Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 47–54

TETRAHEDRON

Versatile, convenient synthesis of pyrimido[1,2,3-*cd*]purinediones

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Received 20 August 2002; revised 9 November 2002; accepted 15 November 2002

Abstract—The alkylation of 3-substituted cycloalkylcarboxamido-6-aminouracil derivatives with 3-bromo-1-propanol followed by ring closure yields 1,3,8-trisubstituted xanthine derivatives bearing a polar hydroxyl group. Use of the more reactive 1,3-dibromopropane or homologous dibromoalkanes for the alkylation reaction results in simultaneous alkylation at N1 and the exocyclic amino group (N^6) yielding imidazo-, pyrimido- and diazepino-pyrimidine derivatives. The pyrimidopyrimidine derivatives can subsequently be cyclised using hexamethyldisilazane at high temperature affording an easy, convenient and general access to tricyclic pyrimido[1,2,3-*cd*]purinediones. Alternatively, 3-substituted 6-amino-5-benzylideneaminouracil derivatives can be reacted with 1,3-dibromopropane followed by an oxidative cyclisation using thionyl chloride to obtain the desired tricyclic pyrimido[1,2,3-*cd*]purinediones, which are sterically fixed analogues of pharmacologically active purine derivatives.

1. Introduction

The pyrimidine and purine ring systems undoubtedly belong to the most ubiquitous heterocycles in nature, as they represent the main structure of many biologically significant compounds, including nucleosides and nucleotides.

For this reason many analogues and derivatives of purine and pyrimidine have been synthesised and developed as pharmacologically active compounds or drugs.[1]

Pharmacologically active purine analogues include tricyclic structures such as imidazo[2,1-*i*]purinones (e.g. PSB-11, a potent A_3 adenosine receptor antagonist),[2] pyrimido[4,5-*b*]indoles (e.g. APEPI, a potent A_1 adenosine receptor antagonist)[3] and imidazo[2,1-*a*]purines (e.g. tricyclic ganciclovir analogues, which are potent antiviral agents)[4,5] (Fig. 1). In general, cyclisation of a molecule results in a reduction of conformational flexibility. Such a rigid fixed conformation may result in an increased affinity to a target structure, if the cyclised structure resembles the bioactive conformation. A well known example is etorphine, a morphine derivative, which contains an additional aliphatic six-membered ring and shows an activity which is 1000-fold higher than that of morphine itself.[6,7] We have now developed a novel, versatile and convenient approach to 2,9-disubstituted 4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-diones, which can be envisaged as xanthine derivatives to which a third ring is attached bridging the N3- and N9-positions (Fig. 2).

Since 1,3,8-trisubstituted xanthines with various substituents are known as highly potent antagonists for adenosine receptors,[8] 4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3*cd*]purine-8,10(9*H*)-diones might be potential new lead structures for novel adenosine receptor ligands.

The activity and selectivity of the xanthine derivatives and other adenosine receptor ligands towards the different adenosine receptor subtypes is largely influenced by their substitution pattern. For this reason variation in positions 2 and 9 of 4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-diones, which are corresponding to position 1 and 8 of xanthines (Fig. 2) is very important. Up to now the synthesis of only few 2,9-disubstituted 4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-diones has been reported in the literature,[9–11] namely such with a methyl substituent in position 9[9,10] and one derivative with a propyl residue in that position. The latter was identified as a side product in the bromination reaction of 8-cyclopropyl-3-(3-hydroxypropyl)-1-propylxanthine at the hydroxypropyl group.[11] The above synthesis which yielded 9-methyl derivatives,[9,10] started from 6-chloro-3-methyl-5-nitrouracil. This starting material is difficult to prepare by a 3-step synthesis giving only moderate yields.[12]

The newly developed synthetic procedure to obtain 2,9-disubstituted 4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3*cd*]purine-8,10(9*H*)-diones allows to easily diversify the substituents in the positions 2 and 9. A recently developed general synthesis of 1,3,8-substituted xanthines[13] (Scheme 1) was applied and modified to give the desired products.

Keywords: pyrimido[1,2,3-*cd*]purinediones; xanthine derivatives; tricyclic purine derivatives; pyrimido[1,6-*a*]pyrimidines; ring closure reaction.

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PII: S0040-4020(02)01485-0

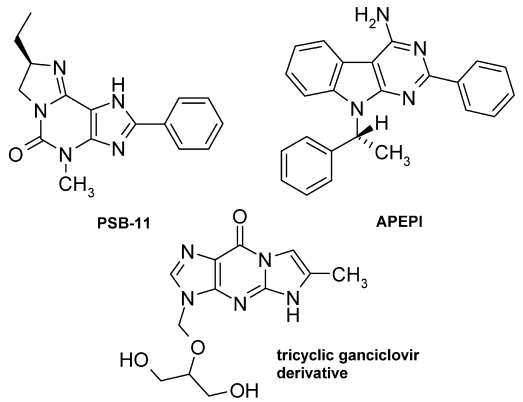


Figure 1. Examples of pharmacologically active tricyclic purine derivatives and analogues.

2. Syntheses

2.1. Synthesis of 1,3,8-trisubstituted xanthines

Initially we prepared 3-hydroxyalkylxanthine derivatives bearing suitable 1-(propyl, butyl) and 8-substituents (phenyl, cycloalkyl) to obtain high A_1 adenosine receptor affinity (Scheme 1). The hydroxyl function was required (i) to increase hydrophilicity and hence water-solubility, which is an important prerequisite for pharmacological activity, and (ii) as a functional group which could be used for prodrug formation or for the attachment of photoaffinity, fluorescence, or other labels.

The general synthesis of 1,3,8-trisubstituted xanthines starts from 3-substituted 5,6-diaminouracils **1a**,**b**, which can be obtained by standard procedures.[14] The compounds **1a** and **1b** were treated with cycloalkyl carboxylic acids or benzoic acid in methanol in the presence of *N'*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide-hydrochloride (EDC) to obtain the corresponding amides **2a**–**e**.[15] In the next step, these amides **2a**–**e** were dissolved in dry dimethylformamide (DMF) in the presence of dry potassium carbonate, and alkylation in position 1 was performed with 3-bromo-1-propanol in analogy to procedures described in the literature.[13,16]

This hydroxyalkylation was the most difficult step in the synthetic route as the yields were generally low (34–43%). All reagents had to be dry and the reaction had to be performed under an argon atmosphere. Besides this, the progress of the reaction was difficult to monitor by TLC due to very similar R_f values of educts and products in common organic solvents. Only after the addition of a few drops of ammonia to the solvent (dichloromethane–methanol), the product spot could be separated from the educt. Finally, the

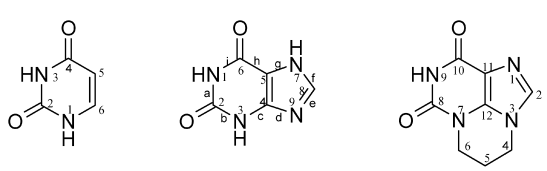
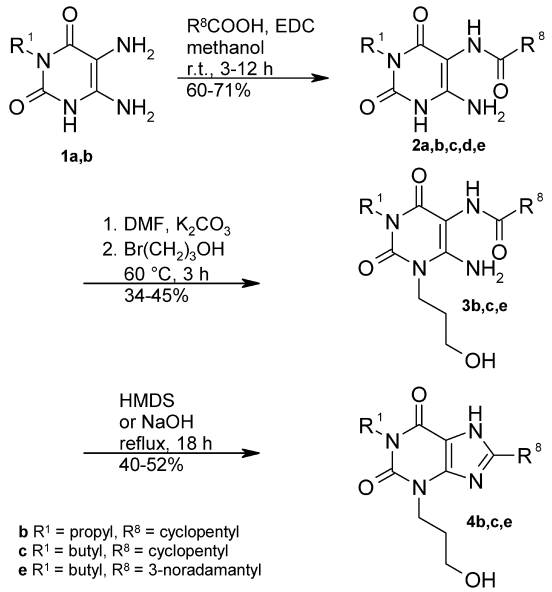


Figure 2. Structures and numbering of uracil, xanthine and 4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-dione.

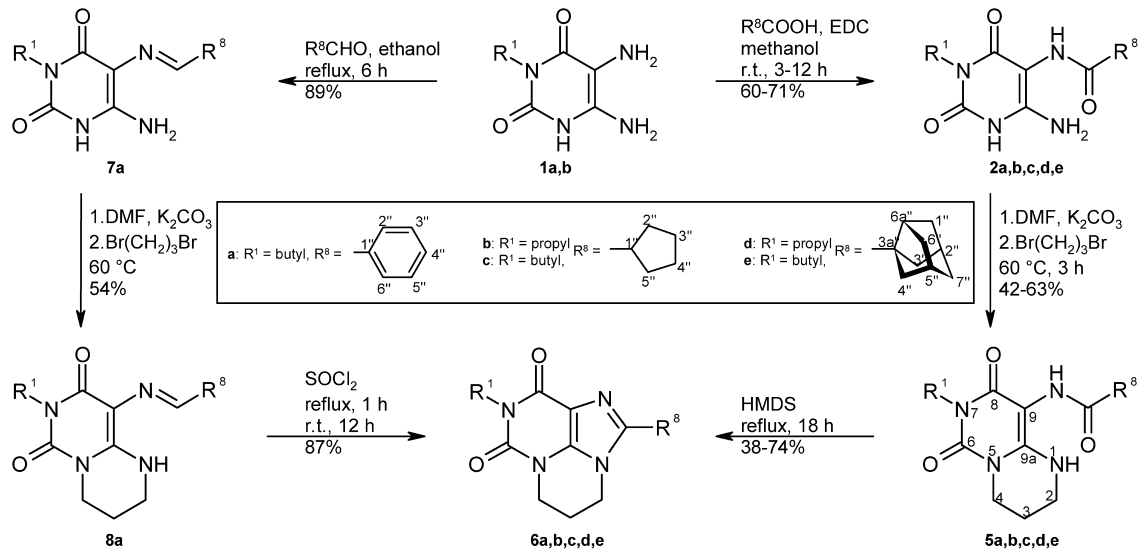


Scheme 1. Synthetic route for 1,3,8-trisubstituted xanthines.

reaction was stopped by the addition of water. Replacement of potassium carbonate by sodium or caesium carbonate as a base did not increase the yields of the alkylation reaction. The subsequent ring closure to obtain the desired 1,3,8-trisubstituted xanthines **4b**,**c**,**e** was carried out under reflux either with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of catalytic amounts of ammonium sulphate or with 10% aqueous sodium hydroxide solution in methanol. The yields were similar with both methods for 8-cyclopentylxanthines, while the latter method could not be employed for the preparation of the 8-(3-noradamantyl)-xanthine derivative **4e** since it was too aggressive, resulting in N1-dealkylation, and amide **2e** was recovered. Only with the milder method using HMDS the desired 1-butyl-3-(3-hydroxypropyl)-8-(3-noradamantyl)xanthine (**4e**) could be obtained (Scheme 2).

2.2. New approach to 2,9-disubstituted 4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-diones

In analogy to the presented synthetic route for the preparation of 3-(3-hydroxypropyl)-substituted xanthine derivatives, the synthesis of 2,9-disubstituted 4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-diones was started from 3-substituted 4,5-diaminouracils **1a**,**b**. 3-Propyl- and 3-butyl-5,6-diaminouracil **1a**,**b** were prepared according to published procedures in high yields.[14] A variety of other substituents, such as saturated and unsaturated alkyl residues or substituents containing an aromatic structure,[14] can also be easily introduced thus allowing a broad variation in the 9-position (R^1) of the final product. Subsequently, the 5,6-diaminouracils **1a**,**b** were transferred to the corresponding amides **2a**–**e** as described above for the preparation of xanthines. In the next step, the additional six-membered ring was introduced by treatment with 1,3-dibromopropane in DMF in the presence of potassium carbonate. 1,3-Dibromopropane is highly reactive and does not only react with the nitrogen in position 1 of the uracil, as 3-bromopropanol does, but also with the amino group attached to position 6 to

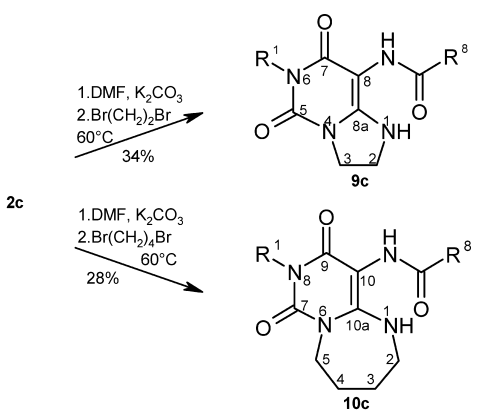


Scheme 2. Synthetic route for 2,9-disubstituted 4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-dione.

give the bicyclic structure **5a**–**e**. These products could be identified by their ^{1}H NMR-spectra: the signal of the 6-amino group of compound **2a**–**e** is shifted downfield in compound **5a**–**e** and corresponds to only one proton. Furthermore the structures of **5a**–**e** were confirmed by high resolution mass spectra. Using a 3-fold excess of 1,3-dibromopropane the desired products **5a**–**e** were obtained in yields of about 50%.

As these yields were quite satisfactory for alkylation reactions involving an intramolecular cyclisation, the method was also examined with homologous dibromoalkane derivatives, including 1,2-dibromoethane, 1,4-dibromobutane, 1,5-dibromopentane, 1,6-dibromohexane and 1,8-dibromooctane. It was found that the analogous intramolecular reaction took place with 1,2-dibromoethane yielding compound **9c** containing a five-membered ring, and with 1,4-dibromobutane yielding a seven-membered ring **10c**. However, with the higher homologues no ring closure could be obtained under the same conditions (Scheme 3).

Treatment of the bicyclic six-membered products **5a**–**e** with HMDS gave the desired disubstituted tricyclic 4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-diones **6a**–**e** in good yields. The final ring closure could not be carried out with other condensing agents, which are generally used in xanthine synthesis, such as aqueous-methanolic sodium hydroxide or methanolic sodium methylate solution. The imidazo[1,2-*c*]pyrimidine derivative **9c** and also the pyrimido[1,6-*a*][1,3]diazepine derivative **10c** could not be cyclised with any of these methods presumably because the expected products of the ring closure are energetically unfavourable.



Scheme 3. Preparation of imidazo[1,2-*c*]pyrimidine derivative **9c** and pyrimido[1,6-*a*][1,3]diazepine derivative **10c**.

An alternative procedure was explored to prepare the tricyclic compound 9-butyl-2-phenyl-4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-dione (**6a**). The 5,6-diaminouracil derivative **1a** was reacted in high yields with benzaldehyde to obtain 6-amino-5-(benzylideneamino)-3-butyl-(1*H*)-pyrimidine-2,4-dione (**7a**).[17] This compound could be converted to the bicyclic product **8a** by reaction with 1,3-dibromopropane in analogy to the preparation of the amide derivatives **5a**–**e**. The final ring closure was achieved oxidatively with thionyl chloride as reagent and solvent,[18] to give the tricyclic product **6a** in good yield.

Preliminary radioligand binding studies indicated that the 2-noradamantyl-substituted pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-diones **6d** and **6e** exhibit high, nanomolar affinity and selectivity for the A_1-adenosine receptor. Comprehensive pharmacological in vitro investigations of the new compounds are currently in progress.

3. Conclusions

In conclusion, we have developed novel approaches to 2,9-disubstituted 4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-diones, which allow the introduction of a variety of substituents in position 2 via aldehydes or carboxylic acids and in position 9 by a convenient alkylation reaction. The tricyclic purine derivatives are of interest as potential new lead structures in drug development. The

3-(3-hydroxypropyl)xanthines, obtained by a recently developed method, may be useful as functionalized adenosine receptor antagonists.

4. Experimental

4.1. General

NMR spectra were recorded on a Varian XL-300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) or a Bruker DRX 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz). Deuterated DMSO was used as solvent and internal standard with the chemical shifts ^{1}H: 2.49 ppm; ^{13}C: 39.7 ppm. All chemical shifts were expressed in ppm according to the internal standard. Coupling constants (*J*) are given in Hertz (Hz). The assignment of the carbon and hydrogen atoms was carried out by the interpretation of 2D-spectra and in comparison with data of similar structures. Atoms of residue R^1 were quoted with $'$, atoms of residue R^8 with $''$ and of R^3 with $'''$. The reactions were monitored by thin layer chromatography (TLC) using aluminium sheets with silica gel 60 F_{254} (Merck). The melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were performed by the Institute of Pharmaceutical Chemistry Endenich, University of Bonn. The mass spectra were collected on an MS-50 A.E.I. (Manchester) mass spectrometer with an ionisation energy of 70 eV.

Compounds **1a** and **1b** were prepared from 6-aminouracil (Fluka) via regioselective alkylation followed by nitrosation and reduction as described.[14] Compound **2b**[15] and **7a**[17] were synthesised as described in the literature. Compounds **4b** and **6b** were prepared with the presented new methods; they gave the same analytical results as described in the literature.[11,15] All solvents were purified and dried before use.

4.2. General procedure for the preparation of compounds 2a–c

To a stirred suspension of compound **1a** or **1b** (5.0 mmol) in methanol (30 mL) first cyclopentane carboxylic acid (0.6 g, 0.55 mL, 5.3 mmol), or benzoic acid (0.65 mg, 5.3 mmol), then *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDC) (1.0 g, 5.2 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. The precipitate was collected by suction filtration and washed with methanol (15 mL) and subsequently with H_2O (15 mL). For analytical purposes, the product was recrystallised from methanol/water.

4.2.1. 6-Amino-5-benzamido-3-butyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (2a). Yield: 1.07 g (71%). Mp 288–289°C. ^{1}H NMR (500 MHz): δ=0.88 (t, 3H, *J*=7.4 Hz, C4′H$_3$), 1.26 (sext, 2H, *J*=7.4 Hz, C3′H$_2$), 1.47 (quint, 2H, *J*=7.4 Hz, C2′H$_2$), 3.72 (t, 2H, *J*=7.4 Hz, C1′H$_2$), 6.04 (br, 2H, NH$_2$), 7.44–7.52 (m, 3H, aromatic-CH), 7.94–7.96 (m, 2H, aromatic-CH), 8.84 (s, 1H, NHCO), 10.44 (s, 1H, N1H). ^{13}C NMR (125 MHz): δ=13.9 (C4′), 19.8 (C3′), 30.0 (C2′), 39.2 (C1′), 87.2 (C5), 128.0 (C3″, C5″), 128.1 (C2″, C6″), 131.3 (C4″), 134.7 (C1″), 150.1, 150.6 (C2, C6), 160.5 (C4), 166.5 (C=O). Calcd for $C_{15}H_{18}N_4O_3$: %C, 59.59; %H, 6.00; %N, 18.53. Found: %C, 59.50; %H, 6.00; %N, 18.51.

4.2.2. 6-Amino-5-cyclopentanecarboxamido-2,4-dioxo-3-propyl-1,2,3,4-tetrahydropyrimidine (2b). Yield: 0.84 g (60%, lit. yield: 93%[15]). Mp 292°C (lit. mp >300°C[15]). ^{1}H NMR and ^{13}C NMR are identical to the data given in literature.[15]

4.2.3. 6-Amino-3-butyl-5-cyclopentanecarboxamido-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (2c). Yield: 0.91 g (62%). Mp 287°C. ^{1}H NMR (500 MHz): δ=0.88 (t, 3H, *J*=7.3 Hz, C4′H$_3$), 1.25 (sext, 2H, *J*=7.3 Hz, C3′H$_2$), 1.46 (quint, 2H, *J*=7.3 Hz, C2′H$_2$), 1.49–1.82 (m, 8H, cyclopentyl-CH$_2$), 2.74 (quint, 1H, *J*=7.8 Hz, C1″H), 3.67 (t, 2H, *J*=7.2 Hz, C1′H$_2$), 5.80 (s, 2H, NH$_2$), 8.25 (s, 1H, NHCO), 10.37 (br, 1H, N1H). ^{13}C NMR (125 MHz): δ=13.7 (C4′), 19.6 (C3′), 25.7 (C3″, C4″), 29.8 (C2′), 30.0 (C2″, C5″), 39.1 (C1′), 44.0 (C1″), 87.6 (C5), 149.9, 149.8 (C2, C6), 160.6 (C4), 175.9 (C=O). MS: *m*/*z*=294.2 (M$^+$, 25), 276.2 ([M−H$_2$O]$^+$, 4), 198.1 (100), 181.1 (18), 142.0 (46), 97.0 (22), 69.1 (86). Calcd for $C_{14}H_{22}N_4O_3$: %C, 57.13; %H, 7.53; %N, 19.03. Found: %C, 57.62; %H, 7.21; %N, 19.38.

4.3. General procedure for the preparation of compounds 2d and 2e

To a suspension of compound **1a** or **1b** (4.0 mmol) in methanol (30 mL) 3-noradamantanecarboxylic acid (0.5 g, 3.0 mmol) and EDC (0.6 g, 3.1 mmol) were added. A clear yellow solution was obtained, from which a light yellow product precipitated after stirring at room temperature for 12 h. The precipitate was collected by suction filtration and washed with methanol (10 mL) and subsequently with water (15 mL). The collected precipitate was proven to be pure product.

4.3.1. 6-Amino-5-(hexahydro-2,5-methanopentalene-3a)-carboxamido-2,4-dioxo-3-propyl-1,2,3,4-tetrahydropyrimidine (2d). Yield: 0.91 g (66%). Mp 295°C. ^{1}H NMR (500 MHz): δ=0.81 (t, 3H, *J*=7.4 Hz, C3′H$_3$), 1.41–1.64 (m, 6H, C2′H$_2$, C1″*H*H, C6″*H*H, C7″H$_2$), 1.80 (m, 4H, C1″*H*H, C3″*H*H, C4″*H*H, C6″*H*H), 2.01 (m, 2H, C3″*H*H, C4″*H*H), 2.23 (m, 2H, C2″H, C5″H), 2.68 (m, 1H, C6a″H), 3.62 (t, 2H, *J*=7.4 Hz, C1′H$_2$), 5.75 (s, 2H, NH$_2$), 7.71 (s, 1H, NHCO), 9.85 (br, 1H, N1H). ^{13}C NMR (125 MHz): δ=11.1 (C3′), 20.9 (C2′), 34.4 (C7″), 36.9 (2H, C2″, C5″), 39.8 (C1′), 42.3 (C6a″), 43.1 (2C, C1″, C6″), 46.8 (2C, C3″, C4″), 54.6 (C3a″), 87.7 (C5), 149.6 (2H, C2, C6), 160.2 (C4), 176.3 (C=O). MS: *m*/*z* (%): 332.2 (M$^+$, 3.5), 184.1 (66), 142.1 (100), 121.1 (14). Calcd for $C_{17}H_{24}N_4O_3$: %C, 62.41; %H, 7.56; %N, 16.17. Found: %C, 62.22; %H, 7.53; %N, 15.86.

4.3.2. 6-Amino-3-butyl-5-(hexahydro-2,5-methanopentalene-3a)-carboxamido-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (2e). Yield: 0.95 g (69%). Mp 278°C. ^{1}H NMR (500 MHz): δ=0.87 (t, 3H, *J*=7.4 Hz, C4′H$_3$), 1.27 (sext, 2H, *J*=7.4 Hz, C3′H$_2$), 1.41–1.56 (m, 6H, C2′H$_2$, C1″*H*H, C6″*H*H, C7″H$_2$), 1.79 (m, 4H, C1″*H*H, C3″*H*H, C4″*H*H, C6″*H*H), 2.01 (m, 2H, C3″*H*H, C4″*H*H), 2.23 (m, 2H, C2″H, C5″H), 2.68 (m, 1H, C6a″H), 3.66 (t, 2H, *J*=7.3 Hz, C1′H$_2$), 5.69 (s, 2H, NH$_2$), 7.70 (s, 1H, NHCO), 10.30 (br, 1H,

N1H). ^{13}C NMR (125 MHz): δ=13.6 (C4′), 19.6 (C3′), 29.7 (C2′), 34.4 (C7″), 36.9 (2C, C2″, C5″), 39.0 (C1′), 42.3 (C6a″), 43.1 (2C, C1″, C6″), 46.8 (2C, C3″, C4″), 54.6 (C3a″), 87.7 (C5), 149.5 (2C, C2, C6), 160.2 (C4), 176.3 (C=O). MS: *m/z*=346.2 (M^+, 23), 198.1 (25), 181.1 (13), 149.1 (52), 142.0 (44), 121.1 (100), 97.0 (22). Calcd for $C_{18}H_{26}N_4O_3$: %C, 61.43; %H, 7.28; %N, 16.85. Found: %C, 60.98; %H, 7.31; %N, 16.54.

4.4. General procedure for the 3-hydroxyalkylation in position 1 of the uracil derivatives

A solution of compound **2b** or **2c** (2.0 mmol) in dried dimethylformamide (DMF) (20 mL) was prepared under an inert atmosphere of argon. Potassium carbonate (0.4 g, 2.9 mmol) was added. The reaction mixture was stirred at room temperature for 6 h and then heated to 80°C for 1 h. After cooling to room temperature the undissolved potassium carbonate was removed from the mixture by suction filtration. The filtrate was heated again to 80°C and 3-bromopropanol (1.4 g, 0.9 mL, 10 mmol) was added. The reaction mixture was stirred for another 12 h under an argon atmosphere at 80°C. As soon as nearly all starting material had disappeared (TLC: dichloromethane/methanol/ammonia (25%)=180:20:1) the solvent was removed by distillation under reduced pressure. The residue was suspended in a mixture of methanol and water (1:1) and the solid material, which was identified as starting material, was filtered off. The methanol was removed under reduced pressure and diethyl ether (20 mL) was added. The mixture was stirred for 3 h. Then it was stored at 4°C until a white pure precipitate was formed, which was isolated by suction filtration and washed twice with cold diethyl ether (20 mL). The products were used without further purification for the next step.

4.4.1. 6-Amino-5-cyclopentanecarboxamido-1-(3-hydroxypropyl)-2,4-dioxo-3-propyl-1,2,3,4-tetrahydropyrimidine (3b). Yield: 0.17 g (25%). Mp 161°C. ^{1}H NMR (300 MHz): δ=0.81 (t, 3H, *J*=7.5 Hz, C3′H$_3$), 1.45–1.83 (m, 12H, C2′H$_2$, C2″H$_2$, cyclopentyl-CH$_2$), 2.75 (quint, 1H, *J*=7.9, C1″H), 3.43 (t, 2H, *J*=5.6 Hz, C3‴H$_2$), 3.69 (t, 2H, *J*=7.3 Hz, C1′H$_2$), 3.87 (t, 2H, *J*=7.0 Hz, C1‴H$_2$), 4.69 (br, 1H, OH), 6.34 (s, 2H, NH$_2$), 8.16 (s, 1H, NHCO). ^{13}C NMR (75 MHz): δ=11.1 (C3′), 20.8 (C2′), 25.7 (2C, C3″, C4″), 29.8 (2C, C2″, C5″), 30.7 (C2‴), 39.8 (C1‴), 41.8 (C1′), 44.0 (C1″), 57.8 (C3‴), 88.1 (C5), 151.3, 150.1 (C2, C6), 158.8 (C4), 175.8 (C=O).

4.4.2. 6-Amino-3-butyl-5-cyclopentanecarboxamido-1-(3-hydroxypropyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (3c). Yield: 0.24 g (34%). Mp 145°C. ^{1}H NMR (300 MHz): δ=0.86 (t, 3H, *J*=7.3, C4′H$_3$), 1.24 (sext, 2H, *J*=7.3, C3′H$_2$), 1.40–1.83 (m, 12H, C2′H$_2$, C2‴H$_2$, cyclopentyl-CH$_2$), 2.74 (quint, 1H, *J*=7.8 Hz, C1″H), 3.43 (t, 2H, *J*=6.1 Hz, C3‴H$_2$), 3.72 (t, 2H, *J*=7.3 Hz, C1′H$_2$), 3.89 (t, 2H, *J*=7.0 Hz, C1‴H$_2$), 4.69 (br, 1H, OH), 6.34 (s, 2H, NH$_2$), 8.15 (s, 1H, NHCO). ^{13}C NMR (75 MHz): δ=14.0 (C4′), 20.0 (C3′), 26.1 (2C, C3″, C4″), 30.1 (C2′), 30.3 (2C, C2″, C5″), 30.9 (C2‴), 39.5 (C1‴), 40.7 (C1′), 44.6 (C1″), 58.3 (C3‴), 88.5 (C5), 152.0, 150.6 (C2, C6), 159.5 (C4), 177.1 (C1″). MS: *m/z*=353.2 (M^+, 49), 334.2 (21), 256.1 (100), 238.1 (24), 97.1 (11), 69.1 (58). HRMS: calcd 352.2111. Found: 352.2110.

4.4.3. 6-Amino-3-butyl-5-(hexahydro-2,5-methanopentalene-3a)-carboxamido-1-(3-hydroxypropyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (3e). When the reaction was completed (TLC), water (20 mL) and diethyl ether (20 mL) were added and the mixture was stirred for 4 h. Then it was stored at 4°C until white solid material precipitated, which was isolated by suction filtration and washed twice with diethyl ether (10 mL). The obtained pure product required no further purification.

Yield: 0.15 g (19%). Mp 172°C. ^{1}H NMR (300 MHz): δ=0.87 (t, 3H, *J*=7.3 Hz, C4′H$_3$), 1.24 (sext, 2H, *J*=7.3 Hz, C3′H$_2$), 1.40–1.68 (m, 6H, C2′H$_2$, C1″*H*H, C6″*H*H, C7″H$_2$), 1.70–1.81 (m, 6H, C1″*H*H, C3″*H*H, C4″*H*H, C6″*H*H, C2‴H$_2$), 2.06 (m, 2H, C3″*H*H, C4″*H*H), 2.23 (m, 2H, C2″H, C5″H), 2.71 (m, 1H, C6a″H), 3.43 (t, 2H, *J*=5.6 Hz, C3‴H$_2$), 3.72 (t, 2H, *J*=7.3 Hz, C1′H$_2$), 3.91 (t, 2H, *J*=6.9 Hz, C1‴H$_2$), 4.72 (m, 1H, OH), 6.25 (s, 2H, NH$_2$), 7.72 (s, 1H, NHCO). ^{13}C NMR (75 MHz): δ=13.6 (C4′), 19.6 (C3′), 29.7 (C2′), 30.7 (C2‴), 34.4 (C7″), 37.0 (2H, C2″, C5″), 39.8 (C1′), 40.0 (C1‴), 42.2 (C6a″), 43.1 (2H, C1″, C6″), 46.7 (2C, C3″, C4″), 54.7 (C3a″), 57.7 (C3‴), 88.5 (C5), 151.3, 150.0 (2H, C2, C6), 158.7 (C4), 176.7 (C=O). MS: *m/z* (%): 404.3 (M^+, 38), 386.3 (12.5), 255.1 (33.5), 238.1 (14), 149.1 (36), 121.1 (100). HRMS: calcd: 404.2425. Found: 404.2429.

4.5. General procedure for the ring closure to obtain 1,3,8-trisubstituted xanthines

Method A. Compound **3b** or **3c** (0.3 mmol) was stirred in a mixture of methanol (10 mL) and aqueous NaOH (10%, 2.0 mL) at 60°C for 24 h. Then water (10 mL) was added and the solution was acidified with concentrated HCl to pH 2–3. The methanol was distilled off under reduced pressure and the aqueous solution was stored at 4°C for 24 h. A white flaky material precipitated, which was isolated by suction filtration and washed with ice-cold water.

Method B. Compound **3b** or **3c** (0.4 mmol) was stirred in 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (10 mL) in the presence of a catalytic amount of ammonium sulphate (ca. 20 mg) under reflux for 48 h. HMDS was removed by distillation under reduced pressure. The oily residue was suspended in water (10 mL) and acidified with concentrated HCl to pH 2–3. The aqueous solution was stored at 4°C until white material precipitated, which was isolated by suction filtration and washed with ice-cold water.

The products were recrystallized from DMSO by the dropwise addition of water.

4.5.1. 8-Cyclopentyl-3-(3-hydroxypropyl)-1-propyl-3,7-dihydropurine-2,6-dione (4b). Yield: 31 mg (32%, method A), 56 mg (44%, method B), lit.[19] yield: 75%. Mp 198°C, lit.[19] mp 207–208°C. ^{1}H NMR was identical to literature data.[19] ^{13}C NMR (75 MHz): δ=11.0 (C3′), 20.7 (C2′), 25.0 (2C, C3″, C4″), 31.0 (C2‴), 31.8 (2C, C2″, C5″), 38.6 (C1″), 40.4 (C1‴), 41.9 (C1′), 58.3 (C3‴), 105.9 (C5), 147.4 (C8), 150.4 (C4), 153.5 (C2), 157.5 (C6). MS: *m/z* (%): 320.2 (M^+; 60), 303.1 (15), 262.1 (34), 234.1 (100), 194 (35), 179.1 (24), 69.1 (24). HRMS: calcd: 320.1848. Found: 320.1847. Calcd for $C_{17}H_{26}N_4O_3$: %C,

59.98; %H, 7.55; %N, 17.49. Found: %C, 59.23; %H, 7.51; %N, 17.11.

4.5.2. 1-Butyl-8-cyclopentyl-3-(3-hydroxypropyl)-3,7-dihydropurine-2,6-dione (4c). Yield: 35 mg (35%, method A), 41 mg (31%, method B). Mp 183°C. ^{1}H NMR (300 MHz): δ=0.84 (t, 3H, J=7.3 Hz, C3′H$_3$), 1.27 (sext, 2H, J=7.4 Hz, C3′H$_2$), 1.45–2.03 (m, 12H, C2′H$_2$, C2‴H$_2$, cyclopentyl-CH$_2$), 3.13 (quint, 1H, J=8.0 Hz, C1″H), 3.42 (t, 2H, J=6.3 Hz, C3‴H$_2$), 3.86 (t, 2H, J=7.3 Hz, C1′H$_2$), 4.02 (t, 2H, J=7.1 Hz, C1‴H$_2$), 4.48 (br, 1H, OH), 13.08 (br, 1H, N7H). ^{13}C NMR (75 MHz): δ=13.3 (C4′), 19.3 (C3′), 24.7 (2C, C3″, C4″), 29.3 (C2′), 30.7 (C2‴), 31.5 (2C, C2″, C5″), 38.4 (C1″), 39.8 (C1‴), 40.1 (C1′), 58.0 (C3‴), 105.7 (C5), 147.1 (C8), 150.1 (C4), 153.2 (C2), 157.2 (C6). MS: m/z (%): 320.2 (M$^+$, 60), 303.1 (15), 262.1 (34), 234.1 (100), 194 (35), 179.1 (24), 69.1 (24). HRMS: calcd: 334.2005. Found: 334.2006. Calcd for $C_{17}H_{26}N_4O_3{\cdot}0.5H_2O$: %C, 59.46; %H, 7.92; %N, 16.31. Found: %C, 59.71; %H, 7.81; %N, 16.28.

4.5.3. 1-Butyl-8-(hexahydro-2,5-methanopentalen-3a-yl)-3-(3-hydroxypropyl)-3,7-dihydropurine-2,6-dione (4e). Compound **3e** (0.2 g, 0.5 mmol) was stirred in HMDS (20 mL) in the presence of a catalytic amount of ammonium sulphate (ca. 20 mg) under reflux for 18 h. Then water (10 mL) was added and the reaction mixture was neutralized with concentrated HCl. The light yellow precipitate was isolated by suction filtration, washed with ice-cold water and purified by column chromatography (dichloromethane/methanol=98:2).

Yield: 64 mg (33%). Mp 182°C. ^{1}H NMR (500 MHz): δ=0.88 (t, 3H, J=7.4 Hz, C4′H$_3$), 1.27 (sext, 2H, J=7.6 Hz, C3′H$_2$), 1.51 (quint, 2H, J=7.4 Hz, C2′H$_2$), 1.61 (m, 4H, C1″*H*H, C6″*H*H, C7″H$_2$), 1.80 (quint, 2H, J=6.8 Hz, C2‴H$_2$), 1.91 (m, 4H, C1″*H*H, C3″*H*H, C4″*H*H, C6″*H*H), 2.12 (m, 2H, C3″*H*H, C4″*H*H), 2.29 (m, 2H, C2″H, C5″H), 2.60 (t, 1H, J=6.8 Hz, C6a″H), 3.41 (q, 2H, J=6.0 Hz, C3‴H$_2$), 3.87 (t, 2H, J=7.4 Hz, C1′H$_2$), 4.02 (t, 2H, J=6.9 Hz, C1‴H$_2$), 4.52 (t, 1H, J=5.5 Hz, OH), 13.02 (s, 1H, N7H). ^{13}C NMR (125 MHz): δ=13.8 (C4′), 19.7 (C3′), 29.8 (C2′), 31.2 (C2‴), 34.3 (C7″), 37.1 (2C, C2″, C5″), 40.3, 40.5 (C1′, C1‴), 43.3 (2C, C1″, C6″), 45.3 (C6a″), 48.4 (2C, C3″, C4″), 49.0 (C3a″), 58.5 (C3‴), 106.8 (C5), 147.7 (C8), 150.8 (C4), 154.0 (C2), 160.1 (C6). MS: m/z (%): 386.2 (M$^+$, 100), 369.2 (49), 286.2 (68). HRMS: calcd: 386.2318. Found: 386.2309. Calcd for $C_{21}H_{30}N_4O_3$: %C, 65.26; %H, 7.82; %N, 14.50. Found: %C, 64.99; %H, 7.83; %N, 14.40.

4.6. General procedure for the preparation of 7,9-disubstituted 1,3,4,6,7,8-hexahydro-2*H*-pyrimido-[1,6-*a*]pyrimidine-6,8-diones

A solution of compound **2a**, **2b**, **2c**, **2d** or **2e** (2.0 mmol) in dried dimethylformamide (DMF) (20 mL) was prepared in an inert atmosphere of argon. Potassium carbonate (0.5 g, 3.6 mmol) was added. The solution was heated at 60°C for 1 h. Then 1,3-dibromopropane (1.98 g, 1.3 mL, 10 mmol) was added. The reaction mixture was stirred for another 2 h under an argon atmosphere. As soon as all starting material had disappeared (TLC: dichloromethane/methanol=9:1), the solvent was removed by distillation under reduced pressure. The products were isolated by gradient column chromatography (dichloromethane/methanol=100:1 to 100:10).

4.6.1. 9-Benzamido-7-butyl-6,8-dioxo-1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,6-*a*]pyrimidine (5a). Yield: 0.37 g (57%). Mp 179–180°C. ^{1}H NMR (500 MHz): δ=0.88 (t, 3H, J=7.4 Hz, C4′H$_3$), 1.26 (sext, 2H, J=7.4 Hz, C3′H$_2$), 1.47 (quint, 2H, J=7.4 Hz, C2′H$_2$), 1.91 (quint, 2H, J=5.8 Hz, C3H$_2$), 3.21 (m, 2H, C4H$_2$), 3.74 (t, 2H, J=7.4 Hz, C1′H$_2$), 3.81 (t, 2H, J=5.8 Hz, C2H$_2$), 7.21 (br, 1H, N1H), 7.45–7.54 (m, 3H, aromatic-CH), 7.96–7.98 (m, 2H, aromatic-CH), 8.81 (s, 1H, NHCO). ^{13}C NMR (125 MHz): δ=13.9 (C4′), 19.8 (C3′), 20.2 (C3), 30.0 (C2′), 38.4 (C4), 40.0 (C1′), 40.8 (C2), 86.2 (C9), 128.1 (2C, C3″, C5″), 128.1 (2C, C2″, C6″), 131.3 (C4″), 134.7 (C1″), 149.5 (C6), 150.2 (C9a), 158.8 (C8), 166.8 (C=O). MS: m/z=342.2 (M$^+$, 46), 237.2 (100), 181.1 (13), 110 (8), 105.1 (18). HRMS: calcd: 342.1692. Found: 342.1693.

4.6.2. 9-Cyclopentanecarboxamido-6,8-dioxo-7-propyl-1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,6-*a*]pyrimidine (5b). Yield: 0.36 g (56%). Mp 179°C. ^{1}H NMR (500 MHz): δ=0.82 (t, 3H, J=7.0 Hz, C3′H$_3$), 1.45–1.93 (m, 12H, C2′H$_2$, C3H$_2$, cyclopentyl-CH$_2$), 2.73 (quint, 1H, J=7.9 Hz, C1″H$_2$), 3.21 (m, 2H, C2H$_2$), 3.68 (t, 2H, J=7.4 Hz, C1′H$_2$), 3.77 (t, 2H, J=6.4 Hz, C4H$_2$), 6.81 (s, 1H, N1H), 8.05 (s, 1H, NHCO). ^{13}C NMR (125 MHz): δ=11.1 (C3′), 20.0 (C3), 20.8 (C2′), 25.6 (2C, C3″, C4″), 29.8 (2C, C2″, C5″), 38.2 (C2), 40.5 (C4), 41.5 (C1′), 44.0 (C1″), 86.3 (C9), 149.8, 148.9 (C6, C9a), 158.3 (C8), 176.0 (C=O). MS: m/z=320.2 (M$^+$, 26), 302.1 (5), 223.1 (100), 181.0 (28), 149.0 (17), 69.1 (26). HRMS: calcd: 320.1848. Found: 320.1850.

4.6.3. 7-Butyl-9-cyclopentanecarboxamido-6,8-dioxo-1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,6-*a*]pyrimidine (5c). Yield: 0.42 g (63%). Mp 186°C. ^{1}H NMR (500 MHz): δ=0.82 (t, 3H, J=7.3 Hz, C4′H$_3$), 1.25 (sext, 2H, J=7.4 Hz, C3′H$_2$), 1.40–1.91 (m, 12H, C2′H$_2$, C3H$_2$, cyclopentyl-CH$_2$), 2.74 (quint, 1H, J=7.9 Hz, C1″H), 3.21 (m, 2H, C2H$_2$), 3.72 (t, 2H, J=7.3 Hz, C1′H$_2$), 3.78 (t, 2H, J=5.8 Hz, C4H$_2$), 6.81 (s, 1H, N1H), 8.05 (s, 1H, NHCO). ^{13}C NMR (125 MHz): δ=11.1 (C4′), 19.6 (C3′), 20.0 (C3), 25.6 (2C, C3″, C4″), 29.8 (3C, C2′, C2″, C5″), 38.2 (C2), 39.7 (C4), 40.5 (C1′), 44.0 (C1″), 86.3 (C9), 149.7, 148.9 (C6, C9a), 158.3 (C8), 176.0 (C=O). MS: m/z=334.3 (M$^+$, 44), 318.2 (5), 237.2 (100), 181.1 (36), 69.1 (23). HRMS: calcd: 334.2005. Found: 334.2014. Calcd for $C_{17}H_{26}N_4O_3$: %C, 61.06; %H, 7.84; %N, 16.75. Found: %C, 60.45; %H, 7.80; %N, 16.25.

4.6.4. 9-(Hexahydro-2,5-methanopentalene-3a)-carboxamido-6,8-dioxo-7-propyl-1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,6-*a*]pyrimidine (5d). Yield: 0.31 g (42%). Mp 194°C. ^{1}H NMR (500 MHz): δ=0.87 (t, 3H, J=7.3 Hz, C3′H$_3$), 1.50–1.61 (m, 6H, C2′H$_2$, C1″*H*H, C6″*H*H, C7″H$_2$), 1.80 (m, 4H, C1″*H*H, C3″*H*H, C4″*H*H, C6″*H*H), 1.91 (m, 2H, C3H$_2$), 2.08 (m, 2H, C3″*H*H, C4″*H*H), 2.24 (m, 2H, C2″H, C5″H), 2.72 (t, 1H, J=6.7 Hz, C6a″H), 3.24 (m, 2H, C4H$_2$), 3.67 (t, 2H, J=7.4 Hz, C1′H$_2$), 3.79 (t, 2H, J=5.8 Hz, C2H$_2$), 6.66 (s, 1H, N1H), 7.61 (s, 1H, NHCO). ^{13}C NMR (125 MHz): δ=11.2 (C3′), 20.8 (C2′), 20.8 (C3), 34.5 (C7″), 36.9 (2C, C2″, C5″), 38.4 (C4), 40.6 (C1′), 41.6 (C2), 42.2 (C6a″), 43.1 (2C, C1″, C6″), 46.8 (2C,

C3″, C4″), 54.7 (C3a″), 86.6 (C9), 149.8, 149.0 (C6, C9a), 158.2 (C8), 176.9 (C=O). MS: *m*/*z*=372.2 (M^+, 43), 223.1 (100), 181.0 (24), 149.1 (41), 121.1 (88). HRMS: calcd: 372.2161. Found: 372.2153.

4.6.5. 7-Butyl-9-(hexahydro-2,5-methanopentalene-3a)-carboxamido-6,8-dioxo-1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,6-*a*]pyrimidine (5e). Yield: 0.40 g (53%). Mp 199°C. ^{1}H NMR (500 MHz): δ=0.87 (t, 3H, *J*=7.3 Hz, C4′H$_3$), 1.25 (sext, 2H, *J*=7.3 Hz, C3′H$_2$), 1.40–1.61 (m, 6H, C2′H$_2$, C1″*H*H, C6″*H*H, C7″H$_2$), 1.80 (m, 4H, C1″*H*H, C3″*H*H, C4″*H*H, C6″*H*H), 1.91 (m, 2H, C3H$_2$), 2.01 (m, 2H, C3″*H*H, C4″*H*H), 2.24 (m, 2H, C2″H, C5″H), 2.73 (t, 1H, *J*=6.7 Hz, C6a″H), 3.24 (m, 2H, C4H$_2$), 3.72 (t, 2H, *J*=7.3 Hz, C1′H$_2$), 3.78 (t, 2H, *J*=5.9 Hz, C2H$_2$), 6.65 (s, 1H, N1H), 7.60 (s, 1H, NHCO). ^{13}C NMR (125 MHz): δ=13.6 (C4′), 19.6 (C3′), 20.1 (C3), 29.8 (C2′), 34.5 (C7″), 37.0 (2H, C2″, C5″), 38.4 (C4), 39.8 (C1′), 40.6 (C2), 42.2 (C6a″), 43.2 (2C, C1″, C6″), 46.8 (2C, C3″, C4″), 54.7 (C3a″), 86.7 (C9), 149.1, 150.0 (C6, C9a), 158.4 (C8), 177.1 (C=O). MS: *m*/*z*=386.3 (M^+, 47.5), 237.1 (100), 181.0 (31), 149.1 (46), 121.1 (100). HRMS: calcd: 386.2318. Found: 386.2311. Calcd for $C_{21}H_{30}N_4O_3$: %C, 65.26; %H, 7.82; %N, 14.50. Found: %C, 65.55; %H, 7.79; %N, 14.05.

4.6.6. 6-Butyl-8-cyclopentanecarboxamido-5,7-dioxo-1,2,3,5,6,7-hexahydroimidazo[1,2-*c*]pyrimidine (9c). Compound **9c** was prepared from compound **2c** in analogy to the method described for compounds **5a**–**e**, but instead of 1,3-dibromopropane 1,2-dibromoethane (1.9 g, 1.3 mL, 10 mmol) was used.

Yield: 0.22 g (34%). Mp 145°C. ^{1}H NMR (300 MHz): δ=0.87 (t, 3H, *J*=7.3 Hz, C4′H$_3$), 1.24 (sext, 2H, *J*=7.4 Hz, C3′H$_2$), 1.40–1.80 (m, 10H, C2′H$_2$, cyclopentyl-CH$_2$), 2.73 (quint, 1H, *J*=7.9 Hz, C1″H), 3.58 (t, 2H, *J*=8.5 Hz, C3H$_2$), 3.69 (t, 2H, *J*=7.3 Hz, C1′H$_2$), 3.97 (t, 2H, *J*=8.6 Hz, C2H$_2$), 7.15 (s, 1H, N1H), 8.38 (s, 1H, NHCO). ^{13}C NMR (75 MHz): δ=13.6 (C4′), 19.5 (C3′), 25.7 (2C, C3″, C4″), 29.9 (C2′), 29.9 (2C, C2″, C5″), 39.4 (C1′), 41.8 (C3), 43.8 (C1″), 44.0 (C2), 85.6 (C8), 148.2, 151.2 (C5, C8a), 160.6 (C7), 175.0 (C=O). MS: *m*/*z*=320.2 (M^+, 29), 302.1 (4), 224.1 (73), 167.0 (37), 149.0 (100), 96.0 (25), 69.1 (38). HRMS: calcd: 320.1848. Found: 320.1839.

4.6.7. 8-Butyl-10-cyclopentanecarboxamido-7,9-dioxo-1,2,3,4,5,7,8,9-octahydropyrimido[1,6-*a*][1,3]diazepine (10c). Compound **10c** was prepared from compound **2c** (1.7 mmol) in analogy to the method described for compounds **5a**–**e**, but instead of 1,3-dibromopropane 1,4-dibromobutane (1.9 g, 1.0 mL, 8.5 mmol) was used.

Yield: 0.16 g (28%). Mp 225–230°C (decomposition). ^{1}H NMR (500 MHz): δ=0.87 (t, 3H, *J*=7.3 Hz, C4′H$_3$), 1.24 (sext, 2H, *J*=7.4 Hz, C3′H$_2$), 1.45 (quint, 2H, *J*=7.3 Hz, C2′H$_2$), 1.48–1.83 (m, 12H, C3H$_2$, C4H$_2$, cyclopentyl-CH$_2$), 2.75 (quint, 1H, *J*=8.0 Hz, C1″H), 3.19 (m, 2H, C5H$_2$), 3.73 (t, 2H, *J*=7.5 Hz, C1′H$_2$), 4.00 (m, 2H, C2H$_2$), 5.76 (s, 1H, N1H), 8.34 (s, 1H, NHCO). ^{13}C NMR (125 MHz): δ=13.8 (C4′), 19.8 (C3′), 25.8 (C3), 25.9 (2C, C3″, C4″), 26.3 (C4), 29.7 (C2′), 30.0 (2C, C2″, C5″), 39.4 (C1′), 44.2 (C1″), 45.7 (C5), 45.9 (C2), 93.39 (C10), 151.1, 155.3, 159.5 (C7, C9, C10a), 175.0 (C=O).

4.7. General procedure for the preparation of 4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-diones

Compound **5a**, **5b**, **5c**, **5d** or **5e** (1.0 mmol) was stirred in HMDS (30 mL) for 18 h under reflux. Then HMDS was removed by distillation under reduced pressure. The product was purified by column chromatography (dichloromethane/methanol=100:2).

4.7.1. 9-Butyl-2-phenyl-4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-dione (6a). Yield: 0.21 g (64%). Mp 210–211°C.

Alternatively compound **6a** was prepared by the following procedure. Compound **8a** (0.2 g, 0.6 mmol) was dissolved in $SOCl_2$ (20 mL) and then refluxed for 1 h. After cooling to room temperature, the reaction mixture was stirred overnight. $SOCl_2$ was removed under reduced pressure and subsequently ice-cold water (30 mL) was added. The precipitate was isolated by suction filtration and purified by recrystallisation from DMF followed by dropwise addition of water.

Yield: 0.17 g (87%). Mp 210–211°C. ^{1}H NMR (500 MHz): δ=0.90 (t, 3H, *J*=7.4 Hz, C4′H$_3$), 1.30 (sext, 2H, *J*=7.4 Hz, C3′H$_2$), 1.52 (quint, 2H, *J*=7.4 Hz, C2′H$_2$), 2.20 (quint, 2H, *J*=5.8 Hz, C5H$_2$), 3.86–3.89 (m, 4H, C1′H$_2$, C4H$_2$), 4.26 (t, 3H, *J*=5.8 Hz, C6H$_2$), 7.49–7.54 (m, 3H, aromatic-CH), 7.76–7.78 (m, 2H, aromatic-CH). ^{13}C NMR (125 MHz): δ=13.9 (C4′), 19.8 (C3′), 21.1 (C5), 29.9 (C2′), 38.8 (C6), 40.3 (C1′), 42.9 (C4), 113.7 (C11), 127.8 (C3″, C5″), 129.0 (C2″, C6″), 129.5 (C4″), 139.5 (C12), 145.1 (C2), 149.7 (C8), 156.8 (C10). MS: *m*/*z* (%)=324.2 (M^+; 100), 307.2 (86), 282.2 (14), 268.1 (28), 225 (100), 197.1 (8), 145.2 (38), 117 (22). HRMS: calcd: 324.1586. Found: 324.1585. Calcd for $C_{18}H_{20}N_4O_2{\cdot}0.5H_2O$: %C, 64.85; %H, 6.35; %N, 16.81. Found: %C, 64.78; %H, 6.12; %N, 16.66.

4.7.2. 2-Cyclopentyl-9-propyl-4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-dione (6b). Yield: 0.11 g (38%). Mp 168°C. ^{1}H NMR and ^{13}C NMR are identical to literature data.[11]

4.7.3. 9-Butyl-2-cyclopentyl-4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-dione (6c). Yield: 0.19 g (60%). Mp 155°C. ^{1}H NMR (500 MHz): δ=0.87 (t, 3H, *J*=7.4 Hz, C4′H$_3$), 1.26 (sext, 2H, *J*=7.4 Hz, C3′H$_2$), 1.47 (quint, 2H, *J*=7.4 Hz, C2′H$_2$), 1.50–2.00 (m, 8H, cyclopentyl-CH$_2$), 2.18 (quint, 2H, *J*=5.7 Hz, C5H$_2$), 3.19 (quint, 1H, *J*=7.9 Hz, 1″H), 3.81 (t, 2H, *J*=5.8 Hz, C4H$_2$), 3.82 (t, 2H, *J*=7.5 Hz, C1′H$_2$), 4.01 (t, 2H, *J*=5.8 Hz, C6H$_2$). ^{13}C NMR (125 MHz): δ=13.9 (C4′), 19.8 (C3′), 20.8 (C5), 25.3 (2C, C3″, C4″), 30.0 (C2′), 30.8 (2C, C2″, C5″), 36.1 (C1″), 38.9 (C6), 40.1 (C4), 40.1 (C1′), 111.8 (C11), 138.9 (C12), 149.8 (C2), 150.5 (C8), 156.7 (C10). MS: *m*/*z* (%)=316.1 (M^+, 58), 299.2 (95), 275 (86), 260 (32), 217 (100). HRMS: calcd: 316.1899. Found: 316.1902.

4.7.4. 2-(Hexahydro-2,5-methanopentalen-3a-yl)-4,5-dihydro-9-propyl-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-dione (6d). Yield: 0.22 g (60%). Mp 182°C. ^{1}H NMR (500 MHz): δ=0.84 (t, 3H, *J*=7.4 Hz, C3′H$_3$), 1.51 (sext,

2H, J=7.4 Hz, C2′H_2), 1.62 (m, 2H, C7″H_2), 1.68 (dd, 2H, J=11.3 Hz, J=2.1 Hz (W-coupling to C3″*H*H, C4″*H*H), C1″*H*H, C6″*H*H), 1.87 (m, 2H, C1″*H*H, C6″*H*H), 1.94 (m, 2H, C3″*H*H, C4″*H*H), 2.10 (dd, 2H, J=10.7, 2.2 Hz (W-coupling to C1″*H*H, C6″*H*H), C3″*H*H, C4″*H*H), 2.19 (quint, 2H, J=5.7 Hz, C5H_2), 2.31 (m, 2H, C2″H, C5″H), 2.82 (t, 1H, J=6.7 Hz, C6a″H), 3.79, 3.80 (m, 4H, C6H_2, C1′H_2), 4.10 (t, 2H, J=5.7 Hz, C4H_2). ^{13}C NMR (125 MHz): δ=11.3 (C3′), 21.0 (C2′), 21.1 (C5), 34.5 (C7″), 36.9 (2C, C2″, C5″), 38.7 (C6), 41.8 (C4), 41.9 (C1′), 42.7 (C6a″), 43.4 (2C, C1″, C6″), 47.9 (2C, C3″, C4″), 48.7 (C3a″), 111.5 (C11), 139.5 (C12), 149.8 (C2, or C6), 151.5 (C8), 156.7 (C2 or C6). MS: m/z (%)=354.3 (M^+, 100), 312 (21), 269 (43). HRMS: calcd: 354.2056. Found: 354.2054.

4.7.5. 9-Butyl-2-(hexahydro-2,5-methanopentalen-3a-yl)-4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-dione (6e). Yield: 0.24 g (63%). Mp 176°C. ^{1}H NMR (500 MHz): δ=0.88 (t, 3H, J=7.4 Hz, C4′H_3), 1.27 (sext, 2H, J=7.5 Hz, C3′H_2), 1.47 (quint, 2H, J=7.4 Hz, C2′H_2), 1.64 (m, 2H, C7″H_2), 1.68 (dd, 2H, J=11.1, 2.2 Hz (W-coupling to C3″*H*H, C4″*H*H), C1″*H*H, C6″*H*H), 1.87 (m, 2H, C1″*H*H, C6″*H*H), 1.94 (dd, 2H, J=10.9, 2.1 Hz (W-coupling to C1″*H*H, C6″*H*H), C3″*H*H, C4″*H*H), 2.10 (m, 2H, C3″*H*H, C4″*H*H), 2.19 (quint, 2H, J=5.7 Hz, C5H_2), 2.32 (m, 2H, C2″H, C5″H), 2.82 (t, 1H, J=6.6 Hz, C6a″H), 3.79 (t, 2H, J=5.8 Hz, C6H_2), 3.84 (t, 2H, J=7.4 Hz, C1′H_2), 4.10 (t, 2H, J=5.7 Hz, C4H_2). ^{13}C NMR (125 MHz): δ=13.9 (C4′), 19.7 (C3′), 21.0 (C5), 30.0 (C2′), 34.5 (C7″), 36.9 (2C, C2″, C5″), 38.8 (C6), 40.1 (C1′), 41.8 (C4), 42.7 (C6a″), 43.5 (2C, C1″, C6″), 47.9 (2C, C3″, C4″), 48.7 (C3a″), 111.5 (C11), 139.5 (C12), 149.8 (C2 or C6), 151.5 (C8), 156.7 (C2 or C6). Calcd for $C_{21}H_{28}N_4O_2$: %C, 68.45; %H, 7.66; %N, 15.20. Found: %C, 68.05; %H, 7.69; %N, 15.04.

4.7.6. 6-Amino-5-(benzylideneamino)-3-butyl-1*H*-pyrimidine-2,4-dione (7a). All analytical data are identical to the data given in literature.[17]

4.7.7. Preparation of 9-(benzylideneamino)-7-butyl-1,2,3,4-tetrahydropyrimido[1,6-*a*]pyrimidine-6,8-dione (8a). A solution of **5a** (2 mmol) in dry dimethylformamide (DMF) (20 mL) containing potassium carbonate (0.5 g, 3.6 mmol) was prepared under an inert atmosphere of argon. The solution was heated up to 60°C for 1 h after which 1,3-dibromopropane (1.98 g, 1 mL, 10 mmol) was added. The reaction mixture was stirred under an inert atmosphere of argon until all starting material had disappeared (TLC dichloromethane/methanol=9:1). The solvent was removed by distillation under reduced pressure. The product was isolated by gradient column chromatography (dichloromethane/methanol=100:1 to 100:10).

Yield: 0.35 g (54%). Mp 187–188°C. ^{1}H NMR (500 MHz): δ=0.87 (t, 3H, J=7.4 Hz, C4′H_3), 1.26 (sext, 2H, J=7.4 Hz, C3′H_2), 1.46 (quint, 2H, J=7.4 Hz, C2′H_2), 1.91 (quint, 2H, J=5.8 Hz, C3H_2), 3.21 (m, 2H, C4H_2), 3.76 (t, 2H, J=7.4 Hz, C1′H_2), 3.81 (t, 2H, J=5.8 Hz, C2H_2), 7.21 (br, 1H, N1H), 7.46–7.54 (m, 3H, aromatic-CH), 7.96–7.98 (m, 2H, aromatic-CH), 8.82 (s, 1H, N=CH). ^{13}C NMR (125 MHz): δ=13.9 (C4′), 19.8 (C3′), 20.2 (C3), 30.0 (C2′), 38.7 (C4), 39.6 (C1′), 40.8 (C2), 97.8 (C9), 127.3 (2C, C3″, C5″), 128.5 (2C, C2″, C6″), 129.0 (C4″), 140.0 (C1″), 148.7 (CH=N), 149.4 (C6), 150.5 (C9a), 156.6 (C8). MS: m/z (%)=326.2 (M^+, 100), 249.2 (17), 181.2 (9), 167.1 (18). HRMS: calcd 326.1743. Found: 326.1743. Calcd for $C_{18}H_{22}N_4O_2{\cdot}0.5H_2O$: %C, 64.46; %H, 6.91; %N, 16.70. Found: %C, 64.80; %H, 6.77; %N, 16.81.

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