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Generation of pyrrolo[2,3-*d*]pyrimidines. Unexpected products in the multicomponent reaction of 6-aminopyrimidines, dimedone, and arylglyoxal

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ABSTRACT

A series of 6-aryl-5-(1-cyclohexen-1-yl)pyrrolo[2,3-*d*]pyrimidines **9a**–**q** were obtained by the three-component reaction between 6-aminopyrimidines **6**, **7**, **8**, dimedone **2**, and arylglyoxal **5a**,**b**. The unexpected cyclization process was established by NMR and X-ray diffraction measurements.

The pyrrolo[2,3-*d*]pyrimidine ring system is a common motif in several natural products and biologically active molecules.[1a] Recently there has been a great interest in the synthesis of pyrrolo[2,3-*d*]pyrimidines due to their proven biological activity and medicinal utility. A number of pyrrolopyrimidine derivatives structurally related to toyocamycin, sangivamycin, and the seco nucleosides of tubercidin have antiviral activity.[1]

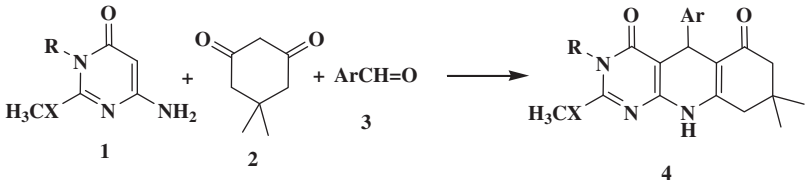
As the pyrrolo[2,3-*d*]pyrimidine heterosystem represents a 7-deazaanalogue of biogenic purine, it is an important class of compounds possessing notable biological activity.[2,3]

We recently reported a three component one-step reaction of 6-aminopyrimidin-4-ones **1** with dimedone **2** and benzaldehydes **3**, which yields pyrimido[4,5-*b*]quinolines[4] **4** via a simple, practical, and a very regioselective procedure (Scheme 1).

In the course of our research aimed at the preparation of bioactive nitrogen-containing heterocycles, we addressed the multicomponent synthesis of fused pyrido[2,3-*d*]pyrimidines.[5]

We report herein an extension of this three-component reaction with aminopyrimidines **1**, dimedone **2**, and arylglyoxales **5**, which yielded the formation of unexpected several pyrrolo[2,3-*d*]pyrimidine derivatives **9a**–**q** (Scheme 2, Table 1).

The structure of all new compounds was determined on the basis of their analytical techniques, 1D and 2D-NMR spectra, and MS, which agree with the proposed structures. Single crystal X-ray dif-



Scheme 1.

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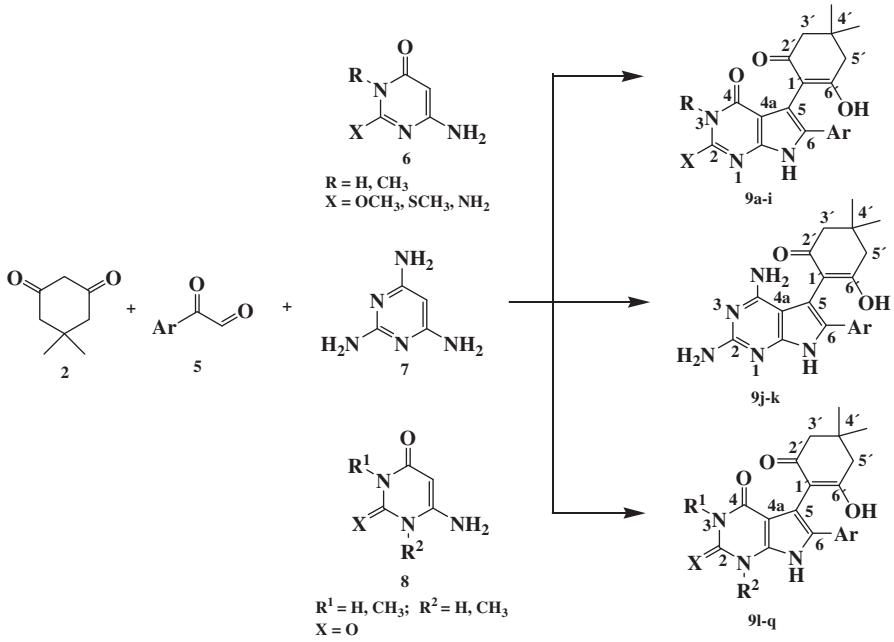
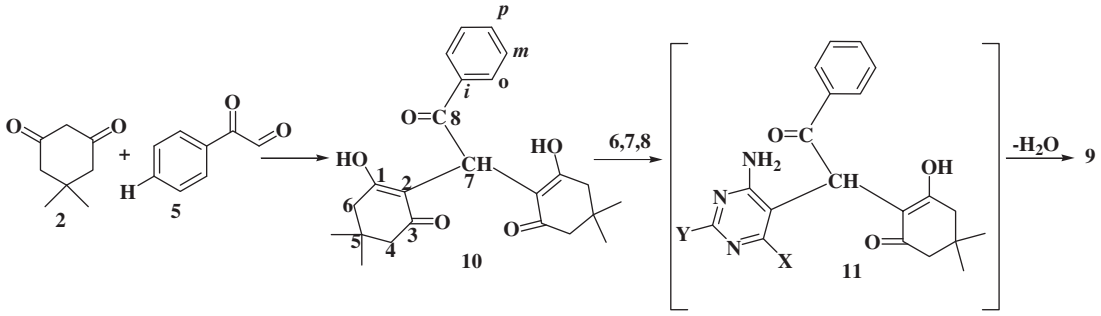


Scheme 2.



Scheme 3.

fraction analysis of compounds **9b**[6] was used to corroborate the postulated structures.[7]

A possible mechanism route for the described three-component reaction is outlined in Scheme 3. We consider that initially the dimedone reacts with the arylglyoxal to give the intermediate **10**. The last one reacts with the 6-aminopyrimidine leading to the formation of intermediate **11**, which suffers the cyclation with loss of a water molecule, to form final pyrrolopyrimidine **9**. As an evidence of this is the fact that the reaction of dimedone with phenylglyoxal led to the formation of product **10**, which was isolated and character-

Table 1
Pyrrolo[2,3-*d*]pyrimidine derivatives

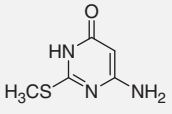
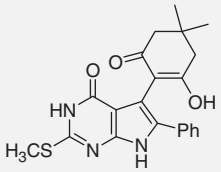
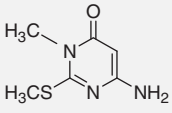
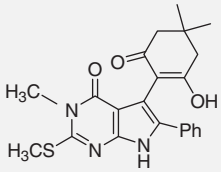
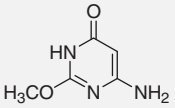
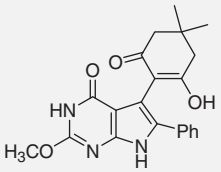
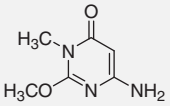
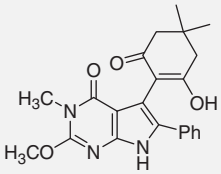
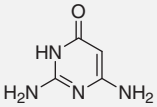
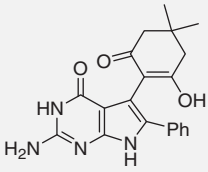
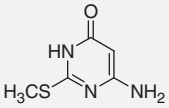
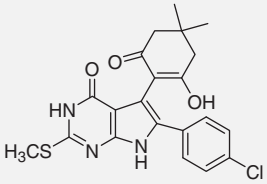
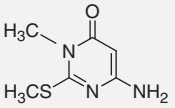
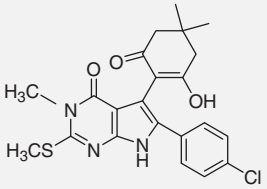
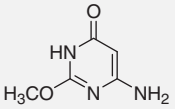
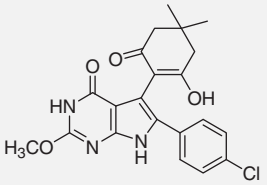
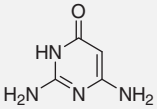
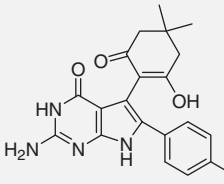
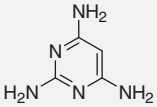
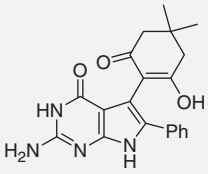
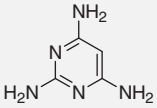
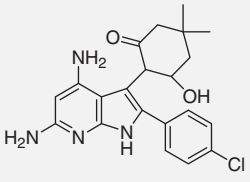
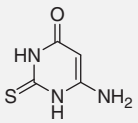
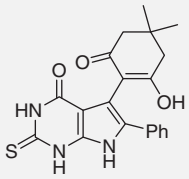
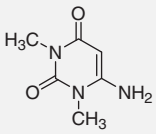
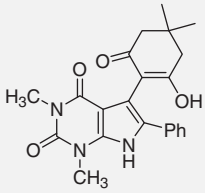
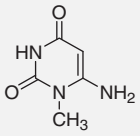
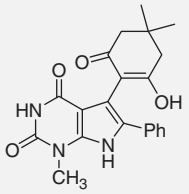
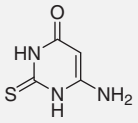
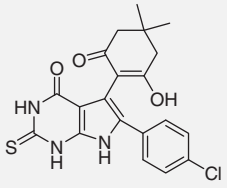
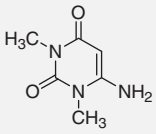
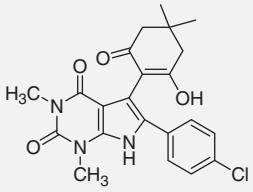
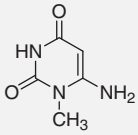
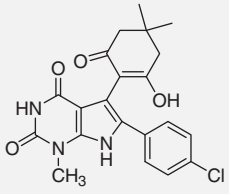
Entry	Pyrimidine	Product	Mp (°C)	%	*m/z*
9a			280–282	50	395
9b			294–295	60	410

Table 1 (*continued*)

Entry	Pyrimidine	Product	Mp (°C)	%	*m/z*
9c			278–280	46	379
9d			296–298	60	393
9e			328–329	46	364
9f			299–301	43	429/431
9g			292–293	39	443/445
9h			262–263	38	413/415
9i			286–288	43	398/400
9j			242–243	41	363
9k			279–281	41	397/399

(*continued on next page*)

Table 1 (*continued*)

Entry	Pyrimidine	Product	Mp (°C)	%	*m/z*
9l			246–248	44	381
9m			299–300	55	393
9n			296–298	53	379
9o			308–309	43	415/417
9p			306–308	40	427/429
9q			295–297	54	413/415

ized.[8] The compound **10** was submitted to the reaction with aminopyrimidines **6** under the same conditions to give compounds **9**.[9]

The described three-component one-step procedure is a simple, practical, and a very regioselective method for the preparation of novel pyrrolo[2,3-*d*]pyrimidines. The biological properties of the new compounds obtained in this research are under investigation.

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7. *General procedure for the preparation of pyrrolo[2,3-d]pyrimidines* **9**. A solution of equimolar amounts of 6-aminopyrimidine **6, 7, 8,** dimedone **2,** and arylglyoxal **5** in ethanol (15 mL) and amounts of catalytic acetic acid was heated for 9 h. Then, the reaction mixture was allowed to cool to ambient temperature, and the resulting solid products were collected by filtration, washed with ethanol, dried in air, and recrystallized from ethanol. *Data for 5-(2-hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-2-(methylsulfanyl)-6-phenyl-3,7-dihydro-4H-pyrrolo[2,3-d]-pyrimidin-4-one* **9a:** White solid, yield 50%, 280–282 °C. ^{1}H NMR (400 MHz DMSO-d_6) δ: 1.05 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 2.16 (s, 2H, H-5′), 2.37 (s, 2H, H-3′), 2.54 (s, 3H, SCH_3), 7.19 (t, 1H, H_p, J = 7.36), 7.28 (t, 2H, H_m J = 7.67), 7.47 (d, 2H, $H_{o''}$, J = 7.47), 9.86 (s, 1H, OH), 11.73 (s, 1H, H-3), 11.88 (s, 1H, H-7). ^{13}C NMR (100 MHz DMSO-d_6) δ: 13.4 (SCH_3), 28.3 (CH_3), 28.9 (CH_3), 32.1 (C-4′), 43.4 (C-3′), 51.1 (C-5′), 106.2 (C-5), 108.1 (C-4a), 109.5 (C-1′), 126.5 (C_o), 126.9 (C_p), 128.6 (C_m), 129.7 (C-6), 133.0 (C_i), 148.9 (C-7a), 154.5 (C-2), 158.8 (C-4), 171.4 (C-2′), 196.4(C-6′). IE EM: *m/z*: 395 (M^+, 98), 380 (100, M^+-CH_3), 297 (34), 270 (48), 167 (31), 140 (35). Anal. Calcd for $C_{21}H_{21}N_3O_3S$: C, 63.78; H, 5.35; N, 10.623; Found: C, 63.59; H, 5.18; N, 10.51.
8. *Preparation of the intermediate 2,2′-(2-oxo-2-phenyl-1,1-ethanediyl)bis(3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one* **10.** This compound was obtained by a modified method described in Ref. 10. A mixture of equimolar amounts of dimedone **2**, arylglyoxal **5,** and amounts of catalytic CdI_2 was subjected to microwave irradiation for 20 s at a temperature of 80 °C (CEM-Discovery). Then, the product obtained is treated with a mixture of ethanol–water, and the resulting solid products were collected by filtration, washed with ethanol, dried in air, and recrystallized from ethanol. White solid, yield 47%, 165–67 °C. ^{1}H NMR (400 MHz $CDCl_3$) δ: 1.09 (s, 6H, CH_3), 1.13 (s, 6H, CH_3), 2.25 (s, 4H, H-4), 2.50 (s, 4H, H-6), 5.42 (s, 1H, H-7), 7.49 (d, 2H, H_o), 7.56 (t, 2H, H_m), 8.28 (d, 1H, H_p). ^{13}C NMR (100 MHz $CDCl_3$) δ: 27.4 (CH_3), 29.0 (CH_3), 32.3 (C-4), 34.2 (C-7), 40.9 (C-5), 50.4 (C-3), 113.1 (C-1), 128.1 (C_m), 129.3 (C_o) 132.8(C_p), 137.3 (C_i), 164.4 (C-2), 196.7 (C-6), 201.5 (C-8). IE EM: *m/z*: 396 (M^+, 1), 273 (100). Anal. Calcd for $C_{24}H_{28}O_5$: C, 72.71; H, 7.12. Found: C, 72.45; H, 6.78.
9. *General procedure for the prepararion of pyrrolo[2,3-d]pyrimidines* **9a** *(R = H, X = SCH$_3$) from the intermediate* **10** *(di-component reaction).* A solution of equimolar amounts of 6-aminopyrimidine **6** and intermediate **10** in ethanol (15 mL) and amounts of catalytic acetic acid was heated for 9 h. Then, the reaction mixture was allowed to cool to ambient temperature, and the resulting solid products were collected by filtration, washed with ethanol, dried in air, and recrystallized from ethanol. Yield 45%.
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