A Green and Efficient Synthesis of Furo[3,4-*e*]pyrazolo[3,4-*b*]-pyridine Derivatives in Water under Microwave Irradiation without Catalyst

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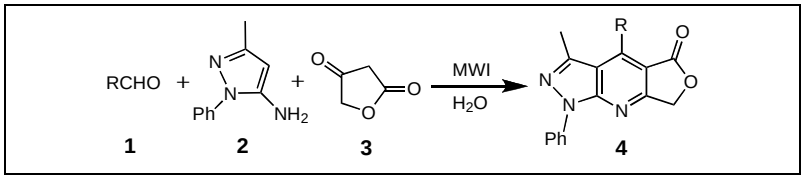

A series of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine analogues of podophylloxin were synthesized *via* three-component reactions of aldehydes, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and tetronic acid in water under microwave irradiation without catalyst. This efficient synthesis not only offers an economical and green synthetic strategy to this class of significant compounds but also enriches the investigations on microwave-assisted synthesis in water.

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INTRODUCTION

Tetronic acid derivatives and their metabolites are interesting and intriguing because of their antibiotic [1], anticoagulant [2], antiepileptic [3], antifungal [4], insecticidal [5], analgesic [6] and anti-inflammatory [7] activities. Recently, these compounds have also been reported as HIV-1 protease inhibitors [8]. Podophyllotoxin, one of the derivatives of tetronic acid, is an antitumor lignan that inhibits microtubule assembly. Attempts to use it for the treatment of human neoplasia were mostly unsuccessful and were complicated by side effects. Extensive structural modifications have been performed in order to obtain more potent and less toxic anticancer agents [9]. However, most modifications were performed on ring B and C (Figure 1), and modification on ring A has had minimal investigation.

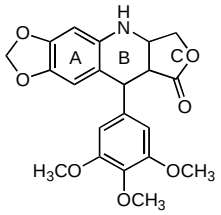


Figure 1. Structure of podophyllotoxin analogue.

Pyrazolo[3,4-*b*]pyridines are attractive targets in organic synthesis due to there interesting biological and pharmacological properties [10] such as vasodialotors, hypoglycemic, anti-inflammatory, analgesic and anti-pyritic activities. It is promising that the modifications on ring A, changed into pyrazole ring, may bring about great changes in bioactivities.

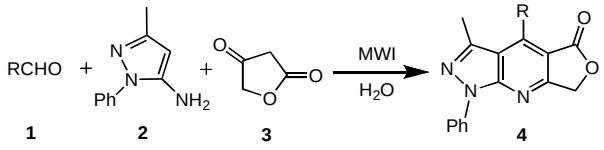
Very recently, Magedov and co-workers have reported the synthesis of dihydropyridopyrazole analogues of podophyllotoxin *via* multi-component condensations using triethylamine as catalyst and ethanol as solvent under traditional heating condition [11]. Moreover, they have found promising anticancer activity of this new scaffold, which will arouse more attentions on the synthesis and pharmacological activities of these types of compounds. Although the above method offered a synthetic approach to this class of important compounds, it still has some disadvantages such as being less economical and environmentally unfriendly since the volatile and flammable or toxic organic reagents, triethylamine and ethanol are used. As a result, developing a green and efficient method on the synthesis of pyridopyrazole analogues of podophyllotoxin is of great significance.

In recent years, microwave-assisted synthesis in water as solvent has become a hot topic of investigation since it combines the two prominent green chemistry principles of "safer solvents" and "energy efficiency" [12]. Among the different solvent alternatives in organic chemistry, water is extremely inexpensive and nontoxic [13]. In addition to these general advantages, several benefits for the reaction are expected when using water as reaction medium for microwave-superheated protocols. First, water is rapidly

heated by microwave irradiation to high reaction temperatures, enabling water to act as a less polar pseudo-organic solvent. Second, precise control of the reaction temperature is easily achieved because of the very high capacity of water. Third, the lack of flammable properties makes the use of water safe also with pressurized exothermic reactions [14].

As a continuation of our efforts on structural modification of podophyllotoxin analogue with green and efficient method [15], we herein report the synthesis of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine derivatives through three-component reactions of aldehydes **1**, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2** and tetronic acid **3** in water under microwave irradiation (MWI) without catalyst (Scheme 1). This efficient synthesis not only offers an economical and green synthetic strategy to this class of significant compounds but also enriches the investigations on microwave-assisted synthesis in water.

Scheme 1



RESULTS AND DISCUSSION

To demonstrate the superiority of water as solvent, in spite of its natural property of being harmless to environment, we compared the synthesis of **4c** in water with other organic solvents including glycol, DMF, glacial acetic acid and ethanol. The mixture of 4-bromophenyl aldehyde **1c** (1 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2** (1 mmol), tetronic acid **3** (1 mmol) and corresponding solvent (2 mL) was irradiated under MWI at 80 °C and 100 W for a given time, then the crude product was purified by recrystallization from EtOH.

Table 1

Solvent optimization for the synthesis of **4c**.

Entry	Solvent	Time (min)	Yield (%)
1	glycol	12	86
2	water	11	85
3	AcOH	15	71
4	DMF	16	63
5	EtOH	18	60

The results (Table 1) reveal that water as solvent can not only improve the yield but also shorten the time of this reaction. Although the yield of the reaction in glycol is a little higher than that in water, considering environmental friendliness and avoidance of using toxic organic reagents, water was preferred as solvent for all further microwave-assisted reactions.

In order to optimize the reaction temperature, the reaction of **1c** (1 mmol), **2** (1 mmol) and **3** (1 mmol) was carried out using water (2 mL) as solvent under MWI (100 W) at temperatures ranging from 70 to 120 °C, with an increment of 10 °C each time. Similarly, the crude product was purified by recrystallization from EtOH. The results are shown in Table 2. The yield of product **4c** was increased and the reaction time was shortened when the temperature was increased from 70 °C to 100 °C (Entries 1–4, Table 2), whereas the yield leveled off when the temperature was further increased to 110 and 120 °C (Entries 5–6, Table 2). So, 100 °C is assigned as the most suitable reaction temperature. Furthermore, we found that the yield of this reaction was affected by the volume of water. The synthesis of **4c** was tested in different volumes of water at 100 °C. The outcomes show that 2.0 mL of water is optimal as solvent since it generates the highest yield of **4c**.

Table 2

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

Entry	T (°C)	Time (min)	Yield (%)
1	70	12	80
2	80	11	85
3	90	8	91
4	100	6	95
5	110	6	95
6	120	6	94

Under these optimized reaction conditions (2.0 mL of water, 100 °C), a series of furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine derivatives **4** were synthesized. The results are illustrated in Table 3. As shown in Table 3, this protocol can be applied not only to aromatic aldehydes with either electron-withdrawing groups (such as nitro or halide groups) or electron-donating groups (such as alkoxyl group), but also to heterocyclic and aliphatic aldehydes with excellent yields under the same conditions. Therefore, the electronic nature of the substrate has no significant effect on this reaction.

Moreover, we also performed the synthesis of **4** in water at 100 °C under standard heating conditions (SC). The results (Table 3) reveal that microwave irradiation efficiently promoted the reactions, resulting in dramatic reduction of reaction time, from hours to minutes, and remarkable increase in yields as well.

Although the detailed mechanism of the above reaction remains to be fully clarified, the formation of furo[3,4-*b*]-pyrazolo[4,3-*e*]pyridine derivatives **4** could be explained by a reaction sequence of condensation, addition, cyclization and dehydration (Scheme 2). First, the condensation of aldehyde **1** and tetronic acid **3** gave the

Table 3

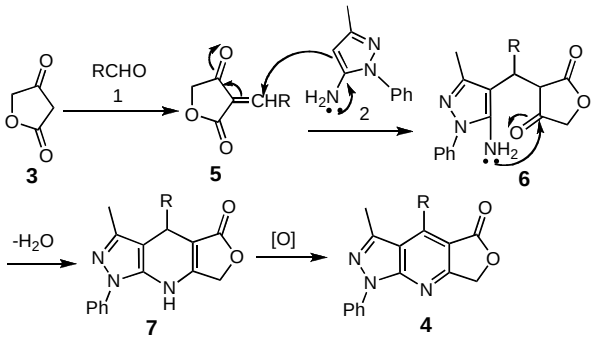
Synthesis of **4** in water at 100 °C under MWI and SC.

Entry	4	1	R	Time (min)		Yield (%)		Mp (°C)
				MWI[c]	SC[d]	MWI[c]	SC[d]	
1	**4a**	**1a**	4-ClC_6H_4	2	150	96	72	230–231
2	**4b**	**1b**	4-FC_6H_4	2	180	97	73	249–250
3	**4c**	**1c**	4-BrC_6H_4	1	180	95	68	222–223
4	**4d**	**1d**	C_6H_5	3	210	95	72	216–218
5	**4e**	**1e**	3-OCH_3-4-OHC_6H_3	2	180	95	74	269–270
6	**4f**	**1f**	2,3-$(CH_3O)_2C_6H_3$	2	180	96	69	243–244
7	**4g**	**1g**	3-$NO_2C_6H_4$	1	180	96	71	265–266
8	**4h**	**1h**	4-$NO_2C_6H_4$	2	210	98	70	297–298
9	**4i**	**1i**	4-$OCH_3C_6H_4$	3	180	94	75	202–204
10	**4j**	**1j**	2,4-$Cl_2C_6H_3$	1	120	97	77	236–238
11	**4k**	**1k**	3,4-$OCH_2OC_6H_3$	2	210	95	74	250–251
12	**4l**	**1l**	4-$N(CH_3)_2C_6H_4$	3	180	96	72	255–256
13	**4m**	**1m**	Thiophen-2-yl	4	240	97	72	258–260
14	**4n**	**1n**	$CH_3CH_2CH_2CH_2$	4	210	97	70	164–165

[c] The time and yields under microwave irradiation conditions. [d] The time and yields under standard heating conditions.

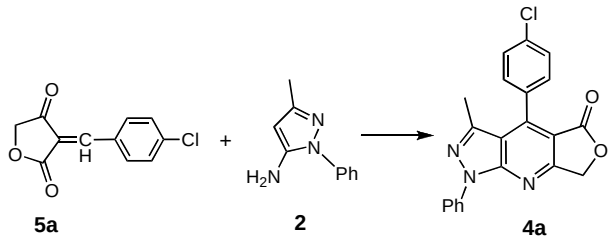
intermediate product **5**. The addition of **2** to **5** then furnished the intermediate product **6**, which upon intermolecular cyclization and dehydration gave rise to **4**.

Scheme 2



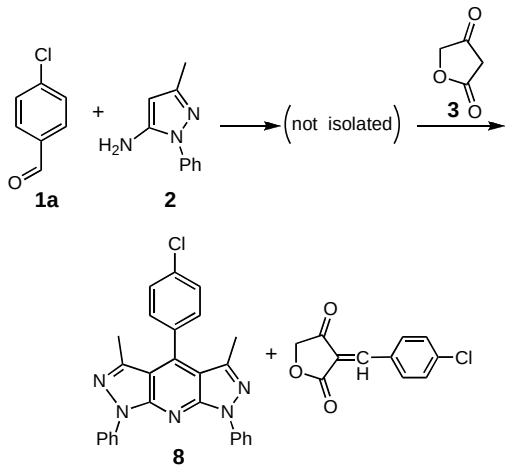
For the aim to support the proposed mechanism, the compound **5a** [16] was firstly prepared from *p*-chlorobenzaldehyde **1a** and tetronic acid **3**. Then **5a** reacted with **2** to afford product **4a** in a yield similar to that obtained in the one-pot reaction (Scheme 3).

Scheme 3



However, *p*-chlorobenzaldehyde **1a** was first condensed with **2** followed by reaction with tetronic acid **3** failed to give the target compound **4a**. Instead, compounds **8** {Mp 250~251°C (249~251°C) [17]} was obtained (Scheme 4).

Scheme 4



All the products were characterized by IR, ^{1}H NMR and elemental analyses. Moreover, the structure of **4a**, **4d**, **4i** and **4m** were also established by X-ray crystallography (Figure 2-5) [18].

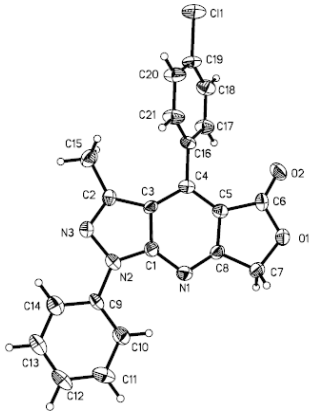


Figure 2. ORTEP diagram of **4a**.

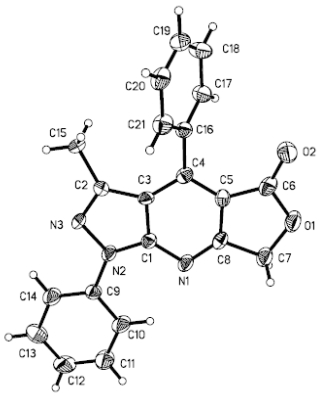


Figure 3. ORTEP diagram of **4d**

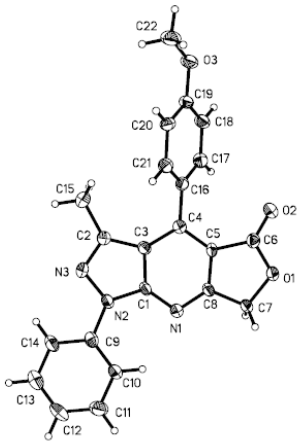


Figure 4. ORTEP diagram of **4i**.

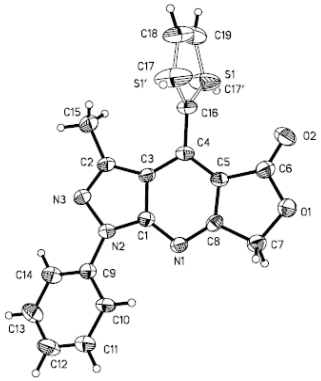


Figure 5. ORTEP diagram of **4m**.

In conclusion, we have developed a green and efficient method on the synthesis of furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine derivatives in water under MWI without catalyst. This method has the notable advantages over the existing ones owing to its features of environmental friendliness, short reaction time, high yield, wide applicability, low-cost and easy operation. On the other hand, this reaction supplies a good example of efficient microwave-assisted synthesis in water as solvent. In addition, this method may provide a shortcut for further investigations on the pharmacological activities of these types of compounds as important and novel podophyllotoxin analogues.

EXPERIMENTAL

Microwave irradiation was carried out in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in XT5 apparatus and are uncorrected. IR spectra were recorded on a FT-IR-Tensor 27 spectrometer. ^{1}H NMR spectra were measured on a DPX 400 spectrometer operating at 400 MHz, using DMSO-d_6 as solvent and TMS as internal standard. Elemental analysis was determined by using a Perkin-Elmer 240c elemental analysis instrument. X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer.

General Procedure for the syntheses of compounds 4 with microwave irradiation. Typically, in a 10 mL Emrys™ reaction vial, aldehyde **1** (1 mmol), 5-amino-3-methyl-1-phenylpyrazol **2** (1 mmol), tetronic acid **3** (1 mmol) and water (2 mL) were mixed and then capped. The mixture was irradiated at 150 W and at 100 °C for a given time. The reaction mixture was cooled to room temperature and poured into water (50 mL), filtered to give the crude product, which was further purified by recrystallization from EtOH.

General Procedure for the syntheses of compounds 4 with conventional heating. A mixture containing aldehyde **1** (1 mmol), 5-amino-3-methyl-1-phenylpyrazol **2** (1 mmol), tetronic acid **3** (1 mmol) and water (2.0 mL) was introduced into a 10 mL Emrys™ reaction vial, capped and then stirred at 100 °C (oil bath temperature) for a given time. The subsequent work-up procedure was the same as in the microwave irradiation reactions.

4-(4-Chlorophenyl)-3-methyl-1-phenyl-1,7-dihydro-5*H*-furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine-5-one (4a). This compound was obtained according to above general procedure; ir (KBr): ν 1761, 1582, 1506, 816cm^{-1}; ^{1}H nmr: δ 8.19 (d, 2H, *J*=8.0 Hz, ArH), 7.67 (d, 2H, *J*=8.0 Hz, ArH), 7.60-7.40 (m, 5H, ArH), 5.50 (s, 2H, CH_2), 2.13 (s, 3H, CH_3). Anal. calcd for $C_{21}H_{14}ClN_3O_2$: C, 67.12; H, 3.75; N, 11.18; found C, 67.33; H, 3.66; N, 11.38.

4-(4-Fluorophenyl)-3-methyl-1-phenyl-1,7-dihydro-5*H*-furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine-5-one (4b). This compound was obtained according to above general procedure; ir (KBr): ν 1756, 1597, 1578, 1512, 830 cm^{-1}; ^{1}H nmr: δ 8.19 (d, 2H, *J*=7.6 Hz, ArH), 7.66 (d, 2H, *J*=7.6 Hz, ArH), 7.58-7.39 (m, 5H, ArH), 5.49 (s, 2H, CH_2), 2.12 (s, 3H, CH_3). *Anal. calcd* for $C_{21}H_{14}FN_3O_2$: C, 70.19; H, 3.93; N, 11.69; found C, 70.02; H, 3.76; N, 11.85.

4-(4-Bromophenyl)-3-methyl-1-phenyl-1,7-dihydro-5*H*-furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine-5-one (4c). This compound was obtained according to above general procedure; ir (KBr): ν 1770, 1577, 1506, 818 cm^{-1}; ^{1}H nmr: δ 8.18 (d, 2H, *J*=8.0 Hz, ArH), 7.78 (d, 2H, *J*=8.0 Hz, ArH), 7.61 (dd, 2H, *J*=7.6, 8.4 Hz, ArH), 7.55 (d, 2H, *J*=8.4 Hz, ArH), 7.41 (t, 1H, *J*=7.6 Hz, ArH), 5.49 (s, 2H, CH_2), 2.12 (s, 3H, CH_3). *Anal. calcd* for $C_{21}H_{14}BrN_3O_2$: C, 60.02; H, 3.36; N, 10.00; found C, 60.21; H, 3.12; N, 10.13.

4-(4-Phenyl)-3-methyl-1-phenyl-1,7-dihydro-5*H*-furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine-5-one (4d). This compound was obtained according to above general procedure; ir (KBr): ν 1752, 1584, 1516, 765, 709 cm^{-1}; ^1H nmr: δ 8.19 (d, 2H, *J*=7.6 Hz, ArH), 7.63-7.41 (m, 8H, ArH), 5.48 (s, 2H, CH_2), 2.08 (s, 3H, CH_3). *Anal. calcd* for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31; found C, 74.04.; H, 4.56; N, 12.22.

4-(3-Methoxyl-4-hydroxylphenyl)-3-methyl-1-phenyl-1,7-dihydro-5*H*-furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine-5-one (4e). This compound was obtained according to above general procedure; ir (KBr): ν 3404, 1767, 1653, 1576, 1512, 821, 801, 703, 709 cm^{-1}; ^1H nmr: δ 9.55 (s, 1H, OH), 8.18 (d, 2H, *J*=7.6 Hz, ArH), 7.62-6.96 (m, 6H, ArH), 5.45 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3). *Anal. calcd* for $C_{22}H_{17}N_3O_4$: C, 68.21; H, 4.42; N, 10.85; found C, 68.08; H, 4.31; N, 110.73.

4-(2,3-Dimethoxyphenyl)-3-methyl-1-phenyl-1,7-dihydro-5*H*-furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine-5-one (4f). This compound was obtained according to above general procedure; ir (KBr): ν 1767, 1586, 1512, 817, 762, 699 cm^{-1}; ^1H nmr: δ 8.18 (d, 2H, *J*=8.0 Hz, ArH), 7.63-7.59 (m, 2H, ArH), 7.41 (t, 1H, *J*=8.0 Hz, ArH), 7.29-7.22 (m, 2H, ArH), 6.93-6.91(m, 1H, ArH), 5.59-5.47(m, 2H, CH_2), 3.92 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 2.07 (s, 3H, CH_3). *Anal. calcd* for $C_{23}H_{19}N_3O_4$: C, 68.82; H, 4.77; N, 10.47; found C, 68.96; H, 4.76; N, 10.61.

4-(3-Nitropheny)-3-methyl-1-phenyl-1,7-dihydro-5*H*-furo-[3,4-*b*]pyrazolo[4,3-*e*]pyridine-5-one (4g). This compound was obtained according to above general procedure; ir (KBr): ν 1773, 1589, 1535, 800, 702 cm^{-1}; ^1H nmr: δ 8.49 (s, 1H, ArH), 8.46 (t, 1H, *J*=7.6 Hz, ArH), 8.19 (d, 2H, *J*=7.6 Hz, ArH), 8.08 (d, 1H, *J*=8.0 Hz, ArH), 7.90 (t, 1H, *J*=8.0 Hz, ArH), 7.62 (t, 2H, *J*=8.0 Hz, ArH), 7.42 (t, 1H, *J*=8.0 Hz, ArH), 5.52 (s, 2H, CH_2), 2.12 (s, 3H, CH_3). *Anal. calcd* for $C_{21}H_{14}N_4O_4$: C, 65.28; H, 3.65; N, 14.50; found C, 65.44; H, 3.76; N, 14.42.

4-(4-Nitropheny)-3-methyl-1-phenyl-1,7-dihydro-5*H*-furo-[3,4-*b*]pyrazolo[4,3-*e*]pyridine-5-one (4h). This compound was obtained according to above general procedure; ir (KBr): ν 1764, 1580, 1517, 837 cm^{-1}; ^1H nmr: δ 8.44 (d, 2H, *J*=8.0 Hz, ArH), 8.20 (d, 2H, *J*=8.0 Hz, ArH), 7.90 (d, 2H, *J*=8.0 Hz, ArH), 7.62 (t, 2H, *J*=8.0 Hz, ArH), 7.42 (t, 1H, *J*=8.0 Hz, ArH), 5.54 (s, 2H, CH_2), 2.11 (s, 3H, CH_3). *Anal. calcd* for $C_{21}H_{14}N_4O_4$: C, 65.28; H, 3.65; N, 14.50; found C, 65.45; H, 3.77; N, 14.30.

4-(4-Methoxyphenyl)-3-methyl-1-phenyl-1,7-dihydro-5*H*-furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine-5-one (4i). This compound was obtained according to above general procedure; ir (KBr): ν 1766, 1608, 1580, 1509, 824 cm^{-1}; ^1H nmr: δ 8.20 (d, 2H, *J*=8.4 Hz, ArH), 7.61 (t, 2H, *J*=8.0 Hz, ArH), 7.53 (d, 2H, *J*=8.4 Hz, ArH), 7.40 (t, 1H, *J*=8.0 Hz, ArH), 7.13 (d, 2H, *J*=8.0 Hz, ArH), 5.47 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 2.16 (s, 3H, CH_3). *Anal. calcd* for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.61; N, 11.31; found C, 71.30; H, 4.46; N, 11.12.

4-(2,4-Dichlorophenyl)-3-methyl-1-phenyl-1,7-dihydro-5*H*-furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine-5-one (4j). This compound was obtained according to above general procedure; ir (KBr): ν 1772, 1578, 1512, 828, 760 cm^{-1}; ^1H nmr: δ 8.19 (d, 2H, *J*=8.4 Hz, ArH), 7.77 (s, 1H, ArH), 7.71-7.43 (m, 5H, ArH), 5.56 (s, 2H, CH_2), 2.11 (s, 3H, CH_3). *Anal. calcd* for $C_{21}H_{13}Cl_2N_3O_2$: C, 61.48; H, 3.19; N, 10.24; found C, 61.32; H, 3.03; N, 10.35.

4-(3,4-Methylenedioxyphenyl)-3-methyl-1-phenyl-1,7-dihydro-5*H*-furo[3,4-*b*]pyrazolo[4,3-*e*]pyrazolo[4,3-e]pyridine-5-one (4k). This compound was obtained according to above general procedure; ir (KBr): ν 1766, 1577, 1508, 842, 798, 756 cm^{-1}; ^1H nmr: δ 8.19 (d, 2H, *J*=7.6 Hz, ArH), 7.61 (t, 2H, *J*=7.6 Hz, ArH), 7.40 (t, 1H, *J*=7.6 Hz, ArH), 7.18 (s, 1H, ArH), 7.13-7.03 (m, 2H, ArH), 6.18 (s, 2H, CH_2), 5.47 (s, 2H, CH_2), 2.19 (s, 3H, CH_3). *Anal. calcd* for $C_{22}H_{15}N_3O_4$: C, 68.57; H, 3.92; N, 10.90; found C, 68.76; H, 3.78; N, 10.69.

4-[4-(Dimethylamino)phenyl]-3-methyl-1-phenyl-1,7-dihydro-5*H*-furo[3,4-*b*]pyrazolo[4,3-*e*]pyridin-5-one (4l). This compound was obtained according to above general procedure; ir (KBr): ν 1760, 1572, 1515, 813 cm^{-1}; ^1H nmr: δ 8.20 (d, 2H, *J*=8.0 Hz, ArH), 7.60 (d, 2H, *J*=8.0 Hz, ArH), 7.44-7.37 (m, 3H, ArH), 6.86 (d, 2H, *J*=8.8 Hz, ArH), 5.42 (s, 2H, CH_2), 3.05 (s, 6H, $2CH_3$), 2.23 (s, 3H, CH_3). *Anal. calcd* for $C_{23}H_{20}N_4O_2$: C, 71.86; H, 5.24; N, 14.57 found C, 71.99; H, 5.13; N, 14.34.

4-(2-Thienyl)-3-methyl-1-phenyl-1,7-dihydro-5*H*-furo[3,4-*b*]-pyrazolo[4,3-*e*]pyridin-5-one (4m). This compound was obtained according to above general procedure; ir (KBr): ν 1761, 1579, 1515, 794, 762, 716 cm^{-1}; ^1H nmr: δ 8.18 (d, 2H, *J*=8.4 Hz, ArH), 7.96 (d, 1H, *J*=8.4 Hz, ArH), 7.62 (t, 2H, *J*=8.0 Hz, ArH), 7.46-7.31 (m, 3H, ArH), 5.48 (s, 2H, CH_2), 2.23 (s, 3H, CH_3). *Anal. calcd* for $C_{19}H_{15}N_3O_2S$: C, 65.31; H, 4.33; N, 12.03 found C, 65.22; H, 4.20; N, 12.14.

4-Butyl-3-methyl-1-phenyl-1,7-dihydro-5*H*-furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine-5-one (4n). This compound was obtained according to above general procedure; ir (KBr): ν 1758, 1592, 1514, 764, 691 cm^{-1}; ^1H nmr: δ 7.68 (d, 2H, *J*=8.4 Hz, ArH), 7.61-7.57 (m, 2H, ArH), 7.41-7.38 (m, 1H, ArH), 5.43 (s, 2H, CH_2), 3.46 (t, 2H, *J*=8.0 Hz, CH_2), 2.79 (s, 3H, CH_3), 1.69-1.67(m, 2H, CH_2), 1.51-1.49 (m, 2H, CH_2), 0.97 (t, 3H, *J*=7.4 Hz, CH_3). *Anal. calcd* for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08; found C, 71.23; H, 5.75; N, 13.01.

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[18] The single-crystal growth was carried out in ethanol and DMF at room temperature. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer (graphite monochromator, MoKa radiation λ = 0.71073 Å). Crystal data for **4a**: Empirical formula $C_{21}H_{14}ClN_3O_2$, yellow, crystal dimension 0.47 x 0.36 x 0.05 mm, monoclinic, space group P2(1)/n, a = 8.599(16) Å, b = 21.95(4) Å, c = 9.900(18) Å, α = 90°, β = 109.38(3) °, γ = 90°, V = 1763(6) Å^3, Mr = 375.80, Z = 4, Dc = 1.416 Mg/m^3 , λ = 0.71073 Å, μ (MOKα) = 0.239 mm^{-1}, F(000) = 776, S = 0.998, R1 = 0.0743, wR2 = 0.1051. Crystal data for **4d**: Empirical formula $C_{21}H_{15}N_3O_2$, yellow, crystal dimension 0.42 x 0.21 x 0.10 mm, monoclinic, space group p2(1)/c, a = 7.067(4) Å, b = 22.439(12) Å, c = 10.871(6) Å, α = 90°, β = 104.909(9) °, γ = 90°, V = 1763(6) Å3, Mr = 341.36, Z = 4, Dc = 1.361 Mg/m^3 , λ = 0.71073 Å, μ (MOKα) = 0.090 mm^{-1}, F(000) = 712, S =1.003, R1 = 0.0687, wR2 = 0.1334. Crystal data for **4i**: Empirical formula $C_{22}H_{17}N_3O_3$, yellow, crystal dimension 0.27 x 0.15 x 0.09 mm, monoclinic, space group P2(1)/c, a = 11.480(4)Å, b = 20.913(7) Å, c = 7.524(3)Å, α = 90°, β = 99.862(6) °, γ = 90°, V = 1779.6(11) Å^3, Mr = 371.39, Z = 4, Dc = 1.386 Mg/m^3, λ = 0.71073 Å, μ (MOKα) = 0.094 mm^{-1}, F(000) = 776, S = 1.007, R1 = 0.0579, wR2 = 0.1109.Crystal data for **4m**: Empirical formula $C_{19}H_{13}N_3O_2S$, yellow, crystal dimension 0.46 x 0.44 x 0.16 mm, monoclinic, space group P2(1)/c, a = 10.878(5) Å, b = 7.356(3) Å, c = 20.498(9)Å, α = 90°, β = 97.448(9) °, γ = 90°, V = 1626.4(12) Å^3, Mr = 347.38, Z = 4, Dc = 1.419 Mg/m^3, λ = 0.71073 Å, μ (MOKα) = 0.217 mm^{-1}, F(000) = 720, S =1.004, R1 = 0.0582, wR2 = 0.0844.