A New Versatile Synthesis of Xanthines with Variable Substituents in the 1-, 3-, 7- and 8-Positions

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A new convenient procedure for the synthesis of a wide range of xanthines has been developed starting from 3-substituted 6-aminouracils. Nitrosation and reduction yields the corresponding 5,6-diaminouracils, which are condensed with carboxylic acids. The resulting amides can be selectively alkylated at the uracil ring nitrogen *N*-1 (corresponding to xanthine *N*-3) under mild conditions. Ring closure and, if desired, alkylation at the 7-position, yields di-, tri-, or tetrasubstituted xanthines in high yields. Sensitive substituents, such as prop-2-ynyl, can be introduced in the 1-position. Variation of the 3-substituent is considerably facilitated in comparison with the standard procedure for the preparation of xanthines.

Xanthines (7*H*-imidazo[4,5-*d*]pyrimidine-2,6(1*H*,3*H*)-diones) derived from the natural plant alkaloids theophylline (1,3-dimethylxanthine) and caffeine (1,3,7-trimethylxanthine) exhibit a variety of pharmacological effects.[1] Since the discovery that xanthines are potent antagonists at adenosine receptors, the interest in this class of compounds has dramatically increased.[2] Xanthines with selectivity for the A1-adenosine receptor subtype are of interest as kidney-protective diuretics and memory-enhancing geriatrics, while xanthines that show selectivity for the A2a receptor subtype may be useful for the treatment of Parkinson's disease.[3] The recent discovery of the novel putative second messenger cyclic ADP ribose (cADPR), a potent stimulator of intracellular calcium release, and the various effects of caffeine and other xanthines on intracellular cADPR receptors and inositol triphosphate (IP_3) receptors have further stimulated the interest in the synthesis and investigation of novel xanthine derivatives.[4]

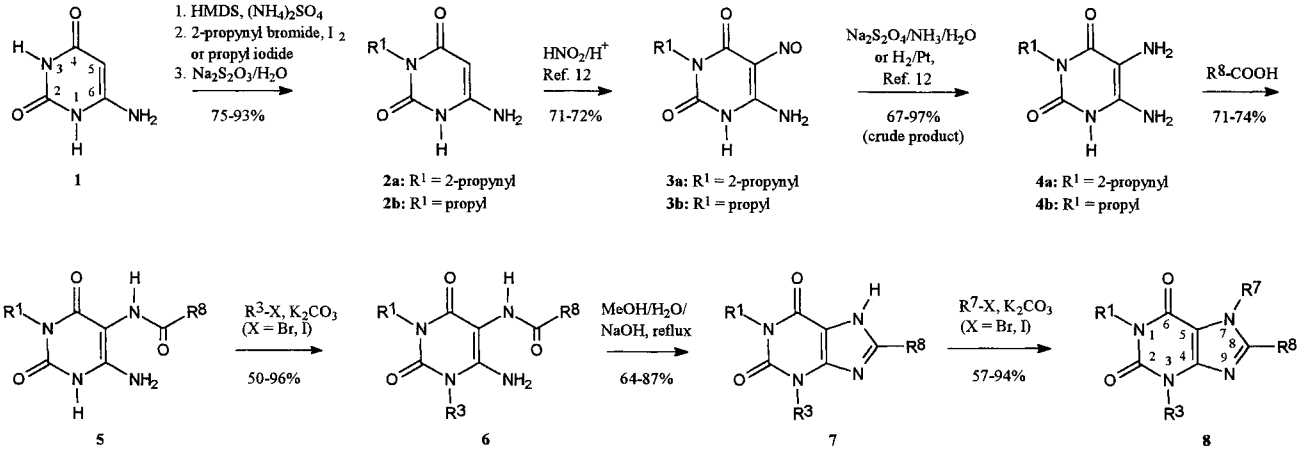
The standard Traube purine synthesis for the preparation of xanthines with different substituents in the 1-, 3-, 7-, and 8-positions starts from monosubstituted ureas, which are condensed with cyanoacetic acid by means of acetic anhydride, followed by alkaline ring closure to obtain the 1-substituted 6-aminouracils.[5] These can be alkylated in the 3-position (corresponding to the 1-position of xanthines) with alkyl bromides or iodides in the presence of sodium hydroxide as base.[5] Nitrosation in the 5-position, reduction to the 5,6-diaminouracils, introduction of what is to become the 8-substituent of the xanthines, ring closure, and final alkylation in the 7-position leads to the 1,3,7,8-tetrasubstituted xanthines.[6] A major drawback of this widely used procedure is the fact that the xanthine 3-substituent has to be introduced already at an early step in the starting urea compound. Monosubstituted ureas, however, are not in all cases readily available, only few derivatives are commercially available, and depending on the substituent, yields can be quite low.[7]

Another problem of the classical xanthine synthesis is that the alkylation of the 1-monosubstituted 6-aminouracils requires harsh reaction conditions, and generally affords only moderate yields.[5] We have been particularly interested in the preparation of 1-(prop-2-ynyl)xanthines (1-propargylxanthines), since some derivatives, such as 3,7-dimethyl-1-propargylxanthine (DMPX), exhibit selectivity for the A2a adenosine receptor subtype.[8] Our attempts to alkylate 6-amino-1-methyluracil with propargyl bromide under the usual conditions in basic medium were unsuccessful due to the high reactivity of alkynes, that are labile under strong basic or acidic conditions and tend to give side reactions, such as hydration of the triple bond.[9,10] An alternative approach to alkylate 6-amino-1-methyluracil after increasing its reactivity by silylation gave only low yields of 6-amino-1-methyl-3-propargyluracil.[9]

Due to these major drawbacks of the classical approach to the synthesis of xanthines we decided to develop an alternative procedure. Recently, we developed the first general synthesis for 3-substituted 6-aminouracils,[11] and based on these starting compounds, we accomplished the synthesis of 1-monosubstituted and various 1,8-disubstituted xanthines.[9,12] Now we have investigated whether these 3-substituted 6-aminouracils could be used for the preparation of xanthines with variable substituents in the 1-, 3-, 7- and 8-positions.

3-Substituted 6-aminouracils **2a**, **2b** were prepared by iodine-catalyzed alkylation of silylated 6-aminouracil, an inexpensive starting compound, with alkyl bromides, or alkyl iodides, respectively, in high yields.[11] The attempted alkylation in the 1-position of 3-substituted 6-aminouracils **2** at this stage resulted in a mixture of compounds which contained mainly 5-substituted products. Therefore, 3-substituted 6-aminouracils **2** were nitrosated in the 5-position,[12] and alkylation at *N*-1 of the nitroso derivatives **3** was attempted. Again, a mixture of products was obtained, containing N^6-alkylated products. We then decided to reduce the 3-substituted 6-amino-5-nitrosouracils **3** to the corresponding 5,6-diaminouracils **4**,[12] which were subsequently condensed with a carboxylic acid to introduce the 8-substituent of the xanthines to afford compounds **5**. At this point, an alkylation of uracil derivatives **5** could easily be performed under very mild conditions in dimethylformamide using alkyl/arylalkyl bromides or iodides and potassium carbonate. The ring nitrogen (*N*-1) could now be selectively alkylated, while the exocyclic amide nitrogen required more drastic conditions for alkylation, e. g. potassium hydroxide as a base, elevated temperature and increased reaction time. After alkylation at *N*-1 (compounds **6**), the imidazole ring could be closed by standard conditions (xanthines **7**), and alkylation at *N*-7 could be performed to afford xanthines **8** (Scheme).

Broad applicability of the new procedure was demonstrated by introducing various substituents. In the 1-



Scheme For R^1, R^3, R^7, and R^8 see Table 1

Table 1. Experimental and Selected Spectral Data for Compounds **5–8**[a]

Compound	R^1	R^2	R^7	R^8	Yield (%)	mp (°C)	^1H or ^{13}C NMR (DMSO-d_6/TMS) δ, J (Hz)
5a	$HC\equiv CCH_2$	–	–	H	72	256	–
5b	$HC\equiv CCH_2$	–	–	(*E*)-3-chlorostyryl	71	289 (dec.)	^1H NMR: 3.05 (t, J = 2.3, 1H, HC≡C), 4.42 (d, J = 2.3, 2H, CH_2N), 6.20 (s, 2H, NH_2), 6.89 (d, J = 15.9, 1H, COCH=CH), 7.41–7.95 (m, 5H, $4H_{arom}$ + COCH=CH), 8.73 (s, 1H, C5-NH), 10.67 (br s, 1H, 1-NH)
5c	Pr	–	–	(*E*)-3-chlorostyryl	74	294–295 (dec.)	^1H NMR: 0.83 (t, J = 7.4, 3H, CH_3), 1.5 (sext, J = 7.4, 2H, CH_2CH_3), 3.66 (t, J = 7.4, 2H, NCH_2), 6.08 (s, 2H, NH_2), 6.9, 7.44 (2d, J = 15.8, 2H, CH=CH), 7.4–7.9 (m, $4H_{arom}$), 8.7 [s, 1H, (5-NH], 10.5 (br s, 1H, 1-NH)[b]
6a	$HC\equiv CCH_2$	$PhCH_2$	–	H	–[c]	–[c]	–
6b	$HC\equiv CCH_2$	Me	–	(*E*)-3-chlorostyryl	96	259	^{13}C NMR: 29.9 (CH_2N), 30.1 (NCH_3), 72.5 (HC≡C), 80.0 (HC≡C), 87.1 (C5), 124.3, 125.9, 127.2, 129.1, 130.9, 133.7, 137.2, 137.3 (C_{arom} + CH=CH), 149.8, 152.4 (C2, C6), 158.1 (C4), 165.0 (NHCO)
6c	$HC\equiv CCH_2$	Pr	–	(*E*)-3-chlorostyryl	–[c]	–[c]	–
6d	$HC\equiv CCH_2$	*i*-Pr	–	(*E*)-3-chlorostyryl	50	123	–
6e	$HC\equiv CCH_2$	$PhCH_2$	–	(*E*)-3-chlorostyryl	86	232–238	–
6f	Pr	Me	–	(*E*)-3-chlorostyryl	95	221–222	^{13}C NMR: 11.2 (CH_3CH_2), 20.9 (CH_3CH_2), 30.0 (NCH_3), 42.0 (CH_2N), 87.4 (C5), 124.4, 125.9, 127.2, 129.1, 130.9, 133.7, 137.1, 137.4 (C_{arom} + CH=CH), 150.4, 151.9 (C2, C6), 159.1 (C4), 165.0 (NHCO)[d]
7a	$HC\equiv CCH_2$	$PhCH_2$	–	H	72	244 (dec.)	^{13}C NMR: 30.2 ($\equiv CCH_2$), 46.2 ($C_6H_5CH_2$), 72.7 (HC≡C), 79.6 (HC≡C), 127.4, 127.9, 128.4, 136.7 (C_6H_5), 106.4 (C5), 141.2 (C8), 147.9 (C4), 150.2 (C2), 153.3 (C6)
7b	$HC\equiv CCH_2$	Me	–	(*E*)-3-chlorostyryl	73	> 300	–
7c	$HC\equiv CCH_2$	Pr	–	(*E*)-3-chlorostyryl	–[c]	–[c]	–
7d	$HC\equiv CCH_2$	*i*-Bu	–	(*E*)-3-chlorostyryl	64	250 (dec.)	–
7e	$HC\equiv CCH_2$	$PhCH_2$	–	(*E*)-3-chlorostyryl	–[c]	–[c]	–
7f[e]	Pr	Me	–	(*E*)-3-chlorostyryl	87	258 (dec.)	–
8a	$HC\equiv CCH_2$	Me	Me	(*E*)-3-chlorostyryl	77	210	–
8b	$HC\equiv CCH_2$	Me	$HC\equiv CCH_2$	(*E*)-3-chlorostyryl	86	236	–
8c	$HC\equiv CCH_2$	Pr	Me	(*E*)-3-chlorostyryl	94	188	–
8d	$HC\equiv CCH_2$	*i*-Bu	Me	(*E*)-3-chlorostyryl	72	189	–
8e	$HC\equiv CCH_2$	$PhCH_2$	Me	(*E*)-3-chlorostyryl	57	228	–
8f	Pr	Me	Me	(*E*)-3-chlorostyryl	91	161–162.5	–

[a] For further NMR data of compounds **5–8**, see Tables 2–4.
[b] IR (KBr): ν = 3329, 3179, 1735, 1646, 1620 cm^{-1}.
[c] Not isolated.
[d] IR (KBr): ν = 3315, 3211, 1704, 1619, 1508, 1456 cm^{-1}.
[e] IR (KBr): ν = 3145, 3089, 3036, 1699, 1643, 1593, 1565, 1495 cm^{-1}.

Table 2. ^{13}C NMR Data of Compounds **5** (DMSO-d_6), δ

Compound	C5	C2, C6	C4	C5-NHCO	R^1	R^8
5a[a]	85.4	149.1, 150.2	161.4	167.2	28.9, 72.4, 79.9	–
5b	86.8	149.2, 150.3	159.6	164.8	28.9, 72.5, 80.0	124.1, 125.9, 127.2, 129.1, 130.9, 133.7, 137.3, 137.4
5c	87.2	149.8	160.6	164.7	11.2, 20.9, 41.0	124.1, 125.9, 127.2, 129.1, 130.8, 133.7, 137.3, 137.4

[a] Mixture of isomers; data of major isomer is given (amide, ca. 70% according to integration of protons in ^1H NMR spectrum); further signals at δ = 29.0, 80.0, 86.2, 149.0, 151.9, 159.4, 160.8.

position a propyl, or a prop-2-ynyl residue, respectively, was introduced; it has been shown before that a wide range of 3-substituted 6-aminouracils is available;[11] thus there should be no limitations for 1-substituents in these syntheses. For the critical introduction of the *N*-3-substituent of the xanthines, that corresponds to *N*-1 of the uracil derivatives, we used reactive alkyl/aryl halides, such as methyl iodide and benzyl bromide, as well as alkyl halides of lower reactivity, such as propyl and isobutyl iodide. It was shown that 8-unsubstituted compounds are accessible (compound **7a**) as well as 8-substituted derivatives **7b–f**. As a substituent in the 8-position we selected the (*E*)-3-chlorostyryl [(*E*)-2-(3-chlorophenyl)ethenyl] residue since it has been reported to confer selectivity for the A2a adenosine receptor subtype to xanthines.[13] The final alkylation in the 7-position has been described before and is performed with alkyl halogenides under very mild conditions, as demonstrated by the introduction of methyl and propargyl residues to give compounds **8a–f**. The new compounds were characterized by their ^1H NMR spectra, melting points and elemental analyses. In addition, for some examples ^{13}C NMR and IR data are provided. The (*E*)-configuration of the (*E*)-styryl-substituted compounds was found to be retained in the reaction sequence as shown by ^1H NMR spectra (J = ca. 16 Hz).

In conclusion, the described syntheses offer a new convenient access to novel xanthines some of which cannot be readily obtained by standard procedures. The new procedure is superior to the standard xanthine synthesis in many cases, and may be the method of choice particularly for the preparation of xanthines with different substituents in the 1-, 3-, 7-, and 8-positions. Biological data of the new compounds will be reported in due course.

Melting points were measured with a Büchi 510 apparatus and are not corrected. The following instruments were used for recording spectra: IR: Perkin-Elmer 1750, MS: Varian MAT 711, ^1H and ^{13}C NMR: Bruker WP-80 or Bruker AC-250; DMSO-d_6 was used as solvent unless otherwise noted. Satisfactory microanalyses were obtained for all isolated compounds: C ± 0.4, H ± 0.27, Cl ± 0.3, N ± 0.4.

6-Amino-3-(prop-2-ynyl)uracil (2a); Typical Procedure:
A suspension of 6-aminouracil (20.0 g, 0.157 mmol) and $(NH_4)_2SO_4$ (1 g) in hexamethyldisilazane (HMDS, 200 mL) was refluxed for 2 h. Within this time the mixture became homogeneous. Excess HMDS was distilled off, at first under atmospheric pressure, then under vacuum. The product was allowed to cool to ca. 40–70 °C, a temperature above the melting point of the compound as it had to be liquid for the subsequent step. A catalytic amount of I_2 (ca. 150 mg) was dissolved in the product, a 80% toluene solution of prop-2-ynyl bromide (20 mL) was added, and the mixture was heated in an oil bath under reflux. After 1.5 h, the progress of the reaction was monitored by TLC (eluent: CH_2Cl_2/MeOH, 9:1) showing only a small quantity of starting material and a little dialkylated product. At this point the mixture was allowed to cool to r.t. and a solution of $Na_2S_2O_3$ (3 g) in H_2O (10 mL) was added. The flask was cooled in an ice bath, and a sat solution of $NaHCO_3$ (ca. 400 mL) was added in small portions over a period of ca. 30 min with vigorous stirring until effervescence ceased, and the gelatinous mixture had turned into a suspension. The precipitate was filtered, washed with cold water (150 mL), toluene (100 mL) and Et_2O (100 mL). Analytical samples were obtained by recrystallization from MeOH; yield: 19.5 g (75%); mp 251 °C (dec) (Lit.[11] mp 251 °C).

MS (EI): m/z (%) = 169 (M^+, 37), 127 (100), 111 (40), 85 (39), 68 (87).

^1H NMR: δ = 2.49 (t, J = 2.3 Hz, 1 H, HC≡C), 4.57 (s, 1 H, 5-H), 4.36 (d, J = 2.3 Hz, 2 H, CH_2N), 6.27 (br s, 2 H, NH_2), 10.49 (br s, 1 H, NH).

^{13}C NMR: δ = 28.2 (CH_2N), 73.0 (HC≡C), 80.3 (HC≡C), 73.8 (C5), 150.3 (C2), 153.9 (C6), 161.9 (C4).

6-Amino-3-propyluracil (**2b**): The preparation of **2b** was performed as described for **2a** from 6-aminouracil (10.0 g, 78.7 mmol) and propyl iodide (11.5 mL, 118 mmol) without the addition of I_2; yield: 24.5 g (93%), mp 275 °C (dec) (Lit.[11] mp 275 °C).

MS (EI): m/z (%) = 165 (M^+, 100), 137 (32), 122 (40), 68 (41).

^1H NMR: δ = 0.80 (t, J = 7.3 Hz, 3 H, CH_3), 1.65 (sext, 2 H, CH_2), 3.95 (t, J = 7.3 Hz, 2 H, CH_2N), 4.53 (s, 1 H, 5-H), 6.14 (br s, 2 H, NH_2), 10.19 (br s, 1 H, NH).

^{13}C NMR: δ = 11.2 (CH_3), 21.0 (CH_3CH_2), 40.2 (CH_2N), 74.2 (C5), 151.4 (C2), 153.9 (C6), 163.1 (C4).

3-Substituted 5,6-Diaminouracils 4a, b:
Compounds **4a** and **4b** were prepared from **2a** and **2b** as described.[12] The labile diaminouracils **4** were generally not purified and used immediately in the subsequent step, even if the compounds were still moist. Analytical samples could be obtained by recrystallization from MeOH.

4a: Yield: 67%; mp 234–238 °C (dec).

^1H NMR: δ = 2.99 (t, J = 2.4 Hz, 1 H, HC≡C), 4.44 (d, J = 2.4 Hz, 2 H, CH_2N), 4.7–5.3 (v br s, 2 H, exchangeable with D_2O, C5-NH_2), 5.70 (br s, 2 H, C6-NH_2).

^{13}C NMR: δ = 28.9 (CH_2N), 72.2 (HC≡C), 80.2 (HC≡C), 95.1 (C5), 143.4 (C6), 148.6 (C2), 159.3 (C4).

4b: Yield: 70%; mp 206 °C (dec).

^1H NMR: δ = 0.79 (t, J = 7.3 Hz, 3 H, CH_3), 1.34 (sext, J = 7.3 Hz, 2 H, CH_3CH_2), 3.65 (t, J = 7.3 Hz, 2 H, CH_2N), 4.7–5.3 (v br s, 2 H, exchangeable with D_2O, C5-NH_2), 5.62 (s, 2 H, C6-NH_2).

For the preparation of **4b**, reduction of **3b** with H_2/Pt was found to be superior to the described reduction with $Na_2S_2O_4$,[12] since the product could be isolated more easily. Compound **3b** (0.50 g, 2.94 mmol) was suspended in MeOH (20 mL). PtO_2 (0.01 g) was added and a stream of H_2 was passed through the suspension. After 2 h the colored suspension had turned white. CH_2Cl_2 (250 mL) was added to dissolve the product. Pt was filtered off and the solvent removed in vacuo to yield 0.45 g (98%) of **4b**.

6-Amino-5-formylamino-3-(prop-2-ynyl)uracil (5a):
Compound **4a** (1.2 g, 6.7 mmol) was dissolved in 98% formic acid (50 mL) and stirred at r.t. for 2 h. Excess formic acid was distilled

Table 3. ^{1}H NMR Data of Representative Examples of Alkylation Products **6** (DMSO-d_6), δ

Compound	C6-NH_2 (br s)	C5-NH (s)	R^1 J (Hz)	R^3 J (Hz)	R^8 J (Hz)
6b	6.87	8.73	3.05 (t, J = 2.3, 1H), 4.49 (d, J = 2.3, 2H)	3.33 (s, 3H)	6.76 (d, J = 15.9, 1H), 7.50–7.97 (m, 5H)
6d	6.73	8.65	3.04 (t, J = 2.3, 1H), 4.47 (d, J = 2.3, 2H)	0.86 (d, J = 6.7, 6H), 2.0 (m, 1H), 3.76 (d, J = 7.6, 2H)	6.87 (d, J = 16.0, 1H), 7.35–7.64 (m, 5H)
6e	6.70	8.71	3.02 (t, J = 2.3, 1H), 4.51 (d, J = 2.3, 2H)	5.53 (s, 2H), 7.28 (s, 5H)	6.87 (d, J = 15.9, 1H), 7.17–7.64 (m, 5H)
6f	6.63	8.64	0.83 (t, J = 7.4, 2H), 1.54 (sext, J = 7.4, 2H), 3.72 (t, J = 7.4, 3H)	3.30 (s, 3H)	6.87 (d, J = 15.9, 1H), 7.35–7.64 (m, 5H)

Table 4. Selected ^{1}H NMR Data of Xanthines **7** and **8** (DMSO-d_6), δ

Compound	R^1 J (Hz)	R^3 J (Hz)	R^7 J (Hz)	R^8 J (Hz)
7a	3.05 (t, J = 2.4, 1H), 4.60 (d, J = 2.4, 2H)	5.19 (s, 2H), 7.30 (s, 5H)	–[a]	8.06 (s, 1H)
7b	2.93 (t, J = 2.3, 1H), 4.62 (d, J = 2.3, 2H)	3.50 (s, 3H)	–[a]	7.16 (d, J = 16.8, 1H), 7.36–7.74 (m, 5H)
7d	3.06 (t, J = 2.4, 1H), 4.61 (d, J = 2.4, 2H)	0.89 (d, J = 6.6, 6H), 2.24 (m, 1H), 3.85 (d, J = 7.5, 2H)	–[a]	7.19–7.69 (m, 6H)
7e	3.05 (t, J = 2.4, 1H), 4.60 (d, J = 2.4, 2H)	5.22 (s, 2H), 7.30 (s, 5H)	–[a]	7.10–7.67 (m, 6H)
7f[b]	0.86 (t, J = 7.3, 3H), 1.57 (sext, J = 7.3, 2H), 3.83 (t, J = 7.3, 2H)	3.46 (s, 3H)	13.38 (v br s, 1H)	7.08, 7.63 (2d, J = 16.2, 2H), 7.30–7.73 (m, 4H)
8a	2.84 (t, J = 2.4, 1H), 4.63 (d, J = 2.4, 2H)	3.50 (s, 3H)	4.04 (s, 3H)	7.22–7.95 (m, 6H)
8b	3.08 (t, J = 2.4, 1H), 4.17 (d, J = 2.4, 2H)	3.48 (s. 3H)	3.10 (t, J = 2.2, 1H), 5.42 (d, J = 2.2, 2H)	7.39–7.94 (m, 6H)
8c	2.87 (t, J = 2.4, 1H), 4.62 (d, J = 2.4, 2H)	0.93 (t, J = 7.2, 3H), 1.82 (sext, J = 7.2, 2H), 4.05 (t, J = 7.2, 2H)	4.05 (s, 3H)	7.24–7.86 (m, 6H)
8d	3.03 (t, J = 2.4, 1H), 4.60 (d, J = 2.4, 2H)	0.86 (d, J = 6.7, 6H), 2.18 (m, 1H), 3.80 (d, J = 7.2, 2H)	4.04 (s, 3H)	7.35–7.95 (m, 6H)
8e	3.01 (t, J = 2.4, 1H), 4.61 (d, J = 2.4, 2H)	5.22 (s, 2H), 7.30 (s, 5H)	4.04 (s, 3H)	7.20–7.92 (m, 6H)
8f[b]	0.85 (t, J = 7.2, 3H), 1.56 (sext, J = 7.2, 2H), 3.81 (t, J = 7.2, 2H)	3.45 (s, 3H)	4.00 (s, 3H)	7.06 (d, J = 15.8, 1H), 7.19–7.79 (m, 5H)

[a] N7-H generally appears as a very broad singlet at 13–14 ppm and could not be seen in some spectra due to rapid exchange.
[b] Recorded in $CDCl_3$/DMSO-d_6 (5 : 1).

off in vacuo, the residue suspended in cold H_2O (10 mL), collected by filtration, washed with cold H_2O, and recrystallized from H_2O. NMR spectra in DMSO-d_6 indicated the existence of at least two isomers, the amide **5a** (structure as shown in Scheme) being the major isomer (ca. 70%).

^{1}H NMR (major isomer): δ = 3.04 (t, J = 1.8 Hz, 1H, HC≡C), 4.42 (d, J = 1.8 Hz, 2H, CH_2N), 6.19 (s, 1.4H, C6-NH_2), 8.05 (s, 0.7H, CHO), 8.64 (s, 0.7H, NHCHO), 10.68 (br s, 1H, 1-NH).

Further signals at: 6.46 (s, 0.6H), 7.69, 7.75 (0.3H), 8.07, 8.12 (0.3H) are assumed to be from the tautomeric *E*- and *Z*-imides (C6-NH_2, N^5=CH–OH and N^5=CH–OH).

3-Substituted 6-Amino-5-(3-chlorocinnamoylamino)uracils 5b, c:
A suspension of **4a**, or **4b** (10 mmol) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.1 g, 11 mmol) and (*E*)-3-chlorocinnamic acid (2.0 g, 11 mmol) in a mixture of MeOH (30 mL) and H_2O (30 mL) was stirred at r.t. overnight. The formed precipitate was collected by filtration, washed with H_2O and subsequently with MeOH.

Alkylation of Uracils 5; General Procedure for the Preparation of 6a–f:
Compound **5a, b**, or **c** (5 mmol) was dissolved in DMF (20 mL). After addition of K_2CO_3 (1.38 g, 10 mmol), the appropriate alkyl/arylalkyl halogenide was added as follows: **6a, 6e**: $PhCH_2I$ (6 mmol); **6b, 6f**: MeI (6 mmol); **6c**: PrI (20 mmol); **6d**: *i*-BuI (50 mmol). The mixture was stirred at r.t. (**6a, b, c, e, f**), or at 50 °C (**6d**) for 48 h. The product was precipitated by the addition of H_2O (30 mL), collected by filtration, and washed with H_2O (50 mL), then with MeOH (10 mL), and finally with Et_2O (10 mL). Further purification was achieved by dissolution in DMF (10 mL) and precipitation by the addition of H_2O (50 mL). Compounds **6a** and **6c** were used in the next step without purification.

Xanthines 7a–f; General Procedure:
Compound **6** (3.0 mmol) was dissolved in a mixture of MeOH (100 mL) and 20% aq NaOH solution (20 mL) and refluxed for 2–3 h. After cooling, the solution was acidified to pH 4 by the addition of conc. HCl, and the formed precipitate was collected by filtration and washed with H_2O. Purification was achieved by dis-

solution in DMF (10 mL) at ca. 80 °C and precipitation by the addition of H_2O (50 mL). Compounds **7c** and **7e** were alkylated to the final tetrasubstituted xanthines **8c** and **8e** without prior purification.

Xanthines 8a–f; General Procedure:
Compound **7** (2.3 mmol) was dissolved in DMF (20 mL), K_2CO_3 (0.64 g, 4.6 mmol) and MeI, or prop-2-ynyl bromide (3.0 mmol) was added. The mixture was stirred at r.t. overnight. Then H_2O (80 mL) was added to precipitate the product which was collected by filtration. The product was treated with 10% aq NaOH solution (15 mL) to dissolve impurities. Further purification was achieved by dissolution in DMF (10 mL) at ca. 80 °C and precipitation by the addition of H_2O (50 mL).

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(1) Stevanovich, V. *Drug News Perspect.* **1989**, *2*, 82.
(2) Müller, C.E.; Scior, T. *Pharm. Acta Helv.* **1993**, *68*, 77.
(3) Williams, M. *Drug Dev. Res.* **1993**, *28*, 438.
(4) Lee, H.C. *J. Biol. Chem.* **1993**, *268*, 293.
Parker, I.; Ivorra, I. *J. Physiol. (London)* **1991**, *433*, 229.
Müller, C.E.; Daly, J.W. *Biochem. Pharmacol.* **1993**, *46*, 1825.
(5) Papesch, V.; Schroeder, E.F. *J. Org. Chem.* **1951**, 1879.
(6) Traube, W. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 3035.
Garst, J.E.; Kramer, G.L.; Wu, Y.J.; Wells, J.N. *J. Med. Chem.* **1976**, *19*, 499.
Review: Gulevskaya, A.V.; Pozharskii, A.I. *Khim. Geterotsikl. Soedin.* **1991**, *1*, 3.
(7) Vishnyakova, T.P.; Golubeva, I.A.; Glebova, E.V. *Russ. Chem. Rev.* **1985**, *54*, 249.
(8) Daly, J.W.; Padgett, W.L.; Shamim, M.T. *J. Med. Chem.* **1986**, *29*, 1305.
(9) Müller, C.E.; Shi, D.; Manning, M.Jr.; Daly, J.W. *J. Med. Chem.* **1993**, *36*, 3341.
(10) Müller, C.E. *J. Org. Chem.* **1994**, *59*, 1928.
(11) Müller, C.E. *Tetrahedron Lett.* **1991**, *32*, 6539.
(12) Müller, C.E. *Synthesis* **1993**, 125.
(13) Jacobson, K.A.; Gallo-Rodriguez, C.; Melman, N.; Fischer, B.; Maillard, M.; van Bergen, A.; van Galen, P.J.M.; Karton, Y. *J. Med. Chem.* **1993**, *36*, 1333.