Convergent Domino *Knoevenagel* Hetero-*Diels–Alder* and Domino Oxidation Hetero-*Diels–Alder* Reactions Encountered in an Unexpected Formation of Novel 5-Aryl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones and 5-Aryl-2,3-dihydro-2-thioxo-1*H*-pyrano[2,3-*d*]pyrimidin-4(5*H*)-ones

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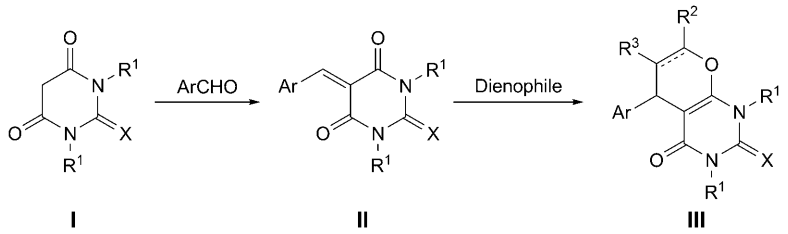
Convergent domino *Knoevenagel* hetero-*Diels–Alder* and domino oxidation hetero-*Diels–Alder* reactions, in which both diene and dienophile are formed under the same reaction conditions *in situ*, are described for the first time, and their application is demonstrated by a one-pot synthesis of novel 5-aryl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones and 5-aryl-2,3-dihydro-2-thioxo-1*H*-pyrano[2,3-*d*]pyrimidin-4(5*H*)-ones.

Introduction. – Domino reactions involving hetero-*Diels–Alder* cycloaddition reaction constitute a powerful strategy for the synthesis of complex organic molecules [1]. Among them, the domino *Knoevenagel* hetero-*Diels–Alder* reaction [1b][2], in which a diene, generated from a 1,3-dicarbonyl compound and an aldehyde, reacts with a dienophile, *e.g.*, an enol ether [3a], alkene [2d][2e], alkyne [3b][3c], or enamine [3d], has been frequently applied for the synthesis of natural products and highly diversified molecules. Whereas, in such reactions, different substrates, *e.g.*, barbituric acids and *Meldrum*'s acid, have been used for generating dienes, dienophiles have not been produced *in situ* but added as reagents. A domino process in which both the diene and the dienophile would be generated *in situ* under the same reaction conditions, and would subsequently react to give a hetero-*Diels–Alder* product, is a challenging concept, which, to the best of our knowledge, has not been encountered in domino sequences involving a hetero-*Diels–Alder* reaction.

5-Unsubstituted barbituric acids **I** undergo the *Knoevenagel* condensation with aldehydes to afford 5-ylidene derivatives **II** [4], which have been reported to react as dienes in a hetero-*Diels–Alder* reaction to give 6/7-substituted 5-aryl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones or their 2-thioxo analogues **III** (X = S) [3] (*Scheme 1*). As fused uracils, these compounds have received considerable attention due to their biological effects, including antiviral [5], antibacterial [6], antifungal [7], and prostate-protective activities [8]. 6,7-Unsubstituted derivatives of **III** have not been obtained by cycloaddition so far. The development of new synthetic strategies for the synthesis of novel 5-aryl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones and their 2-thioxo analogs is, therefore, of significant relevance. 5-Arylidenebarbituric acid derivatives **II** obtained by *Knoevenagel* condensation can also be easily reduced at the exocyclic C=C bond [9], so they can be considered as models of redox coenzymes such

as FAD and NAD, and used as oxidants for mild oxidation of alcohols [10] and thiols [11].

Scheme 1. *Synthesis of 5-Aryl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H,5H*)-diones and Their 2-Thioxo Analogs* via *Consecutive* Knoevenagel *Condensation and Hetero*-Diels–Alder *Cycloaddition*



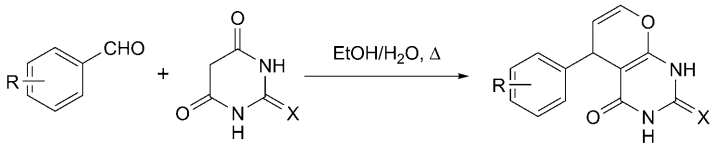
R^1 = H, alkyl; X = O, S

Results and Discussion. – In the course of our research on novel antibacterial compounds [12][13], we discovered an unexpected synthesis of novel 6,7-unsubstituted 5-aryl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones and their 2-thioxo analogues **3a**–**3l** in a catalyst-free, one-pot reaction, which was performed simply by heating barbituric or 2-thiobarbituric acid with a benzaldehyde derivative, **1a**–**1g**, in EtOH/H_2O[1]). Application of microwave irradiation substantially reduced the reaction times (from 3 d to *ca.* 1–2 h) but did not significantly influence the reaction yields (*Table*). This is, to the best of our knowledge, the first domino *Knoevenagel* hetero-*Diels–Alder* reaction in which both diene and dienophile are formed *in situ*. The conversion in fact comprises two interconnected domino reaction sequences: *i*) a domino *Knoevenagel* hetero-*Diels–Alder* reaction, and *ii*) a domino oxidation hetero-*Diels–Alder* reaction, both converging in products **3a**–**3l** (*Scheme 2*). The sequences can thus be described as convergent domino *Knoevenagel* hetero-*Diels–Alder* and domino oxidation hetero-*Diels–Alder* reactions.

A proposed mechanism for the reaction of barbituric (= pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) or 2-thiobarbituric acid (= 2,3-dihydro-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione) (**2a** and **2b**, resp.) and substituted benzaldehydes **1a**–**1g** in EtOH/H_2O leading to 5-aryl-1*H*-pyrano[2,3-*d*]-pyrimidinones and 5-aryl-2,3-dihydro-2-thioxo-1*H*-pyrano-[2,3-*d*]pyrimidin-4(5*H*)-ones **3a**–**3l** is depicted in *Scheme 3*. First, *Knoevenagel* condensation of an aromatic aldehyde **1a**–**1g** with **2a** or **2b** affords a 5-benzylidenebarbituric acid **A**, which, due to its readily reducible exocyclic C=C bond, is responsible for oxidation of EtOH to acetaldehyde (MeCHO) [10]. It is noteworthy that MeCHO enters the following reaction step in its enol form, **B** (R^1 = H). As a dienophile, it reacts with **A** in a hetero-*Diels–Alder* reaction to give, after elimination of H_2O from intermediate **C**, the fused products **3a**–**3l**. Alternatively, formation of ethyl vinyl ether, **B** (R^1 = Et) from MeCHO and EtOH, and elimination of EtOH from

[1]) So far, only 6- and 7-substituted derivatives of **III** have been obtained by cycloaddition. Only two 6,7-unsubstituted derivatives of **III** (R^1 = Me, R^2 = R^3 = H, Ar = Ph or 4-MeO–C_6H_4) are known. They were obtained as side-products by elimination of a substituent at C(7) (see [3d]).

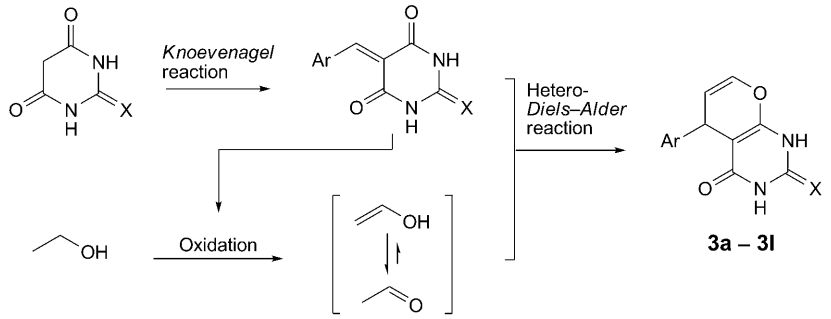
Table. *Synthesis of 5-Aryl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H,5H*)-diones and Their 2-Thioxo Analogs* **3a**–**3l**[a])



Entry	**1**	R	**2**	X	Product	Yield [%][b])	
						Method A	*Method B*
1	**1a**	H	**2a**	S	**3a**	24	23
2	**1b**	3-NO_2	**2b**	O	**3b**	56	35[c])
3	**1b**	3-NO_2	**2a**	S	**3c**	34	33
4	**1c**	4-NO_2	**2b**	O	**3d**	58	46
5	**1c**	4-NO_2	**2a**	S	**3e**	58	40
6	**1d**	3-CN	**2b**	O	**3f**	58	57[c])
7	**1d**	3-CN	**2a**	S	**3g**	26	44
8	**1e**	4-CN	**2b**	O	**3h**	58	46
9	**1e**	4-CN	**2a**	S	**3i**	46	60
10	**1f**	4-COOH	**2b**	O	**3j**	44	42[c])
11	**1f**	4-COOH	**2a**	S	**3k**	20	27
12	**1g**	4-COOMe	**2b**	O	**3l**	28	30

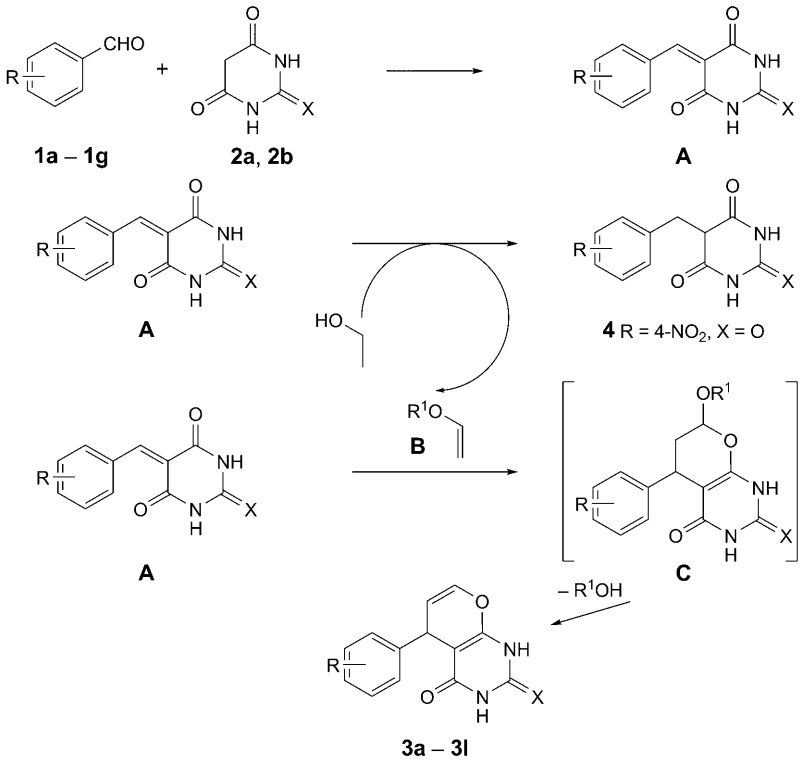
[a]) Reaction conditions: **1** (1 mmol), **2** (1 mmol), and EtOH/H_2O 1:1, reflux, 3 d (*Method A*) or microwave irradiation: 120°, 30 W, 40 min (*Method B*). [b]) Yield of isolated pure product; yields were calculated considering that 100% yield corresponds to the conversion of 1 mmol of **1a**–**1g** to 0.5 mmol of **3a**–**3l**, which is in agreement with the reaction mechanism depicted in *Scheme 3*. [c]) Reaction time: 2 h.

Scheme 2. *Formation of 5-Aryl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H,5H*)-diones and Their 2-Thioxo Analogs by Convergent Domino* Knoevenagel *Hetero-*Diels–Alder *and Domino Oxidation Hetero-*Diels–Alder *Reactions*



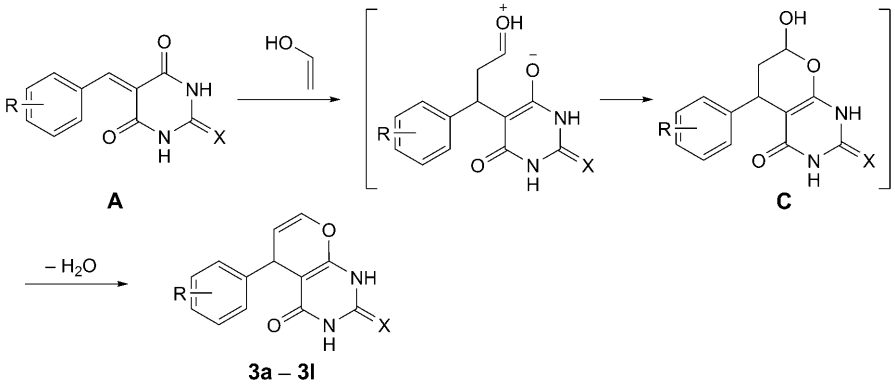
intermediate **C** could be anticipated. A formal domino *Knoevenagel* hetero-*Diels–Alder* reaction has been proposed previously for the reaction of ethyl vinyl ether with various benzaldehydes and 1,3-dimethylbarbituric acid [3a]. An alternative mecha-

Scheme 3. *Mechanistic Proposal for the Synthesis of 5-Aryl-1*H*-pyrano[2,3-*d*]pyrimidinones and 5-Aryl-2,3-dihydro-2-thioxo-1*H*-pyrano[2,3-*d*]-pyrimidin-4(5*H*)-ones* **3a**–**3l**



nistic explanation for the formation of **3a**–**3l** could be a *Michael* addition of the enol form of MeCHO at the 5-benzylidenebarbituric acid **A**, followed by the cyclization to **C** and subsequent elimination of H_2O (*Scheme 4*). Yields compiled in the *Table* were calculated considering that 100% yield corresponds to the conversion of 1 mmol of **1a**–**1g** to 0.5 mmol of **3a**–**3l**, which is in agreement with the described reaction mechanism. According to *Yoneda et al.* [10], the oxidizing ability of 5-benzylidene-barbituric acids depends on the electron density in the C=C bond and, hence, on the number and strength of electron-withdrawing substituents on the aromatic ring. This explains why the reaction proceeds well with nitro-, carboxy- and cyanobenzaldehydes, but not with 4-hydroxybenzaldehyde. Although oxidation of several alcohols with 5-arylidene-barbituric acids has been described [10], in our hands the reaction with other alcohols (PrOH, i-PrOH) was not successful, indicating that steric factors in the dienophile might play a role. To verify the proposed reaction mechanism, we heated 5-(4-nitrobenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**A**, R = 4-NO_2, X = O) in EtOH/H_2O and obtained the product **3d** in 30% yield, indicating that the *Knoevenagel* condensation indeed occurs first. To confirm that the oxidation of EtOH to MeCHO and the reduction of the exocyclic C=C bond of 5-arylidene-barbituric acids take place in the next step, we examined the reaction of 4-nitrobenzaldehyde and barbituric acid

Scheme 4. *Alternative Mechanism for the Synthesis of* **3a – 3l**



(**2a**) in EtOH/H_2O. After filtering off the product **3d** from the mixture, the reduced derivative, 5-(4-nitrobenzyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4**), was isolated from the mother liquid by column chromatography. The reaction gave identical results under Ar atmosphere, thus excluding a possible oxidation of EtOH[2]) by atmospheric O_2. Finally, we sought to establish whether MeCHO reacts with 5-(4-nitrobenzylidene)-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**A**; R = 4-NO_2, X = O) in a hetero-*Diels–Alder* reaction. To this end, 4-nitrobenzaldehyde and barbituric acid (**2a**) were reacted in pure H_2O at 100° to give first 5-(4-nitrobenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**A**; R = 4-NO_2, X = O). After subsequent addition of MeCHO, crystals formed in the reaction mixture were filtered off and confirmed to be identical to product **3d**. The formation of **3d** from **1c**, **2a**, and MeCHO in the absence of EtOH thus excludes the intermediacy of ethyl vinyl ether (**B**; R^1 = Et). All these experiments support a three-component convergent domino reaction mechanism for the formation of 5-aryl-1*H*-pyrano[2,3-*d*]pyrimidinones and 5-aryl-2,3-dihydro-2-thioxo-1*H*-pyrano[2,3-*d*]pyrimidin-4(5*H*)-ones **3a – 3l**, comprising a hetero *Diels–Alder* reaction of 5-arylidene-barbituric acid **A** with the enol of MeCHO, both formed *in situ*, as proposed in *Scheme 3*.

Conclusions. – In conclusion, we have described the first convergent domino *Knoevenagel* hetero-*Diels–Alder* and domino oxidation hetero-*Diels–Alder* reactions, in which both diene and dienophile are formed *in situ* under the same reaction conditions, and demonstrated their application in a surprising one-pot synthesis of novel 6,7-unsubstituted 5-aryl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones and 5-aryl-2,3-dihydro-2-thioxo-1*H*-pyrano[2,3-*d*]pyrimidin-4(5*H*)-ones **3a – 3l**. Although, in this particular case, the overall yields of products **3a – 3l** were low, possibly due to interference of competing reactions[3]), we assume that the reported strategy of

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[2]) EtOH with less than 0.001% MeCHO content was used.

[3]) Acetaldehyde, which is formed *in situ*, can compete with benzaldehyde **1a – 1g** for barbituric acids **2a** and **2b** as a substrate for the *Knoevenagel* reaction. Additionally, the *Knoevenagel* product **A** can undergo *Michael* addition with a second molecule of barbituric acid.

generating both the diene and the dienophile *in situ* in two converging domino processes could open new opportunities for sequential transformations which include hetero-*Diels–Alder* reaction.

Experimental Part

General. All reagents were used as received from commercial sources without further purification unless otherwise indicated. Anal. TLC: *Merck* silica gel (*60 F_{254}*) plates (0.25 mm), components visualized with UV light. Column chromatography (CC): silica gel *60* (particle size 240–400 mesh; *Merck*). Microwave-assisted reactions were conducted in a sealed glass vessel (capacity 10 ml) on a *CEM Discover* microwave synthesizer (*CEM Corporation*, USA) with a built-in pressure measurement sensor and operator-selectable power output from 0 to 300 W. The temp. was monitored using an IR temp. sensor mounted under the reaction vessel. All experiments were performed using a high-speed stirring option. M.p.: *Reichert* hot stage microscope; uncorrected. IR Spectra: *Perkin–Elmer 1600* FT-IR spectrometer. ^{1}H- and ^{13}C-NMR spectra: at 300 and 75 MHz, resp., on a *Bruker AVANCE DPX300* spectrometer in (D_6)DMSO or D_2O with TMS as the internal standard at 25°. Spectra were assigned using gradient COSY, HSQC and DEPT experiments. MS: *VG Analytical Autospec Q* mass spectrometer. Microanalyses: *Perkin-Elmer C,H,N analyzer 240 C*. All reported yields are yields of purified products.

*General Procedure for the Preparation of 5-Phenyl-1*H*-pyrano[2,3-*d*]pyrimidine-4(3*H*,5*H*)-ones and Their 2-Thioxo Analogs* **3a**–**3l**. *Method A* (*Conventional Heating* ([i])). A suspension of benzaldehyde **1a**–**1g** (1.00 mmol) and barbituric or 2-thiobarbituric acid (**2a** or **2b**, resp.; 1.00 mmol) in EtOH/H_2O 1:1 (20 ml) was refluxed for 3 d, then the mixture was cooled to r.t., and the product was filtered off and washed with EtOH.

Method B (*Microwave-Assisted Synthesis* ([ii])). A suspension of benzaldehyde **1a**–**1g** (1.00 mmol), and **2a** or **2b** (1.00 mmol) in EtOH/H_2O 1:1 (3 ml) was heated in a sealed 10-ml glass vessel in a microwave reactor for 1–2 h (*Table*) at 120° (power, 30 W; ramp time, 3 min). The mixture was cooled to r.t., and the product was filtered off and washed with EtOH.

*1,2,3,5-Tetrahydro-5-phenyl-2-thioxo-4*H*-pyrano[2,3-*d*]pyrimidin-4-one* (**3a**). Yield: 31 mg (24%[i]), 30 mg (23%[ii]). Orange crystals. M.p. 276–279°. IR (KBr): 3441, 3078, 2895, 1651, 1597, 1574, 1556, 1526, 1450, 1430, 1379, 1324, 1308, 1223, 1175, 1152, 998, 848, 787, 758, 687. ^{1}H-NMR (300 MHz, (D_6)DMSO): 7.49–7.51 (*m*, H–C(3′), H–C(4′), H–C(5′)); 7.68–7.71 (*m*, H–C(2′), H–C(6′)); 7.79 (*d*, ^3J = 15.3, H–C(5)); 8.06 (*d*, ^3J = 12.0, H–C(7)); 8.45 (*dd*, ^3J(5,6) = 15.3, ^3J(6,7) = 12.0, H–C(6)); 12.31 (br. *s*, NH); 12.34 (br. *s*, NH). ^{13}C-NMR (75 MHz, (D_6)DMSO): 116.8; 125.5; 129.7; 130.2; 132.4; 136.2; 154.6; 155.5; 161.7 (arom. C, C=O); 162.2 (arom. C, C=O); 179.4 (C=S). ESI-MS: 257 ([M – H]$^-$). HR-MS: 257.0381 ([M – H]$^-$, $C_{13}H_9N_2O_2S^-$; calc. 257.0385). Anal. calc. for $C_{13}H_{10}N_2O_2S$ (258.30): C 60.45, H 3.90, N 10.85; found: C 60.42, H 3.78, N 10.94.

*1,5-Dihydro-5-(3-nitrophenyl)-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione* (**3b**). Yield: 80 mg (56%[i]), 50 mg (35%[ii]). Yellow crystals. M.p. 286–288°. IR (KBr): 3527, 3185, 3056, 2836, 1743, 1668, 1600, 1562, 1520, 1438, 1413, 1377, 1359, 1322, 1304, 1216, 1172, 1107, 1008, 998, 810, 794, 754, 736. ^{1}H-NMR (300 MHz, (D_6)DMSO): 7.73–7.82 (*m*, H–C(5), H–C(5′)); 7.97 (*d*, ^3J = 11.7, H–C(7)); 8.09 (*d*, ^3J = 7.8, H–C(6′)); 8.25–8.28 (*m*, H–C(4′)); 8.40 (*s*, H–C(2′)); 8.49 (*dd*, ^3J(5,6) = 15.6, ^3J(6,7) = 11.7, H–C(6)); 11.27 (br. *s*, NH); 11.31 (br. *s*, NH). ^{13}C-NMR (75 MHz, (D_6)DMSO): 118.3; 123.6; 125.8; 127.3; 131.7; 134.8; 137.8; 149.2; 149.8; 151.2; 153.1; 163.7 (C=O); 163.8 (C=O). ESI-MS: 286 ([M – H]$^-$). HR-MS: 286.0476 ([M – H]$^-$, $C_{13}H_8N_3O_5^-$; calc. 286.0464). Anal. calc. for $C_{13}H_9N_3O_5$ (287.23): C 54.36. H 3.16, N 14.63; found: C 54.15, H 3.11, N 14.64.

*1,2,3,5-Tetrahydro-5-(3-nitrophenyl)-2-thioxo-4*H*-pyrano[2,3-*d*]pyrimidin-4-one* (**3c**). Yield: 52 mg (34%[i]), 50 mg (33%[ii]). Yellow crystals. M.p. > 350°. IR (KBr): 3487, 3091, 2893, 2595, 1706, 1674, 1599, 1532, 1452, 1435, 1373, 1351, 1320, 1292, 1224, 1211, 1172, 1152, 1100, 1002, 880, 812, 785, 736, 666. ^{1}H-NMR (300 MHz, (D_6)DMSO): 7.78 (*t*, ^3J = 7.8, H–C(5′)); 7.88 (*d*, ^3J = 15.6, H–C(5)); 8.02 (*d*, ^3J = 11.7, H–C(7)); 8.14 (*d*, ^3J = 7.8, H–C(6′)); 8.28–8.31 (*m*, H–C(4′)); 8.44 (*t*, ^4J = 1.8, H–C(2′)); 8.52 (*dd*, ^3J(5,6) = 15.6, ^3J(6,7) = 11.7, H–C(6)); 12.38 (br. *s*, NH); 12.41 (br. *s*, NH). ^{13}C-NMR (75 MHz, (D_6)DMSO): 118.4; 123.8; 126.0; 127.5; 131.7; 135.0; 137.7; 149.2; 150.7; 154.0; 161.5 (arom. C, C=O);

162.0 (arom. C, C=O); 179.5 (C=S). ESI-MS: 302 ([$M-H$]$^-$). HR-MS: 302.0244 ([$M-H$]$^-$, $C_{13}H_8N_3O_4S^-$; calc. 302.0236). Anal. calc. for $C_{13}H_9N_3O_4S$ (303.29): C 51.48, H 2.99, N, 13.85; found: C 51.33, H 2.96, N 13.75.

*1,5-Dihydro-5-(4-nitrophenyl)-2*H-*pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione* (**3d**). Yield: 83 mg (58%[i]), 66 mg (46%[ii]). Yellow crystals. M.p. >350°. IR (KBr): 3526, 3176, 3030, 2878, 1756, 1715, 1668, 1590, 1568, 1520, 1447, 1417, 1374, 1336, 1318, 1224, 1172, 1001, 844, 794, 754, 748. ^{1}H-NMR (300 MHz, (D$_6$)DMSO): 7.79 (*d*, ^3J = 15.6, H–C(5)); 7.90 (*d*, ^3J = 8.7, H–C(2′), H–C(6′)); 8.00 (*d*, ^3J = 11.7, H–C(7)); 8.30 (*d*, ^3J = 8.7, H–C(3′), H–C(5′)); 8.53 (*dd*, ^3J(5,6) = 15.6, ^3J(6,7) = 11.7, H–C(6)); 11.29 (br. *s*, NH); 11.33 (br. *s*, NH). ^{13}C-NMR (75 MHz, (D$_6$)DMSO): 118.8; 125.2 (C(3′), C(5′)); 128.7 (C(6)); 130.2 (C(2′), C(6′)); 142.3; 148.9; 149.4 (C(5)); 151.1; 152.7 (C(7)); 163.6 (C=O); 163.7 (C=O). EI-MS: 287 (M^+, 100), 270 (42), 257 (8), 240 (13). HR-MS: 287.0550 (M^+, $C_{13}H_9N_3O_5^+$; calc. 287.0542). Anal. calc. for $C_{13}H_9N_3O_5$ (287.23): C 54.36, H 3.16, N 14.63; found: C 54.30, H 3.06, N 14.78.

*1,2,3,5-Tetrahydro-5-(4-nitrophenyl)-2-thioxo-4*H-*pyrano[2,3-*d*]pyrimidin-4-one* (**3e**). Yield: 88 mg (58%[i]), 61 mg (40%[ii]). Orange crystals. M.p. >350°. IR (KBr): 3488, 3075, 2887, 2592, 2441, 1711, 1665, 1593, 1564, 1520, 1446, 1416, 1379, 1340, 1315, 1296, 1214, 1172, 995, 841, 786, 746. ^{1}H-NMR (300 MHz, (D$_6$)DMSO): 7.85 (*d*, ^3J = 15.3, H–C(5)), 7.92 (*d*, ^3J = 9.0, H–C(2′), H–C(6′)); 8.03 (*d*, ^3J = 11.7, H–C(7)); 8.31 (*d*, ^3J = 9.0, H–C(3′), H–C(5′)); 8.54 (*dd*, ^3J(5,6) = 15.3, ^3J(6,7) = 11.7, H–C(6)); 12.38 (br. *s*, NH); 12.41 (br. *s*, NH). ^{13}C-NMR (75 MHz, (D$_6$)DMSO): 118.8; 125.2; 128.9; 130.4; 142.2; 149.0; 150.3; 153.6; 161.5 (arom. C, C=O); 162.0 (arom. C, C=O); 179.5 (C=S). ESI-MS: 302 ([$M-H$]$^-$). HR-MS: 302.0243 ([$M-H$]$^-$, $C_{13}H_8N_3O_4S^-$; calc. 302.0236). Anal. calc. for $C_{13}H_9N_3O_4S$ (303.29): C 51.48, H 2.99, N 13.85; found: C 51.37, H 2.81, N 13.83.

*3-(1,3,4,5-Tetrahydro-2,4-dioxo-2*H-*pyrano[2,3-*d*]pyrimidin-5-yl)benzonitrile* (**3f**). Yield: 77 mg (58%[i]), 76 mg (57%[ii]). Yellow crystals. M.p. 308–310°. IR (KBr). 3526, 3384, 3252, 2845, 2492, 2232 (CN), 1731, 1690, 1603, 1558, 1427, 1397, 1366, 1314, 1292, 1211, 1176, 1040, 1005, 956, 837, 793, 758, 676. ^{1}H-NMR (300 MHz, (D$_6$)DMSO): 7.65–7.70 (*m*, H–C(5), H–C(5′)); 7.89 (*d*, ^3J = 7.5, H–C(4)); 7.94–7.98 (*m*, H–C(6), H–C(7′)); 8.08 (*s*, H–C(2)); 8.45 (*dd*, ^3J(5,6) = 15.6, ^3J(6,7) = 11.7, H–C(6′)); 11.26 (br. *s*, NH); 11.30 (br. *s*, NH). ^{13}C-NMR (75 MHz, (D$_6$)DMSO): 113.3; 118.1; 119.1; 127.0; 131.3; 132.9; 133.3; 134.7; 137.3; 150.1; 151.2; 153.3; 163.6 (C=O); 163.8 (C=O). ESI-MS: 266 ([$M-H$]$^-$). HR-MS: 266.0570 ([$M-H$]$^-$, $C_{14}H_8N_3O_3^-$; calc. 266.0566). Anal. calc. for $C_{14}H_9N_3O_3$ (267.24): C 62.92, H 3.39, N 15.72; found: C 62.62, H 3.26, N 15.62.

*3-(1,3,4,5-Tetrahydro-4-oxo-2-thioxo-2*H-*pyrano[2,3-*d*]pyrimidin-5-yl)benzonitrile* (**3g**). Yield: 37 mg (26%[i]), 62 mg (44%[ii]). Orange crystals. M.p. 285–289°. IR (KBr): 3560, 3254, 3125, 3084, 3017, 2891, 2571, 2234 (CN), 1708, 1674, 1595, 1553, 1525, 1434, 1380, 1314, 1296, 1242, 1216, 1184, 1144, 997, 844, 817, 786, 734, 674. ^{1}H-NMR (300 MHz, (D$_6$)DMSO): 7.69 (*t*, ^3J = 7.8, H–C(5)); 7.76 (*d*, ^3J = 15.6, H–C(5′)); 7.93 (*d*, ^3J = 7.8, H–C(4)); 7.99–8.03 (*m*, H–C(6), H–C(7′)); 8.13 (*s*, H–C(2)); 8.47 (*dd*, ^3J(5,6) = 15.6, ^3J(6,7) = 11.7, H–C(6′)); 12.36 (br. *s*, NH); 12.39 (br. *s*, NH). ^{13}C-NMR (75 MHz, (D$_6$)DMSO): 113.3; 118.2; 119.1; 127.3; 131.3; 133.1; 133.4; 135.0; 137.3; 151.1; 154.2; 161.5 (arom. C, C=O); 162.0 (arom. C, C=O); 179.5 (C=S). ESI-MS: 282 ([$M-H$]$^-$). HR-MS: 282.0336 ([$M-H$]$^-$, $C_{14}H_8N_3O_2S^-$; calc. 282.0337). Anal. calc. for $C_{14}H_9N_3O_2S$ (283.31): C 59.35, H 3.20, N 14.83; found: C 58.95, H 3.12, N 14.66.

*4-(1,3,4,5-Tetrahydro-2,4-dioxo-2*H-*pyrano[2,3-*d*]pyrimidin-5-yl)benzonitrile* (**3h**). Yield: 77 mg (58%[i]), 61 mg (46%[ii]). Yellow crystals. M.p. 316–318°. IR (KBr): 3613, 3350, 3055, 2827, 2228 (CN), 1732, 1693, 1556, 1417, 1372, 1322, 1300, 1209, 1168, 1004, 871, 846, 824, 792, 756. ^{1}H-NMR (300 MHz, (D$_6$)DMSO): 7.74 (*d*, ^3J = 15.6, H–C(5′)); 7.83 (*d*, ^3J = 8.4, H–C(2), H–C(6)); 7.93 (*d*, ^3J = 8.4, H–C(3), H–C(5)); 7.99 (*d*, ^3J = 11.7, H–C(7′)); 8.50 (*dd*, ^3J(5,6) = 15.6, ^3J(6,7) = 11.7, H–C(6′)); 11.27 (br. *s*, NH); 11.31 (br. *s*, NH). ^{13}C-NMR (75 MHz, (D$_6$)DMSO): 113.3; 118.4; 119.4; 128.0; 129.8; 133.8; 140.4; 150.1; 151.1; 153.0; 163.6 (C=O); 163.7 (C=O). ESI-MS: 266 ([$M-H$]$^-$). HR-MS: 266.0570 ([$M-H$]$^-$, $C_{14}H_8N_3O_3^-$; calc. 266.0566). Anal. calc. for $C_{14}H_9N_3O_3$ (267.24): C 62.92, H 3.39, N 15.72; found: C 62.67, H 3.30, N 15.68.

*4-(1,3,4,5-Tetrahydro-4-oxo-2-thioxo-2*H-*pyrano[2,3-*d*]pyrimidin-5-yl)benzonitrile* (**3i**). Yield: 65 mg (46%[i]), 85 mg (60%[ii]). Orange crystals. M.p. 310–313°. IR (KBr): 3364, 3271, 3087, 3017, 2887, 2584, 2224 (CN), 1682, 1599, 1531, 1447, 1413, 1369, 1318, 1279, 1227, 1201, 1166, 1145, 1003, 826, 801, 657. ^{1}H-NMR (300 MHz, (D$_6$)DMSO): (*d*, ^3J = 15.6, H–C(5′)); 7.84 (*d*, ^3J = 8.4, H–C(2), H–C(6)); 7.93 (*d*,

^3J = 8.4, H–C(3), H–C(5)); 8.02 (*d*, ^3J = 11.7, H–C(7′)); 8.50 (*dd*, ^3J(5,6) = 15.6, ^3J(6,7) = 11.7, H–C(6′)); 12.37 (br. *s*, NH); 12.40 (br. *s*, NH). ^{13}C-NMR (75 MHz, (D_6)DMSO): 113.5; 118.6; 119.4; 128.3; 129.9; 133.9; 140.4; 151.1; 153.8; 161.5 (arom. C, C=O); 162.0 (arom. C, C=O); 179.5 (C=S). ESI-MS: 282 ([M – H]$^-$). HR-MS: 282.0349 ([M – H]$^-$, $C_{14}H_8N_3O_2S^-$; calc. 282.0337). Anal. calc. for $C_{14}H_9N_3O_2S$ (283.31): C 59.35, H 3.20, N 14.83; found: C 59.26, H 3.11, N 14.78.

*4-(1,3,4,5-Tetrahydro-2,4-dioxo-2*H*-pyrano[2,3-*d*]pyrimidin-5-yl)benzoic Acid* (**3j**). Yield: 63 mg (44%[i]), 60 mg (42%[ii]). Yellow crystals. M.p. > 350°. IR (KBr): 3550, 3284, 3054, 2847, 2652, 2519, 1731, 1694, 1607, 1598, 1568, 1549, 1506, 1440, 1415, 1383, 1319, 1295, 1238, 1214, 1175, 1113, 1052, 1013, 961, 848, 827, 790, 767. ^{1}H-NMR (300 MHz, (D_6)DMSO): 7.73 – 7.78 (*m*, H–C(3), H–C(5), H–C(5′)); 8.00 – 8.04 (*m*, H–C(2), H–C(6), H–C(7′)); 8.50 (*dd*, ^3J(5,6) = 15.6, ^3J(6,7) = 11.7, H–C(6′)); 11.25 (br. *s*, NH); 11.29 (br. *s*, NH); 13.14 (br. *s*, COOH). ^{13}C-NMR (75 MHz, (D_6)DMSO): 117.8; 127.1; 129.4; 130.9; 133.2; 140.1; 151.2; 151.4; 153.6; 163.7 (C=O); 163.9 (C=O); 167.6 (C=O). ESI-MS: 285 ([M – H]$^-$). HR-MS: 285.0501 ([M – H]$^-$, $C_{14}H_9N_2O_5^-$; calc. 285.0511). Anal. calc. for $C_{14}H_{10}N_2O_5$ (286.24): C 58.74, H 3.52, N 9.79; found: C 58.46, H 3.43, N 9.66.

*4-(1,3,4,5-Tetrahydro-4-oxo-2-thioxo-2*H*-pyrano[2,3-*d*]pyrimidin-5-yl)benzoic Acid* (**3k**). Yield: 30 mg (20%[i]), 41 mg (27%[ii]). Orange crystals. M.p. > 350°. IR (KBr): 3360, 3148, 3092, 2888, 2668, 2541, 1693, 1660, 1607, 1555, 1532, 1417, 1380, 1300, 1224, 1172, 1147, 1104, 998, 847, 787, 766. ^{1}H-NMR (300 MHz, (D_6)DMSO): 7.77 – 7.84 (*m*, H–C(3), H–C(5), H–C(5′)); 8.01 – 8.07 (*m*, H–C(2), H–C(6), H–C(7′)); 8.51 (*dd*, ^3J(5,6) = 15.6, ^3J(6,7) = 12.0, H–C(6′)); 12.35 (br. *s*, NH); 12.38 (br. *s*, NH); 13.15 (br. *s*, COOH). ^{13}C-NMR (75 MHz, (D_6)DMSO): 118.0; 127.4; 129.6; 131.0; 133.4; 140.0; 152.4; 154.5; 161.6 (arom. C, C=O); 162.1 (arom. C, C=O); 167.6 (C=O); 179.5 (C=S). ESI-MS: 301 ([M – H]$^-$). HR-MS: 301.0290 ([M – H]$^-$, $C_{14}H_9N_2O_4S^-$; calc. 301.0283). Anal. calc. for $C_{14}H_{10}N_2O_4S$ (302.31): C 55.62, H 3.33, N 9.27; found: C 55.27, H 3.35, N 8.95.

*Methyl 4-(1,3,4,5-Tetrahydro-2,4-dioxo-2*H*-pyrano[2,3-*d*]pyrimidin-5-yl)benzoate* (**3l**). Yield: 42 mg (28%[i]), 45 mg (30%[ii]). Yellow crystals. M.p. 296 – 300°. IR (KBr): 3468, 3218, 3079, 2957, 2809, 1739, 1694, 1716, 1678, 1606, 1427, 1379, 1309, 1279, 1264, 1213, 1179, 1106, 1000, 958, 827, 766, 696. ^{1}H-NMR (300 MHz, (D_6)DMSO): 3.88 (*s*, Me); 7.73 – 7.81 (*m*, H–C(3), H–C(5), H–C(5′)); 8.00 – 8.06 (*m*, H–C(2), H–C(6), H–C(7′)); 8.51 (*dd*, ^3J(5,6) = 15.6, ^3J(6,7) = 12.0, H–C(6′)); 11.26 (br. *s*, NH); 11.30 (br. *s*, NH); 13.14 (br. *s*, COOH). ^{13}C-NMR: compound could not be dissolved in sufficient concentration in any known solvent. ESI-MS: 299 ([M – H]$^-$). HR-MS: 299.0670 ([M – H]$^-$, $C_{15}H_{11}N_2O_5^-$; calc. 299.0668). Anal. calc. for $C_{15}H_{12}N_2O_5$ (300.27): C 60.00, H 4.03, N 9.33; found: C 59.79, H 3.88, N 9.34.

*5-(4-Nitrobenzyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**4**). Yield: 42 mg (32%). Orange crystals. M.p. > 300° ([14]: 265 – 266°). IR (KBr): 3427, 3157, 3013, 2928, 2853, 1674, 1654, 1616, 1508, 1490, 1387, 1368, 1350, 1175, 1111, 860, 834, 807, 774, 700. ^{1}H-NMR (300 MHz, (D_6)DMSO): 3.49 (*s*, CH_2); 7.45 (*d*, ^3J = 8.7, H–C(2), H–C(6)); 8.05 (*d*, ^3J = 8.7, H–C(3), H–C(5)); 9.08 (br. *s*, NH); signal for CH not seen. ^{13}C-NMR (75 MHz, D_2O + 10 µl 40% NaOD): 28.4 (CH_2); 89.0 (CH); 123.2 (arom. C); 128.2 (arom. C); 145.2 (arom. C); 151.7 (arom. C); 159.5 (C=O); 171.3 (C=O). ESI-MS: 262 ([M – H]$^-$). HR-MS: 262.0461 ([M – H]$^-$, $C_{11}H_8N_3O_5^-$; calc. 262.0464).

Preparation of **3d** *from 5-(4-Nitrobenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione.* 5-(4-Nitrobenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (100 mg, 383 µmol) was heated to reflux for 3 d in EtOH/H_2O 1:1 (20 ml), then the mixture was cooled to r.t., and the product filtered off and washed with EtOH to afford 22 mg (20%) of yellow crystals. The product was identical to the one obtained according to the *General Procedure* for the preparation of **3a** – **3l**.

Preparation of **3d** *from MeCHO.* 4-Nitrobenzaldehyde (250 mg, 1.65 mmol) and barbituric acid (**2a**; 212 mg, 1.65 mmol) were dissolved in H_2O (40 ml) at 100°, the soln. was cooled to r.t., and acetaldehyde (280 µl, 4.96 mmol) was added. The mixture was heated at 100° for 1 h, and the product was filtered off, and washed with H_2O and EtOH to give 309 mg (65%) of yellow crystals. The product was identical to the one obtained according to the *General Procedure* for the preparation of **3a** – **3l**.

This work was supported by the *EU FP6 Project EUR-INTAFAR* (LSHM-CT-2004-512138) and by the *Slovenian Research Agency* (Grant P1-0208).

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Received August 27, 2010