A MILD METHOD FOR THE PREPARATION OF 8-SUBSTITUTED XANTHINES FROM 5,6-DIAMINOURACILS

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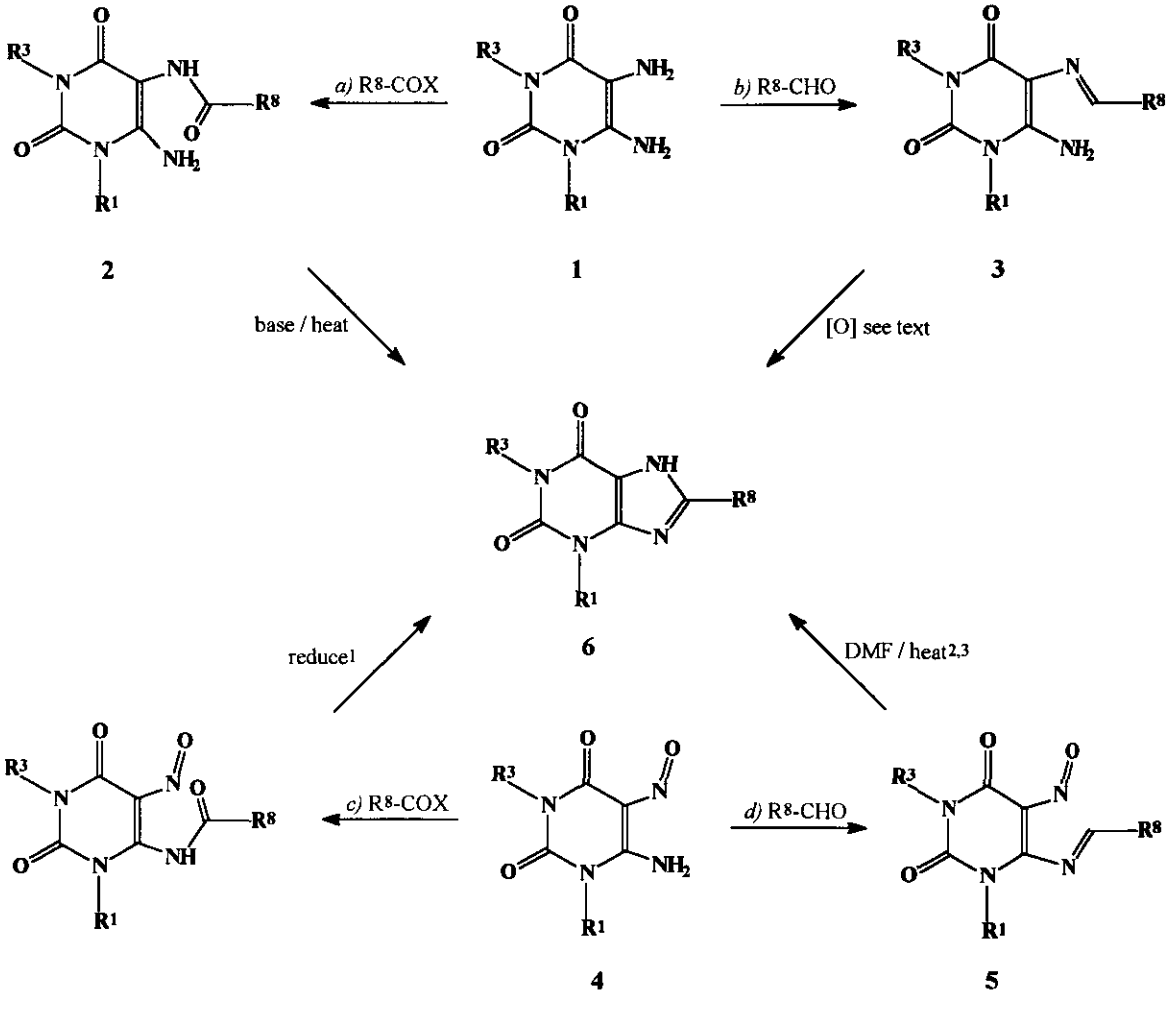
Abstract *- The Schiff base derivatives (3), prepared from the respective 5,6-diaminouracil (1) and aldehydes can be mildly oxidatively cyclized with m-CPBA in MeCN to afford C-8 substituted xanthines (6).*

Xanthines, a class of compounds commonly used clinically as bronchodilators, central nervous system stimulants and diuretics, are usually prepared by one of several conceptually similar methods:



The condensation of a 5,6-diaminouracil (**1**) with either *a)* a carboxylic acid (or derivative) or *b)* an aldehyde, followed by ring closure of the amino-acylamino (**2**) or 6-amino-5-iminouracil (**3**) intermediate respectively, *c)* acylation of a 6-amino-5-nitrosouracil (**4**) followed by reduction of the nitroso function and concomitant cyclization[1] or *d)* Schiff base formation followed by heating of the nitroso-Schiff base (**5**) in DMF.[2,3] This gives rise to 8-substituted (R8) xanthines (**6**). Of these, *a)* and *b)* are the most commonly employed routes. Where available, trialkyl orthoesters can be used instead of carboxy derivatives and condensed with diaminouracils to afford xanthines directly.[4]

Often these preparations can be effected in one-pot, although in many cases the reaction conditions for the ring closure can be forcing. Commonly employed procedures for this step include aqueous inorganic bases at reflux (*Route a)*) as well as oxidative cyclization of **3** using I_2/DME/50°C,[5] DEAD/DMF/100°C,[6] DEAD/glyme/reflux,[7a] DEAD(neat)/heat,[7b] $SOCl_2$/reflux,[8] $HgCl_2$/DMSO/rt,[9] $FeCl_3$/EtOH/reflux,[10] $FeCl_3$/AcOH,[11] benzaldehyde/Pd/SiO_2/benzene/reflux (one pot),[12] EtOH/reflux (aldehyde employed as sodium sulphite adduct)[13] or NBS/$CHCl_3$/reflux[14] (*Route b)*). The diaminouracil (**1**) may also be heated with the respective aldehyde, albeit only at elevated temperatures (refluxing nitrobenzene[12]) to provide the xanthine directly without added oxidant.

We expect, that most of the methods for oxidative cyclization cited herein have some drawbacks regarding their general applicability. Recently we tried to prepare some xanthines and found in several cases for example, that the temptingly mild oxidative cyclization of amino Schiff-base type intermediates (**3**) employing ferric chloride in refluxing ethanol[10] did not yield the desired xanthines. Iodine in DME[5] at elevated temperatures on the other hand did provide the expected result, albeit often in low yield with the added annoyance of generally tedious work-up, isolation and purification procedures.

From a completely different angle it is to be expected at least that **many, if not all of the oxidative cyclization conditions cited above will not be suitable in the burgeoning field of combinatorial chemistry** due to the incompatibility of reagents,[5,8,12,14] reaction temperature,[6-8,10,12-14] or ease and/or unpleasantness of execution[5,8,9,12] with current solid phase chemistry technology.

We have found, that *m*-CPBA in acetonitrile is a mild and convenient oxidant, **which avoids all of the abovementioned drawbacks in this regard and effects the clean oxidative cyclization of amino Schiff-bases (3) to the respective 8-substituted xanthines (6) at room temperature.** In most cases the product precipitates in pure form from solution and can be filtered directly and recrystallised from a suitable solvent if necessary.

The **Table** shows the xanthines prepared by this method. The intermediate Schiff bases (**3**) were used directly in the subsequent oxidative cyclization without purification. In all cases the products were high melting solids, most often precipitating from the reaction in pure form. Some strongly electron deficient

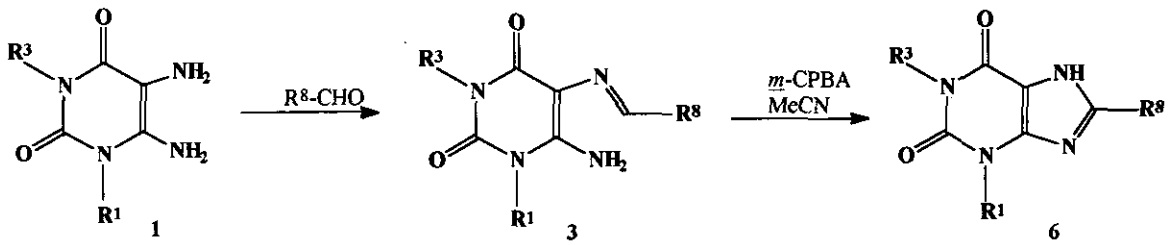


Table 1: Preparation of 8-substituted xanthines (**6**)

R^{1} a)	R^{3}	R^{8} a)	Imine b)	Yield / %	Xanthine c)	Yield / %
Me	Me	*o*-F-Ph	**3a**	92	**6a**[15]	71
Me	Me	*p*-F-Ph	**3b**	95	**6b**[15]	73
Propenyl	Me	*p*-HO-Ph	**3c**	67	**6c**	87
Me	Me	*o*-HO-Ph	**3d**	81	**6d**[15]	90
Me	Me	*p*-Me-Ph	**3e**	93	**6e**[8, 15]	83
Me	Me	*p*-Me_2N-Ph	**3f**	69	**6f**[8, 15]	70
Me	Me	*o*-HO_2C-Ph	**3g**	81	**6g**[15]	57
Me	Me	*p*-O_2N-Ph	**3h**	99	**6h**[15,16]	44
Me	Me	*p*-Diphenyl	**3i**	89	**6i**[15]	88
Me	Me	Styryl	**3j**	86	**6j**[17]	90
Me	Me	2-Furyl	**3k**	93	**6k**[18]	85
Me	Me	Cyclohexyl	**3l**	d)	**6l**[19]	68
p-Acetamidobenzyl[20]	*n*-Pr	2-Pyridyl e)	**3m**	83 f)	**6m**[15, 16]	0 g)
p-Acetamidobenzyl	*n*-Pr	*p*-HO_2CCH_2O-Ph	**3n**	87 f)	**6n**[20]	69

a) Commercially available reagents were used directly.
b) Intermediates (**3**) were pure solids (TLC, NMR) which were filtered off and used without further purification.
c) Products precipitated in pure form from the reaction mixture. Known xanthines (**6a, b, d-l, n**) are very high melting (>300°C) solids and gave satisfactory NMR and MS spectra.
d) **6l** isolated directly after 7 days. With shorter reaction times **3l/6l** mixtures were obtained.
e) We thank Ms. Paola Ciceri for performing this reaction.
f) Yield for two steps: C-5 nitroso hydrogenation and direct 5,6-diaminouracil condensation with appropriate aldehydes (cf. ref. 21)
g) **3m** insoluble in MeCN. No reaction in DMF.

aldehydes unfortunately were poor in this protocol. Thus *p*-CN- (not shown) and *p*-O_2N- (**h**) as well as pyridine-2-carbaldehyde (**m**) derived imines gave low (or no) yields of xanthine in the cyclization step.

It is interesting to note the different effects of the aromatic moiety upon the reaction rate in the two steps of this sequence. In the first step from aldehyde to Schiff base (**1** → **3**) the aldehyde, acting as an electrophile, reacts fast in the case of electron poor benzaldehyde derivatives (p. ex. **a**, **b**, **h**, **m**), in the

second step however, where the imine function reacts as a nucleophile in the oxidative cyclization, the reverse is true; i.e. electron rich aromatic substrates react faster (p. ex. **3c-f**). A comparison of cases **e** and **h** is instructive. As expected, Schiff base formation proceeded in high yield in both cases, although **1** → **3h** (electron poor: instantaneous) was much faster than **1** → **3e** (electron rich: 2 h). Matters were reversed in the oxidative cyclization. Not only did the *p*-nitrophenyl derived imine (**3h**) give a much lower yield of product (**6h**) than *p*-methylimine (**3e**), but its' reaction with *m*-CPBA was also much slower: **3h** → **6h** (electron poor: >7 h) > **3e** → **6e** (electron rich: instantaneous).

We believe this method to be a useful addition to current oxidative cyclization methodology for the synthesis of xanthines. In view of generally good yields as well as ease of execution and product isolation it should be considered amongst first-choice methods for the preparation of this important class of compounds.

EXPERIMENTAL

Melting points are not corrected. ^{1}H NMR (200, 300, 360 MHz) spectra were recorded on Varian *Gemini-200*, Varian *Unity Plus* and Bruker *AM-360* instruments respectively using residual solvent protons as references. IR spectra were recorded on a Bruker *IFS 66* apparatus and MS on VG *70-SE* and Finnigan *GCQ-MAT* instruments. Analytical TLC was done on precoated *Kieselgel 60* F_{254} glass plates (Merck) or plastic sheets (Macherey-Nagel, *Polygram SIL G/UV*$_{254}$). AR grade solvents (Fluka, Vetec) and commercial reagents (Fluka, Aldrich) were used without further purification in all cases. N3-Methyl-N1-propenyl-5,6-diaminouracil was obtained from the Novartis (*ex*-Sandoz)-*Kilolabor*.

Procedure for the preparation of N1-*p*-acetamidobenzyl-N3-*n*-propyl-5,6-diaminouracil:- (The entire six-step procedure was carried out without purification of intermediates in close analogy to established procedures.[20,21] Products were clean by TLC, NMR and MS, in all cases amenable to further transformation. In practice, material could be stored at any intermediate stage. The final 5,6-diaminouracil (**1n**) itself however decomposed with time, so that material was best stored at the penultimate 6-amino-5-nitroso stage, using the ethanol solution of the product resulting from Raney Nickel nitroso group hydrogenation, immediately for the Schiff base (**3n**) preparation; *vide infra*.): N-*p*-Nitrobenzyl-N'-*n*-propylurea (56.6 g, 239 mmol) was suspended in Ac_2O (230 mL) and treated with cyanoacetic acid (24.4 g, 286 mmol). The light-beige suspension was stirred at 50°C for 20 h and concentrated *in vacuo*. The resultant oil was dissolved in an equal volume of toluene and again concentrated. The residue was now dissolved in EtOAc, washed with saturated aq $NaHCO_3$ (3x) and brine, dried (Na_2SO_4), filtered and concentrated to afford a red-brown oil (100 g) which was taken up in EtOH (300 mL) and crystallised to

obtain light-yellow crystals of **N-cyanoacetyl-N-*n*-propyl-N′-*p*-nitrobenzylurea** (53.5 g, 74%), mp 80-81°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.22 (br s, 1H), 8.20 (d, J = 7.5 Hz, 2H), 7.48 (d, J = 7.5 Hz, 2H), 4.58 (d, J = 7 Hz, 2H), 3.80 (s, 2H), 3.66 (t, J = 7 Hz, 2H), 1.69 (m, 2H), 0.99 (t, J = 7 Hz, 3H). All of this material (53.5 g, 176 mmol) was dissolved in warm EtOH (700 mL) (50°C) and the yellow solution diluted with water (270 mL), brought to 40°C and treated with conc NaOH solution (3.7 mL, 28 mmol). The temperature rose to 46°C and the now light-brown, clear solution was stirred for 1h at rt. Concentration *in vacuo* to approx 400 mL resulted in the separation of yellow crystals which were filtered, washed with EtOH/H_2O and dried to afford **N1-*p*-nitrobenzyl-N3-*n*-propyl-6-aminouracil** (39.1g), mp 190-192°C. The mother liquor was further concentrated to 200 mL, giving a second crop (10 g), mp 180-185°C. Both (combined yield: 92%) were suitable (TLC, NMR) as such for the next step, in which the foregoing product (10g, 32.9 mmol) and PtO_2 (300 mg) were suspended in EtOH (200 mL) and hydrogenated at rt and 1 atm pressure for 3h. Filtration through *celite* and concentration gave a yellow foam (9.15 g, 100%), which was dissolved in pyridine (100 mL), cooled to 0°C and treated with Ac_2O (3.42 mL, 36.2 mmol). After stirring at 0°C for 2h, the reaction mixture was concentrated *in vacuo* and the solid, bright-yellow residue slurried in water (200 mL), worked through with a glass rod, filtered and washed with more water. The residue was now treated in a likewise fashion with Et_2O (200 mL) and finally dried *in vacuo* to afford **N1-*p*-acetamidobenzyl-N3-*n*-propyl-6-aminouracil** as a light-beige powder (9.4 g, 91%), clean by TLC/NMR and used without further purification. The thus prepared 6-aminouracil (9.2 g, 29 mmol) was suspended in MeOH (100 mL) and AcOH (100 mL) and treated dropwise during 20 min with a solution of $NaNO_2$ (8.035 g, 116 mmol) in water (30 mL) resulting in a violet solution. Stirring continued at rt for 3 h, after which the precipitate was filtered to give a violet powder (2 g, Fraction A). The mother liquor was diluted with water (1 L) resulting in a brown suspension which was filtered off (1.36 g, Fraction B). The filtrate was now extracted with EtOAc (3x), the organic phases dried (Na_2SO_4), filtered and concentrated to afford a violet solid (2g) which was worked through with Et_2O, filtered, washed and dried to afford more violet powder (1.33 g, Fraction C). The aqueous phase from the EtOAc-extraction was concentrated to 100 mL and the precipitated product filtered, washed with water and dried to give more of the **N1-*p*-acetamidobenzyl-N3-*n*-propyl-6-amino-5-nitrosouracil** as a violet powder (4.3 g, Fraction D); (total yield: Fractions A-D: 8.99 g, 89%; Fractions A and D pure, used as such in the next step; Fractions B and C impure). ^{1}H NMR (200 MHz, DMSO-d_6) δ 13.22 (br s, 1H), 9.98 (s, 1H), 9.20 (br s, 1H), 7.52 (d, J = 9 Hz, 2H), 7.20 (d, J = 9 Hz, 2H), 5.08 (s, 2H), 3.90 (m, 2H), 2.04 (s, 3H), 1.63 (m, 2H), 0.91 (t, J = 7 Hz, 3H); IR (KBr) ν_{max} 3306, 2966, 1723, 1672, 1631(sh), 1600, 1517, 791 cm^{-1}; MS (CI) *m/z* 345 (M^+, 7), 328 (17), 215 (25), 148 (50), 106 (100). This pure 5-nitrosouracil (1 g, 2.9 mmol) and Raney Nickel (100 mg) were suspended in EtOH (20 mL) and hydrogenated at rt and 1 atm for 4 h. The mixture was filtered and the clear filtrate (TLC: single spot) was

used immediately in the subsequent condensation step to Schiff base (**3n**) as described below. In another run, evaporation of a portion of the EtOH-solution provided **1n** as a thick gum. ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.04 (br s, 1H), ≅9.3 - ≅5.7 (br, 2H), 7.52 (d, J = 9 Hz, 2H), 7.15 (d, J = 9 Hz, 2H), 6.19 (s, 2H), 5.10 (s, 2H), 3.79 (m, 2H), 2.03 (s, 3H), 1.52 (m, 2H), 0.83 (t, J = 7 Hz, 3H); MS (EI) *m/z* 331 (M^+, 8), 302 (5), 261 (8), 184 (16), 164 (12), 148 (82), 121 (73), 106 (100).

General procedure for the preparation of 8-substituted xanthines: The 5,6-diamino-1,3-disubstituted uracil (**1**) (3-7 mmol) in EtOH (50-100 mL) was stirred with an appropriate aldehyde (1 equiv) until completion of imine formation as indicated by TLC. Filtration provided the Schiff bases (**3**) (a second crop was usually obtained by concentration of the mother liquor to a smaller volume, refrigeration and filtration) which was dissolved in acetonitrile (50-100 mL), treated with 85% *m*-CPBA (1-1.5 equiv) and stirred at rt until completion of reaction by TLC. Excessive reaction times were not detrimental to yields. The precipitated products were filtered and washed to give pure xanthines (**6**).

N1,N3-Dimethyl-8-*o*-fluorophenylxanthine (**6a**): mp >300°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.74 (br s, 1H), 7.96 (ddd, J = 8, 8, 1.5 Hz, 1H), 7.55 (m, 1H), 7.40 (m, 2H), 3.49 (s, 3H), 3.27 (s, 3H); MS (EI) *m/z* 274 (M^+, 20), 217 (1), 156 (57), 139 (100).

N1,N3-Dimethyl-8-*p*-fluorophenylxanthine (**6b**): mp >300°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.84 (br s, 1H), 8.18 (dd, J = 9, 5.5 Hz, 2H), 7.37 (t, J = 9 Hz, 2H), 3.50 (s, 3H), 3.27 (s, 3H); MS (EI) *m/z* 274 (M^+, 100), 245 (8), 217 (6), 189 (4), 122 (13).

N3-Methyl-N1-propenyl-8-*p*-hydroxyphenylxanthine (**6c**): mp >300°C, fine white needles from AcOH; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.54 (br s, 1H), 10.03 (s, 1H), 7.96 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.96 (m, 1H), 5.16 (br s, 1H), 5.11 (br d, J = 1 Hz, 1H), 4.64 (br d, J = 5 Hz, 2H), 3.26 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.5, 154.0, 150.7, 150.5, 148.1, 132.5, 128.3, 119.6, 116.8, 115.7, 107.0, 44.8, 27.8; IR (KBr) ν_{max} 3287, 3179, 1699, 1646, 1618, 1591 cm^{-1}; MS (EI) *m/z* 298 (M^+, 100), 281 (39), 241 (24), 212 (23), 120 (22); Anal. Calcd for $C_{15}H_{14}N_4O_3.1/3H_2O$: C, 59.1, H, 4.8, N, 18.4. Found: C, 58.9, H, 4.6, N, 18.4.

N1,N3-Dimethyl-8-*o*-hydroxyphenylxanthine (**6d**): mp >300°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ >11.5 (br s, 1H), 8.09 (dd, J = 7.5, 1.5 Hz, 1H), 7.37 (ddd, J = 7.5, 7.5, 2 Hz, 1H), 7.03-6.94 (m, 2H), 3.50 (s, 3H), 3.28 (s, 3H); MS (EI) *m/z* 272 (M^+, 100), 215 (31), 187 (24), 120 (32).

N1,N3-Dimethyl-8-*p*-methylphenylxanthine (**6e**): mp >300°C (lit.,[8] mp >300°C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.03 (d, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 2H), 3.50 (s, 3H), 3.26 (s, 3H), 2.36 (s, 3H); MS (EI) *m/z* 270 (M^+, 100), 241 (9), 213 (8), 118 (38).

N1,N3-Dimethyl-8-*p*-dimethylaminophenylxanthine (6f): mp >300°C (lit.,[8] mp >300°C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19 (dd, J = 9, 5.5 Hz, 2H), 7.37 (t, J = 9 Hz, 2H), 3.50 (s, 3H), ≅3.30 (6H, obscured by water peak), 3.27 (s, 3H); MS (EI) *m/z* 299 (M^+, 100), 242 (6), 214 (27), 147 (16).

N1,N3-Dimethyl-8-*p*-carboxyphenylxanthine (6g): mp >300°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.06 (d, J = 8 Hz, 1H), 7.96(d, J = 7.5 Hz, 1H), 7.57 (dd, J = 7.5, 7.5 Hz, 1H), 7.49(dd, J = 8, 7.5 Hz, 1H), 7.10 (br s, 2H), 3.49 (s, 3H), 3.26 (s, 3H); MS (EI) *m/z* 300 (M^+,35), 282 (100), 256 (8), 225 (37), 197(22).

N1,N3-Dimethyl-8-*p*-nitrophenylxanthine (6h): mp >300°C (lit.,[16] mp >300°C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 14.38 (br s, 1H), 8.37 (s, 4H), 3.52 (s, 3H), 3.28 (s, 3H); MS (EI) *m/z* 301 (M^+, 100), 272 (11), 255 (11), 198 (11).

N1,N3-Dimethyl-8-*p*-diphenylxanthine (6i): mp >300°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.50 (br t, J = 7 Hz, 2H), 7.41 (br t, J = 7.5 Hz, 1H), 3.53 (s, 3H), 3.28 (s, 3H); MS (EI) *m/z* 332 (M^+, 100), 303 (5), 275 (6), 246 (4), 179 (42).

N1,N3-Dimethyl-8-styrylxanthine (6j): mp >280°C (lit.,[17] mp >280°C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.71-7.62 (m, 3H), 7.43 (m, 3H), 7.06 (d, J = 16.5 Hz, 1H), 3.50 (s, 3H), 3.28 (s, 3H); MS (EI) *m/z* 282 (M^+, 47), 281 (100), 267 (5), 224 (21), 196 (12), 103 (2).

N1,N3-Dimethyl-8-(2′-furyl)xanthine (6k): mp >300°C (lit.,[18] mp 347°C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.92 (br s, 1H), 7.91 (d, J = 2 Hz, 1H), 7.22 (d, J = 3.5 Hz, 1H), 6.70 (dd, J = 3.5, 2 Hz, 1H), 3.46 (s, 3H), 3.25 (s, 3H); MS (EI) *m/z* 246 (M^+, 100), 217 (9), 189 (10), 161 (7), 94 (8).

N1,N3-Dimethyl-8-cyclohexylxanthine (6l): mp 264,5-265,5°C (lit.,[19] mp 261°C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.1 (br s, 1H), 3.40 (s, 3H), 3.21 (s, 3H), 2.72 (dddd, J = 12, 12, 3, 3 Hz, 1H), 1.92-1.18 (m, 10H); MS (EI) *m/z* 262 (M^+, 18), 207 (61), 194 (100).

N1-*p*-Acetamidobenzyl-N3-*n*-propyl-6-amino-5-*p*-carboxymethyloxybenzylideniminouracil (3n): ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.98 (s, 1H), 9.70 (s, 1H), 7.85 (d, J = 9 Hz, 2H), 7.54 (d, J = 9 Hz, 2H), 7.32 (s, 2H), 7.20 (d, J = 9 Hz, 2H), 6.94 (d, J = 9 Hz, 2H), 5.21 (br s, 2H), 4.72 (s, 2H), 3.81 (m, 2H), 2.02 (s, 3H), 1.58 (m, 2H), 0.86 (t, J = 7 Hz, 3H).

N3-*p*-Acetamidobenzyl-N1-*n*-propyl-8-*p*-carboxymethyloxyphenylxanthine (6n): mp 280°C (dec); ^{1}H NMR (360 MHz, DMSO-d_6) δ >13.0 (s, 1H), 9.89 (s, 1H), 8.08 (d, J = 8 Hz, 2H), 7.50 (d, J = 8 Hz, 2H), 7.34 (d, J = 8 Hz, 2H), 7.05 (d, J = 8 Hz, 2H), 5.17 (s, 2H), 4.75 (s, 2H), 3.88 (m, 2H), 2.02 (s, 3H), 1.59 (m, 2H), 0.88 (t, J = 7 Hz, 3H); IR (KBr) ν_{max} 3429, 3187, 2963, 1697, 1649, 1611, 1530, 1479, 1180,

1079, 836 cm^{-1}; MS (ESI) *m/z* 492 (MH^+, 100). Hydrolysis of **6n** in aq NaOH provided the free aniline, a known adenosine receptor antagonist. mp 260°C (dec)(lit.,[20] mp 261°C (dec)).

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