Chemoselectivity of Multicomponent Condensations of Barbituric Acids, 5-Aminopyrazoles, and Aldehydes

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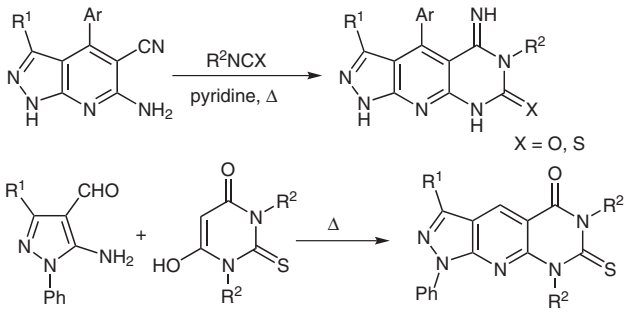
Abstract: Multicomponent cyclocondensations between 5-aminopyrazoles, barbituric acids, and aromatic aldehydes under conventional thermal heating, microwave irradiation, or ultrasonic irradiation were studied and the temperature regime was found to be the main factor in controlling their chemoselectivity. At high temperatures the starting materials react in two different ways yielding pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines or their dihydro analogues depending on the nature of the N-substituent in the 5-aminopyrazole. Treatment at room temperature results in a new four-component reaction giving previously undisclosed heterocyclic compounds, 4,6-diaryl-1,4,6,7-tetrahydro-2′*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]s. Facile multipurpose three-component selective procedures to new spiroheterocycles are proposed.

Key words: heterocycles, multicomponent reactions, selectivity, ultrasonication, microwave-assisted synthesis

The efficient synthesis of organic compounds by an 'ideal procedure'[1] is one of the most important objectives in modern synthetic chemistry for drug discovery and related fields. Organic reactions should preferably be facile and fast and the resulting products should be easily and rapidly purified. Multicomponent reactions[2] and the application of 'non-classical' conditions, like controlled microwave[3] and ultrasonic[4] irradiation, are powerful tools in modern chemistry for the optimization of reactions and the efficient preparation of new target compounds. The use of these methods and their combinations in high-throughput organic synthesis has become particularly popular within the last fifteen years and numerous examples of such condensations for the construction of heterocycles with interesting properties have been reported in the literature.[2–4]

The importance of azolopyrimidines in medicinal chemistry is widely known: many of these fused nitrogen heterocycles are known as cardiovascular vasodilators, calcium channel blocking agents, and potassium channel inhibitors and openers.[5] An interesting class of such heterocycles is the azolopyridopyrimidines, which possess antimycobacterial, fungicidal, anticancer, and antihistamic activities and they are effective as central analgetics and for the treatment of insomnia.[6] Some derivatives of pyrazolopyridines have been also found to be useful in agriculture[7] and for coloring wool, silk, and polyamides.[8]

A facile and widespread synthetic approach to azolopyridines and pyrimidines is the multicomponent cyclocondensation of aminoazoles with CH-acids and carbonyl compounds, which sometimes can lead to the formation of several different reaction products;[9] their selectivity may be efficiently tuned by application of microwave and ultrasonic irradiation.[9e,h,i] However, the multicomponent synthesis of pyrazolopyridopyrimidines involving barbituric acid as a building block has not been described in the literature and only unsuccessful attempts at similar condensations have been communicated.[10] The usual way to pyrazolopyridopyrimidines is by the modification of vicinal aminocarbonitriles or aminoamides of azolopyridines, obtained by three-component reaction of aminoazole, aldehyde, and malononitrile or cyanoacetamide (Scheme 1).[11] This method allows the synthesis of diverse types of the target heterocycles, but cannot be conducted as an efficient one-pot procedure. Another way includes reaction of 5-aminopyrazole-4-carbaldehydes with active methylene compounds, for example barbituric acids and cyclic 1,3-diketones, and leads to pyrazolopyridopyrimidines in high yields.[12] However, this route does not give the possibility of introducing substituents into the pyridine ring (Scheme 1).



Scheme 1

Four-component condensations involving two equivalents of barbituric acid and one equivalent of aldehyde and ammonia leading to the formation of dihydropyridine ring are also known.[13]

Therefore, in the present work the multicomponent reactions of 5-aminopyrazoles **1**, barbituric acids **2**, and aro-

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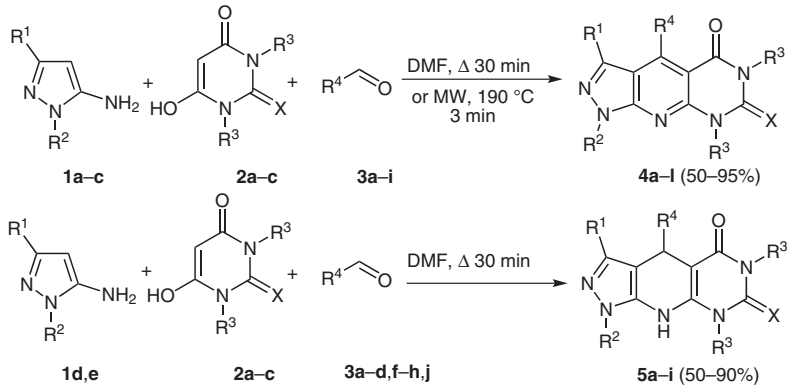


Scheme 2

matic aldehydes **3** were studied under conventional heating, microwave irradiation, or ultrasonic irradiation at various temperatures. It was established that the three-component reaction of 5-amino-3-methyl-1-phenyl-1*H*-pyrazole (**1a**) with barbituric acids **2a**,**b** and aldehydes **3a**–**h** in boiling *N*,*N*-dimethylformamide for 30 minutes gave heteroaromatized 4-arylpyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines **4a**–**l** (Scheme 2, Table 1). The work-up procedure was simple and consisted of the addition of ethanol to the reaction mixture, filtration, and drying on air at room temperature, which allowed the target heterocycles **4a**–**l** to be obtained in 50–95% yields with purity ~95% according to ^{1}H NMR.

From the other hand, it was unexpectedly found that refluxing of the equimolar mixture of N-unsubstituted 3-methyl- and 3-phenyl-5-aminopyrazoles **1d**,**e** with barbituric acids **2a**–**c** and aromatic aldehydes **3a**–**d**,**f**–**h**,**j** in *N*,*N*-dimethylformamide for 30 minutes after an identical work up procedure led to 4-aryl-4,9-dihydropyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines **5a**–**i** in 50–90% yields (Scheme 2, Table 1). It should be noted that in case of compound **5b** impurities of the corresponding heteroaromatized heterocycle (~5%) were also observed in the ^{1}H NMR spectrum.

As the possible reason for the different reaction products in the case of aminoazoles **1a** and **1d**,**e**, we considered the influence of the N-phenyl substituent which enlarges the electron-donor properties of the aminoazole moiety and this can result in easier oxidation of the pyridine ring. The multicomponent reactions involving barbituric acid **2a**, aldehyde **3g**, and 5-amino-3-methyl-1-(4-nitrophenyl)-1*H*-pyrazole (**1b**), containing a nitrophenyl electron-withdrawing substituent, however, also led to oxidized heterocycle **4j**. The reaction with participation of 5-amino-1,3-dimethyl-1*H*-pyrazole (**1c**), barbituric acids **2a**,**c**, and aldehydes **3e**,**i** gave the same result, compounds **4k** and **4l** were the sole isolated products after cooling and addition of ethanol to the reaction mixture.

Table 1 Synthesis of Pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines **4a**–**l**, **5a**–**i**

Entry	5-Aminopyrazole			Barbituric acid			Aldehyde		Product	Yield (%)
		R^1	R^2		R^3	X		R^4		
1	**1a**	Me	Ph	**2a**	H	O	**3a**	4-EtC_6H_4	**4a**	95[a]
2	**1a**	Me	Ph	**2a**	H	O	**3b**	4-$MeSC_6H_4$	**4b**	60[a]
3	**1a**	Me	Ph	**2a**	H	O	**3c**	4-$O_2NC_6H_4$	**4c**	95[a]
4	**1a**	Me	Ph	**2a**	H	O	**3d**	4-NCC_6H_4	**4d**	90[a]
5	**1a**	Me	Ph	**2a**	H	O	**3e**	4-$MeOC_6H_4$	**4e**	75[a]
6	**1a**	Me	Ph	**2a**	H	O	**3f**	2,4,5-$(MeO)_3C_6H_2$	**4f**	85[a]
7	**1a**	Me	Ph	**2b**	H	S	**3a**	4-EtC_6H_4	**4g**	65[a]
8	**1a**	Me	Ph	**2b**	H	S	**3g**	4-ClC_6H_4	**4h**	55[a]
9	**1a**	Me	Ph	**2b**	H	S	**3h**	3,4-$(HO)_2C_6H_3$	**4i**	50[a]
10	**1b**	Me	4-$O_2NC_6H_4$	**2a**	H	O	**3g**	4-ClC_6H_4	**4j**	55[a]
11	**1c**	Me	Me	**2a**	H	O	**3e**	4-$MeOC_6H_4$	**4k**	50[a]

Table 1 Synthesis of Pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines **4a–l**, **5a–i** (continued)

Entry	5-Aminopyrazole			Barbituric acid			Aldehyde		Product	Yield (%)
		R^1	R^2		R^3	X		R^4		
12	**1c**	Me	Me	**2c**	Me	O	**3i**	4-MeC_6H_4	**4l**	50[a]
13	**1d**	Me	H	**2a**	H	O	**3a**	4-EtC_6H_4	**5a**	85
14	**1d**	Me	H	**2c**	Me	O	**3b**	4-$MeSC_6H_4$	**5b**	50
15	**1d**	Me	H	**2a**	H	O	**3c**	4-$O_2NC_6H_4$	**5c**	75
16	**1d**	Me	H	**2a**	H	O	**3d**	4-NCC_6H_4	**5d**	85
17	**1d**	Me	H	**2a**	H	O	**3f**	2,4,5-$(MeO)_3C_6H_2$	**5e**	70
18	**1d**	Me	H	**2a**	H	O	**3h**	3,4-$(HO)_2C_6H_3$	**5f**	55
19	**1d**	Me	H	**2a**	H	O	**3j**	2-HO-3-$EtOC_6H_3$	**5g**	90
20	**1e**	Ph	H	**2a**	H	O	**3g**	4-ClC_6H_4	**5h**	75
21	**1e**	Ph	H	**2b**	H	S	**3g**	4-ClC_6H_4	**5i**	55

[a] Under MW irradiation.

Application of controlled microwave irradiation (temperatures from 150 to 190 °C) to carry out multicomponent reaction involving N-unsubstituted pyrazoles **1d**,**e** did not give positive results, as it was expected, and led to complicated mixtures of several inseparable products. However, using the microwave field to promote the reaction of 5-aminopyrazoles **1a–c** with barbituric acids and aldehydes was successful. It was established that three-component reactions of aromatic aldehydes **3a–i** and barbituric acids **2a–c** with aminopyrazoles **1a–c** can be efficiently carried out under microwave irradiation in ethanol instead of *N*,*N*-dimethylformamide at 170 °C for five minutes. The most preferable microwave-assisted procedure for the synthesis of pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines **4**, from the viewpoint of yields and purity of the target compounds. consisted of the treatment of the starting building blocks in *N*,*N*-dimethylformamide under microwave irradiation at 190 °C for three minutes.

Surprisingly, it was observed that the multicomponent reaction involving 4-(methylsulfanyl)benzaldehyde (**3b**), 5-amino-3-methyl-1-phenyl-1*H*-pyrazole (**1a**), and barbituric acid **2a** in boiling *N*,*N*-dimethylformamide sometimes passed in an unusual manner yielding, according to ^1H NMR and mass spectra, hitherto undisclosed 3-methyl-4,6-bis[4-(methylsulfanyl)phenyl]-1-phenyl-1,4,6,7-tetrahydro-2′*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]-2′,4′,6′(1′*H*,3′*H*)-trione (**6a**).

Taking into account our previous results in tuning the chemoselectivity of multicomponent reactions with participation of similar starting compounds by application of high-temperature microwave-assisted and low-temperature ultrasonic-promoted procedures[9e,h,i] we tried to carry out this four-component cyclocondensation under sonication at room temperature. It was found that treatment of two equivalent of aromatic aldehyde **3b**,**e**,**g** with one equivalent of barbituric acid **2a–c** and aminopyrazoles **1a**,**d** in *N*,*N*-dimethylformamide in ultrasonic bath for three hours yielded spiro compounds **6a–f** in 63–98% yields (Method A, Scheme 3, Table 2).

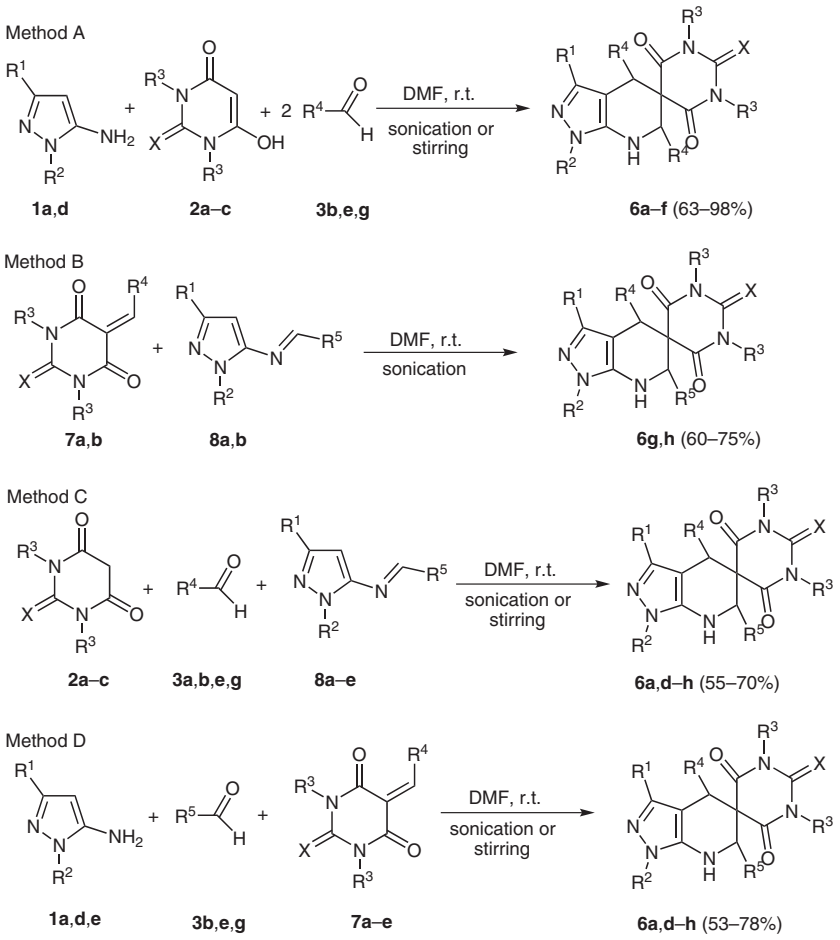
It was additionally established that simple intensive stirring of the same starting compounds in *N*,*N*-dimethylformamide at room temperature with magnetic stirring for 2–3 hours also allowed the target spiroheterocycles **6a–f** to be obtained in lower yields. It is interesting that a recent report[9h] found that multicomponent condensations of 5-aminopyrazoles with cyclic 1,3-diketones and aldehydes under ultrasonic irradiation at room temperature yielded Biginelli-type dihydropyrimidines, which were not observed in our case. On the other hand, the formation of similar spiro compounds was described for the four-component treatment of barbituric acid, urea, and aldehydes.[14]

A main disadvantage of the new four-component reaction is the impossibility of introducing two different substituents R^4 in positions 4 and 6. To avoid this limitation we developed a two-component procedure consisted of the reaction of arylidenebarbituric acids **7a**,**b** and azomethines **8a**,**b**; treatment of these compounds in *N*,*N*-dimethylformamide under sonication for three hours yielded spiroheterocycles **6g**,**h** (Method B, Scheme 3, Table 2).

However, this method requires the preliminary synthesis of two starting compounds (**6** and **7**) and this makes the procedure less efficient and facile. Taking into account such inconveniences, two additional three-component synthetic pathways to target compounds **6** were elaborated.

Heterocycles **6a**,**d–h** were obtained by treatment of azomethines **8a–e** with barbituric acids **2a–c** and corresponding aromatic aldehydes **3a**,**b**,**g**,**e** at room temperature under sonication or simple stirring of the reaction mixture for three hours in 55–70% yields (Method C, Scheme 3, Table 2). The most convenient and effective

procedure for the synthesis spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]s **6** consists of the three-component reaction of arylidenebarbituric acids **7a–e**, 5-aminopyrazoles **1a**,**d**,**e**, and aldehydes **3b**,**e**,**g** under ultrasonic irradiation or with magnetic stirring at ambient conditions (Method D, Scheme 3, Table 2).



Scheme 3

Table 2 Synthesis of Spiropyrazolo[3,4-*b*]pyridine-5,5′-pyrimidines **6a–h**

Entry	Substrates	Method	Substituents						Product	
			R^1	R^2	R^3	R^4	R^5	X		Yield[a] (%)
1	**1a** + **2a** + **3b** (2 equiv)	A	Me	Ph	H	4-$MeSC_6H_4$	–	O	**6a**	95
2	**1a** + **2a** + **3e** (2 equiv)	A	Me	Ph	H	4-$MeOC_6H_4$	–	O	**6b**	98
3	**1a** + **2a** + **3g** (2 equiv)	A	Me	Ph	H	4-ClC_6H_4	–	O	**6c**	80
4	**1a** + **2b** + **3g** (2 equiv)	A	Me	Ph	H	4-ClC_6H_4	–	S	**6d**	82
5	**1d** + **2c** + **3e** (2 equiv)	A	Me	H	Me	4-$MeOC_6H_4$	–	O	**6e**	80
6	**1e** + **2c** + **3b** (2 equiv)	A	Ph	H	Me	4-$MeOC_6H_4$	–	O	**6f**	63
7	**7a** + **8a**	B	Me	H	H	4-EtC_6H_4	4-$MeOC_6H_4$	O	**6g**	75
8	**7b** + **9b**	B	Me	Ph	Me	4-$MeSC_6H_4$	4-$MeOC_6H_4$	O	**6h**	60
9	**2a** + **3b** + **8c**	C	Me	Ph	H	4-$MeSC_6H_4$	4-$MeSC_6H_4$	O	**6a**	70
10	**2b** + **3g** + **8d**	C	Me	Ph	H	4-ClC_6H_4	4-ClC_6H_4	S	**6d**	70
11	**2c** + **3e** + **8a**	C	Me	H	Me	4-$MeOC_6H_4$	4-$MeOC_6H_4$	O	**6e**	55

Table 2 Synthesis of Spiropyrazolo[3,4-*b*]pyridine-5,5′-pyrimidines **6a–h** (continued)

Entry	Substrates	Method	Substituents						Product	
			R^1	R^2	R^3	R^4	R^5	X		Yield[a] (%)
12	**2c** + **3b** + **8e**	C	Ph	H	Me	4-$MeOC_6H_4$	4-$MeOC_6H_4$	O	**6f**	55
13	**2a** + **3a** + **8a**	C	Me	H	H	4-EtC_6H_4	4-$MeOC_6H_4$	O	**6g**	65
14	**2c** + **3b** + **8b**	C	Me	Ph	Me	4-$MeSC_6H_4$	4-$MeOC_6H_4$	O	**6h**	55
15	**1a** + **3b** + **7c**	D	Me	Ph	H	4-$MeSC_6H_4$	4-$MeSC_6H_4$	O	**6a**	75
16	**1a** + **3g** + **7d**	D	Me	Ph	H	4-ClC_6H_4	4-ClC_6H_4	S	**6d**	78
17	**1d** + **3e** + **7e**	D	Me	H	Me	4-$MeOC_6H_4$	4-$MeOC_6H_4$	O	**6e**	53
18	**1e** + **3b** + **7e**	D	Ph	H	Me	4-$MeOC_6H_4$	4-$MeOC_6H_4$	O	**6f**	54
19	**1d** + **3e** + **7a**	D	Me	H	H	4-EtC_6H_4	4-$MeOC_6H_4$	O	**6g**	65
20	**1a** + **3e** + **7b**	D	Me	Ph	Me	4-$MeSC_6H_4$	4-$MeOC_6H_4$	O	**6h**	55

[a] Under sonication.

It should be noted that in Methods B and C if the reaction mixture is refluxed, instead of ultrasonication or stirring at room temperature, this leads to decomposition of azomethines **8** and formation of two isomeric products with reverse location of the R^4 and R^5 substituents (see result of X-ray analysis for compound **6h**).

In addition, it was established that compounds **6a–h** under both refluxing in boiling *N*,*N*-dimethylformamide and microwave irradiation at 150–180 °C could not be rearranged into pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines **4** or **5** and only numerous products of decomposition were found after the above-mentioned treatments.

The structures of heterocycles of type **4**, **5**, and **6** were established by elemental analyses in combination with MS and NMR spectroscopic data and X-ray diffraction analysis. The ^{1}H NMR spectra of pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines **4a–l** are very simple and exhibit the signals of pyrimidine NH and terminal functional groups as well as of aryl rings. However, even together with information obtained from MS and ^{13}C NMR spectra these data did not give structure proof of the compounds synthesized. Finally X-ray diffraction analysis carried out for heterocycle **4a** showed that it has a structure of 4-(4-ethylphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (Figure 1).

^{1}H NMR spectra of heterocyclic compounds **5a–i** together with signals of functional groups and aromatic rings contain two additional singlets at ca. δ = 5 and 11–12 assigned to methylene and amino groups of dihydropyridine moiety, respectively.

MS spectra and elemental analysis of compounds **6a–h** showed that these heterocycles contain fragments of two molecules of aromatic aldehyde, one pyrimidine and one pyrazole ring. ^{1}H NMR spectra exhibit the following signals: singlets of methylene protons and amino group of tetrahydropyridine ring at δ = ~4.8, 4.9, and 6.0–6.5, respectively, pyrimidine NH singlets at δ = 10–12 (for compounds **6a–d**,**g**), multiplets of aromatic rings, and necessary signals of other functional groups. ^{13}C NMR spectra of other signals contain a signal for the spiro-carbon at δ = ca. 65. All this data allowed us to suggest the spiroheterocyclic structure for compounds **6a–h**. Finally, this structure was proved by X-ray diffraction data obtained for crystal of **6h** obtained in boiling *N*,*N*-dimethylformamide (Figure 2).

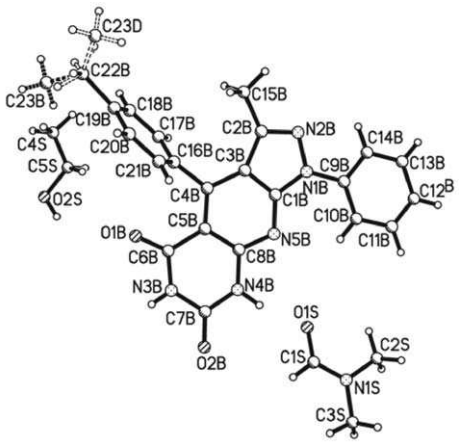


Figure 1 Structure of compound **4a** (X-ray diffraction data)

In summary, the article describes the development of chemoselective cyclocondensations based on multicomponent treatment between 5-aminopyrazoles, barbituric acids, and aromatic aldehydes. It was established that temperature was the main factor in controlling the direction of the reaction studied. Under reflux or microwave irradiation at high temperatures (170–190 °C) the starting materials react in two different ways, in the case of N-substituted aminopyrazoles the reaction yields pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines or their dihydro analogues when the N-substituent is absent. Sonication of the same reaction mixture or simple stirring at room tem-

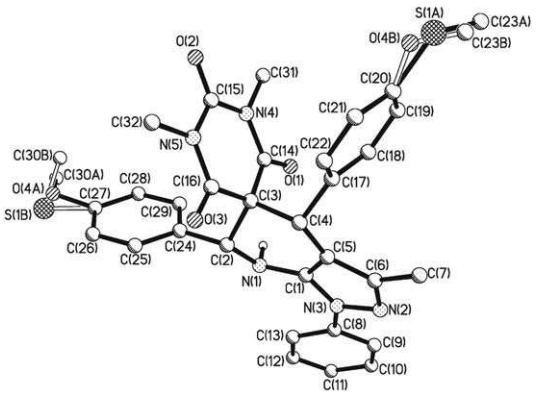


Figure 2 Structure of compound **6h** (X-ray diffraction data)

perature leads to a new four-component reaction yielding previously undisclosed heterocyclic compounds, 4,6-diaryl-1,4,6,7-tetrahydro-2′*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]s.

Melting points were obtained on a standard melting point apparatus in open capillary tubes. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 400 and 200 MHz (100 and 50 MHz for ^{13}C) on Jeol Lambda 400 and Varian Mercury VX-200 spectrometers. LR-MS were measured on a GC-MS Varian 1200L (ionizing voltage 70 eV). Elemental analysis was made on a EuroVector EA-3000. TLC analyses were performed on pre-coated (silica gel 60 HF_{254}) plates.

Sonication was carried out with help of standard ultrasonic bath producing irradiation at 44.2 kHz in round-bottom flasks equipped with a condenser.

Microwave experiments were performed using the Emrys™ Creator EXP and Emrys™ Initiator reactors from Biotage AB (Uppsala, Sweden) possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz. Experiments were carried out in sealed microwave process vials using high absorbance level settings and IR temperature monitoring. Reaction times reflect irradiation times at the set reaction temperature (fixed hold times).

All solvents and chemicals were obtained from standard commercial vendors and were used without any further purification.

The synthesis of the starting 5-aminopyrazoles **1a**–**e** were carried out by the described procedures.[15] Arylidenebarbituric acids **7a**–**e** and Schiff bases **8a**–**e** obtained according known methods.[16,17]

X-ray Diffraction Analysis of Compounds 4a *and* 6h

The colorless crystals of **4a** 2 ($C_{23}H_{19}N_5O_2$)·C_3H_7NO·C_6H_6O) are triclinic. At –173 K, a = 11.522(6), b = 13.364(8), c = 16.369(4) Å, a = 79.58(4)°, b = 84.30(4)°, g = 63.27(6)°, V = 2214(2) Å^3, Mr = 914.03, Z = 2, space group P$\bar{1}$, d_{calc} = 1.371 g/m^3, μ (MoKα) = 0.093 mm^{-1}, F(000) = 964. Intensities of 13853 reflections (7323 independent, R_{int} = 0.037) were measured on the 'Xcalibur-3' diffractometer (graphite monochromated MoKα radiation, CCD detector, ω-scanning, $2\Theta_{max}$ = 50°).

The colorless crystals of **6h** ($C_{32}H_{31}N_5O_4S$) are triclinic. At 293 K, a = 8.180(1), b = 10.823(2), c = 17.503(3) Å, a = 107.23(1)°, b = 94.75(1)°, g = 96.92(1)°, V = 1457.7(4) Å^3, Mr = 581.68, Z = 2, space group P$\bar{1}$, d_{calc} = 1.325 g/m^3, μ (MoKα) = 0.157 mm^{-1}, F(000) = 612. Intensities of 9458 reflections (4877 independent, R_{int} = 0.032) were measured on the 'Xcalibur-3' diffractometer (graphite monochromated MoKα radiation, CCD detector, ω-scanning, $2\Theta_{max}$ = 50°).

The structures were solved by direct method using SHELXTL package.[18] The restrains for the bond lengths (Csp^3–Csp^3 1.54 Å, C_{Ar}–O 1.37 Å, Csp^3–O 1.42 Å, C_{Ar}–S 1.77 Å, Csp^3–S 1.79 Å) in the disordered fragments were applied in the refinement of the structures. Positions of the hydrogen atoms were located from electron density difference maps and refined by 'riding' model with U_{iso} = nU_{eq} of the carrier atom (n = 1.5 for methyl group and n = 1.2 for other hydrogen atoms). The hydrogen atom of the structure **6h** participating in the formation of the hydrogen bond was refined in isotropic approximation.

Full-matrix least-squares refinement of the structures against $F2$ in anisotropic approximation for non-hydrogen atoms using 7155 (**4a**), 4824 (**6h**) reflections was converged to: wR_2 = 0.081 (R_1 = 0.042 for 2690 reflections with $F > 4\sigma(F)$, S = 0.708) for structure **4a** and wR_2 = 0.194 (R_1 = 0.066 for 2842 reflections with $F > 4\sigma(F)$, S = 0.926) for structure **6h**.[19]

4-Aryl-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines 4a–l; General Procedure

A mixture of 5-aminopyrazole **1a**–**c** (1.30 mmol, 1 equiv), barbituric acid **2a**–**c** (1.30 mmol, 1 equiv), and aromatic aldehyde **3a**–**i** (1.3 mmol, 1 equiv) in DMF (2 mL), contained in a round-bottom flask equipped with condenser, was refluxed for 30 min. The mixture was cooled and EtOH (20 mL) was added. The mixture was allowed to stand and then filtered to give a solid product that was washed with EtOH and dried on air at r.t.

4-Aryl-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines 4a–l; General Procedure for Microwave-Assisted Reactions

A mixture of 5-aminopyrazole **1a**–**c** (1.30 mmol, 1 equiv), barbituric acid **2a**–**c** (1.30 mmol, 1 equiv), and aromatic aldehyde **3a**–**i** (1.3 mmol, 1 equiv) in DMF (2 mL), contained in a sealed microwave vial, was heated in a single mode microwave reactor at 190 °C for 3 min with magnetic stirring. The mixture was cooled to r.t. by compressed air and EtOH (20 mL) was added. The mixture was allowed to stand and then filtered to give a solid product which was washed with EtOH and dried on air at r.t.

The reaction was also carried out in EtOH (2 mL) at 150 °C for 5 min. In this case the precipitate formed was filtered after cooling of the mixture without addition of any other solvent.

4-(4-Ethylphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4a)

Colorless solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.25 (t, J = 7.5 Hz, 3 H, CH_3), 1.70 (s, 3 H, CH_3), 2.69 (q, J = 7.5 Hz, 2 H, CH_3), 7.17–8.24 (m, 9 H_{arom}), 11.28 (s, 2 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.8, 153.2, 151.4, 150.7, 150.3, 145.5, 143.7, 139.1, 133.7, 129.5, 128.0, 127.3, 126.3, 120.7, 114.2, 104.2, 28.5, 16.0, 14.4.

MS (EI, 70 eV): m/z (%) = 397 (100) [M$^+$], 398 (29.5), 396 (26.8).

Anal. Calcd for $C_{23}H_{19}N_5O_2$: C, 69.51; H, 4.82; N, 17.62. Found: C, 69.48; H, 4.78; N, 17.60.

3-Methyl-4-[4-(methylsulfanyl)phenyl]-1-phenyl-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4b)

Colorless solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.80 (s, 3 H, CH_3), 2.54 (s, 3 H, SCH_3), 6.24–8.25 (m, 9 H_{arom}), 11.16 (s, 1 H, NH), 11.76 (s, 1 H, NH).

MS (EI, 70 eV): m/z (%) = 415 (100) [M$^+$], 416 (38.5), 417 (13.3).

Anal. Calcd for $C_{22}H_{17}N_5O_2S$: C, 63.60; H, 4.12; N, 16.86. Found: C, 63.63; H, 4.09; N, 16.84.

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 (4c)
Yellow solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.74 (s, 3 H, CH_3), 7.29–8.35 (m, 9 H_{arom}), 11.27 (s, 1 H, NH), 11.86 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.8, 152.8, 150.3, 150.0, 147.5, 147.3, 144.7, 138.5, 137.8, 134.5, 129.4, 129.2, 126.1, 123.0, 122.8, 120.4, 113.4, 103.9, 14.2.

MS (EI, 70 eV): *m*/*z* (%) = 414 (100) [M$^+$], 415 (23.5).

Anal. Calcd for $C_{21}H_{14}N_6O_4$: C, 60.87; H, 3.41; N, 20.28. Found: C, 60.91; H, 3.45; N, 20.30.

4-(4-Cyanophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4d)
Colorless solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.71 (s, 3 H, CH_3), 7.28–8.23 (m, 9 H_{arom}), 11.24 (s, 1 H, NH), 11.83 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.3, 152.5, 150.0, 149.8, 148.2, 144.4, 141.2, 138.4, 131.3, 129.0, 128.7, 125.8, 120.3, 118.6, 112.8, 110.7, 103.4, 39.5, 13.7.

MS (EI, 70 eV): *m*/*z* (%) = 394 (100) [M$^+$], 395 (25.9), 393 (24.1).

Anal. Calcd for $C_{22}H_{14}N_6O_2$: C, 67.00; H, 3.58; N, 21.31. Found: C, 66.98; H, 3.61; N, 21.29.

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)
Colorless solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.76 (s, 3 H, CH_3), 3.82 (s, 3 H, OCH_3), 6.98–8.24 (m, 9 H_{arom}), 11.11 (s, 1 H, NH), 11.70 (s, 1 H, NH).

MS (EI, 70 eV): *m*/*z* (%) = 399 (100) [M$^+$], 398 (40.6), 400 (16.6).

Anal. Calcd for $C_{22}H_{17}N_5O_3$: C, 66.16; H, 4.29; N, 17.53. Found: C, 66.13; H, 4.33; N, 17.51.

3-Methyl-1-phenyl-4-(2,4,5-trimethoxyphenyl)-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4f)
Yellow solid; mp 276–277 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.87 (s, 3 H, CH_3), 3.64 (s, 6 H, 2 OCH_3), 3.87 (s, 3 H, OCH_3), 6.78–8.24 (m, 7 H_{arom}), 11.10 (s, 1 H, NH), 11.63 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.4, 153.0, 150.3, 150.1, 149.8, 148.2, 145.4, 142.5, 138.7, 129.3, 126.0, 120.5, 115.6, 114.2, 113.5, 104.6, 97.9, 56.4, 56.2, 55.8, 13.5.

MS (EI, 70 eV): *m*/*z* (%) = 459 (100) [M$^+$], 428 (47.8), 460 (26.2), 444 (18.5).

Anal. Calcd for $C_{24}H_{21}N_5O_5$: C, 62.74; H, 4.61; N, 15.24. Found: C, 62.77; H, 4.60; N, 15.22.

4-(4-Ethylphenyl)-3-methyl-1-phenyl-7-thioxo-1,6,7,8-tetrahydro-5*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidin-5-one (4g)
Colorless solid; mp 281–282 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.25 (t, *J* = 7.8 Hz, 3 H, CH_3), 1.74 (s, 3 H, CH_3), 2.7 (q, *J* = 7.8 Hz, 2 H, CH_3), 7.19–8.30 (m, 9 H_{arom}), 12.27 (s, 1 H, NH), 13.10 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.2, 159.2, 151.9, 151.3, 150.1, 145.6, 144.0, 139.0, 133.2, 129.5, 128.1, 127.3, 126.2, 120.4, 115.0, 105.9, 28.5, 15.9, 14.4.

MS (EI, 70 eV): *m*/*z* (%) = 413 (100) [M$^+$], 414 (30.9), 412 (25.1), 384 (17.8).

Anal. Calcd for $C_{23}H_{19}N_5OS$: C, 66.81; H, 4.63; N, 16.94. Found: C, 66.85; H, 4.60; N, 16.96.

4-(4-Chlorophenyl)-3-methyl-1-phenyl-7-thioxo-1,6,7,8-tetrahydro-5*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidin-5-one (4h)
Yellow solid; mp 297–298 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.82 (s, 3 H, CH_3), 7.32–8.34 (m, 9 H_{arom}), 12.35 (s, 1 H, NH), 13.2 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.9, 159.1, 151.5, 149.7, 149.2, 145.1, 138.6, 134.5, 133.0, 129.7, 129.2, 127.7, 126.0, 120.1, 114.3, 105.6, 14.1.

MS (EI, 70 eV): *m*/*z* (%) = 419 (100) [M$^+$], 420 (32.2), 421 (23.9).

Anal. Calcd for $C_{21}H_{14}ClN_5OS$: C, 60.07; H, 3.36; N, 16.68. Found: C, 60.04; H, 3.32; N, 16.66.

4-(3,4-Dihydroxyphenyl)-3-methyl-1-phenyl-7-thioxo-1,6,7,8-tetrahydro-5*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidin-5-one (4i)
Yellow solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.85 (s, 3 H, CH_3), 6.50–8.25 (m, 8 H_{arom}), 9.03 (s, 1 H, OH), 9.10 (s, 1 H, OH), 11.10 (s, 1 H, NH), 11.70 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.7, 161.5, 153.0, 151.7, 150.5, 150.3, 150.0, 145.4, 144.7, 138.8, 129.3, 126.8, 120.4, 119.0, 115.6, 115.0, 114.1, 104.0, 89.1, 80.3, 14.0.

MS (EI, 70 eV): *m*/*z* (%) = 417 (100) [M$^+$], 416 (26.8), 415 (18.9).

Anal. Calcd for $C_{21}H_{15}N_5O_3S$: C, 60.42; H, 3.62; N, 16.78. Found: C, 60.45; H, 3.60; N, 16.77.

4-(4-Chlorophenyl)-3-methyl-1-(4-nitrophenyl)-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4j)
Yellow solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.71 (s, 3 H, CH_3), 7.3–8.55 (m, 8 H_{arom}), 11.26 (s, 1 H, NH), 11.88 (s, 1 H, NH).

MS (EI, 70 eV): *m*/*z* (%) = 448 (100) [M$^+$], 450 (38.6), 449 (32.8).

Anal. Calcd for $C_{21}H_{13}ClN_6O_4$: C, 56.20; H, 2.92; N, 18.72. Found: C, 56.18; H, 2.89; N, 18.71.

4-(4-Methoxyphenyl)-1,3-dimethyl-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4k)
Yellow solid; mp 288–289 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.70 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 3.86 (s, 3 H, NCH_3), 6.95–7.19 (m, 4 H_{arom}), 11.02 (s, 1 H, 1 NH), 11.60 (s, 1 H, 1 NH).

MS (EI, 70 eV): *m*/*z* (%) = 337 (100) [M$^+$], 336 (50.6), 338 (13.2).

Anal. Calcd for $C_{17}H_{15}N_5O_3$: C, 60.53; H, 4.48; N, 20.76. Found: C, 60.51; H, 4.47; N, 20.74.

1,3,6,8-Tetramethyl-4-(4-methylphenyl)-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (4l)
Yellow solid; mp 221–223 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.68 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 3.14 (s, 3 H, CH_3), 3.66 (s, 3 H, CH_3), 3.94 (s, 3 H, CH_3), 7.09–7.27 (m, 4 H_{arom}).

MS (EI, 70 eV): *m*/*z* (%) = 349 (100) [M$^+$], 348 (60.9), 350 (23.8).

Anal. Calcd for $C_{19}H_{19}N_5O_2$: C, 65.32; H, 5.48; N, 20.04. Found: C, 65.29; H, 5.51; N, 20.05.

4-Aryl-4,9-dihydro-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidines 5a–i; General Procedure

A mixture of 5-aminopyrazole **1d**,**e** (1.30 mmol, 1 equiv), barbituric acid **2a**–**c** (1.30 mmol, 1 equiv), and aromatic aldehyde **3a**–**d**,**f**–**h**,**j** (1.3 mmol, 1 equiv) in DMF (2 mL), contained in a round-bottom flask equipped with condenser, was refluxed for 30 min. The mixture was cooled and EtOH (20 mL) was added. The mixture was allowed to stand and then filtered to give the solid product, which was washed with EtOH and dried on air at r.t.

4-(4-Ethylphenyl)-3-methyl-4,9-dihydro-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (5a)

Colorless solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.1 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.88 (s, 3 H, CH_3), 2.5 (q, *J* = 7.5 Hz, 2 H, CH_2), 4.82 (s, 1 H, 4-CH), 6.98–7.07 (m, 4 H_{arom}), 8.71 (s, 1 H, NH), 9.94 (s, 1 H, NH), 10.44 (s, 1 H, 9-NH), 11.80 (s, 1 H, 1-NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.4, 150.5, 147.3, 145.1, 141.3, 127.6, 103.0, 87.3, 34.7, 28.2, 16.0, 10.0.

MS (EI, 70 eV): *m*/*z* (%) = 323 (23.4) [M$^+$], 218 (100), 175 (26.6).

Anal. Calcd for $C_{17}H_{17}N_5O_2$: C, 63.15; H, 5.30; N, 21.66. Found: C, 63.17; H, 5.27; N, 21.63.

3,6,8-Trimethyl-4-[4-(methylsulfanyl) phenyl]-4,9-dihydro-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (5b)

Colorless solid; mp 195–196 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.90 (s, 3 H, CH_3), 2.38 (s, 3 H, SCH_3), 3.04 (s, 3 H, NCH_3), 3.44 (s, 3 H, NCH_3), 4.94 (s, 1 H, 4-CH), 7.03–7.14 (m, 4 H_{arom}), 9.8 (s, 1 H, 9-NH), 11.92 (s, 1 H, 1-NH).

MS (EI, 70 eV): *m*/*z* (%) = 369 (15.9) [M$^+$], 246 (100), 247 (15.3), 137 (15.20).

Anal. Calcd for $C_{18}H_{19}N_5O_2S$: C, 58.52; H, 5.18; N, 18.96. Found: C, 58.55; H, 5.20; N, 18.93.

3-Methyl-4-(4-nitrophenyl)-4,9-dihydro-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (5c)

Yellow solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.86 (s, 3 H, CH_3), 5.05 (s, 1 H, 4-CH), 7.4–8.1 (m, 4 H_{arom}), 8.92 (s, 1 H, NH), 10.08 (s, 1 H, NH), 10.55 (s, 1 H, 9-NH), 11.92 (s, 1 H, 1-NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.4, 155.2, 150.4, 147.6, 146.1, 145.6, 136.4, 129.1, 123.7, 101.5, 86.2, 35.5, 9.9.

MS (EI, 70 eV): *m*/*z* (%) = 340 (22.6) [M$^+$], 218 (100), 175 (38.7), 338 (51.1).

Anal. Calcd for $C_{15}H_{12}N_6O_4$: C, 52.94; H, 3.55; N, 24.70. Found: C, 52.91; H, 3.52; N, 24.69.

4-(4-Cyanophenyl)-3-methyl-4,9-dihydro-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (5d)

Colorless solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.85 (s, 3 H, CH_3), 4.98 (s, 1 H, 4-CH), 7.33–7.68 (m, 4 H_{arom}), 8.87 (s, 1 H, NH), 10.04 (s, 1 H, NH), 10.53 (s, 1 H, 9-NH), 11.90 (s, 1 H, 1-NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.4, 153.2, 150.5, 147.8, 145.7, 136.3, 132.4, 128.9, 119.5, 109.0, 101.7, 86.3, 35.6, 9.9.

MS (EI, 70 eV): *m*/*z* (%) = 320 (16.5) [M$^+$], 218 (100), 175 (34.6), 219 (12.6).

Anal. Calcd for $C_{16}H_{12}N_6O_2$: C, 60.00; H, 3.78; N, 26.24. Found: C, 59.97; H, 3.81; N, 26.23.

3-Methyl-4-(2,4,5-trimethoxyphenyl)-4,9-dihydro-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (5e)

Colorless solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.85 (s, 3 H, CH_3), 3.55 (s, 3 H, OCH_3), 3.72 (s, 6 H, 2 OCH_3), 5.11 (s, 1 H, 4-CH), 6.52–6.58 (m, 2 H_{arom}), 8.61 (s, 1 H, NH), 9.88 (s, 1 H, NH), 10.37 (s, 1 H, 9-NH), 11.68 (s, 1 H, 1-NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.3, 150.8, 150.6, 148.3, 147.8, 145.9, 143.3, 135.5, 128.1, 114.3, 103.1, 99.8, 86.8, 57.3, 57.1, 56.3, 28.6, 9.8.

MS (EI, 70 eV): *m*/*z* (%) = 385 (50.0) [M$^+$], 354 (100), 153 (65.5), 168 (60.4).

Anal. Calcd for $C_{18}H_{19}N_5O_5$: C, 56.10; H, 4.97; N, 18.17. Found: C, 56.14; H, 4.95; N, 18.16.

4-(3,4-Dihydroxyphenyl)-3-methyl-4,9-dihydro-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (5f)

Colorless solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.90 (s, 3 H, CH_3), 4.68 (s, 1 H, 4-CH), 6.4–6.54 (m, 3 H_{arom}), 8.49 (s, 1 H, OH), 8.65 (s, 1 H, OH), 8.70 (s, 1 H, NH), 9.91 (s, 1 H, NH), 10.45 (s, 1 H, 9-NH), 11.78 (s, 1 H, 1-NH).

MS (EI, 70 eV): *m*/*z* (%) = 325 (40.7) [M$^+$], 110 (100), 174 (67.7), 217 (88.3).

Anal. Calcd for $C_{15}H_{13}N_5O_4$: C, 55.05; H, 4.00; N, 21.40. Found: C, 55.02; H, 4.03; N, 21.38.

4-(3-Ethoxy-2-hydroxyphenyl)-3-methyl-4,9-dihydro-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (5g)

Colorless solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.31 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.86 (s, 3 H, CH_3), 3.94 (q, *J* = 6.9 Hz, 2 H, CH_3), 5.2 (s, 1 H, 4-CH), 6.32–6.66 (m, 3 H_{arom}), 8.78 (s, 1 H, NH), 8.84 (s, 1 H, OH), 10.03 (s, 1 H, NH), 10.60 (s, 1 H, 9-NH), 11.80 (s, 1 H, 1-NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.6, 150.2, 147.9, 147.5, 146.1, 143.6, 135.7, 134.9, 121.0, 119.4, 110.9, 102.9, 87.1, 64.4, 28.1, 15.3, 9.8.

MS (EI, 70 eV): *m*/*z* (%) = 355 (100) [M$^+$], 218 (73.2), 110 (75.0), 138 (46.8).

Anal. Calcd for $C_{17}H_{17}N_5O_4$: C, 57.46; H, 4.82; N, 19.71. Found: C, 57.44; H, 4.80; N, 19.70.

4-(4-Chlorophenyl)-3-phenyl-4,9-dihydro-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (5h)

Colorless solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 5.25 (s, 1 H, 4-CH), 7.12–7.49 (m, 9 H_{arom}), 9.06 (s, 1 H, NH), 10.05 (s, 1 H, NH), 10.55 (s, 1 H, 9-NH), 12.66 (s, 1 H, 1-NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.8, 150.4, 147.5, 146.8, 146.0, 138.3, 130.8, 129.8, 129.5, 129.2, 128.6, 128.1, 126.7, 101.9, 87.4, 31.2.

MS (EI, 70 eV): *m*/*z* (%) = 391 (30) [M$^+$], 280 (100), 393 (17.0), 237 (19.8).

Anal. Calcd for $C_{20}H_{14}ClN_5O_2$: C, 61.31; H, 3.60; N, 17.87. Found: C, 61.33; H, 3.57; N, 17.86.

4-(4-Chlorophenyl)-3-phenyl-7-thioxo-1,4,6,7,8,9-hexahydro-5*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidin-5-one (5i)

Colorless solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 5.29 (s, 1 H, 4-CH), 7.1–7.49 (m, 9 H_{arom}), 8.85 (s, 1 H, NH), 10.60 (s, 1 H, NH), 12.02 (s, 1 H, 9-NH), 12.75 (s, 1 H, 1-NH).

MS (EI, 70 eV): *m*/*z* (%) = 407 (29.9) [M$^+$], 296 (100), 409 (18.8), 219 (28.4).

Anal. Calcd for $C_{20}H_{14}ClN_5OS$: C, 58.89; H, 3.46; N, 17.17. Found: C, 58.86; H, 3.49; N, 17.14.

4,6-Aryl-1,4,6,7-tetrahydro-2′*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]s 6a–f; General Procedure for Method A

A mixture of 5-aminopyrazole **1a**,**d** (1.30 mmol, 1 equiv), barbituric acid **2a**–**c** (1.30 mmol, 1 equiv), and aldehyde **3b**,**e**,**g** (2.6 mmol, 2 equiv) in DMF (1 mL), contained in a round-bottom flask, was sonicated in ultrasonic bath at r.t. for 3 h. Then EtOH (30 mL) was added and the mixture was allowed to stand; it was filtered to give the solid product, which was washed with EtOH and dried on air at r.t.

This synthesis can be also carried out with intensively magnetic stirring instead of ultrasonication with some lower yields.

4,6-Aryl-1,4,6,7-tetrahydro-2′*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]s 6g,h; General Procedure for Method B

A mixture of arylidenebarbituric acid **7a**,**b** (2 mmol, 1 equiv) and appropriate Schiff base **8a**,**b** (2 mmol, 1 equiv) in DMF (1 mL), contained in a round-bottom flask equipped with a condenser, was refluxed for 30 min. The mixture was cooled, EtOH (30 mL) was added, and the mixture was allowed to stand; it was filtered to give the solid product, which was washed with EtOH and dried on air at r.t.

4,6-Aryl-1,4,6,7-tetrahydro-2′*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]s 6a,d–h; General Procedure for Method C

A mixture of barbituric acid **2a**–**c** (1.30 mmol, 1 equiv), aromatic aldehyde **3a**,**b**,**e**,**g** (1.3 mmol, 1 equiv), and Schiff base **8a**–**e** in DMF (1 mL), contained in a round-bottom flask, was sonicated in an ultrasonic bath at r.t. for 3 h. Then EtOH (30 mL) was added and the mixture was allowed to stand; it was filtered to give the solid product, which was washed with EtOH and dried on air at r.t.

4,6-Aryl-1,4,6,7-tetrahydro-2′*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]s 6a,d–h; General Procedure for Method D

A mixture of 5-aminopyrazole **1a**,**d**,**e** (1.30 mmol, 1 equiv), aromatic aldehyde **3b**,**e**,**g** (1.3 mmol, 1 equiv), and arylidenebarbituric acid **7a**–**e** in DMF (1 mL), contained in a round-bottom flask, was sonicated in ultrasonic bath at r.t. for 3 h. Then EtOH (30 mL) was added and the mixture was allowed to stand; it was filtered to give the solid product, which was washed with EtOH and dried on air at r.t.

3-Methyl-4,6-bis[4-(methylsulfanyl)phenyl]-1-phenyl-1,4,6,7-tetrahydro-2′*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]-2′,4′,6′(1′*H*,3′*H*)-trione (6a)

Colorless solid; mp 281–282 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.59 (s, 3 H, CH_3), 2.43 (s, 6 H, 2 SCH_3), 4.71 (d, *J* = 7.5 Hz, 1 H, 6-CH), 4.88 (s, 1 H, 4-CH), 6.16 (d, *J* = 7.5 Hz, 1 H, 7-NH), 7.01–7.82 (m, 13 H_{arom}), 11.11 (br s, 2 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.3, 167.2, 149.2, 145.5, 144.4, 139.6, 139.2, 137.9, 133.0, 132.2, 129.0, 128.7, 125.5, 125.5, 125.3, 121.0, 102.1, 65.8, 57.3, 46.2, 14.3, 14.2, 13.92.

MS (EI, 70 eV): *m*/*z* (%) = 569 (13) [M$^+$], 307 (100), 306 (37), 308 (21), 442 (20).

Anal. Calcd For $C_{30}H_{27}N_5O_3S_2$: C, 63.25; H, 4.78; N, 12.29. Found: C, 63.22; H, 4.80; N, 12.26.

4,6-Bis(4-methoxyphenyl)-3-methyl-1-phenyl-1,4,6,7-tetrahydro-2′*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]-2′,4′,6′(1′*H*,3′*H*)-trione (6b)

Colorless solid; mp 219–220 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.57 (s, 3 H, CH_3), 3.71 (s, 6 H, 2 OCH_3), 4.68 (d, *J* = 7.6 Hz, 1 H, 6-CH), 4.84 (s, 1 H, 4-CH), 6.06 (d, *J* = 7.6 Hz, 1 H, 7-NH), 6.83–7.82 (m, 13 H_{arom}), 11.02 (s, 1 H, NH), 11.18 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.9, 167.8, 159.8, 159.2, 149.6, 145.9, 144.8, 140.0, 129.8, 129.3, 128.9, 128.4, 125.6, 121.4, 114.2, 102.8, 66.0, 58.0, 55.6, 55.5, 46.7, 14.3.

MS (EI, 70 eV): *m*/*z* (%) = 537 (14) [M$^+$], 291 (100), 290 (53), 246 (61), 184 (64).

Anal. Calcd For $C_{30}H_{27}N_5O_5$: C, 67.03; H, 5.06; N, 13.03. Found: C, 67.05; H, 5.02; N, 13.02.

4,6-Bis(4-chlorophenyl)-3-methyl-1-phenyl-1,4,6,7-tetrahydro-2′*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]-2′,4′,6′(1′*H*,3′*H*)-trione (6c)

Colorless solid; mp 255–256 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.59 (s, 3 H, CH_3), 4.77 (d, *J* = 7.3 Hz, 1 H, 6-CH), 4.94 (s, 1 H, 4-CH), 6.35 (d, *J* = 7.3 Hz, 1 H, 7-NH), 7.06–7.8 (m, 13 H_{arom}), 11.17 (s, 1 H, NH), 11.36 (s, 1 H, NH).

MS (EI, 70 eV): *m*/*z* (%) = 547 (14.1) [M$^+$], 549 (10.1), 294 (100.0), 295 (85.0), 296 (35.0).

Anal. Calcd For $C_{28}H_{21}Cl_2N_5O_3$: C, 61.55; H, 3.87; N, 12.82. Found: C, 61.51; H, 3.85; N, 12.80.

4,6-Bis(4-chlorophenyl)-3-methyl-1-phenyl-2′-thioxo-1,4,6,7-tetrahydro-2′*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]-4′,6′(1′*H*,3′*H*)-dione (6d)

Colorless solid; mp 210–211 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.58 (s, 3 H, CH_3), 4.7 (d, *J* = 7.3 Hz, 1 H, 6-CH), 4.97 (s, 1 H, 4-CH), 6.45 (d, *J* = 7.3 Hz, 1 H, 7-NH), 7.06–7.8 (m, 13 H_{arom}), 12.2 (s, 1 H, NH), 12.3 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.7, 170.2, 164.9, 145.7, 144.6, 139.9, 135.9, 134.8, 131.1, 133.0, 130.4, 129.4, 129.0, 125.8, 121.8, 101.9, 66.5, 58.6, 46.6, 14.4.

MS (EI, 70 eV): *m*/*z* (%) = 561 (17) [M$^+$], 562 (11), 563 (4.7), 295 (100), 297 (98), 266 (96).

Anal. Calcd For $C_{28}H_{21}Cl_2N_5O_2S$: C, 59.79; H, 3.76; N, 12.45. Found: C, 59.72; H, 3.74; N, 12.44.

4,6-Bis(4-methoxyphenyl)-1′,3,3′-trimethyl-1,4,6,7-tetrahydro-2′*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]-2′,4′,6′(1′*H*,3′*H*)-trione (6e)

Yellow solid; mp 225–226 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.52 (s, 3 H, CH_3), 2.74 (s, 3 H, NCH_3), 2.79 (s, 3 H, NCH_3), 3.66 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 4.68 (d, *J* = 7.3 Hz, 1 H, 6-CH), 4.88 (s, 1 H, 4-CH), 5.83 (d, *J* = 7.3 Hz, 1 H, 7-NH), 6.75–7.06 (m, 8 H_{arom}), 11.54 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.4, 164.6, 162.5, 159.6, 158.7, 152.5, 149.7, 135.3, 131.9, 130.1, 129.0, 128.4, 114.6, 113.7, 100.1, 66.2, 60.4, 55.1, 54.9, 45.8, 28.0, 27.3, 11.2.

MS (EI, 70 eV): *m*/*z* (%) = 489 (29.7) [M$^+$], 216 (100), 273 (74.6), 274 (68), 490 (20).

Anal. Calcd For $C_{26}H_{27}N_5O_5$: C, 63.79; H, 5.56; N, 14.31. Found: C, 63.82; H, 5.54; N, 14.30.

4,6-Bis(4-methoxyphenyl)-1′,3′-dimethyl-3-phenyl-1*H*-1,4,6,7-tetrahydro-2′*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]-2′,4′,6′(1′*H*,3′*H*)-trione (6f)
Yellow solid; mp 156–157 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.67 (s, 3 H, NCH_3), 2.83 (s, 3 H, NCH_3), 3.49 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 4.81 (d, *J* = 7.3 Hz, 1 H, 6-CH), 5.28 (s, 1 H, 4-CH), 6.02 (d, *J* = 7.3 Hz, 1 H, 7-NH), 6.40–7.10 (m, 13 H_{arom}), 12.07 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.6, 164.6, 162.5, 159.6, 158.2, 149.6, 129.8, 128.6, 128.5, 128.2, 127.6, 127.1, 126.8, 113.7, 113.0, 99.6, 65.8, 60.6, 55.1, 54.8, 46.4, 35.7, 30.7, 28.1, 27.3.

MS (EI, 70 eV): *m*/*z* (%) = 551 (30.8) [M^+], 277 (100), 273 (70.6), 274 (62.2).

Anal. Calcd For $C_{31}H_{29}N_5O_5$: C, 67.50; H, 5.30; N, 12.70. Found: C, 67.47; H, 5.33; N, 12.67.

4-(4-Ethylphenyl)-6-(4-methoxyphenyl)-3-methyl-1*H*-1,4,6,7-tetrahydro-2′*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]-2′,4′,6′(1′*H*,3′*H*)-trione (6g)
Yellow solid; mp 219–220 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.11 (t, *J* = 7.6 Hz, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 2.56 (q, *J* = 7.6 Hz, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 4.66 (d, *J* = 7.3 Hz, 1 H, 6-CH), 4.80 (s, 1 H, 4-CH), 5.78 (d, *J* = 7.3 Hz, 1 H, 7-NH), 6.79–7.15 (m, 8 H_{arom}), 9.95 (s, 1 H, NH), 10.85 (s, 1 H, NH), 11.06 (s, 1 H, NH).

MS (EI, 70 eV): *m*/*z* (%) = 459 (31) [M^+], 457 (55), 332 (39.5), 215 (52).

Anal. Calcd For $C_{25}H_{25}N_5O_4$: C, 65.35; H, 5.48; N, 15.24. Found: C, 65.37; H, 5.51; N, 15.23.

6-(4-Methoxyphenyl)-1′,3,3′-trimethyl-4-[4-(methylsulfanyl)phenyl]-1-phenyl-1,4,6,7-tetrahydro-2′*H*-spiro[pyrazolo[3,4-*b*]pyridine-5,5′-pyrimidine]-2′,4′,6′(1′*H*,3′*H*)-trione (6h)
Colorless solid; mp 252–253 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.59 (s, 3 H, CH_3), 2.41 (s, 3 H, SCH_3), 2.77 (s, 3 H, NCH_3), 2.84 (s, 3 H, NCH_3), 3.69 (s, 3 H, OCH_3), 4.76 (d, *J* = 7.3 Hz, 1 H, 6-CH), 4.95 (s, 1 H, 4-CH), 6.24 (d, *J* = 7.3 Hz, 1 H, 7-NH), 6.80–7.80 (m, 13 H_{arom}).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.2, 164.9, 159.6, 158.9, 149.6, 145.5, 144.2, 139.6, 138.0, 133.0, 132.8, 132.2, 132.0, 129.0, 128.7, 128.1, 125.6, 125.5, 121.1, 113.8, 101.9, 66.5, 58.6, 55.0, 46.6, 28.2, 27.5, 14.2, 13.9.

MS (EI, 70 eV): *m*/*z* (%) = 581 (93) [M^+], 565 (37.8), 290 (100), 426 (54.9), 306 (40.1).

Anal. Calcd For $C_{32}H_{31}N_5O_4S$: C, 66.07; H, 5.37; N, 12.04. Found: C, 66.03; H, 5.33; N, 12.03.

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