 120 and 130°C (Table 1, entries 9 and 10). Therefore, 110°C was choosen as the most suitable reaction temperature.

Moreover, we found that the yield of this reaction was affected by the volume of water. The synthesis of **4e** was tested in different volumes of water at 110°C. The results show that 1.5 mL of water was optimal as solvent because it generated the most yield of **4e**.

Under these optimized reaction conditions (1.5 mL of water, 110°C), a series of novel pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines **4** was synthesized under MWI, and the results are summarized in Table 2. To test the efficiency and applicability of this green synthetic approach, different aldehydes were employed in the reactions. As illustrated in Table 2, this protocol could be applied not only to the aromatic aldehydes with either electron-withdrawing groups such as nitro or halide groups or electron-donating groups such as an alkoxyl group but also to heterocyclic

Table 2. Synthesis of **4** under microwave irradiation

Entry	**4**	R	Time (min)	Yield (%)	Mp (°C)
1	**4a**	4-FC_6H_4	7	86	>300
2	**4b**	4-ClC_6H_4	6	85	>300
3	**4c**	2,4-$Cl_2C_6H_3$	5	88	>300
4	**4d**	C_6H_5	10	84	>300
5	**4e**	4-BrC_6H_4	5	86	>300
6	**4f**	3-$NO_2C_6H_4$	7	87	>300
7	**4g**	Thien-2-yl	9	80	>300
8	**4h**	4-$CH_3OC_6H_4$	8	82	>300
9	**4i**	3,4-$(CH_3O)_2C_6H_3$	10	84	>300
10	**4j**	Benzo[*d*][1,3]dioxol-5-yl	8	83	>300
11	**4k**	3,4,5-$(CH_3O)_3C_6H_2$	10	81	>300
12	**4l**	4-$NO_2C_6H_4$	6	83	>300



Scheme 2. The reasonable mechanism for the formation of product **4**.

aldehydes with excellent yields. So, it was concluded that the electronic nature of the substituents on aldehydes has no significant effect on this reaction.

The structures of all the synthesized compounds were established on the basis of their spectroscopic data and high-resolution mass spectrometry (HRMS).

A reasonable mechanism for the formation of product **4** is outlined in Scheme 2. The formation of **4** is expected to proceed via initial condensation of aldehyde **1** with 1-methylbarbituric acid **3** to give an intermediate **5**. Then, it undergoes Michael addition with **2** to give an open-chain intermediate **6**, which is subsequently cyclized, dehydrated, and dehydrogenated to afford the aromatized product **4**.

CONCLUSION

In brief, we have realized a green and facile approach to the synthesis of polyfunctionalized pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines via microwave-assisted multicomponent reactions of aldehydes, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, and 1-methylbarbituric acid in water without catalyst. This protocol has the prominent advantages of environmental friendliness, short reaction time, excellent yields, low cost, easy operation, and broad scope of applicability. At the same time, this efficient synthesis cannot only offer a green synthetic strategy to highly fused heterocyclic compounds but also enrich the investigations on microwave-assisted multicomponent reactions in water.

EXPERIMENTAL

MWI was carried out in a monomodal Emrys Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined on an XT5 apparatus and are uncorrected. Infrared (IR) spectra were recorded on an Fourier transform (FT)–IR Tensor 27 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a DPX 400 spectrometer operating at 400 MHz and 100 MHz, respectively, using dimethylsulfoxide (DMSO-d_6) as solvent and tetramethylsilane (TMS) as an internal standard. HRMS (ESI) was determined on a microtof-QII HRMS/MS instrument (Bruker).

General Procedure for the Synthesis of Compounds 4 Under Microwave Irradiation

Typically, in a 10-mL Emrys reaction vial, aldehyde **1** (1 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2** (1 mmol), 1-methylbarbituric acid **3** (1 mmol), and water (1.5 mL) were mixed, and then the vial was capped. The mixture was irradiated at 200 W and 110°C for a given time. The reaction mixture was cooled to room temperature, poured into water, and filtered to give the crude product, which was further purified by recrystallization from ethanol (EtOH) to give pure pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines **4**.

4-(4-Fluorophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo-[4′,3′:5,6]pyrido [2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4a). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.12 (s, 1H, NH), 8.27 (d, 2H, $J = 8.4$ Hz, ArH), 7.57 (t, 2H, $J = 8.0$ Hz, ArH), 7.38–7.42 (m, 3H, ArH), 7.35 (d, 2H, $J = 8.4$ Hz, ArH), 3.12 (s, 3H, CH_3), 1.81 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3109, 3043, 2950, 2833, 1719, 1667, 1589, 1568, 1512, 1443, 1412, 1379, 1351, 1222, 1159, 1039, 1015, 842, 811, 757, 734, 691, 659, 609. HRMS (ESI) m/z: calc. for $C_{22}H_{16}FN_5O_2$: 402.1361 $[M + H]^+$:found: found: 402.1352 $[M + H]^+$.

4-(4-Chlorophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo-[4′,3′:5,6]pyrido [2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4b). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.11 (s, 1H, NH), 8.26 (d, 2H, $J = 8.0$ Hz, ArH), 7.55–7.58 (m, 4H, ArH), 7.34–7.40 (m, 3H, ArH), 3.12 (s, 3H, CH_3), 1.82 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 163.3, 153.54 152.7, 152.2, 151.8, 151.7, 147.3, 140.9, 137.5, 135.1, 131.8, 131.6, 130.1, 128.4, 122.7, 122.6, 116.0, 114.7, 105.7, 29.4, 16.5. IR(KBr, ν, cm^{-1}): 3107, 3036, 2949, 2834, 1717, 1667, 1589, 1567, 1494, 1439, 1411, 1379, 1350, 1315, 1271, 1210, 1088, 1038, 1016, 838, 810, 758, 734, 690, 608. HRMS (ESI) m/z: calc. for $C_{22}H_{16}ClN_5O_2$: 418.1066 $[M + H]^+$, found: 418.1061 $[M + H]^+$.

4-(2,4-Dichlorophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo-[4′,3′:5,6]pyrido [2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4c). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.25 (s, 1H, NH), 8.26 (d, 2H, $J = 8.4$ Hz, ArH), 7.85 (s, 1H, ArH), 7.56–7.60 (m, 3H, ArH), 7.44 (d, 1H, $J = 8.0$ Hz, ArH), 7.38 (t, 1H, $J = 7.6$ Hz, ArH), 3.14 (s, 3H, CH_3), 1.87 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 163.1, 153.5, 152.6, 152.4, 148.2, 146.8, 140.7, 136.6, 136.1, 134.3, 133.0, 131.6, 130.7, 129.5, 128.4, 122.7, 115.3, 105.7, 29.5, 15.7. IR (KBr, ν, cm^{-1}): 3108, 3045, 2951, 2833, 1716, 1667, 1589, 1569, 1496, 1442, 1411, 1380, 1350, 1315, 1275, 1210, 1122, 1100, 1040, 860, 835, 790, 758, 690, 609. HRMS (ESI) m/z: calc. for $C_{22}H_{16}Cl_2N_5O_2$: 452.0676 $[M + H]^+$, found: 452.0665 $[M + H]^+$.

3,6-Dimethyl-1,4-diphenyl-1*H*-pyrazolo-[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4d). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.10 (s, 1H, NH), 8.27 (d, 2H, $J = 7.6$ Hz, ArH), 7.57 (t, 2H, $J = 7.6$ Hz, ArH), 7.48–7.50 (m, 3H, ArH), 7.33–7.38 (m, 3H, ArH), 3.12 (s, 3H, CH_3), 1.74 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 163.1, 153.4, 153.1, 152.7, 152.0, 147.3, 140.9, 138.5, 131.4, 130.1, 129.9, 129.8, 128.0, 122.4, 116.1, 105.4, 29.4, 16.1. IR (KBr, ν, cm^{-1}): 3105, 3055, 2946, 2830, 1716, 1663, 1589, 1565, 1503, 1443, 1411,

1378, 1347, 1312, 1272, 1210, 1197, 1123, 1041, 810, 756, 690, 608. HRMS (ESI) m/z: calc. for $C_{22}H_{17}N_5O_2$: 384.1460 $[M+H]^+$, found: 384.1462 $[M+H]^+$.

4-(4-Bromophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo-[4′,3′:5,6]pyrido [2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4e). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.14 (s, 1H, NH), 8.26 (d, 2H, $J=8.0$ Hz, ArH), 7.70 (d, 2H, $J=8.4$ Hz, ArH), 7.57 (d, 2H, $J=8.0$ Hz, ArH), 7.37 (d, 1H, $J=8.0$ Hz, ArH), 7.32 (d, 2H, $J=8.4$ Hz, ArH), 3.12 (s, 3H, CH_3), 1.82 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 161.2, 151.3, 150.6, 149.9, 149.6, 145.2, 138.5, 135.6, 130.8, 129.8, 129.4, 126.3, 121.4, 120.6, 113.7, 103.4, 27.2, 14.2. IR (KBr, ν, cm^{-1}): 3113, 3045, 2953, 2831, 1719, 1667, 1598, 1584, 1493, 1444, 1408, 1353, 1314, 1270, 1213, 1196, 1124, 1079, 1037, 1011, 836, 811, 790, 765, 748, 693, 657, 609. HRMS (ESI) m/z: calc. for $C_{22}H_{16}BrN_5O_2$: 462.0561 $[M+H]^+$: found: 462.0553 $[M+H]^+$.

3,6-Dimethyl-4-(3-nitrophenyl)-1-phenyl-1*H*-pyrazolo-[4′,3′:5,6]pyrido [2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4f). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.16 (s, 1H, NH), 8.38 (d, 1H, $J=8.0$ Hz, ArH), 8.27 (s, 1H, ArH), 8.26 (d, 2H, $J=8.0$ Hz, ArH), 7.87 (d, 1H, $J=7.6$ Hz, ArH), 7.82 (t, 1H, $J=7.6$ Hz, ArH), 7.57 (t, 2H, $J=8.0$ Hz, ArH), 7.36 (t, 1H, $J=7.6$ Hz, ArH), 3.11 (s, 3H, CH_3), 1.77 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 163.5, 153.5, 152.7, 152.3, 150.0, 149.6, 147.1, 140.8, 140.3, 136.7, 131.8, 131.6, 128.4, 125.3, 124.9, 122.7, 115.9, 114.7, 105.8, 29.5, 16.7. IR (KBr, ν, cm^{-1}): 3239, 3079, 2960, 2926, 1735, 1663, 1590, 1571, 1530, 1507, 1444, 1412, 1378, 1347, 1208, 1178, 1125, 1044, 907, 884, 840, 810, 753, 728, 689, 609. HRMS (ESI) m/z: calc. for $C_{22}H_{16}N_6O_4$: 429.1306 $[M+H]^+$: found: 429.1292 $[M+H]^+$.

3,6-Dimethyl-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 (4g). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.11 (s, 1H, NH), 8.25 (d, 2H, $J=8.0$ Hz, ArH), 7.80 (d, 1H, $J=4.4$ Hz, Thiophene-H), 7.57 (t, 2H, $J=8.0$ Hz, ArH), 7.36 (t, 1H, $J=7.2$ Hz, ArH), 7.21 (t, 1H, $J=4.4$ Hz, Thiophene-H), 7.13 (d, 1H, $J=4.4$ Hz, Thiophene-H), 3.15 (s, 3H, CH_3), 1.93 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 162.8, 153.5, 152.6, 151.9, 147.3, 146.0, 140.8, 137.4, 131.5, 129.8, 129.5, 129.0, 128.3, 122.6, 117.1, 106.9, 29.4, 15.6. IR (KBr, ν, cm^{-1}): 3438, 3244, 3069, 2953, 1717, 1669, 1590, 1572, 1495, 1437, 1377, 1353, 1279, 1207, 1141, 1044, 854, 826, 805, 753, 707, 692, 657, 618. HRMS (ESI) m/z: calc. for $C_{20}H_{15}N_5O_2S$: 390.1020 $[M+H]^+$: found: 390.1014 $[M+H]^+$.

4-(4-Methoxyphenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo-[4′,3′:5,6]pyrido [2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4h). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.07 (s, 1H, NH), 8.27 (d, 2H, $J=8.4$ Hz, ArH), 7.56 (t, 2H, $J=7.6$ Hz, ArH), 7.35 (t, 1H, $J=7.6$ Hz, ArH), 7.26 (d, 2H, $J=8.4$ Hz, ArH), 7.05 (d, 2H, $J=8.4$ Hz, ArH), 3.86 (s, 3H, OCH_3), 3.12 (s, 3H, CH_3), 1.83 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 163.2, 161.4, 153.6, 153.4, 152.7, 152.1, 147.5, 141.0, 131.5, 131.3, 130.4, 128.2, 122.6, 116.5, 115.4, 105.8, 57.5, 29.4, 16.6. IR (KBr, ν, cm^{-1}): 3106, 2998, 2954, 2836, 1716, 1668, 1589, 1566, 1514, 1440, 1412, 1380, 1351, 1246, 1176, 1036, 836, 812, 760, 692, 609. HRMS (ESI) m/z: calc. for $C_{23}H_{19}N_5O_3$: 414.1561 $[M+H]^+$: found: 414.1566 $[M+H]^+$.

4-(3,4-Dimethoxyphenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo-[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4i). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.05 (s, 1H, NH), 8.26 (d, 2H, $J = 7.6$ Hz, ArH), 7.56 (t, 2H, $J = 7.6$ Hz, ArH), 7.35 (t, 1H, $J = 7.6$ Hz, ArH), 7.06 (d, 1H, $J = 8.0$ Hz, ArH), 6.94 (s, 1H, ArH), 6.84 (d, 1H, $J = 8.0$ Hz, ArH), 3.85 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.13 (s, 3H, CH_3), 1.86 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 160.9, 151.3, 151.2, 150.5, 149.9, 148.7, 148.2, 145.4, 138.7, 129.3, 128.5, 126.0, 120.4, 120.0, 114.3, 111.9, 111.1, 103.6, 55.8, 55.7, 27.2, 14.2. IR (KBr, ν, cm^{-1}): 3113, 3045, 2953, 2831, 1719, 1667, 1584, 1493, 1444, 1408, 1353, 1314, 1270, 1124, 1037, 1011, 836, 811, 765, 748, 693, 609. HRMS (ESI) m/z: calc. for $C_{24}H_{21}N_5O_4$: 444.1667 $[M + H]^+$: found: 444.1660 $[M + H]^+$.

4-(1,3-Benzodioxol-5-yl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo-[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4j). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.08 (s, 1H, NH), 8.26 (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), 7.03 (d, 1H, $J = 8.0$ Hz, ArH), 6.94 (s, 1H, ArH), 6.78 (d, 1H, $J = 8.0$ Hz, ArH), 6.14 (d, 2H, $J = 5.6$ Hz, CH_2), 3.14 (s, 3H, CH_3), 1.91 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 163.0, 161.1, 151.4, 151.1, 150.6, 150.0, 145.3, 144.5, 138.8, 136.4, 129.5, 129.4, 128.0, 127.8, 127.5, 126.2, 120.6, 118.8, 114.7, 114.0, 103.5, 27.2, 14.0. IR (KBr, ν, cm^{-1}): 3308, 3064, 2987, 2895, 1727, 1674, 1588, 1571, 1494, 1440, 1377, 1351, 1235, 1117, 1037, 933, 804, 751, 691, 662, 646, 624, 582. HRMS (ESI) m/z: calc. for $C_{23}H_{17}N_5O_4$: 428.1354 $[M + H]^+$: found: 428.1347 $[M + H]^+$.

3,6-Dimethyl-1-phenyl-4-(3,4,5-trimethoxyphenyl)-1*H*-pyrazolo-[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4k). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.08 (s, 1H, NH), 8.25 (d, 2H, $J = 7.2$ Hz, ArH), 7.56 (t, 2H, $J = 7.2$ Hz, ArH), 7.33–7.37 (m, 1H, ArH), 6.65 (s, 2H, ArH), 3.76 (s, 9H, OCH_3), 3.15 (s, 3H, CH_3), 1.89 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 163.0, 154.8, 153.5, 153.1, 152.7, 152.1, 147.7, 140.9, 139.4, 134.0, 131.5, 128.3, 122.7, 116.3, 107.6, 105.6, 62.7, 58.5, 29.4, 16.1. IR (KBr, ν, cm^{-1}): 3105, 3062, 3041, 2940, 2829, 1720, 1668, 1587, 1567, 1506, 1462, 1411, 1380, 1355, 1317, 1236,1127, 1040, 1013, 860, 814, 788, 751, 688, 667, 651, 585. HRMS (ESI) m/z: calc. for $C_{25}H_{23}N_5O_5$: 474.1772 $[M + H]^+$: found: 474.1770 $[M + H]^+$.

3,6-Dimethyl-4-(4-nitrophenyl)-1-phenyl-1*H*-pyrazolo-[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione 4l. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.18 (s, 1H, NH), 8.37 (d, 2H, $J = 8.4$ Hz, ArH), 8.26 (d, 2H, $J = 8.0$ Hz, ArH), 7.68 (d, 2H, $J = 8.4$ Hz, ArH), 7.58 (t, 2H, $J = 8.0$ Hz, ArH), 7.37 (t, 1H, $J = 8.0$ Hz, ArH), 3.12 (s, 3H, CH_3), 1.80 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 161.2, 151.3, 150.5, 150.1, 148.3, 147.4, 144.8, 143.8, 138.6, 129.4, 129.3, 129.3, 126.3, 123.0, 120.6, 120.5, 114.7, 113.2, 103.4, 27.2, 14.3. IR (KBr, ν, cm^{-1}): 3109, 3057, 2955, 2839, 1720, 1668, 1587, 1570, 1517, 1496, 1445, 1408, 1343, 1271, 1211, 1124, 1037, 858, 843, 811, 761, 694, 608. HRMS (ESI) m/z: calc. for $C_{22}H_{16}N_6O_4$: 429.1306 $[M + H]^+$: found: 429.1302 $[M + H]^+$.

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