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Easy Access to 1*H*-Pyrrolo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8(3*H*,7*H*)-tetraone and Selectively N^7-Substituted Analogues through Key Synthons

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To synthesize unsubstituted pyrrolo[3′,4′:5,6] pyrido[2,3-*d*]-pyrimidine-2,4,6,8-tetraone, we have developed new synthon 4-formyl-3-hydroxy-2,5-dioxo-2,5-dihydro-1*H*-pyrrole, which was then treated under mild conditions with 6-amino-uracil. This new synthetic pathway could be extended to the preparation of N^7-selectively substituted heterocycles by starting either from this new synthon or from its *N*-substituted analogues. Examples of N^1,N^7-disubstituted and N^1,N^3,N^7-trisubstituted derivatives are also described. We have thus developed new synthons that lead to easy access to the unsubstituted pyrrolo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8-tetraone skeleton and to selectively N^7-substituted analogues.

Introduction

In connection with their similarities to DNA bases, pyrimidinediones constitute a major class of heterocyclic compounds, which have various pharmaceutical applications[1]. N^1,N^3-Unsubstituted pyrimidinediones possess antineoplastic and antiviral activities, for example.[2] The bicyclic N^1,N^3-unsubstituted pyrido[2,3-*d*]pyrimidinedione structural motif has also received much attention and shows biological activity as antineoplastic,[3] antiviral,[4] antiasthmatic and antiallergics.[5]

Many tricyclic heterocycles in which a pyrido[2,3-*d*]pyrimidine-2,3(1*H*,3*H*)-dione nucleus is fused with a six-membered ring have been described, particularly in the 5-deazaflavin series. Despite the potential biological interest of analogues fused with a five-membered cycle or heterocycle, few papers concerning these linear tricyclic heterocyclic series have been published.[6] These observations and our interest in active molecular design for drugs led us to attempt an efficient synthetic pathway to the synthesis of 1*H*-pyrrolo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8(3*H*,7*H*)-tetraone (**1**) and selectively N^7-substituted derivatives (Figure 1).

To the best of our knowledge, only one publication reports the synthesis of this heterocyclic skeleton. 7-Phenyl-1,3-dimethyl derivative **6** has been obtained under solid-state microwave irradiation[6] or under classical thermal conditions in benzene[6] by reacting *N*-phenylmaleimide (**5**) with 6-amino-1,3-dimethyl-5-formyluracil (**4**), which was prepared from commercially available 6-amino-1,3-dimethyluracil (**3**;[7] Scheme 1).

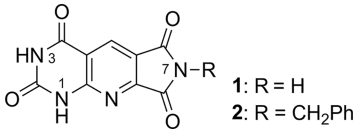
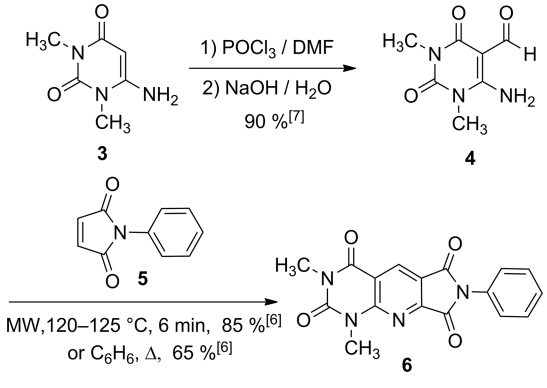


Figure 1. Structure of compounds **1** and **2**.



Scheme 1.

This pathway is very efficient for the preparation of trisubstituted heterocycles. However, a classical approach is not appropriate for the synthesis of the unsubstituted core that involves very insoluble starting materials. A solventless approach requires particular materials and cannot be used for the preparation of N^1,N^3-dimethyl-substituted heterocycles (vide infra).

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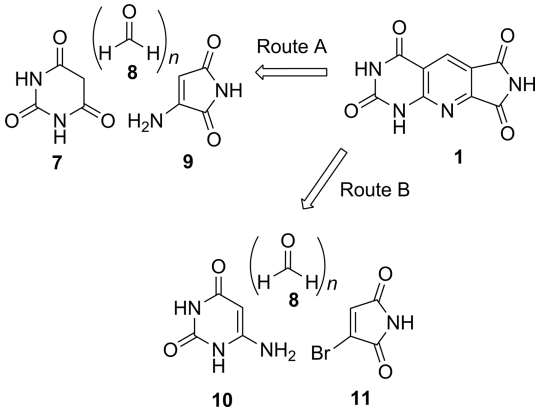
In this paper, we describe an original and easy access to unsubstituted heterocyclic skeleton **1** and to selectively N^7-substituted analogues. N^7-Benzyl compound **2**, which was chosen as a model, was synthesized by two different routes. Furthermore, we have also investigated the possibility that these new processes could be extended to the preparation of N^1,N^7-disubstituted and N^1,N^3,N^7-trisubstituted analogues.

Results and Discussion

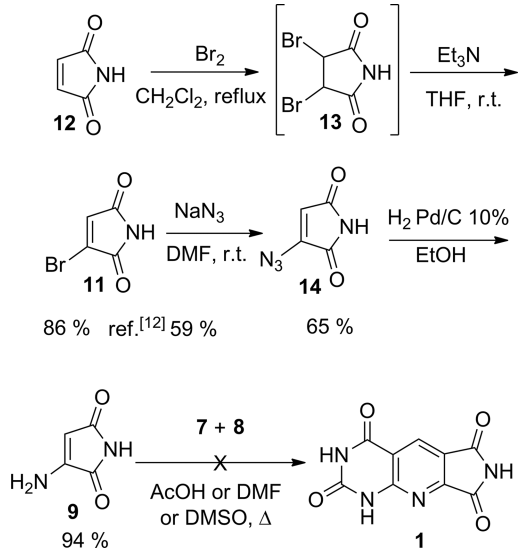
In 1882, Hantzsch described the synthesis of symmetrical 1,4-dihydropyridines under mild conditions by condensation of two equivalents of a β-dicarbonyl compound with one equivalent of an aldehyde in the presence of ammonia.[8] Subsequent oxidation afforded the corresponding pyridines. Later, it was shown that same products can been prepared by using an aldehyde, an α-methylenic ketone and a ketimine, and that the scope of this synthesis can be extended to asymmetrical dihydropyridines.[9a,9b] The synthetic potential of the unsymmetrical Hantzsch reaction has been recognized and illustrated by the synthesis of numerous polyhydroquinolines.[9c,9d] Enantioselective organocatalytic syntheses have also been described.[9e] Based on these extensions of the Hantzsch reaction, our group has developed simple and convenient reactions for the synthesis of various tricyclic nitrogen heterocycles[10] and specially pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones, which have been obtained by a three-component one-pot reaction that involves barbituric acid, paraformaldehyde, and anilines.[11] In continuation to this work, two "three-component one-pot" strategies have been envisaged for the preparation of unsubstituted compound **1** (Scheme 2).



Scheme 2.

Route A, in which aniline has been replaced by aminomaleimide (**9**), and Route B, which uses commercially available 6-aminouracil (**10**) and bromomaleimide (**11**), which is more easily accessible than the hydroxymaleimide.

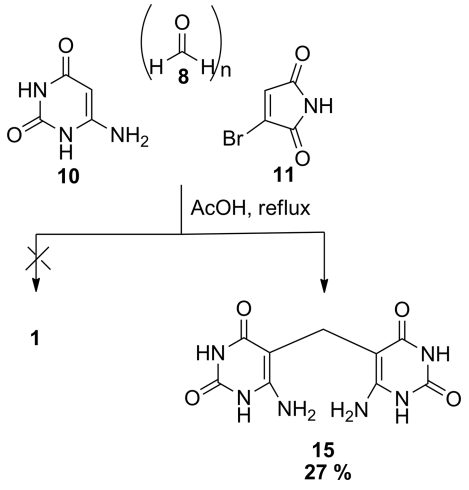
Route A. The synthesis of aminomaleimide (**9**) was realized in two steps and 61% overall yield from bromomaleimide (**11**) by reaction with sodium azide in dimethylformamide (DMF) at room temperature and catalytic reduction of resulting azido derivative **14** (Scheme 3). Bromomaleimide (**11**) was prepared by dibromination of maleimide (**12**) and subsequent elimination of hydrobromhydric acid in accordance with the method previously described by Baker.[12] However, replacement of chloroform by dichloromethane in the first step and modification of the work up allowed us to improve the yield to 86% from 59%.



Scheme 3.

With the aminomaleimide in hand, it was used in the three-component reaction with paraformaldehyde (**8**) and barbituric acid (**7**). However, regardless of the conditions used [reflux temperatures in AcOH, DMF or dimethyl sulfoxide (DMSO)], several inseparable derivatives were obtained. Replacement of the latter by 6-chlorouracil was also unsuccessful.

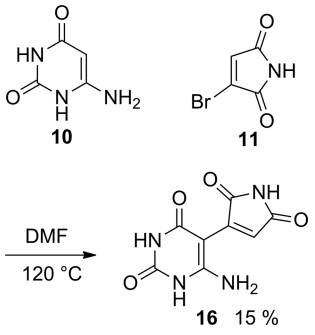
Route B. According to the literature 6-aminouracil could react either as an enamine or as a classical amine.[13] Consequently, we expected that in the first step of the envisaged one-pot reaction, the amino group of **10** would substitute the bromine of **11**. Unfortunately, in an equimolar mixture of compounds **10**, **8** and **11** in acetic acid at reflux tempera-



Scheme 4.

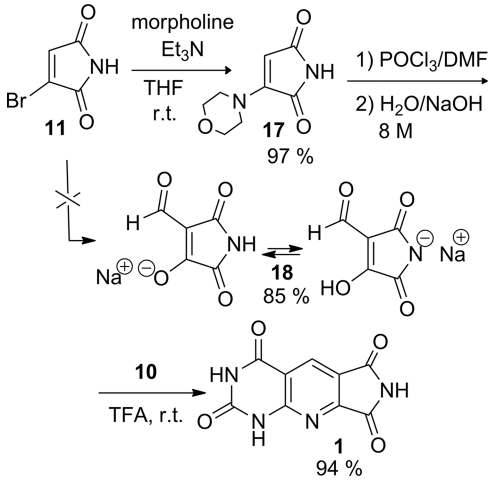
tures, the 6-aminouracil reacted as an enamine on the paraformaldehyde to give a small amount of bis(4-amino-2,6-dioxo-5-tetrahydropyrimidinyl)methane[14] (**15**; Scheme 4).

In an attempt to carry out the synthesis in a two-step procedure, compounds **10** and **11** were heated in DMF. Only a small amount of **16** was isolated from the multicompound reaction mixture (Scheme 5).



Scheme 5.

Therefore, we envisaged a multi-step synthesis in which the formyl group was first introduced on the maleimide moiety. Compound **1** was obtained in accordance to this procedure through key synthon **18**, isolated as its sodium salt (Scheme 6). Direct Vilsmeier formylation on bromomaleimide (**11**) was not possible. To increase the reactivity of the pyrrolidinedione toward electrophilic substitution, bromomaleimide (**11**) was substituted by morpholine and the Vilsmeier reaction was performed on resulting morpholino derivative **17**. During classical alkaline work-up for the hydrolysis of the iminium intermediate, the vinylamide function was also hydrolyzed to give **18** in 85% yield.



Scheme 6.

The structure of sodium salt **18** was confirmed by elemental analysis ($C_5H_2N\ NaO_4{\cdot}H_2O$), a strong molecular ion peak at m/z = 140 $[M - Na]^-$, and NMR spectroscopic data. As expected, the ^1H NMR spectrum presents only two signals (δ = 9.20 and 10.07 ppm). It is well known that several isomeric forms could co-exist in this type of heterocycle and that interpretation of the ^{13}C NMR spectroscopic data is not easy.[15]

For compound **18**, partial assignment could be achieved by analysis of the HSQC and HMBC spectra that show a ^1J coupling between the proton at δ = 9.20 ppm and the carbonyl at δ = 179.7 ppm, a ^2J coupling between the proton at δ = 9.20 ppm and the carbon at δ = 102.1 ppm and a ^3J coupling between the proton at δ = 9.20 ppm and the carbonyl at δ = 167.6 ppm. Other signals have been attributed by analysis with similar structures described in the literature (Figure 2).[16]

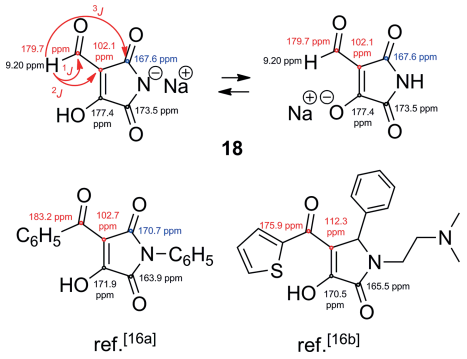


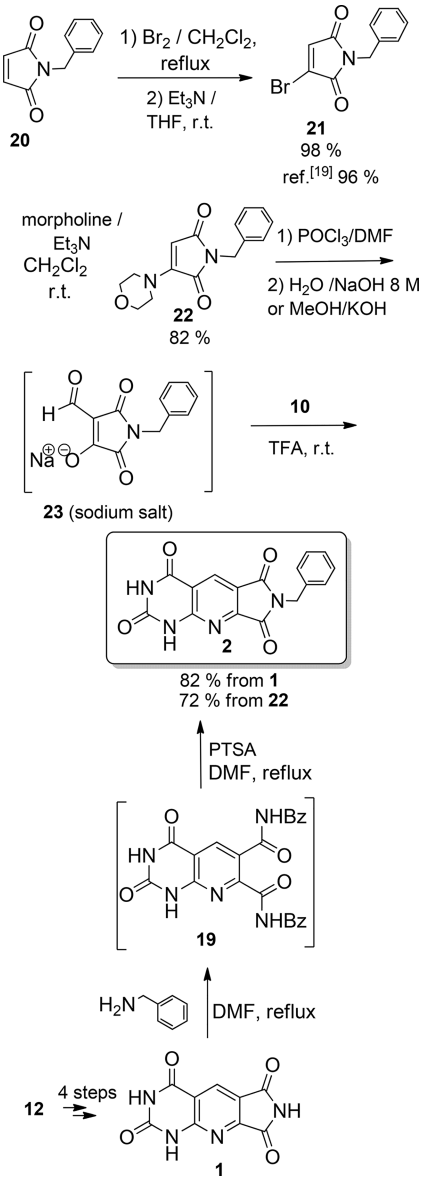
Figure 2. NMR data for compound **18** compared to literature data.

It is noteworthy that the carbonyl at δ = 179.7 ppm appears as a strong signal and carbonyls at 177.4 and 173.5 ppm as very weak signals. However, it is well known that relaxation times of carbon atoms tend to vary more widely than those for protons and that consequently their signals may be missed or not fully accumulated specially for quaternary carbons.[17] The ultimate proof of the structure was the synthesis of desired heterocycle **1** by condensation of synthon **18** with 6-aminouracil (**10**) in trifluoroacetic acid (TFA; Scheme 6).

Derivative **1** was isolated in pure 94% yield by simple filtration. According to this procedure, 1*H*-pyrrolo[3′,4′:5,6]-pyrido[2,3-*d*]pyrimidine-2,4,6,8(3*H*,7*H*)-tetraone (**1**) has been synthesized in four steps and in 67% overall yield from commercially available maleimide (**12**) and aminouracil (**10**).

The pK_a of the three NH of **1** are of the same order of magnitude (calculated pK_a in water[18] = 7.05, 7.38, 8.42 for N^1, N^3 and N^7, respectively). Consequently, selective N^7-alkylation of **1** was believed to be difficult. To obtain the N^7-substituted heterocycles, two synthetic pathways were explored (Scheme 7).

In a first classical sequential one-pot procedure, *N*-benzyl derivative **2**, chosen as a model, was synthesized in 82% yield from **1**. The imide ring of compound **1** was opened by reaction with two equivalents of benzylamine in DMF at reflux temperatures, and then resulting diamide **19** was cyclized with two equivalents of *p*-toluenesulfonic acid (PTSA).



Scheme 7.

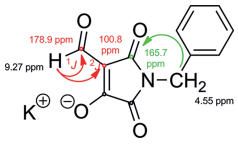


Figure 3. Compound **23** (potassium salt).

erocycle **2** by condensation with 6-aminouracil (**10**) in TFA (Scheme 7).

According to these procedures, 7-benzyl-1*H*-pyrrolo-[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8(3*H*,7*H*)-tetraone (**2**) has been synthesized either in five steps and 55% overall yield from maleimide (**12**) or in four steps with 58% overall yield from *N*-benzylmaleimide (**20**). For the preparation of N^7-benzylated analogue, the two synthetic pathways gave similar overall yields. However, the first route is more versatile because the N^7-substituent is introduced in the last step.

We have shown that the scope of the reaction could be extended to the synthesis of other *N7*-selectively substituted heterocycles (Figure 4). Good yields have been obtained by reaction of **1** with various benzylamines (unsubstituted, electron-rich and electron-poor substituted benzylamines), with phenylethylamine (compound **27**) and with an alicyclic amine (compound **28**). Attempts with aniline have not given good results so far.

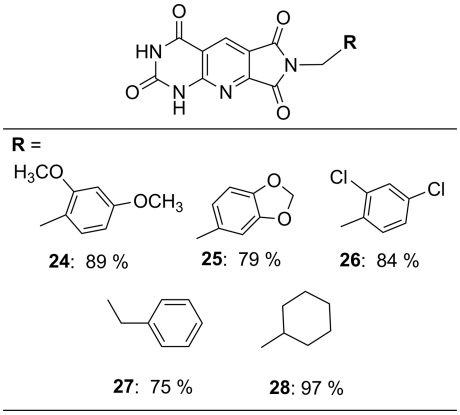


Figure 4. Other *N*-substituted derivatives.

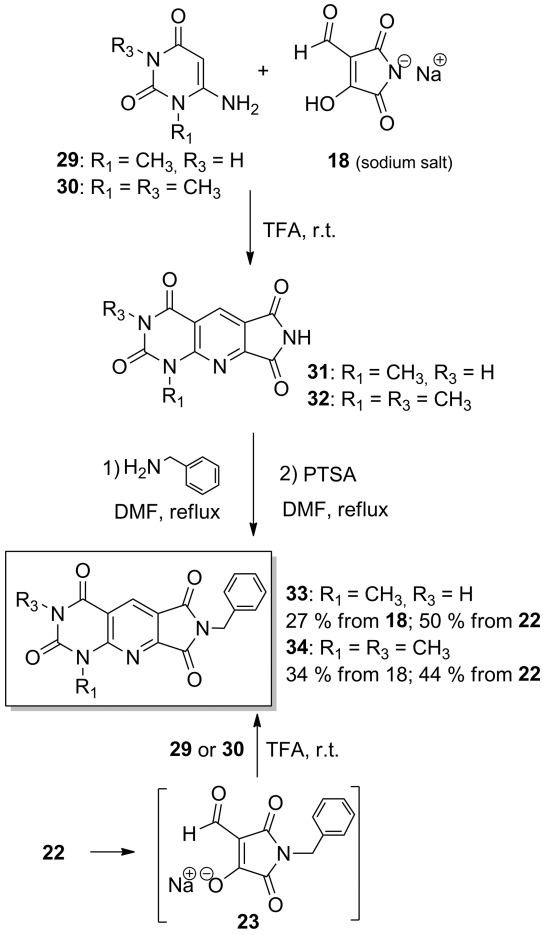
Alternatively, compound **2** was obtained from *N*-benzylmaleimide (**20**) by the same sequence as used for compound **1**: bromination of **20** into **21** in accordance with the procedure previously described,[19] substitution by morpholine to give **22**, Vilsmeier reaction and condensation with 6-aminouracil (**10**). Compound **2** was obtained from synthon **23** as the sodium salt, without isolation.

To characterize **23**, a small amount of potassium salt has been prepared (hydrolysis of the iminium intermediate with KOH/MeOH) and purified. Contrary to *N*-unsubstituted synthon **18**, the ^{13}C NMR spectrum of compound **23** does not present any signal for the enol carbon and one of the carbonyl of the imide group even if a Bruker AC 600 Spectrometer is used (Figure 3).

The structure of compound **23** was confirmed by elemental analysis ($C_{12}H_8KNO_4$) and by isolation of desired het-

To investigate the possibility of extending these reaction schemes to the preparation of di- or trisubstituted derivatives, 1-methyl-7-benzyl compound **33** and 1,3-dimethyl-7-benzyl derivative **34** were synthesized in accordance with the two synthetic pathways by using either 1-methyl-6-aminouracil (**29**) or 1,3-dimethyl-6-aminouracil (**30**) as starting materials (Scheme 8).

Interestingly, for the preparation of 1,3-dimethyl heterocycle **32**, we have tried to use the methods previously described in the literature[6] for the synthesis of compound **6** (Scheme 1). However, no reaction occurred when carbaldehyde **4** and maleimide (**12**) were heated to reflux in tetrahydrofuran (THF). Under microwave irradiation in the same solvent, several products were obtained. To increase the solubility of the starting materials, THF was replaced by DMF, but without success.



Scheme 8.

Conclusions

In order to synthesize pyrrolo[3′,4′:5,6] pyrido[2,3-*d*]pyrimidine-2,4,6,8-tetraone (**1**), we have developed new synthon 4-formyl-3-hydroxy-2,5-dioxo-2,5-dihydro-1*H*-pyrrole (**18**). We have shown that this new synthetic pathway could be extended to the preparation of N^7-selectively substituted derivatives starting from **18** or its *N*-substituted analogues. The use of these synthons for easy and versatile syntheses of other heterocyclic skeletons is now under investigation.

Experimental Section

General Remarks: Melting points were measured with a Stuart SMP3 melting point apparatus. TLC was carried out with Merck GF 254 silica-gel plates. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 300 or AC 400 spectrometers with [D_6]DMSO as both solvent and internal standard. IR spectra were obtained with a Perkin–Elmer 1600 spectrophotometer. Mass spectra were recorded with a Q-TOF Waters spectrometer. Elemental analyses were performed at the C.N.R.S. Analysis Laboratory, Gif-sur-Yvette.

Bromomaleimide (11): To maleimide (4.00 g, 40 mmol) in CH_2Cl_2 (80 mL) was added bromine (2.5 mL, 50 mmol) in CH_2Cl_2 (20 mL) dropwise. The reaction mixture was heated to reflux for 2.5 h and left to cool to room temperature over 1 h. The solvent was removed under reduced pressure. To eliminate the last traces of bromine, the resulting solid was stirred in CH_2Cl_2 and the solvent was removed under reduced pressure (three times). The crude 2,3-dibromosuccinimide was dissolved in THF (80 mL) and Et_3N (6 mL, 40 mmol) in THF (40 mL) was added over a 5 min period at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h. The solid was removed by filtration and the solvent removed under vacuum. The crude product was purified by silica-gel column chromatography (cyclohexane/EtOAc, 8:2) to afford a pale yellow powder (6.21 g, 0.0344 mol) in 86% yield, m.p. 152 °C (ref.[12] 148–151 °C).

3-Azido-1*H*-pyrrole-2,5-dione (14): A solution of 3-bromomaleimide (**11**; 1.0 g, 5.70 mmol) and sodium azide (2.22 g, 34.2 mmol) in DMF (5 mL) was stirred for 3 h at room temperature. After addition of H_2O (50 mL) to the reaction mixture and extraction with CH_2Cl_2, the organic layers were dried with anhydrous sodium sulfate, and the solvent removed under vacuum. The residue was washed with ligroin to give a crude brown solid (0.51 g, 65%). Unstable azide **14** was used without purification. ^{1}H NMR (300 MHz): δ = 6.14 (s, 1 H, CH), 11.02 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz): δ = 109.3 (CH), 144.2 (C-N^3), 167.8 (C=O), 171.0 (C=O) ppm. IR (solid): $\tilde{\nu}$ = 3215, 3124, 2294, 2133, 2094, 1774, 1697, 1605, 1370, 1330, 1303, 1247, 1133, 1043 cm^{-1}.

3-Amino-1*H*-pyrrole-2,5-dione (9): A solution of azide **14** (0.24 g, 1.74 mmol) in EtOH (20 mL) was hydrogenated for 2 h at room temperature in the presence of Pd/C (10%; 56 mg) under a hydrogen atmosphere. After filtration through a pad of Celite, the solvent was removed under reduced pressure to afford quite pure compound **9** as an orange powder (0.91 g, 94%) which was used without further purification in the next step. ^{1}H NMR (400 MHz): δ = 4.71 (s, 1 H, CH), 7.10 (br. s, 2 H, NH_2), 10.02 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz): δ = 86.1 (CH), 151.3 (H_2N-C), 169.7 (C=O), 174.1 (C=O) ppm. IR (solid): $\tilde{\nu}$ = 3380, 3171, 3101, 2736, 1761, 1705, 1629, 1603, 1400, 1345, 1271, 1186, 1116 cm^{-1}.

Bis(4-amino-2,6-dioxo-5-tetrahydropyrimidinyl)methane (15): A solution of paraformaldehyde (**8**; 15 mg, 0.5 mmol), 3-bromomaleimide (**11**; 88 mg, 0.5 mmol), and 6-aminouracil (**10**; 64 mg, 0.5 mmol) was heated to reflux in glacial AcOH (5 mL) for 18 h. After filtration of the hot solution, the purple precipitate was purified by sequential heating to reflux in AcOH and in H_2O. The resulting precipitate was filtered off to give compound **15** (46 mg, 27%) as a white powder, m.p. 352 °C (ref.[14] 360 °C). ^{1}H NMR (300 MHz): δ = 3.02 (s, 2 H, CH_2), 6.73 (br. s, 4 H, 2NH_2), 10.24 (s, 2 H, 2NH), 10.48 (s, 2 H, 2NH) ppm. ^{13}C NMR (75 MHz): δ = 16.30 (CH_2), 85.3 (2***C***=C-N), 150.3 (2C=O), 154.1 (2C=*C*-N), 166.2 (2C=O) ppm. IR (solid): $\tilde{\nu}$ = 3343, 3160, 2985, 2787, 1707, 1592, 1527, 1456, 1387, 1161, 1092, 1018 cm^{-1}.

6-Amino-5-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (16): A solution of 3-bromomaleimide (**11**; 88 mg, 0.5 mmol) and 6-aminouracil (**10**; 64 mg, 0.5 mmol) in DMF (5 mL) was stirred at 120 °C for 48 h. The solvent was removed under reduced pressure and the crude product was purified by silica-gel column chromatography (CH_2Cl_2/MeOH, 9:1) to afford compound **16** (17 mg, 15%) as a yellow powder, m.p. 364 °C. ^{1}H NMR (300 MHz): δ = 6.85 (s, 1 H, CH), 7.35 (s, 2 H, NH_2), 10.67 (s, 1 H, NH), 10.80 (br. s, 2 H, 2NH) ppm. ^{13}C NMR (75 MHz): δ = 79.8 (-*C*=C-NH_2), 125.1 (-C=*C*H-), 141.7 (-C=*C*-NH_2), 150.0 (-*C*=CH), 154.4 (C=O), 163.2 (C=O), 173.0 (C=O), 174.1 (C=O) ppm. IR (solid): $\tilde{\nu}$ = 3407, 3239, 3024, 2921, 1762, 1698, 1612, 1541, 1512, 1453, 1400, 1339, 1287, 1225, 1125, 1028 cm^{-1}. MS (ESI$^-$): *m*/*z* = 221 [M – H]$^-$.

3-Morpholino-1*H*-pyrrole-2,5-dione (17): To a solution of 3-bromomaleimide (**11**; 0.78 g, 4.44 mmol) in THF (29 mL), triethylamine (682 μL, 4.88 mmol) and morpholine (427 μL, 4.88 mmol) were added dropwise. After 1 h of stirring at room temperature, the solvent was removed under reduced pressure. The residue was washed with EtOH (13 mL) and filtered off to give **17** as a yellow powder (0.797 g, 97%), m.p. 239 °C. ^{1}H NMR (400 MHz): δ = 3.64 (m, 8 H, 4CH_2), 5.11 (s, 1 H, CH), 11.30 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz): δ = 47.3 (2CH_2), 66.1 (2CH_2), 91.0 (-C=*C*H-), 150.8 (-C=*C*-N), 169.0 (C=O),171.8 (C=O) ppm. IR (solid): $\tilde{\nu}$ = 3117, 3036, 2994, 2925, 2871, 2747, 1710, 1621, 1597, 1466, 1452, 1432, 1348, 1303, 1261, 1238, 1111, 1065, 1034 cm^{-1}. $C_8H_{10}N_2O_3 \cdot 0.25H_2O$: calcd. C 51.47, H 5.67, N 15.01; found C 51.39, H 5.49, N 14.75.

4-Formyl-3-hydroxy-2,5-dioxo-2,5-dihydro-1*H*-pyrrole, Sodium Salt (18): Under vigorous stirring, $POCl_3$ (0.4 mL, 4.3 mmol) was added dropwise to a suspension of compound **17** (400 mg, 2.15 mmol) in DMF (0.7 mL) over a 4 min period to avoid the temperature of the reaction mixture rising above 20 °C. The reaction mixture was stirred at room temperature for 2 h. After cooling and addition of H_2O (2 mL), the suspension was basified with an aqueous NaOH (8 M) to pH of 9–10. The mixture was then stirred at 40 °C overnight. The precipitate was filtered off, washed with a 1:1 H_2O/EtOH mixture (10 mL) and vacuum-dried with P_2O_5 to give salt **18** (339 mg, 85%) of as a light yellow powder, m.p. 313 °C. ^{1}H NMR (400 MHz): δ = 9.20 (s, 1 H, O=CH), 10.07 (s, 1 H, NH or OH) ppm. ^{13}C NMR (75 MHz): δ = 102.1 (-*C*=C-O), 167.6 (C=O), 173.5 (C=O), 177.4 (-C=*C*-O), 179.7 (HC=O strong signal) ppm. IR (solid): $\tilde{\nu}$ = 3404, 3181, 3077, 2695, 1790, 1744, 1720, 1676, 1653, 1626, 1590, 1468, 1401, 1365, 1329, 1231, 1095 cm^{-1}. MS (ESI$^-$): *m*/*z* = 140 [M – Na]$^-$. $C_5H_2NNaO_4 \cdot H_2O$ (181.1): calcd. C 33.16, H 2.23, N 7.74; found C 33.18, H 2.00, N 7.74.

1*H*-Pyrrolo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8(3*H*,7*H*)-tetraone (1): To a solution of 6-aminouracil (**10**; 221 mg, 1.74 mmol) in TFA (11 mL) was added synthon **18** sodium salt (315 mg, 1.58 mmol). After stirring overnight at room temperature, the resulting precipitate was filtered off, washed with EtOH (5× 1 mL) and Et_2O (5× 2 mL). To eliminate the last traces of TFA, the resulting solid was stirred in EtOH and the solvent was removed under reduced pressure (five times) to give pure compound **1** (347 mg, 94%) as a yellow powder, m.p. > 410 °C. ^{1}H NMR (300 MHz): δ = 8.45 (s, 1 H, H_5), 11.82 (s, 1 H, H1 or H3 or H7), 11.84 (s, 1 H, H1 or H3 or H7), 12.44 (s, 1 H, H1 or H3 or H7) ppm. ^{13}C NMR (75 MHz): δ = 113.2 (Cq), 122.5 (Cq), 131.9 (CH), 150.5 (C=O), 157.1 (Cq), 157.4 (Cq), 162.0 (C=O), 166.9 (C=O), 167.0 (C=O) ppm. IR (solid): $\tilde{\nu}$ = 3300, 3067, 3003, 2916, 2800, 1782, 1729, 1706, 1671, 1606, 1534, 1470, 1407, 1372, 1300, 1279, 1106, 1042, 1010, 890, 850, 817, 790, 740, 726 cm^{-1}. $C_9H_4N_4O_4 \cdot 0.25H_2O$ (236.7): calcd. C 45.68, H 1.92, N 23.67; found C 45.47, H 1.85, N 23.39.

1-Benzyl-3-morpholino-1*H*-pyrrole-2,5-dione (22): To a solution of 1-benzyl-3-bromomaleimide (**21**;[19] 3.41 g, 12.8 mmol) in CH_2Cl_2 (50 mL), Et_3N (1.79 mL, 12.8 mmol) and morpholine (1.23 mL, 14.1 mmol) were added dropwise. After 3 h of stirring at room temperature, the organic layer was washed with H_2O (3× 30 mL), dried with anhydrous sodium sulfate, and the solvent was removed under vacuum. The resulting residue was washed with MeOH (40 mL) to give **22** (2.87 g, 82%) as a yellow powder, m.p. 133 °C. ^{1}H NMR (400 MHz): δ = 3.67 (m, 8 H, 4CH_2), 4.53 (s, 2 H, CH_2-Ph), 5.26 (s, 1 H, CH), 7.20–7.35 (m, 5 H, Har) ppm. ^{13}C NMR (75 MHz): δ = 40.5 (CH_2-Ph), 47.4 (2CH_2), 66.0 (2CH_2), 89.1 (-C=*C*H-), 127.7 (2CHar), 127.8 (CHar), 129.0 (2CHar), 137.7 (Cq), 150.6 (-C=*C*-N), 167.0 (C=O), 170.4 (C=O) ppm. IR (solid): $\tilde{\nu}$ = 2994, 2877, 1747, 1698, 1617, 1587, 1497, 1454, 1432, 1406, 1390, 1346, 1304, 1282, 1255, 1240, 1209, 1133, 1120, 1100, 1077, 1043, 1028 cm^{-1}. $C_{15}H_{16}N_2O_3$ (272.30): calcd. C 66.16, H 5.92, N 10.29; found C 66.01, H 5.96, N 10.35.

1-Benzyl-4-formyl-3-hydroxy-2,5-dioxo-2,5-dihydro-1*H*-pyrrole, Potassium Salt (23): Under vigorous stirring, $POCl_3$ (2 mL, 21.5 mmol) was added dropwise to a suspension of compound **22** (1.0 g, 3.68 mmol) in DMF (8 mL) over a period of 4 min to avoiding the temperature of the reaction mixture rising above 20 °C. The reaction mixture was stirred at room temperature for 1 h. After removal of the solvent under reduced pressure, H_2O (20 mL) was added and the reaction mixture was stirred at room temperature for 20 h. The resulting precipitate was filtered off and vacuum-dried with P_2O_5. To a suspension of iminium salt in MeOH (3 mL) a methanolic KOH solution (536 mg in 15 mL, 9.5 mmol) was added. The mixture was then stirred at room temperature overnight. The precipitate was filtered off, washed with cold MeOH (2 mL) and vacuum-dried with P_2O_5 to give **23** potassium salt (446 mg, 45%) as a white powder, m.p. 238–240 °C. ^{1}H NMR (400 MHz): δ = 4.55 (s, 2 H, CH_2), 7.20–7.25 (m, 5 H, 5Har), 9.27 (s, 1 H, O=CH) ppm. ^{13}C NMR (75 MHz): δ = 39.8 (CH_2), 100.8 (-*C*=C-O), 127.5 (CH), 127.7 (2CH), 128.9 (2CH), 138.3 (Cq), 165.7 (C=O), 178.9 (C=O strong signal) ppm. IR (solid): $\tilde{\nu}$ = 3030, 2797, 2728, 1766, 1709, 1661, 1569, 1542, 1495, 1455, 1428, 1398, 1342, 1273, 1108, 925 cm^{-1}. $C_{12}H_8KNO_4$ (269.30): calcd. C 53.52, H 2.99, N 5.20; found C 53.20, H 2.96, N 4.99.

7-Benzyl-1*H*-pyrrolo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8-(3*H*,7*H*)-tetraone (2). Synthesis f**rom 1**: To a suspension of **1** (70 mg, 0.30 mmol) in DMF (444 μL) benzylamine (66 μL, 0.60 mmol) was added. The reaction mixture was heated to reflux temperatures for 2 h. To the solution, PTSA (115 mg, 0.6 mmol) was added and reflux temperatures were maintained for 10 min. The resulting precipitate was filtered off and washed with water (3× 2 mL) to give pure **2** as a white powder (80 mg, 82%).

Synthesis from 22: $POCl_3$ (0.2 mL, 2.15 mmol) was added dropwise under vigorous stirring to a suspension of compound **22** (500 mg, 1.83 mmol) in DMF (6 mL) over a period of 4 min to avoid the temperature of the reaction mixture rising above 20 °C. The reaction mixture was stirred at room temperature for 30 min. After removal of the solvent under reduced pressure, H_2O (40 mL) was added. The resulting suspension was basified with an aqueous NaOH (8 M) to pH of 9–10. The mixture was then stirred at room temperature for 48 h. The solvent was removed under reduced pressure and crude product **23** was used without further purification. A solution of crude compound **23** and 6-aminouracil (**10**; 234 mg, 1.83 mmol) in TFA (12 mL) was stirred for 48 h at room temperature. The solvent was removed under reduced pressure. Addition of EtOH (25 mL) to the oily residue gave a precipitate, which was filtered and washed with EtOH (5× 1 mL) and then with Et_2O (5× 2 mL). To eliminate the last traces of TFA, the resulting solid was stirred in EtOH and the solvent was removed under reduced pressure (five times) to give pure compound **2** (426 mg, 72%) as a white powder, m.p. 352 °C. ^{1}H NMR (300 MHz): δ = 4.81 (s, 2 H, CH_2), 7.29–7.35 (m, 5 H, Har), 8.52 (s, 1 H, H5), 11.88 (s, 1 H, H1 or H3), 12.51 (s, 1 H, H1 or H3) ppm. ^{13}C NMR (75 MHz): δ = 41.6 (CH_2), 113.2 (Cq), 121.6 (Cq), 127.9 (2CH), 128.0 (Cq), 129.0 (2CH), 132.0 (CH), 136.7 (CH), 150.5 (C=O), 156.5 (Cq), 157.5 (Cq), 161.9 (C=O), 165.6 (C=O), 165.7 (C=O) ppm. IR (solid): $\tilde{\nu}$ = 3207, 3033, 1709, 1661, 1626, 1609, 1533, 1496, 1471, 1457, 1433, 1414, 1391, 1355, 1339, 1303, 1283, 1249, 1208, 1186, 1153, 1117, 1102, 1077, 1039, 1030, 1002 cm^{-1}. $C_{16}H_{10}N_4O_4 \cdot 0.5H_2O$ (331.3): calcd. C 58.01, H 3.35, N 16.91; found C 58.39, H 3.11, N 16.92.

1*H*-7-(2,4-Dimethoxybenzyl)-pyrrolo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8(3*H*,7*H*)-tetraone (24): Compound **24** was prepared by using 2,4-dimethoxybenzylamine (90 μL, 0.60 mmol) in accordance with the same procedure and work up as described for compound **2** (from **1**). Reaction time: 2 h and 15 h, yield 89%, m.p. 295 °C. ^{1}H NMR (300 MHz): δ = 3.73 (s, 3 H, OMe), 3.78 (s, 3 H, OMe), 4.69 (s, 2 H, CH_2-N), 6.43 (dd, $J_{H5'-H6'}$ = 8.1, $J_{H5'-H3'}$ = 2.1 Hz, 1 H, H5′), 6.55 (d, $J_{H3'-H5'}$ = 2.1 Hz, 1 H, H3′), 7.09 (d, $J_{H6'-H5'}$ = 8.1 Hz, 1 H, H6′), 8.50 (s, 1 H, H5), 11.87 (s, 1 H, H1), 12.50 (s, 1 H, H3) ppm. ^{13}C NMR (75 MHz): δ = 36.5 (CH_2-N), 55.3 (OMe), 55.6 (OMe), 98.3 (CH), 104.5 (CH), 112.8 (Cq), 115.7 (Cq), 121.2 (Cq), 128.8 (CH), 131.4 (CH), 150.0 (Cq), 156.0 (Cq), 157.0 (CO), 157.5 (Cq), 160.1 (CO), 161.5 (CO), 165.0 (CO), 165.1 (Cq) ppm. IR (solid): $\tilde{\nu}$ = 3232, 3101, 3030, 2813, 1775, 1735, 1708, 1689, 1606, 1589, 1528, 1511, 1450, 1435, 1369, 1382, 1335, 1272, 1295, 1211, 1185, 1161, 1136, 1062, 1035, 1027, 966, 943, 933, 918, 853, 817 cm^{-1}. $C_{18}H_{14}N_4O_6$·0.5H_2O (391.3): calcd. C 55.24, H 3.86, N 14.32; found C 55.14, H 3.79, N 14.24.

7-(3,4-Methylenedioxybenzyl)-1*H*-pyrrolo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8(3*H*,7*H*)-tetraone (25): Compound **25** was prepared in accordance with the same procedure and work up as described for compound **2** by using 3,4-methylenedioxybenzylamine (83 mg, 0.60 mmol). Reaction times: 2 h and 17 h, yield 79%, m.p. 352 °C. ^{1}H NMR (300 MHz): δ = 4.70 (s, 2 H, CH_2-N), 5.98 (s, 2 H, O-CH_2-O), 6.83 (d, $J_{H5'-H6'}$ = 7.8 Hz, 1 H, H6′), 6.86 (d, $J_{H5'-H6'}$ = 7.8 Hz, 1 H, H5′), 6.91 (s, 1 H, H2′), 8.49 (s, 1 H, H5), 11.93 (s, 1 H, H1), 12.41 (s, 1 H, H3) ppm. ^{13}C NMR (75 MHz): δ = 41.0 (CH_2-N), 101.1 (O-CH_2-O), 108.3 (2CH), 112.7 (Cq), 121.2 (CH, Cq), 130.0 (Cq), 131.5 (CH), 146.6 (Cq), 147.4 (Cq), 150.1 (CO), 156.1 (Cq), 157.1 (Cq), 161.5 (CO), 165.1 (CO), 165.2 (CO) ppm. IR (solid): $\tilde{\nu}$ = 3204, 3045, 2895, 2859, 1947, 1804, 1742, 1707, 1678, 1618, 1533, 1500, 1491, 1442, 1428, 1384.1366, 1337, 1320, 1282, 1244, 1196, 1152, 1111, 1097, 1032, 976, 947, 934, 924, 848, 839, 808 cm^{-1}. $C_{17}H_{10}N_4O_6$·0.25H_2O (370.8): calcd. C 55.07, H 2.85, N 14.24; found C 55.84, H 3.00, N 15.45.

7-(2,4-Dichlorobenzyl)-1*H*-pyrrolo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8(3*H*,7*H*)-tetraone (26): Compound **26** was prepared in accordance with the same procedure and work up as described for compound **2** by using 2,4-dichlorobenzylamine (80 μL, 0.60 mmol). Reaction times: 2 h and 17 h, yield 84%, m.p. 367 °C. ^{1}H NMR (300 MHz): δ = 4.85 (s, 2 H, CH_2-N), 7.39 (dd, $J_{H5'-H6'}$ = 8.3, $J_{H5'-H3'}$ = 1.5 Hz, 1 H, H5′), 7.47 (d, $J_{H5'-H6'}$ = 8.3 Hz, 1 H, H6′), 7.68 (d, $J_{H3'-H5'}$ = 1.5 Hz, 1 H, H3′), 8.52 (s, 1 H, H5), 11.82 (s, 1 H, H1), 12.52 (s, 1 H, H3) ppm. ^{13}C NMR (75 MHz): δ = 55.0 (CH_2-N), 112.8 (Cq), 121.2 (Cq), 127.5 (CH), 128.9 (CH), 130.5 (CH), 131.6 (Cq), 132.4 (CH), 132.7 (Cq), 133.0 (Cq), 150.1 (CO), 156.1 (Cq), 157.1 (Cq), 161.5 (CO), 165.0 (CO), 165.1 (CO) ppm. IR (solid): $\tilde{\nu}$ = 3049, 2930, 2786, 1784, 1722, 1682, 1646, 1605, 1566, 1535, 1474, 1450, 1414, 1398, 1378, 1340, 1318, 1287, 1254, 1197, 1187, 1151, 1119, 1102, 1072, 1045, 998, 989, 959, 934, 858, 831, 813 cm^{-1}. $C_{16}H_8Cl_2N_4O_4$·DMF: calcd. C 49.15, H 3.26, N 15.09; found C 48.72, H 3.30, N 14.85.

7-Phenylethyl-1*H*-pyrrolo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8(3*H*,7*H*)-tetraone (27): Compound **27** was prepared in accordance with the same procedure and work up as described for compound **2** by using phenylethylamine (72 μL, 0.60 mmol). Reaction times: 5 h and 17 h, yield 75%, m.p. 360 °C ^{1}H NMR (300 MHz): δ = 2.92 (t, J = 6.9 Hz, 2 H, CH_2-Ph), 3.84 (t, J = 6.9 Hz, 2 H, CH_2-N), 7.15–7.32 (m, 5 H, Har), 8.46 (s, 1 H, H5), 11.85 (s, 1 H, H1), 12.47 (s, 1 H, H3) ppm. ^{13}C NMR (75 MHz): δ = 33.6 (CH_2-Ph), 39.0 (CH_2-N), 112.8 (Cq), 121.0 (Cq), 126.5 (CH), 128.5 (2CH), 128.7 (2CH), 131.3 (CH), 138.2 (Cq), 150.0 (CO), 155.8 (Cq), 157.0 (Cq), 161.5 (CO), 165.0 (CO), 165.1 (CO) ppm. IR (solid): $\tilde{\nu}$ = 3604, 3478, 3164, 3028, 3055, 2817, 1778, 1740, 1697, 1674, 1604, 1540, 1497, 1466, 1455, 1437, 1398, 1383, 1338, 1287, 1241, 1188, 1150, 1116, 1107, 1040, 1028, 987, 905, 866, 807 cm^{-1}. $C_{17}H_{12}N_4O_4$·0.75H_2O: calcd. C 58.62, H 3.86, N 16.09; found C 58.48, H 3.89, N 16.13.

7-Cyclohexylmethyl-1*H*-pyrrolo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8(3*H*,7*H*)-tetraone (28): Compound **28** was prepared in accordance with the same procedure and work up as described for compound **2** by using cyclohexylmethylamine (78 μL, 0.60 mmol). Reaction times: 2 h and 17 h, yield 97%, m.p. 390–392 °C. ^{1}H NMR (400 MHz): δ = 0.87–1.00 (m, 2 H, CH_2), 1.07–1.23 (m, 3 H, CH, CH_2), 1.55–1.74 (m, 6 H, 3CH_2), 3.43 (d, $J_{CH2N-CH}$ = 5.2 Hz, 2 H, CH_2-N), 8.46 (s, 1 H, H5), 11.84 (s, 1 H, H1), 12.46 (s, 1 H, H3) ppm. ^{13}C NMR (100 MHz): δ = 25.2 (2CH_2), 25.8 (CH), 30.3 (2CH_2), 36.6 (CH_2), 43.9 (CH_2-N), 112.6 (Cq), 121.1 (Cq), 131.3 (CH), 150.0 (CO), 155.9 (Cq), 157.0 (Cq), 161.5 (CO), 165.4 (CO), 165.6 (CO) ppm. IR (solid): $\tilde{\nu}$ = 3208, 2925, 2849, 1775, 1703, 1660, 1625, 1610, 1533, 1468, 1449, 1387, 1362, 1336, 1304, 1282, 1242, 1187, 1164, 1078, 1041, 1012, 955, 936, 916, 866, 836, 813 cm^{-1}. $C_{16}H_{16}N_4O_4$·0.5H_2O (337.3): calcd. C 56.97, H 5.09, N 16.61; found C 57.30, H 4.78, N 16.61.

1-Methyl-1*H*-pyrrolo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8-(3*H*,7*H*)-tetraone (31): Compound **31** was prepared in accordance with the same procedure and work up as described for compound **1** by using 6-amino-1-methyluracil (**29**; 117 mg, 0.829 mmol) in TFA (6 mL) and synthon **18** (150 mg, 0.753 mmol). Reaction time: 24 h at room temperature. Compound **31** (105 mg, 57%) was isolated as a yellow powder, m.p. 312 °C. ^{1}H NMR (400 MHz): δ = 3.57 (s, 3 H, Me), 8.52 (s, 1 H, H5), 11.86 (s, 1 H, H3 or H7), 12.12 (s, 1 H, H3 or H7) ppm. ^{13}C NMR (75 MHz): δ = 29.6 (Me), 114.5 (Cq), 122.3 (Cq), 132.0 (CH), 150.7 (C=O), 156.4 (Cq), 157.0 (Cq), 160.9 (C=O), 166.8 (C=O), 166.9 (C=O) ppm. IR (solid): $\tilde{\nu}$ = 3515, 3304, 3187, 3061, 2803, 1786, 1754, 1738, 1692, 1615, 1602, 1505, 1472, 1416, 1397, 1381, 1346, 1313, 1292, 1181, 1121, 1074, 993, 947, 849, 818 cm^{-1}. $C_{10}H_6N_4O_4$·H_2O (264.2; 246.18): calcd. C 45.46, H 3.05, N 21.21; found C 45.09, H 2.63, N 20.80.

7-Benzyl-1-methyl-1*H*-pyrrolo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8(3*H*,7*H*)-tetraone (33): Compound **33** was prepared by the same procedures as used for compound **2**.

Synthesis f**rom 31:** N^3,N^7-unsubstituted heterocycle **31** (50 mg, 0.203 mmol), DMF (1 mL), benzylamine (45 μL, 0.406 mmol) and PTSA (77 mg, 0.406 mmol). Reaction times: 2 h and 21 h to give a white powder (32 mg, 47%).

Synthesis from 22: Step 1, compound **22** (500 mg, 1.83 mmol), $POCl_3$ (0.2 mL, 2.15 mmol), DMF (6 mL). Step 2, crude compound **23** (sodium salt), 6-amino-1-methyluracil (**29**; 258 mg, 1.8 mmol) and TFA (18 mL). Reaction time: 18 h at room temperature; purification by silica-gel column chromatography (CH_2Cl_2/EtOAc, 8.5:1.5 to 7.5:2.5) to give compound **33** (303 mg, 50%) as a white powder, m.p. 294 °C. ^{1}H NMR (400 MHz): δ = 3.56 (s, 3 H, Me), 4.83 (s, 2 H, CH_2), 7.29–7.35 (m, 5 H, 5Har), 8.57 (s, 1 H, H5), 12.16 (s, 1 H, H3) ppm. ^{13}C NMR (75 MHz): δ = 29.6 (Me), 41.7 (CH_2), 114.5 (Cq), 121.4 (Cq), 128.0 (2CH, Cq), 129.0 (2CH), 132.0 (CH), 136.6 (CH), 150.7 (C=O), 155.8 (Cq), 157.0 (Cq), 160.9 (C=O), 165.5 (C=O), 165.6 (C=O) ppm. IR (solid): $\tilde{\nu}$ = 3182, 3128, 3068, 2838, 1775, 1698, 1614, 1599, 1508, 1494, 1473, 1456, 1431, 1390, 1373, 1350, 1307, 1273, 1210, 1197, 1158, 1122, 1111, 1101, 1072, 1039, 1027, 995, 981, 952, 920, 903, 826, 817 cm^{-1}. $C_{17}H_{12}N_4O_4$ (336.31): calcd. C 60.71, H 3.60, N 16.66; found C 60.26, H 3.64, N 16.59.

1,3-Dimethyl-1*H*-pyrrolo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8-(3*H*,7*H*)-tetraone (32): Compound **32** was prepared in accordance with the same procedure and work up as described for compound **1** by using 6-amino-1,3-dimethyluracil (**30**; 144 mg, 0.928 mmol) in TFA (6 mL) and synthon **18** (168 mg, 0.844 mmol). Reaction time: 72 h at room temperature. Compound **32** (160 mg, 73%) was isolated as a yellow powder, m.p. 327 °C. ^{1}H NMR (400 MHz): δ = 3.34 (s, 3 H, Me), 3.65 (s, 3 H, Me), 8.58 (s, 1 H, H5), 11.87 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz): δ = 28.9 (Me), 30.5 (Me), 113.6 (Cq), 122.5 (Cq), 132.4 (CH), 151.1 (C=O), 155.6 (Cq), 156.4 (Cq), 160.6 (C=O), 166.7 (C=O), 166.8 (C=O) ppm. IR (solid): $\tilde{\nu}$ = 3365, 3171, 3056, 2755, 1778, 1711, 1651, 1612, 1599, 1507, 1464, 1414, 1399, 1386, 1357, 1317, 1290, 1190, 1159, 1140, 1105, 1067, 1041, 991, 962, 818 cm^{-1}. $C_{11}H_8N_4O_4 \cdot 0.25H_2O$ (264.7): calcd. C 49.91, H 3.24, N 21.17; found C 50.04, H 3.18, N 21.14.

1,3-Dimethyl-7-benzyl-1*H*-pyrrolo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8(3*H*,7*H*)-tetraone (34): Compound **34** was prepared by the same procedures as used for compound **2**.

Synthesis from 32: *N*-unsubstituted heterocycle **32** (50 mg, 0.192 mmol), DMF (1 mL), benzylamine (41 µL, 0.384 mmol) and PTSA (77 mg, 0.406 mmol). Reaction times: 2 h and 46 h to give a white powder (32 mg, 47%).

Synthesis from 22: Step 1, compound **22** (500 mg, 1.83 mmol), $POCl_3$ (0.2 mL, 2.15 mmol) and DMF (6 mL). Step 2, crude compound **23** (sodium salt), 6-amino-1,3-dimethyluracil (**30**; 284 mg, 1.83 mmol) and TFA (12 mL). Reaction time: 48 h at room temperature. Purification by silica-gel column chromatography (CH_2Cl_2/EtOAc, 10:0 to 9.7:0.3) to give a white powder (277 mg, 44%), m.p. 243 °C. ^{1}H NMR (400 MHz): δ = 3.34 (s, 3 H, Me), 3.66 (s, 3 H, Me), 4.84 (s, 2 H, CH_2), 7.28–7.36 (m, 5 H, 5Har), 8.65 (s, 1 H, H5) ppm. ^{13}C NMR (75 MHz): δ = 28.9 (Me), 30.6 (Me), 41.7 (CH_2), 113.6 (Cq), 121.6 (Cq), 128.0 (2CH, Cq), 129.0 (2CH), 132.4 (CH), 136.7 (CH), 151.1 (C=O), 155.6 (Cq), 155.8 (Cq), 160.6 (C=O), 165.5 (C=O), 165.6 (C=O) ppm. IR (solid): $\tilde{\nu}$ = 3061, 3036, 2960, 1780, 1717, 1661, 1615, 1602, 1514, 1497, 1471, 1456, 1427, 1415, 1385, 1364, 1349, 1337, 1313, 1286, 1208, 1108, 1094, 1074, 1055, 1027, 990, 970, 934, 923, 906, 843, 818, 805 cm^{-1}. $C_{18}H_{14}N_4O_4$ (350.33): calcd. C 61.71, H 4.03, N 15.99; found C 61.41, H 4.05, N 16.02.

Supporting Information (see footnote on the first page of this article): ^{1}H, ^{13}C and J-MOD NMR spectra for all new compounds are available. Spectra recorded with a Bruker AC 600 spectrometer are also available

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