Two-Step Synthetic Approach to 6-Substituted Pyrido[2,3-*d*]pyrimidine(1*H*,3*H*)-2,4-diones from 6-Amino-, 6-Alkylamino-, and 6-Arylamino-1,3-dimethyluracils*

Kerstin Bischoff, Ulrich Girreser, Dieter Heber, and Martin Schütt

Pharmazeutisches Institut, Abteilung für Pharmazeutische Chemie, Christian-Albrechts-Universität Kiel, Gutenbergstraße 76, D-24118 Kiel

Reprint requests to Prof. Dr. Dieter Heber. Fax: +49(431)8801352,
E-mail: dheber@pharmazie.uni-kiel.de

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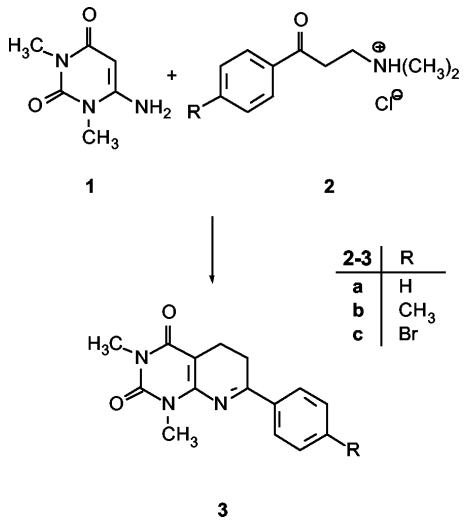
The Mannich reaction of 7-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidines **3**, easily accessible by condensation of 6-amino-1,3-dimethyluracil **(1)** with Mannich bases **2a** – **c**, gives rise to a mixture of 7-aryl-6-(*N*,*N*-dimethylaminomethyl)pyrido[2,3-*d*]pyrimidines **6** and **7** as well as 1,2-bis-(7-arylpyrido[2,3-*d*]pyrimidin-6-yl)ethane **13** the ratio of which depends on the reaction conditions and the amine used. 6-Alkylamino-1,3-dimethyluracils **15** – **18** were converted to the corresponding 5-(3-oxo-3-phenylpropyl)uracils **19** – **22** by condensation with the Mannich base **2a**. Ring closure of **19** – **22** was performed by Vilsmeier formylation to afford the 8-alkyl- and 7,8-diaryl-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbaldehydes **9** – **12** *via* the corresponding iminium salts **27** – **30**.

Key words: Cyclization, 6-Amino-1,3-dimethyluracil, Mannich Bases, Pyrido[2,3-*d*]pyrimidines, Ene Reaction

Introduction

Among the methods for the preparation of substituted 1,3-dimethylpyrido[2,3-*d*]pyrimidine(1*H*,3*H*)-2,4-diones the condensation of 6-amino-1,3-dimethyluracil (**1**) with electrophilic reagents represents a frequently employed procedure [1 – 7]. In this process the substitution pattern of the anellated pyridine ring system is determined by the structure of the bis-electrophile. We succeeded in directly introducing a substituent in position 6 of the pyridopyrimidine by the condensation of **1** with arylalkanone Mannich bases **2** affording the oxidation product of **3** (Scheme 1), described already by Troschütz and Roth [1]. With modified reaction conditions only the 5,6-dihydro derivatives **3** were isolated in yields of 50 – 80% without purification by column chromatography [8]. The aza-analogous arylalkyl ketone moiety of the anellated pyridine ring system **3** should allow an electrophilic attack at position 6 and lead to pyridopyrimidines with interesting pharmacological activities. Compounds of this type are known for their anticancer and antibacterial activities [9, 10] and are therefore important targets in medicinal chemistry. Reviewing this concept we employed the Vilsmeier formylation of **3** and isolated novel 6-substituted 1,3-dimethyl-7-phenylpyrido-[2,3-*d*]pyrimidine(1*H*,3*H*)-2,4-diones **4** and **5** (Fig. 1) depending on the reaction conditions [8].



Scheme 1. Pyrido[2,3-*d*]pyrimidines **3** from 6-amino-1,3-dimethyluracil (**1**) and aryl-alkanone Mannich bases **2**.

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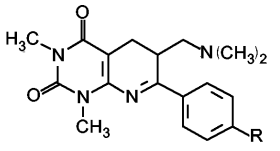

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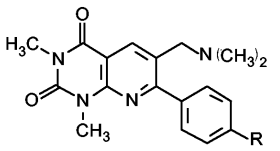

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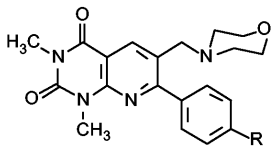


7

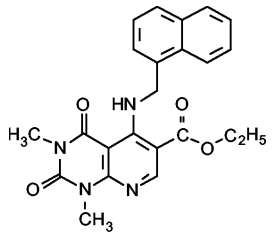
4–7	R
a	H
b	CH_3
c	Br

Fig. 1. Constitution of the pyrido[2,3-*d*]pyrimidines **4** – **7**.

As part of our continuing interest in the reactivity of the methylene group towards electrophiles [8] the Mannich reaction should produce analogous compounds **6** and **7** (Fig. 1). In addition, 6-substituted pyridopyrimidines were of interest for our project on compounds acting at adenosine receptors. Within the scope of our structure-activity studies concerning the affinity of amino-substituted pyrido[2,3-*d*]pyrimidines for A_1- and A_{2A}-adenosine receptors we found that the pyridopyrimidine **8** (Fig. 2) was a highly effective A_1-receptor antagonist with a K_i value of 5 nM at rat and 25 nM at human A_1-receptors [11]. We decided to investigate the influence of substituents at position 7 and 8 on the affinity for adenosine receptors. We synthesized compounds with electron withdrawing groups at position 6 and 7 and in addition an alkyl or phenyl substituent at the nitrogen atom. Starting from 6-alkyl- and 6-phenylamino-1,3-dimethyluracils we prepared the compounds **9** – **12**.

Results and Discussion

5,6-Dihydropyrido[2,3-*d*]pyrimidines **3** reacted with *N*,*N*-dimethylaminomethylene chloride (Eschenmoser's salt) as well as morpholine hydrochloride and paraformaldehyde in ethanolic solution to afford *via* the Mannich compounds **4** and **5** their oxidation products **6** and **7** (Scheme 2). As expected, aminomethylation in position 6 had occurred, and the analytical and spectroscopic data of **6** and **7**, namely IR, ^{1}H and ^{13}C NMR data (*cf.* Experimental Section) are in agreement with the proposed structure. TLC of the reaction mixture showed the formation of a by-product, the structure of which seemed to be always identical independent of the amine used. In order to isolate this novel compound we carried out the reaction at higher temperature using *N*,*N*-dimethylformamide as solvent. We identified the structure of this unexpected compound as 1,2-bis-(pyrido[2,3-*d*]pyrimidin-6-yl)ethane **13** (Scheme 2). The ^{1}H NMR spectrum shows the ethylene bridge as a singlet with 4 magnetically equivalent protons. The dimeric structure was unequivocally established by the mass spectrum (ESI, *cf.* Experimental Section).



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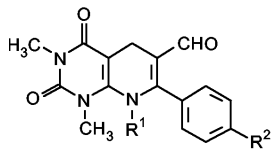


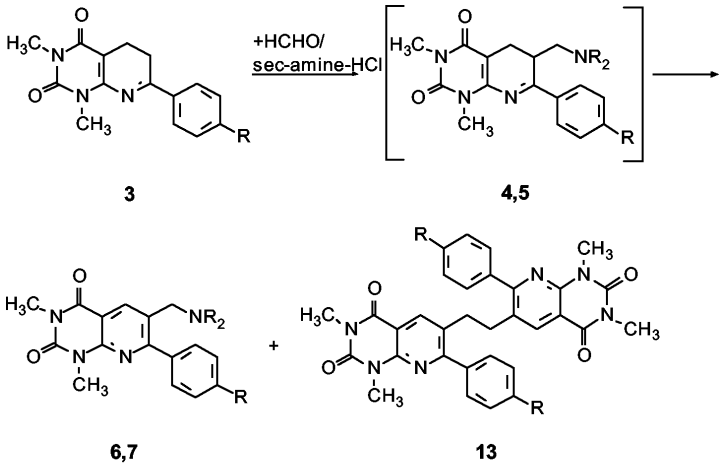
9–12

	R^1
9	CH_3
10	C_3H_7
11	$CH_2C_6H_5$
12	C_6H_5

9–12	R^2
a	H
b	OCH_3
c	Br

Fig. 2. Constitution of the pyrido[2,3-*d*]pyrimidines **8** – **12**.

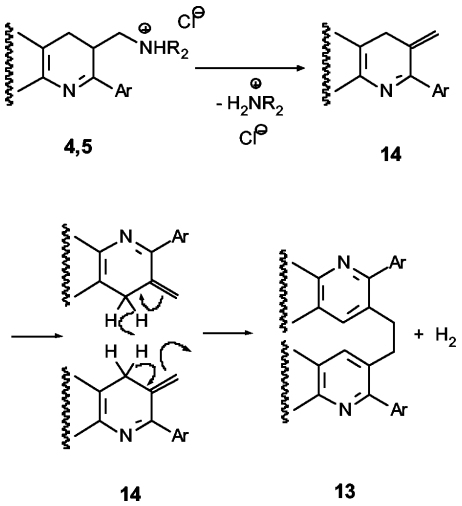
We would like to discuss two different reaction mechanisms both initiated by elimination of the amine as the key step of the oxidative dimerization to afford the ethylene compound **13** at elevated temperatures. In analogy to the intramolecular Cope rearrangement both exocyclic sp^2-hybridized vinyl carbon



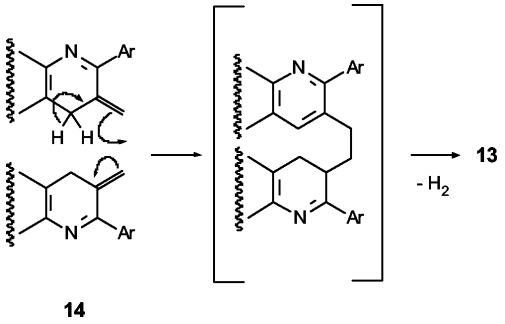
3-7,13	R
a	H
b	CH_3
c	Br

	sec-amine
6	$NH(CH_3)_2$
7	HN⟨⟩O

Scheme 2. Pyrido[2,3-*d*]pyrimidines **6**, **7**, and **13** by Mannich reaction of 5,6-dihydropyrido[2,3-*d*]pyrimidines **3**.



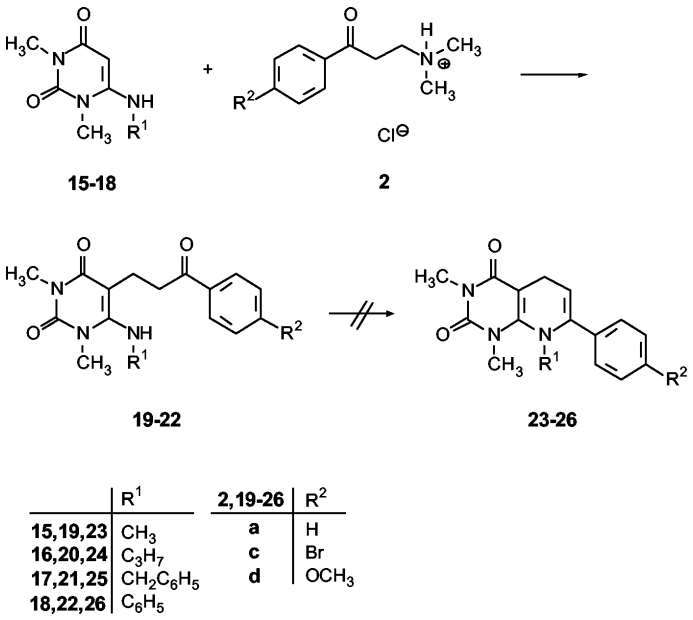
Scheme 3. Reaction mechanism suggested for the formation of 1,2-bis(pyrido[2,3-*d*]pyrimidin-6-yl)ethane **13** through the intermolecular Cope reaction.



Scheme 4. Reaction mechanism suggested for the formation of bis(pyrido[2,3-*d*]pyrimidin-6-yl)ethane **13** through the ene reaction.

atoms form the sp^3-hybridized carbon atoms of the ethylene moiety. In this connection the double bonds are shifted to the anellated pyridine ring releasing hydrogen. The reaction mechanism may be formulated as an intermolecular Cope reaction (Scheme 3) or as an ene reaction (Scheme 4). Since enophile **14** would act both as an ene, the addition of the double bond at the olefin moiety with two allylic hydrogen atoms gives rise to an ethylene intermediate substituted by the anellated dihydropyridine ring system which is then oxidized to **13**.

N^6-Substituted 6-amino-1,3-dimethyluracils **19**–**22** were prepared by nucleophilic substitution of 6-chloro-1,3-dimethyluracil with appropriate amines to form the pyrimidines **15**–**18** [12–14] followed by Michael addition of the acrylophenone formed by amine elimination of the ketone Mannich bases **2**. Ring closure to pyrido[2,3-*d*]pyrimidines **25**–**28** in analogy to the formation of **3** described in the literature [8] did not occur (Scheme 5). Instead, the 5-(3-oxo-3-phenyl)propyl substituted uracils **19**–**22** were isolated and their Vilsmeier formylation was successfully performed using a mixture of *N*,*N*-dimethylformamide and phosphorous oxychloride to afford



	R^1	2,19-26	R^2
15,19,23	CH_3	**a**	H
16,20,24	C_3H_7	**c**	Br
17,21,25	$CH_2C_6H_5$	**d**	OCH_3
18,22,26	C_6H_5		

Scheme 5. Attempted cyclization of the uracils **15** – **18** using ketone Mannich bases **2**.

the pyrido[2,3-*d*]pyrimidine-6-carboxaldehydes **9** – **12** (Scheme 6).

Conclusions

We have demonstrated that the aza-analogous aryl-alkyl ketone moiety of the anellated pyridines is also available to aminomethylation reactions. Depending on temperature and solvent we isolated pyrido[2,3-*d*]pyrimidines **6**, **7** and **13**. Different mechanisms for the formation of the dimer **13** were discussed. As to our best knowledge this is a type of Mannich reaction characterized for the first time. Contrary to **1**, N^6-substituted 6-amino-1,3-dimethyluracils **15** – **18** gave no ring closure with aryl ketone Mannich bases **2**. But under Vilsmeier conditions a novel cyclization to substituted pyrido[2,3-*d*]pyrimidines was developed.

Experimental Section

General methods

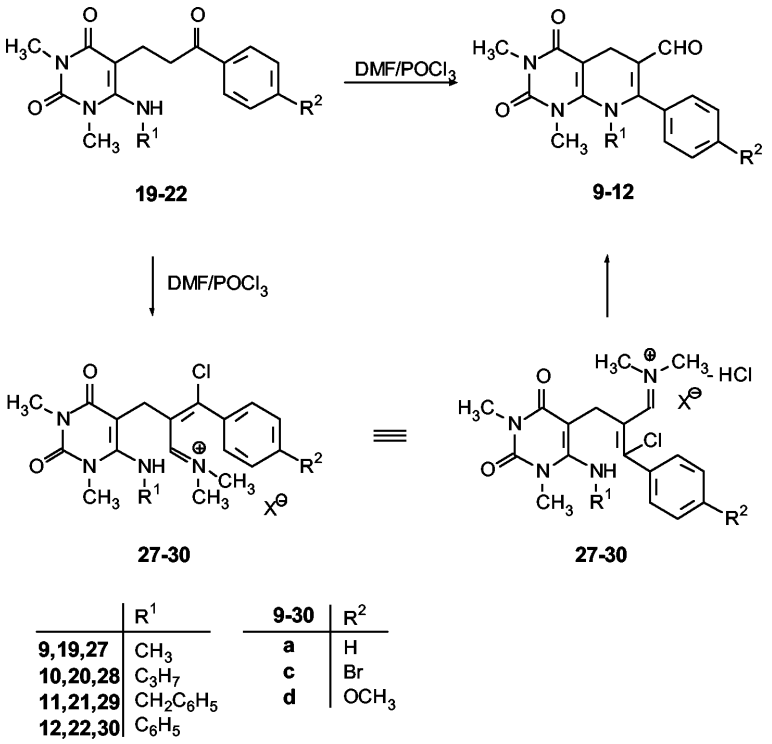
Melting points are uncorrected and were recorded with a Stuart Scientific, SMP03 melting point apparatus, ^{1}H and ^{13}C NMR spectra (internal Me_4Si) were recorded using a Bruker ARX 300 spectrometer (δ given in ppm, J in Hz), IR spectra (KBr pellet) were measured on a Perkin-Elmer FT-IR 16 PC spectrometer, ESI-MS spectra were taken on a Bruker LC esquire mass spectrometer (ESI) in a MeOH/water mixture by direct infusion; EI (electron impact) mass spectra were obtained with an ionization energy of 70 eV using a HP 5989 mass spectrometer and a direct inlet probe with a tungsten wire; m/z values are reported followed by the relative intensity in parentheses; elemental analysis was performed by the Microanalytical Laboratory of the Institute of Inorganic Chemistry, University of Kiel. Macherey-Nagel Polygram® SIL G/UV_{254} on plastic sheets was used for TLC monitoring.

Synthesis of 7-arylpyrido[2,3-d]pyrimidines (**6a** – **c**)

A mixture of 7-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidines **3a** – **c** (4 mmol) and *N*,*N*-dimethylaminomethylene chloride (10 mmol) in ethanol (80 ml, 160 ml for **6c**) was heated to 65 °C for 3 h. After cooling to room temperature the reaction mixture was concentrated under reduced pressure. Ethyl acetate (50 ml) was added to the residue and heated. The boiling mixture was filtered and the solid formed was washed two times with boiling ethyl acetate (50 ml). The precipitate was solved in water (100 ml). To the unsolvable residue after filtration was added 2 ml ammonia (3 N). The solid formed was collected by filtration, dried and purified by crystallization from diethyl ether (**6a**) or ethanol (**6b**, **c**).

1,3-Dimethyl-6-(N,N-dimethylaminomethyl)-7-phenyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (**6a**)

M. p. 136 °C (Et_2O); yield 400 mg (31%). – IR: ν = 1712 (C=O), 1666 (C=O), 1606 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (s, 6H, $N(CH_3)_2$), 3.46 (s, 2H, 6-CH_2), 3.51 (s, 3H, N^3-CH_3), 3.75 (s, 3H, N^1-CH_3), 7.49 (m_c, 3H, 3'-H, 4'-H), 7.77 (m_c, 2H, 2'-H), 8.58 (s, 1H, 5-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.5 (N^3-CH_3), 29.5 (N^1-CH_3), 45.0 ($N(CH_3)_2$), 60.0 (6-CH_2),



	R^1
9,19,27	CH_3
10,20,28	C_3H_7
11,21,29	$CH_2C_6H_5$
12,22,30	C_6H_5

9-30	R^2
a	H
c	Br
d	OCH_3

Scheme 6. Projected cyclization of the uracils **15**–**18** using ketone Mannich bases **2**.

109.0 (C-4a), 127.8 (C-6), 128.1 (C-2'), 129.2 (C-4'), 129.7 (C-3'), 139.0 (C-1'), 140.2 (C-5), 149.2 (C-8a), 151.7 (C-2), 161.5 (C-4), 163.6 (C-7). – ESI-MS: $m/z = 325$ [(M+H)$^+$]. – $C_{18}H_{20}N_4O_2$ (324.39): calcd. C 66.65, H 6.21, N 17.27; found C 66.92, H 6.30, N 17.14.

1,3-Dimethyl-6-(N,N-dimethylaminomethyl)-7-(4-methylphenyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (**6b**)

M. p. 166–167 °C (EtOH); yield 700 mg (52%). – IR: $\nu =$ 1702 (C=O), 1652 (C=O), 1604 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.25$ (s, 6H, N(CH_3)$_2$), 2.44 (s, 3H, 4'-CH_3), 3.45 (s, 2H, 6-CH_2), 3.50 (s, 3H, N^3-CH_3), 3.73 (s, 3H, N^1-CH_3), 7.28 (m_c, 2H, 3'-H), 7.69 (m_c, 2H, 2'-H), 8.55 (s, 1H, 5-H). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.4$ (4'-CH_3), 28.4 (N^3-CH_3), 29.4 (N^1-CH_3), 45.0 (N(CH_3)$_2$), 60.1 (6-CH_2), 108.7 (C-4a), 127.7 (C-6), 128.9 (C-2'), 129.7 (C-3'), 136.2 (C-1'), 139.4 (C-4'), 140.2 (C-5), 149.2 (C-8a), 151.8 (C-2), 161.5 (C-4), 163.6 (C-7). – ESI-MS: $m/z = 339$ [(M+H)$^+$]. – $C_{19}H_{22}N_4O_2$ (338.41): calcd. C 67.44, H 6.55, N 16.56; found C 67.52, H 6.62, N 16.26.

7-(4-Bromophenyl)-1,3-(dimethyl)-6-(N,N-dimethylaminomethyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (**6c**)

M. p. 146–147 °C (EtOH); yield 600 mg (37%). – IR: $\nu =$ 1708 (C=O), 1662 (C=O), 1606 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.23$ (s, 6H, N(CH_3)$_2$), 3.40 (s, 2H, 6-CH_2), 3.51 (s, 3H, N^3-CH_3), 3.73 (s, 3H, N^1-CH_3), 7.61 (m_c, 2H, 3'-H), 7.75 (m_c, 2H, 2'-H), 8.52 (s, 1H, 5-H). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.5$ (N^3-CH_3), 29.5 (N^1-CH_3), 44.9 (N(CH_3)$_2$), 60.1 (6-CH_2), 109.0 (C-4a), 124.0 (C-4'), 127.6 (C-6), 131.3 (C-2'), 131.5 (C-3'), 137.8 (C-1'), 140.6 (C-5), 149.3 (C-8a), 151.6 (C-2), 161.4 (C-4), 162.5 (C-7). – ESI-MS: $m/z = 403$ [(M+H)$^+$, ^{79}Br]. – $C_{18}H_{19}N_4O_2Br$ (403.28): calcd. C 53.61, H 4.75, N 13.89; found C 53.74, H 4.78, N 13.66.

Synthesis of 7-arylpyrido[2,3-d]pyrimidines (**7a**–**c**)

A mixture of 7-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine **3a**–**c** (4 mmol), morpholine hydrochloride (8 mmol) and paraformaldehyde (10 mmol) was reacted as described for compounds **6a**–**c**. Products **7a**–**c** were purified by crystallization from ethanol.

1,3-Dimethyl-6-(morpholinomethyl)-7-phenyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (**7a**)

M. p. 166 °C (EtOH); yield 900 mg (64%). – IR: $\nu =$ 1708 (C=O), 1662 (C=O), 1608 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.42$ (t, $J = 4.6$ Hz, 4H, morpholine N-CH_2), 3.52 (s, 3H, N^3-CH_3), 3.53 (s, 2H, 6-CH_2), 3.68 (t, $J = 4.6$ Hz, 4H, morpholine O-CH_2), 3.75 (s, 3H, N^1-CH_3), 7.49 (m_c, 3H, 3'-H, 4'-H), 7.74 (m_c, 2H, 2'-H), 8.57 (s, 1H,

5-H). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.5$ (N^3-CH_3), 29.5 (N^1-CH_3), 53.1 (morpholine N-CH_2), 59.1 (6-CH_2), 66.9 (morpholine O-CH_2), 107.9 (C-4a), 127.7 (C-6), 128.2 (C-2'), 129.3 (C-4'), 129.5 (C-3'), 138.9 (C-1'), 140.1 (C-5), 149.4 (C-8a), 151.7 (C-2), 161.5 (C-4), 163.9 (C-7). – ESI-MS: $m/z = 367$ [$(M+H)^+$]. – $C_{20}H_{22}N_4O_3$ (366.42): calcd. C 65.56, H 6.05, N 15.21; found C 65.84, H 6.12, N 15.21.

1,3-Dimethyl-7-(4-methylphenyl)-6-(morpholinomethyl)-1,2,3,4-tetrahydropyrido-[2,3-d]pyrimidine-2,4-dione (**7b**)

M. p. 173 – 174 °C (EtOH); yield 900 mg (60%). – IR: $\nu =$ 1704 (C=O), 1654 (C=O), 1602 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.43$ (t, $J = 4.6$ Hz, 4H, morpholine N-CH_2), 2.45 (s, 3H, 4'-CH_3), 3.52 (s, 3H, N^3-CH_3), 3.53 (s, 2H, 6-CH_2), 3.69 (t, $J = 4.6$ Hz, 4H, morpholine O-CH_2), 3.74 (s, 3H, N^1-CH_3), 7.29 (m_c, 2H, 3'-H), 7.67 (m_c, 2H, 2'-H), 8.56 (s, 1H, 5-H). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 21.4 (4'-CH_3), 28.5 (N^3-CH_3), 29.5 (N^1-CH_3), 53.2 (morpholine N-CH_2), 59.2 (6-CH_2), 66.9 (morpholine O-CH_2), 108.7 (C-4a), 126.5 (C-6), 128.9 (C-2'), 129.6 (C-3'), 136.1 (C-1'), 139.5 (C-4'), 140.1 (C-5), 149.3 (C-8a), 151.7 (C-2), 161.6 (C-4), 163.9 (C-7). – ESI-MS: $m/z = 381$ [$(M+H)^+$]. – $C_{21}H_{24}N_4O_3$ (380.45): calcd. C 66.30, H 6.36, N 14.73; found C 66.90, H 6.52, N 15.00.

7-(4-Bromophenyl)-1,3-dimethyl-6-(morpholinomethyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (**7c**)

M. p. 149 – 150 °C (EtOH); yield 460 mg (34%). – IR: $\nu =$ 1708 (C=O), 1660 (C=O), 1610 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.44$ (t, $J = 4.2$ Hz, 4H, morpholine N-CH_2), 3.48 (s, 2H, 6-CH_2), 3.51 (s, 3H, N^3-CH_3), 3.68 (t, $J = 4.5$ Hz, 4H, morpholine O-CH_2), 3.73 (s, 3H, N^1-CH_3), 7.62 (m_c, 2H, 3'-H), 7.71 (m_c, 2H, 2'-H), 8.52 (s, 1H, 5-H). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.5$ (N^3-CH_3), 29.5 (N^1-CH_3), 53.1 (morpholine N-CH_2), 59.3 (6-CH_2), 66.9 (morpholine O-CH_2), 109.0 (C-4a), 124.0 (C-4'), 126.4 (C-6), 131.3 (C-2'), 131.4 (C-3'), 137.8 (C-1'), 140.5 (C-5), 149.5 (C-8a), 151.6 (C-2), 161.4 (C-4), 162.8 (C-7). – ESI-MS: $m/z = 445$ [$(M+H)^+$, ^{79}Br]. – $C_{20}H_{21}N_4O_3Br$ (445.32): calcd. C 53.94, H 4.75, N 12.58; found C 54.33, H 5.03, N 12.45.

Synthesis of 8-alkyl-7-aryl-2,4-dioxo-5,8-dihydropyrido-[2,3-d]pyrimidine-6-carbaldehydes (**9 – 12**)

To phosphoryl chloride (3.0 g) was added *N*,*N*-dimethylformamide (3.0 g) drop by drop at 15 – 35 °C and the mixture stirred for 1 h at r. t. After adding the uracil derivative (**19 – 22**) (1 mmol) the solution was stirred overnight. The mixture was poured onto ice-water and made alkaline with $NaHCO_3$. The solid formed was collected by filtration and purified by crystallization.

1,3,8-Trimethyl-2,4-dioxo-7-phenyl-1,3,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbaldehyde (**9a**)

M. p. 217 °C (EtOH); yield 174 mg (56%). – IR: $\nu =$ 1698 (C=O), 1670 (C=O), 1590 (C=C), 1465 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]-DMSO): $\delta = 2.91$ (s, 3H, N^8-CH_3), 3.38 (s, 3H, N^3-CH_3), 3.42 (s, 2H, 5-H), 3.50 (s, 3H, N^1-CH_3), 7.42 (m_c, 2H, Ar), 7.55 (m_c, 3H, Ar), 9.34 (s, 1H, CHO). – ^{13}C NMR (75 MHz, [D_6]-DMSO): $\delta = 19.0$ (C-5), 28.3 (N^3-CH_3), 34.6 (N^1-CH_3), 40.7 (N^8-CH_3), 97.1 (C-4a), 120.4 (C-6), 129.2 (C-2'), 130.6 (C-3'), 131.2 (C-4'), 131.4 (C-1'), 149.2 (C-8a), 152.7 (C-2), 159.9 (C-7), 161.7 (C-4), 190.6 (CHO). – EI-MS: $m/z = 311$ [M^+] (71), 296 (100). – $C_{17}H_{17}N_3O_3$ (311.34): calcd. C 65.58, H 5.50, N 13.50; found C 65.69, H 5.54, N 13.50.

7-(4-Bromophenyl)-1,3-dimethyl-2,4-dioxo-8-propyl-1,3,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbaldehyde (**10c**)

M. p. 171 °C (isopropanol); yield 180 mg (43%). – IR: $\nu = 1704$ (C=O), 1654 (C=O), 1636 (C=O), 1600 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.78$ (t, $J =$ 7.4 Hz, 3H, 3"-H), 1.47 (sext, $J = 7.5$ Hz, 2H, 2"-H), 3.16 (t, $J = 7.6$ Hz, 2H, 1"-H), 3.37 (br s, 5H, N^3-CH_3, 5-H), 3.49 (s, 3H, N^1-CH_3), 7.30 (m_c, 2H, 2'-H), 7.65 (m_c, 2H, 3'-H), 9.36 (s, 1H, CHO). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.0$ (C-3"), 19.1 (C-2"), 22.2 (C-5), 28.3 (N^3-CH_3), 34.3 (N^1-CH_3), 53.8 (C-1"), 99.2 (C-4a), 123.3 (C-6), 125.8 (C-4'), 132.0 (C-2'), 132.5 (C-1', -3'), 148.3 (C-8a), 152.7 (C-2), 157.9 (C-7), 161.5 (C-4), 190.1 (CHO). – EI-MS: $m/z = 417$ [M^+, ^{79}Br] (29), 419 [M^+, ^{81}Br] (30), 376 (100). – $C_{19}H_{20}N_3O_3Br$ (418.29): calcd. C 54.56, H 4.82, N 10.05; found C 53.72, H 5.05, N 10.08.

8-Benzyl-7-(4-bromophenyl)-1,3-dimethyl-2,4-dioxo-1,3,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbaldehyde (**11c**)

M. p. 217 – 219°C (Isopropanol); yield 380 mg (81%). – IR: $\nu = 1700$ (C=O), 1658 (C=O), 1634 (C=O), 1580 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.10$ (s, 2H, 5-H), 3.39 (s, 3H, N^3-CH_3), 3.64 (s, 3H, N^3-CH_3), 4.56 (s, 2H, CH_2), 6.88 (m_c, 2H, 2"-H), 7.18 (m_c, 2H, 2'-H), 7.26 (m_c, 3H, 3"-H, 4"-H), 7.65 (m_c, 2H, 3'-H), 9.30 (s, 1H, CHO). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.9$ (C-5), 28.3 (^{3}N-CH_3), 34.4 (^{1}N-CH_3), 55.7 (CH_2), 99.8 (C-4a), 124.3 (C-6), 125.9 (C-4'), 127.9 (C-2"), 129.0 (overlapping, C-2', C-3"), 130.5 (C-1'), 132.4 (overlapping, C-3', C-4"), 134.9 (C-1"), 148.4 (C-8a), 152.6 (C-2), 157.5 (C-7), 161.4 (C-4), 190.1 (CHO). – EI-MS: $m/z = 169$ (100). – $C_{23}H_{20}N_3O_3Br$ (466.34): calcd. C 59.24, H 4.32, N 9.01; found C 56.15, H 4.77, N 8.49.

1,3-Dimethyl-2,4-dioxo-7,8-diphenyl-1,3,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbaldehyde (**12a**)

M. p. 245 °C (EtOH); yield 210 mg (56%). – IR: $\nu = 1698$ (C=O), 1654 (C=O), 1642 (C=O), 1598 (C=C) cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.06$ (s, 3H, N^3-CH_3), 3.40 (s, 3H, N^1-CH_3), 3.56 (s, 2H, 5-H), 6.85 (m_c, 2H, 2"-H), 7.17 (m_c, 3H, 3"-H, 4"-H), 7.25 (m_c, 2H, 3'-H), 7.39 (m_c, 2H, 2'-H), 7.47 (m_c, 1H, 4'-H), 9.25 (s, 1H, CHO). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.8$ (C-5), 29.1 (N^3-CH_3), 33.9 (N^1-CH_3), 99.3 (C-4a), 122.9 (C-6), 128.5 (C-2"), 128.7 (C-4"), 129.2 (C-2'), 130.2 (C-3", 131.1 (C-4'), 131.7 (C-3"), 133.2 (C-1'), 143.2 (C-1"), 148.9 (C-8a), 152.8 (C-2), 159.9 (C-7), 162.5 (C-4), 192.0 (CHO). – EI-MS: $m/z = 373$ [M^+] (87), 77 (100). – $C_{22}H_{19}N_3O_3$ (373.42): calcd. C 70.76, H 5.13, N 11.25; found C 70.56, H 5.26, N 11.54.

Synthesis of bis(pyrido[2,3-d]pyrimidin-6-yl)ethanes (**13a – c**)

A mixture of 7-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidines **3a – c** (4 mmol) and *N*,*N*-dimethylaminomethylene chloride (8 mmol) in DMF (20 ml) was heated at 125 °C for 2 h. After cooling the reaction mixture to room temperature the solid formed was collected by filtration, washed with water and ethanol, dried and purified by crystallization from DMF.

1,2-Bis(1,3-dimethyl-2,4-dioxo-7-phenyl-1H,3H-pyrido[2,3-d]pyrimidin-6-yl]ethane (**13a**)

M. p. 305 – 306 °C (DMF); yield 380 mg (34%). – IR: $\nu = 1708$ (C=O), 1670 (C=O), 1606 (C=C) cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.98$ (s, 4H, 6-CH_2), 3.47 (s, 6H, N^3-CH_3), 3.70 (s, 6H, N^1-CH_3), 7.30 (m_c, 4H, 2'-H), 7.39 (m_c, 6H, 3'-H, 4'-H), 8.05 (s, 2H, 5-H). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 29.1$ (N^3-CH_3), 30.1 (N^1-CH_3), 33.7 (6-CH_2), 109.9 (C-4a), 129.0 (C-6), 129.3 (C-3'), 129.6 (two overlapping signals C-2', C-4'), 139.5 (C-1', C-5), 149.4 (C-8a), 152.2 (C-2), 161.9 (C-4), 163.6 (C-7). – ESI-MS: $m/z = 561$ [$(M+H)^+$]. – $C_{32}H_{28}N_6O_4$ (560.62): calcd. C 68.56, H 5.03, N 14.99; found C 68.05, H 5.16, N 15.24.

1,2-Bis[1,3-dimethyl-7-(4-methylphenyl)-2,4-dioxo-1H,3H-pyrido[2,3-d]pyrimidin-6-yl]ethane (**13b**)

M. p. 323 – 324 °C (DMF); yield 350 mg (30%). – IR: $\nu = 1712$ (C=O), 1670 (C=O), 1606 (C=C) cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.37$ (s, 6H, 4'-CH_3), 3.01 (s, 4H, 6-CH_2), 3.49 (s, 6H, N^3-CH_3), 3.70 (s, 6H, N^1-CH_3), 7.14 (m_c, 8H, phenyl-H), 8.00 (s, 2H, 5-H). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.2$ (4'-CH_3), 29.4 (N^3-CH_3), 29.4 (N^1-CH_3), 33.1 (6-CH_2), 109.1 (C-4a), 128.6 (C-2'), 128.8 (C-3'), 136.0 (C-1'), 138.9 (C-6), 139.1 (C-1', C-5), 148.7 (C-8a), 151.6 (C-2), 161.1 (C-4), 162.8 (C-7). – ESI-MS: $m/z = 589$ [$(M+H)^+$]. – $C_{34}H_{32}N_6O_4$ (588.67): calcd. C 69.37, H 5.48, N 14.28; found C 69.65, H 5.54, N 14.54.

1,2-Bis[7-(4-bromophenyl)-1,3-dimethyl-2,4-dioxo-1H,3H-pyrido[2,3-d]pyrimidin-6-yl]ethane (**13c**)

M. p. > 350 °C (DMF); yield 420 mg (29%). – IR: $\nu = 1706$ (C=O), 1666 (C=O), 1602 (C=C) cm^{-1}. NMR data could not be obtained because of insolubility. – ESI-MS: $m/z = 719$ [$(M+H)^+$, ^{79}Br]. – $C_{32}H_{26}N_6O_4Br_2$ (718.41): calcd. C 53.50, H 3.65, N 11.70; found C 53.41, H 3.64, N 11.51.

Synthesis of 6-substituted 1,3-dimethyl-5-(3-oxo-3-phenylpropyl)uracils (**19 – 22**)

A solution of 6-substituted 1,3-dimethyluracils (**15 – 18**) (4 mmol) and arylalkanone Mannich bases **2a**,**c – d** (8 mmol) was refluxed in ethanol/water (1 : 1, 20 ml). After cooling to room temperature the solid product filtered and recrystallized from isopropanol. If no solid was formed the solvent was removed under reduced pressure and diethyl ether was added to the residue. This mixture was stirred vigorously, the precipitate filtered and crystallized from isopropanol.

1,3-Dimethyl-6-methylamino-5-(3-oxo-3-phenylpropyl)-uracil (**19a**)

M. p. 128 °C (isopropanol); yield 800 mg (66%). – IR: $\nu = 1696$ (C=O), 1682 (C=O), 1630 (C=O), 1595 (C=C) cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.80$ (m_c, 2H, 1'-H), 2.87 (d, $J = 5.8$ Hz, 3H, NH-CH_3), 3.32 (s, 3H, N^3-CH_3), 3.40 (m_c, 2H, 2'-H), 3.43 (s, 3H, N^1-CH_3), 5.69 (br q, $J = 5.6$ Hz, 1H, NH), 7.44 (m_c, 2H, 3"-H), 7.56 (tt, $J = 7.4$ Hz, $J = 1.5$ Hz, 1H, 4"-H), 7.97 (m_c, 2H, 2"-H). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.1$ (C-1'), 28.6 (N^3-CH_3), 33.7 (N^1-CH_3), 34.8 (NH-CH_3), 38.5 (C-2'), 98.2 (C-4a), 128.9 (C-1"), 129.3 (C-4"), 134.2 (C-2"), 137.2 (C-3"), 153.3 (C-6), 156.0 (C-2), 164.4 (C-4), 202.6 (C-3').– EI-MS: $m/z = 301$ [M^+] (8), 169 (100). – $C_{16}H_{19}N_3O_3$ (301.35): calcd. C 63.77, H 6.36, N 13.94; found C 63.50, H 6.40 N 13.80.

1,3-Dimethyl-5-[3-oxo-3-phenylpropyl]-6-propylamino-uracil (**20a**)

M. p. 131 – 132 °C (isopropanol); yield 500 mg (38%). – IR: $\nu = 3294$ (NH), 1694 (C=O), 1686 (C=O), 1634 (C=O), 1598 (C=C) cm^{-1}. – ^1H NMR (300 MHz, [D_6]-DMSO): $\delta = 0.90$ (t, $J = 7.4$ Hz, 3H, 3"'-H), 1.57 (sext, $J = 7.3$ Hz, 2H, 2"'-H), 2.69 (t, $J = 7.3$ Hz, 2H, 1'-H), 3.01 (q, $J = 7.0$ Hz, 2H, 1"'-H), 3.15 (s, t, $J = 7.3$ Hz, 5H, N^3-CH_3, 2'-H), 3.32 (s, 3H, N^1-CH_3), 5.60 (t, $J = 6.5$ Hz, 1H, NH), 7.52 (br tt, $J = 7.5$ Hz, 2H, 3"-H), 7.63 (m_c, 1H, 4"-H), 7.97 (m_c, 2H, 2"-H). – ^{13}C NMR (75 MHz,

[D$_6$]-DMSO): δ = 11.2 (C-3"'), 19.7 (C-2"'), 23.1 (C-1'), 27.6 (N^3-CH$_3$), 32.6 (N^1-CH$_3$), 37.8 (C-2'), 48.4 (C-1"'), 94.4 (C-5), 127.8 (C-3"), 128.6 (C-2"), 133.1 (C-4"), 136.5 (C-1"), 151.6 (C-6), 153.5 (C-2), 162.5 (C-4), 200.2 (C-3'). – EI-MS: m/z = 329 [M$^+$] (10), 197 (100). – $C_{18}H_{23}N_3O_3$ (329.40): calcd. C 65.63, H 7.04, N 12.76; found C 65.83, H 7.08, N 12.65.

5-[3-(4-Bromophenyl)-3-oxopropyl]-1,3-dimethyl-6-propylaminouracil (**20c**)

M. p. 162 °C (EtOH); yield 700 mg (43%). – IR: ν = 3306 (NH), 1685 (C=O), 1640 (C=O), 1601 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 0.88 (t, J = 7.4 Hz, 3H, 3"'-H), 1.55 (sext, J = 7.3 Hz, 2H, 2"'-H), 2.66 (t, J = 7.3 Hz, 2H, 1'-H), 3.00 (t, J = 7.0 Hz, 2H, 1"'-H), 3.13 (t , J = 4.7 Hz, 2'-H), 3.13 (s, 3H, N^3-CH$_3$), 3.31 (s, 3H, N^1-CH$_3$), 5.57 (d, J = 6.4 Hz, 1H, NH), 7.72 (dt, J = 8.6 Hz, J = 2.1 Hz, 2H, 3"-H), 7.89 (dt, J = 8.6 Hz, J = 2.1 Hz, 2H, 2"-H). – ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 11.2 (C-3"'), 19.7 (C-1'), 23.1 (C-2"'), 27.6 (N^3-CH$_3$), 32.6 (N^1-CH$_3$), 37.8 (C-2'), 48.4 (C-1"'), 94.2 (C-5), 127.2 (C-4"), 129.9 (C-2"), 131.7 (C-3"), 135.5 (C-1"), 151.6 (C-2), 153.4 (C-6), 162.5 (C-4), 199.4 (C-3'). – EI-MS: m/z = 407 [M$^+$, ^{79}Br] (4), 409 [M$^+$, ^{81}Br] (4), 210 (100). – $C_{18}H_{22}N_3O_3Br$ (408.30): calcd. C 52.95, H 5.43, N 10.29; found C 53.04, H 5.66, N 10.67.

5-[3-(4-Methoxyphenyl)-3-oxopropyl]-1,3-dimethyl-6-propylaminouracil (**20d**)

M. p. 131 – 132 °C (isopropanol); yield 400 mg (28%). – IR: ν = 3326 (NH), 1694 (C=O), 1672 (C=O), 1636 (C=O), 1610 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 0.90 (t, J = 7.4 Hz, 3H, 3"'-H), 1.56 (sext, J = 7.4 Hz, 2H, 2"'-H), 2.66 (t, J = 7.4 Hz, 2H, 1'-H), 3.00 (q, J = 6.7 Hz, 2H, 1"'-H), 3.08 (t, J = 7.4 Hz, 2H, 2'-H), 3.15 (s, 3H, N^3-CH$_3$), 3.31 (s, 3H, N^1-CH$_3$), 3.84 (s, 3H, O-CH$_3$), 5.62 (t, J = 6.5 Hz, 1H, NH), 7.03 (m$_c$, 2H, 3"-H), 7.96 (m$_c$, 2H, 2"-H). – ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 11.2 (C-3"'), 19.8 (C-1'), 23.1 (C-2"'), 27.5 (N^3-CH$_3$), 32.5 (N^1-CH$_3$), 37.3 (C-2'), 48.4 (C-1"'), 55.4 (O-CH$_3$), 94.6 (C-5), 113.8 (C-3"), 129.4 (C-1"), 130.1 (C-2"), 151.6 (C-6), 153.3 (C-2), 162.4 (C-4"), 163.0 (C-4), 198.5 (C-3'). – EI-MS: m/z = 359 [M$^+$] (9), 197 (100). – $C_{19}H_{25}N_3O_4$ (359.43): calcd. C 63.49, H 7.01, N 11.69; found C 63.55, H 7.07, N 11.58.

6-Benzylamino-1,3-dimethyl-5-(3-oxo-3-phenylpropyl)-uracil (**21a**)

M. p. 107 °C (isopropanol); yield 700 mg (46%). – IR: ν = 1684 (C=O), 1670 (C=O), 1634 (C=O), 1616 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 2.54 (t, J = 7.4 Hz, 2H, 1'-H), 2.95 (t, J = 7.4 Hz, 2H, 2'-H), 3.13 (s, 3H, N^3-CH$_3$), 3.38 (s, 3H, N^1-CH$_3$), 4.26 (d, J = 7.0 Hz, 2H, NH-CH$_2$), 6.11 (t, J = 7.1 Hz, 1H, NH), 7.23 (m$_c$, 1H, 4"'-H), 7.31 (m$_c$, 4H, 2"'-H, 3"'-H), 7.50 (m$_c$, 2H, 3"-H), 7.62 (m$_c$, 1H, 4"-H), 7.89 (m$_c$, 2H, 2"-H). – ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 19.5 (C-1'), 27.6 (N^3-CH$_3$), 32.9 (N^1-CH$_3$), 37.7 (C-2'), 49.8 (NH-CH$_2$), 95.4 (C-5), 127.3 (C-4"'), 127.6 (C-2"'), 127.8 (C-3"'), 128.4 (C-2"), 128.6 (C-3"), 133.1 (C-4"), 136.5 (C-1"), 138.8 (C-1"'), 151.7 (C-6), 152.9 (C-2), 162.5 (C-4), 200.0 (C-3'). – EI-MS: m/z = 377 [M$^+$] (4), 91 (100). – $C_{22}H_{23}N_3O_3$ (377.45): calcd. C 70.01, H 6.14, N 11.13; found C 69.94, H 6.18, N 11.15.

6-Benzylamino-5-[3-(4-bromophenyl)-3-oxopropyl]-1,3-dimethyluracil (**21c**)

M. p. 140 °C (isopropanol); yield 187 mg (41%). – IR: ν = 1682 (C=O), 1632 (C=O), 1600 (C=C), 1456 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 2.64 (t, J = 7.8 Hz, 2H, 1'-H), 2.91 (t, J = 7.4 Hz, 2H, 2'-H), 3.13 (s, 3H, N^3-CH$_3$), 3.38 (s, 3H, N^1-CH$_3$), 4.25 (d, J = 7.0 Hz, 2H, NH-CH$_2$), 6.09 (t, J = 7.0 Hz, 1H, NH), 7.28 (m$_c$, 5H, Ar-H"'), 7.71 (dt, J = 8.6 Hz, J = 2.1 Hz, 2H, 3"-H), 7.81 (dt, J = 8.6 Hz, J = 2.1 Hz, 2H, 2"-H). – ^{13}C NMR (75 MHz, [D$_6$]-DMSO/CDCl$_3$): δ = 19.4 (C-1'), 27.6 (N^3-CH$_3$), 32.9 (N^1-CH$_3$), 37.7 (C-2'), 49.8 (NH-CH$_2$), 98.3 (C-5), 127.1 (C-4"), 127.3 (C-4"'), 127.6 (C-2"'), 128.4 (C-3"'), 129.8 (C-2"), 131.7 (C-3"), 135.5 (C-1"), 138.8 (C-1"'), 151.7 (C-2), 152.9 (C-6), 162.4 (C-4), 199.2 (C-3'). – EI-MS: m/z = 455 [M$^+$, ^{79}Br] (1), 457 [M$^+$, ^{81}Br] (1), 91 (100). – $C_{22}H_{22}N_3O_3Br$ (456.34): calcd. C 57.90, H 4.86, N 9.21; found C 57.80, H 5.17, N 9.56.

6-Anilino-1,3-dimethyl-5-(3-oxo-3-phenylpropyl)uracil (**22a**)

M. p. 200 °C (isopropanol); yield 680 mg (47%). – IR: ν = 1704 (C=O), 1682 (C=O), 1640 (C=O), 1606 (C=C) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 2.64 (m$_c$, 2H, 1'-H), 3.11 (m$_c$, 2H, 2'-H), 3.17 (s, 3H, N^3-CH$_3$), 3.25 (s, 3H, N^1-CH$_3$), 6.81 (d, J = 7.5 Hz, 2H, 2"'-H), 6.90 (t, J = 7.4 Hz, 1H, 4"'-H), 7.25 (t, J = 7.5 Hz, 2H, 3"'-H), 7.46 (t, J = 7.5 Hz, 2H, 3"-H), 7.59 (tt, J = 7.4 Hz, J = 1.8 Hz, 1H, 4"-H), 7.87 (d, J = 7.0 Hz, 2H, 2"-H), 8.30 (s, 1H, NH). – ^{13}C NMR (75 MHz, [D$_6$]-DMSO/CDCl$_3$): δ = 20.1 (C-1'), 27.7 (N^3-CH$_3$), 31.5 (N^1-CH$_3$), 37.3 (C-2'), 103.5 (C-5), 115.8 (C-2"'), 120.6 (C-4"'), 127.6 (C-3"), 128.4 (C-2"), 129.3 (C-3"'), 132.9 (C-4"), 136.2 (C-1"), 143.0 (C-6), 146.7 (C-1"'), 151.5 (C-2), 162.8 (C-4), 199.6 (C-3'). – EI-MS: m/z = 363 [M$^+$] (24), 258 (100). – $C_{21}H_{21}N_3O_3$ (363.42): calcd. C 69.41, H 5.82, N 11.56; found C 69.54, H 5.87, N 11.76.

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