A_1 Adenosine Receptor Antagonists as Ligands for Positron Emission Tomography (PET) and Single-Photon Emission Tomography (SPET)†

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The high affinity of 8-cyclopentyl-1,3-dipropylxanthine (CPX) for the A_1 adenosine receptor (A_1AR) provides a good lead for developing radioligands suitable for positron emission tomography (PET) and single-photon emission tomography (SPET). This study tested the hypothesis that the kinds of chemical modifications made in the synthesis of CPX analogues containing carbon-11, fluorine-18, or radioiodine will not alter affinity for the A_1AR. This report describes the synthesis and radioligand binding assays of unlabeled CPX analogues having methyl, 2-methoxyethyl, 2-fluoropropyl, or 3-fluoropropyl substituents, respectively, at either N-1 (**13a**−**d**) or N-3 (**8a**−**d**) or an (*E*)-3-iodoprop-2-en-1-yl substituent at N-3 (**8f**). Compounds **8d**,**f** and **13b**,**d** antagonized the binding of [^{3}H]CPX to the A_1AR of rat brain with affinities similar to those of CPX; compound **8c** was twice as potent as CPX. Analogues **8a**,**b** and **13a** were less potent than CPX, but for each the K_i of antagonism was ≥0.5 nM. Attempts to iodinate the 8-(4-hydroxyphenyl) analogue of CPX failed, probably because the xanthine substituent strongly deactivated the phenol toward electrophilic iodination. In summary, several of the modifications of the propyl groups of CPX needed to produce ligands for imaging by PET and SPET preserve or enhance affinity for the A_1AR.

Single-photon emission tomography (SPET) and positron emission tomography (PET) are widely used techniques for medical imaging. PET also serves as a means for assessing tissue metabolism in vivo[1] and for studying receptor density and function.[2] Imaging a pharmacological receptor requires a ligand that has (a) selectivity and high affinity for the receptor, ideally a K_D < 1 nM, so that imaging can distinguish specific binding to the receptor from unspecific binding to "background" structures; (b) pharmacodynamic properties that enable it to traverse the boundaries between compartments, for example, the blood−brain barrier, and thereby to achieve effective concentrations at the receptors of interest; and (c) metabolism that is either negligible or generates metabolites that clear rapidly and do not interfere with measurements of specifically bound ligand. The design of ligands must also take into account (d) the requirements of no-carrier-added (nca) radiosynthesis that ensures the high specific radioactivity on which the imaging of bound ligand depends and, (e) since the medically useful β^+-emitting radionuclides have short half-lives, the provisions for incorporating longer-lived γ-emitting isotopes such as those of iodine for studies of tissue distribution and metabolism as well as for SPET.

The clinical importance of the A_1 adenosine receptor (A_1AR) makes it an attractive target for radionuclide imaging. The A_1AR is neuromodulatory, inhibiting synaptic transmission.[3] In the brain those tonic inhibitory influences may prevent seizures.[4] Brief periods of hypoxia can reduce receptor density greatly.[5] Recent work indicates that the A_1AR plays an essential role in cerebral protection by ischemic preconditioning.[6] In the heart A_1ARs coupled to muscarinic potassium channels mediate the bradycardia and heart block caused by ischemia[7,8] and perhaps the bradyarrhythmias that occur in a substantial number of patients after heart transplantation.[9] A_1ARs in the renal juxtaglomerular apparatus inhibit renin release,[10] and receptors coupled to bicarbonate channels in the epithelium of the proximal tubule promote sodium reabsorption.[11]

This report describes the synthesis and structure−activity relationships of some A_1AR antagonists that, if radiolabeled, would be of interest as potential ligands for SPET and PET. The ligands are analogues of 8-cyclopentyl-1,3-dipropylxanthine (CPX), which, owing to its high selectivity and affinity for the A_1AR,[14,15] is the prototypical A_1AR antagonist.[16] The ligands for PET include some methyl analogues of CPX obtainable by carbon-11 methylation of a suitable precursor, as well as surrogates for fluorine-18-labeled radioligands. The single ligand suitable only for SPET has an N-3 substituent that contains iodine. Although the present project aims ultimately at the development of radioligands, the intermediate steps described here evaluate only the pharmacological impact of the chemical modifications caused by radiolabeling and do so with unlabeled compounds. The aim was to obtain target ligands

† Dedicated to Professor G. Stöcklin on the occasion of his 65th birthday.

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as directly as possible, and so some of the syntheses are inappropriate for nca syntheses of radioligands. However, in those instances we prepared some of the precursors for radiolabeling.

Pharmacodynamic studies in rats support the candidacy of CPX as a brain-imaging agent. [^{3}H]CPX administered intravenously penetrated into the brain to the extent of 0.8% of the injected dose/g at 5 min. That level remained stable for 15 min. Unlabeled CPX displaced 45−70% of bound [^{3}H]CPX.[12] Ishikawa et al.[13] synthesized [^{11}C]KF15372, an 8-dicyclopropylmethyl analogue of CPX, and demonstrated specific uptake in mouse brain.

Chemistry

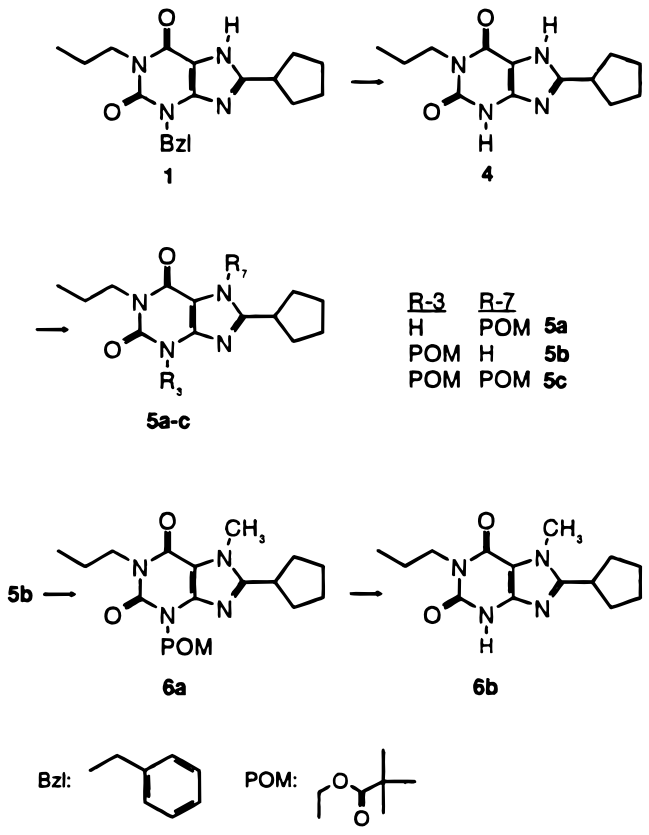
The syntheses of the 1- and 3-substituted 8-cyclopentylxanthines followed a well-known route, namely, the condensation of a urea with cyanoacetic acid, cyclization in alkali to form a uracil, nitrosation and reduction of the nitroso group to form a diaminouracil that is acylated, and, finally, cyclization of the amidouracil to form a xanthine.[17−19] The syntheses had two features in common. First, they proceeded from unsymmetrical ureas, either *N*-benzylurea or *N*-benzyl-*N*′-propylurea. Second, both syntheses called for alkylations at N-3 that required prior protection of N-7 to ensure that the alkylations at N-3 would be regioselective.

Proceeding from benzylureas served two purposes. First, the benzyl group exerted steric control over the condensation of the urea with cyanoacetic acid. The condensation of cyanoacetic acid with an unsymmetrical urea occurs at either of the nitrogens but favors the nitrogen bearing the smallest (least hindering) substituent.[17] Because a benzyl group is so much larger than a hydrogen or propyl substituent, the nitrogen forming the cyanoacetamide is more likely to be N-3 of the intermediate uracil and, ultimately, N-1 of the xanthine. Proceeding from *N*-benzyl-*N*′-propyluracil appeared by TLC to give only one xanthine, but reverse-phase HPLC showed that the product was a 4:1 mixture of two xanthines. Reference to an authentic sample established that 3-benzyl-8-cyclopentyl-1-propylxanthine, **1,** was the more polar major product. Presumably, the other isomer was 1-benzyl-8-cyclopentyl-3-propylxanthine. Fractional crystallization of the isomers was not successful, but the 7-POM derivatives (see below) separated easily on crystallization from methanol. By contrast, benzylurea gave one product, 3-benzyl-8-cyclopentylxanthine, **2**. Second, the benzyl group also served as a protecting group that is easily removable by catalytic transfer hydrogenation (CTH).[20]

Alkylation at N-7 of **1** with di-*tert*-butyl pyrocarbonate, $(boc)_2O$, chloromethyl methyl ether, MOM-Cl, or chloromethyl pivalate, POM-Cl, generated the *tert*-butoxycarbonyl (BOC), methoxymethyl (MOM), and pivaloyloxymethyl (POM) derivatives **3a**−**c**, respectively, for evaluation of the suitability of those protecting groups. In a subsequent step hydrogenolysis cleaved the *t*-BOC and MOM groups, and thus, they were not useful. The POM group resisted hydrogenolysis and, just as importantly, underwent removal by alkali.

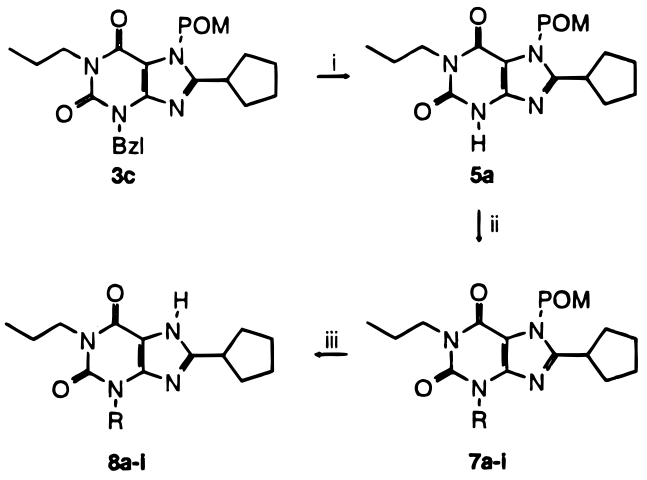
The initial plan to synthesize the 3-substituted 8-cyclopentyl-1-propylxanthines called for debenzylation of **1** to form 8-cyclopentyl-1-propylxanthine, **4**, which was

Scheme 1



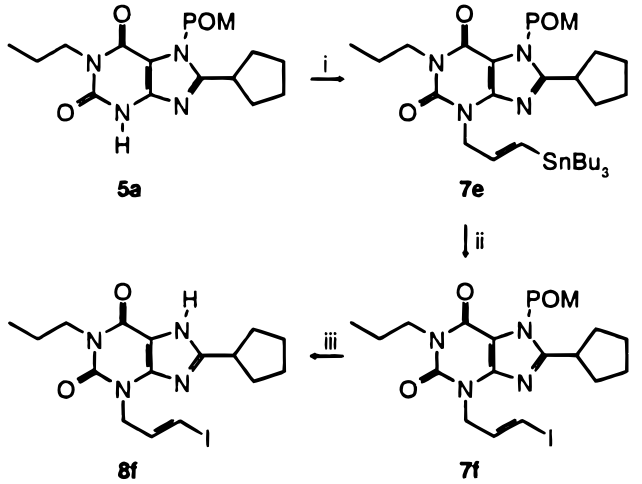
then to undergo protection of N-7 followed by alkylation at N-3 (Scheme 1). The reaction of POM-Cl with **4** could, in principle, produce three products: the desired 7-POM derivative **5a** as well as the 3-POM derivative **5b** and the 3,7-bis-POM derivative **5c**. The original description[21] of the protection of xanthines by the POM group indicated that the reaction of 1-methylxanthine with POM-Cl gives a mixture of **5a**,**c**. On the basis of that information, **4**, the monosubstituted product of the reaction with POM-Cl, underwent alkylation with iodomethane to form **6a**, which was then deprotected. Unexpectedly, that product, **6b**, was 300-fold less potent than CPX. ^{1}H NMR analysis of the products of the reaction of POM-Cl with **4** showed that the monosubstituted product was the 3-POM derivative **5b** rather than the expected 7-POM derivative **5a**. That structural assignment was based on the following evidence: (a) The resonance for the proton on the unsubstituted nitrogen was at 13.5 ppm, which is characteristic of an N-7 rather than an N-3 proton;[22] (b) the unambiguous synthesis of 8-cyclopentyl-1-propyl-7-POM-xanthine, **5a**, by the debenzylation of **3c** gave a product that had an NH resonance at 11.7 ppm, characteristic of a 3-H xanthine;[22] (c) the alkylation of the mono-POM derivative with methyl iodide gave a product, **6a**, having a methyl proton resonance at 3.84 ppm, that expected of a 7-methyl rather than a 3-methyl substituent, which would have a resonance at about 3.4 ppm;[22,23] (d) the methylation of authentic **5a** gave a product, 8-cyclopentyl-1-propyl-3-methyl-7-POM-xanthine, **7a**, that had the expected methyl resonance at 3.38 ppm; and (e) in parallel with the shifts of the methyl resonances, the resonance of the methylene moiety of the POM group of **5a** at 6.25 ppm was further downfield than that

Scheme 2[a]



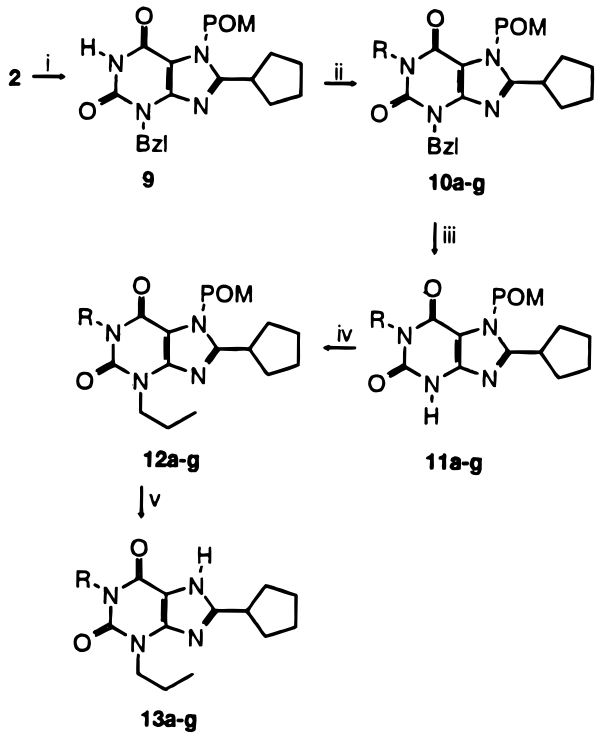
[a] (i) NH_4CO_2H, PD/C, MeOH, reflux; (ii) RX, K_2CO_3, DMF; (iii) NAOH, reflux.

Scheme 3[a]



[a] (i) (*E*)-Bu_3Sn-CH=Ch-CH_2-OTos, DMF, K_2CO_3, rt; (ii) I_2, DCM, rt; (iii) NaOH, reflux.

Scheme 4[a]



[a] (i) POM-Cl, K_2CO_3, DMF; (ii) RX, K_2CO_3, DMF; (iii) NH_4CO_2H, Pd/C, MeOH, reflux; (iv) $CH_3(CH_2)_2I$, K_2CO_3, DMF; (v) 2 N NaOH, reflux.

resonance of **5b**, which was at 6.15 ppm. Thus, proceeding from **5b** had yielded 8-cyclopentyl-7-methyl-3-POM-1-propylxanthine, **6a**, and, after deprotection, 8-cyclopentyl-7-methyl-1-propylxanthine, **6b**. Further, that result showed that to use the POM group for the protection of N-7, it was essential to first protect N-3 with a benzyl group.

The synthesis of the 3-substituted CPX analogues (Scheme 2) began with the fractional crystallization of **3c** to remove the unwanted 1-benzyl-3-propyl isomer. The ^{1}H NMR spectrum of **3c** was a convenient way to follow that separation. Two crystallizations usually sufficed to remove the unwanted isomer, as shown by the disappearance of its benzylic resonance at 5.15 ppm. Removal of the 3-benzyl group by CTH[21] gave 8-cyclopentyl-7-(pivaloyloxymethyl)-1-propylxanthine, **5a**. CTH required elevated temperatures (bath temperatures of 140 °C) and anhydrous conditions, specifically, anhydrous methanol as the solvent and excess ammonium formate dried over P_4O_{10} as the hydrogen donor. Regioselective alkylation with either methyl iodide, 2-chloroethyl methyl ether, 1-bromo-2-fluoropropane, or 1-bromo-3-fluoropropane provided **7a**−**d**, respectively. Because the scope of the project included iodinated ligands and because vinylic iodides tend to resist metabolism,[24] we alkylated **5a** with (*E*)-3-(tri-*n*-butylstannyl)prop-2-en-1-yl *p*-toluenesulfonate,[25, 26] obtaining the intermediate (*E*)-3-[3-(tributylstannyl)-1-prop-2-en-1-yl]xanthine, **7e**, which was then reacted with iodine to give the (*E*)-3-(3-iodoprop-2-en-1-yl)xanthine, **7f** (Scheme 3). Alkaline cleavage of the POM groups of **7a**−**f** completed the syntheses of **8a**−**f**.

The reactions in Scheme 2 include the preparations of precursors for the nca synthesis of carbon-11-labeled **8a,b** and fluorine-18-labeled **8c**,**d**. The precursor for carbon-11-labeled **8a** is **5a**. The alkylation of **5a** with chloroethanol followed by deprotection of the intermediate **7g** gave **8g**, the precursor of carbon-11-labeled **8b**.

The synthesis of **8c**,**d** labeled with fluorine-18 proceeds from the 2- and 3-hydroxypropyl analogues, **8h**,**i**. Since 1-halo-2-propanols cyclize to the oxiranes under the conditions of alkylation, **5a** was alkylated with chloroacetone and then reduced by CTH in methanol to yield **7h** as a mixture of isomers. The alkylation of **5a** with 3-bromopropanol yielded **7i**. Deprotection of **7h**,**i** in alkali gave **8h**,**i**. Alkylation of **5a** by chloroethanol gave intermediate **7g** and, following deprotection, **8g**. Compound **7g** serves as a precursor for carbon-11-labeled **8b**. An alternative approach suited to the nca synthesis of **8f** began with the alkylation of **5a** with propargyl chloride to give the 3-(prop-2-yn-1-yl) derivative **7j**. However, **7j** did not react with tributyltin hydride, and so we abandoned that approach.

The synthesis of the 1-substituted CPX analogues (Scheme 4) from 3-benzyl-8-cyclopentylxanthine, **2**, began with the protection of N-7 by a POM group to give **9**. Alkylation of **9** at N-1 with either iodomethane,

2-chloroethyl methyl ether, 1-bromo-2-fluoropropane, or 1-bromo-3-fluoropropane formed **10a**−**d**. Successive steps included debenzylation to the 3-H xanthines, **11a**−**d**, alkylation with 1-iodopropane to form the 3-propylxanthines, **12a**−**d**, and removal of the POM groups to form the 1-methyl, 1-ethoxymethyl, 1-(2-fluoropropyl), and 1-(3-fluoropropyl) analogues of CPX, **13a**−**d**. The syntheses of the 1-(2-hydroxyethyl) and 1-(3-hydroxypropyl) analogues of CPX, **13e**,**g**, precursors of carbon-11-labeled **13b** and fluorine-18-labeled **13d**, followed those of **8g**,**i**. The synthesis of the 1-(2-hydroxypropyl) analogue of CPX, **13f**, began with the alkylation of **9** with chloroacetone, but differed from the synthesis of **8h** in that CTH simultaneously reduced the 2-keto group during debenzylation rather than in a separate step.

The project plan included iodophenyl derivatives of CPX because 8-phenyltheophylline and its 1,3-dialkyl congeners are useful investigational tools. Since phenols are strongly activated for iodination, the known[27] 1,3-dipropyl-8-(4-hydroxyphenyl)xanthine, **14**, seemed a suitable precursor. Surprisingly, **14** resisted the usual methods for electrophilic iodination.[28] Those methods included (a) elemental iodine applied to a solution of the xanthine in 35% aqueous ammonia or (b) NaI with, as an oxidant, either NaOCl,[29] chloramine T, iodogen,[30] or $HgO-HBF_4$ supported on silica gel.[31] The best explanation for the unreactivity of the phenolic moiety of **14** is that the xanthine must be a profoundly inactivating substituent.

Results and Discussion

Table 1 lists the chemical characteristics of the CPX analogues.

Table 2 summarizes the results of the radioligand binding assays. Modifications of the 3-propyl group (analogues **8a**−**d**,**f**) were well-tolerated. All of the analogues had values of K_i < 0.5 nM. (±)-8-Cyclopentyl-3-(2-fluoropropyl)-1-propylxanthine, **8c**, was twice as potent as CPX, and the least active, 8-cyclopentyl-3-(2-methoxyethyl)-1-propylxanthine, **8b**, was only 3-fold less potent than CPX. Because **8c** is a racemate, the possibility remains that one isomer might be even more potent. The iodinated analogue, **8f**, was only 1.4-fold less potent than CPX. Generally, the modifications of the 1-propyl group (analogues **13a**−**d**) reduced affinity, though only modestly. The least potent analogue, **13c**, had a K_i slightly above 1 nM and was only 8-fold less potent than CPX. The other 1-substituted analogues had values of K_i in the subnanomolar range.

In summary, several chemical modifications of the 1- and 3-propyl groups of CPX have little impact on affinity for the A_1 adenosine receptor. Since the CPX analogues studied here are surrogates for ligands labeled with carbon-11, fluorine-18, or radioiodine, such radioligands could be useful agents for imaging by PET and SPET. CPX analogues radiolabeled in the C-8 substituent are not promising because the present experiments show that 1,3-dipropyl-8-(4-hydroxyphenyl)xanthine is refractory to iodination. The low potency of 1,3-dipropyl-8-(3-fluorocyclopentyl)xanthine[32] suggests that fluorination of the cyclopentane moiety affects potency.

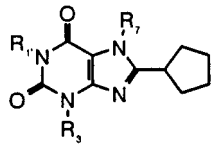
Experimental Section

Melting points were measured on an Electrothermal apparatus and are uncorrected. Elemental analyses were performed by MHW Laboratories, Tucson, AZ, and by the Zentralabteilung für chemische Analysen at the Forschungszentrum Jülich, and are within ±0.4% of calculated composition. Thin-layer chromatography employed precoated silica gel sheets (Polygram, Macherey-Nagel, Düren, Germany) developed with ethyl acetate−hexane, 1:1 (solvent A) or 3:1 (solvent B), or chloroform−methanol, 95:5 (solvent C). A Bruker WP-80 spectrometer provided 80-MHz NMR spectra. Resonances are reported as chemical shifts (δ) downfield from a TMS internal standard. Refluxing over Mg turnings and distillation dried methanol for CTH. Drying of ammonium formate was over P_4O_{10} at room temperature and atmospheric pressure. CTH employed equal weights of substrate and 10% Pd−C and a 10-fold molar excess of ammonium formate for times and temperatures indicated in individual experiments. Purification of dimethylformamide (DMF) consisted of distillation and storage in a light-proof container over 4A molecular sieves. Storage over 4A molecular sieves dried CH_2Cl_2 and toluene. Other solvents and reagents were used as supplied by the vendors. Analytical HPLC used a 250- × 4-mm column of C-18 silica gel, eluted with methanol−water (64:36, v/v). Table 1 lists the solvents used for purification by crystallization or liquid chromatography.

3-Benzyl-8-cyclopentyl-1-propylxanthine (1). A solution of *N*-benzyl-*N*′-propylurea (96.1 g, 0.5 mol) and cyanoacetic acid (40.2 g, 0.55 mol) in acetic anhydride (200 mL) was stirred for 3 h at 70 °C and evaporated. The syrupy residue was mixed with water (500 mL) and then basified with 5 N NaOH. Refrigeration overnight deposited a solid that was filtered off and crystallized from methanol−water. Yield 123 g, 95%, of the 6-aminouracil as silky white needles. A solution of the aminouracil (30 g, 116 mmol) in 80% acetic acid (200 mL) and ethanol (400 mL) was stirred at 40 °C during the dropwise addition of a solution of $NaNO_2$ (12 g, 174 mmol) in water (100 mL) over a 2-h period. Stirring continued for an additional 30 min, at which time TLC (solvent C) showed the reaction was complete. Cooling on ice and filtration collected the nitrosouracil, which was washed with water and dried. Yield 28.5 g, 85%. The nitrosouracil was suspended in water (100 mL), heated to 85 °C and, stirred during the addition of solid sodium dithionite in portions until the red color disappeared. The cooled solution was extracted with ethyl acetate (5 × 50 mL), and the organic phases were pooled, dried over $MgSO_4$, and evaporated to a thick syrup that was then dried at high vacuum to remove traces of moisture. Yield of the diaminouracil was 25.9 g, 95%. A solution of cyclopentanecarbonyl chloride, freshly prepared from cyclopentanecarboxylic acid (11.3 g, 99 mmol) and $SOCl_2$ (8.0 mL, 110 mmol) and dissolved in dry CH_2Cl_2 (50 mL), was added dropwise to a stirred solution of the diaminouracil in dry CH_2Cl_2 (50 mL). After 15 min HPLC showed that a more polar product had completely replaced the starting material. The gummy residue after evaporation was dissolved in ethanol (100 mL) and 1 N NaOH (100 mL) and refluxed overnight. Cooling and acidification with HCl precipitated essentially pure product that was filtered off and crystallized. ^{1}H NMR ($CDCl_3$) δ: 0.85 (t, 3H, $CH_2CH_2CH_3$), 1.2−2.3 (m, 10H, $CH_2CH_2CH_3$ and cyclopentyl CH_2), 2.85−3.45 (m, 1H, cyclopentyl *H*-1), 3.85 (m, 2H, $CH_2CH_2CH_3$), 5.25 (s, 2H, $CH_2C_6H_5$), 7.2−7.5 (m, 5H, C_6H_5), 13.08 (br s, 1H, N^7H).

3-Benzyl-8-cyclopentylxanthine (2). A solution of 6-amino-1-benzyluracil[15] (34.2 g, 157 mmol) in glacial acetic acid (100 mL), ethanol (100 mL), and water (200 mL) was cooled in an ice bath and stirred during the dropwise addition of a solution of $NaNO_2$ (14 g, 200 mmol) in water (50 mL). Stirring continued for an additional 30 min. The nitrosouracil was filtered off, washed with water, suspended in water (250 mL), and heated to 85 °C. The addition of solid sodium dithionite discharged the purple color and precipitated a bright-green solid that was filtered off and freeze-dried. Yield 27.0 g, 74%.

Table 1. Characteristics of Xanthines

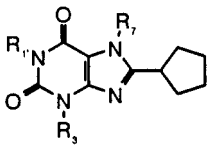


no.	$R_1-R_3-R_7$	yield, %	purification[a]	mp, °C	formula	anal.[b]
1	Pr−Bz−H	64[c]	M	221	$C_{20}H_{24}N_4O_2$	C,H,N
2	H−Bz−H	54[c]	Et−W	>300	$C_{17}H_{18}N_4O_2$	C,H,N
3a	Pr−Bz−BOC	100	DCM	131	$C_{25}H_{32}N_4O_4$	C,H,N
3b	Pr−Bz−MOM	56	PE	131	$C_{22}H_{28}N_4O_3$	C,H,N
3c	Pr−Bz−POM	92	M	134	$C_{26}H_{34}N_4O_4$·DMF	C,H,N
4	Pr−H−H	83	M	>300	$C_{13}H_{18}N_4O_2$	C,H,N
5a	Pr−H−POM	92	M	127	$C_{19}H_{28}N_4O_4$	C,H,N
5b	Pr−POM−H	12	LC H−E, 1:1	157	$C_{19}H_{28}N_4O_4$	C,H,N
5c	Pr−POM−POM	35	LC H−E, 1:1	141	$C_{25}H_{38}N_4O_6$	C,H,N
6a	Pr−POM−Me	91	PE	69−71	$C_{20}H_{30}N_4O_4$	C,H,N
6b	Pr−H−Me	77	EC	151	$C_{14}H_{20}N_4O_2$	C,H,N
7a	Pr−Me−POM	93	H	93	$C_{20}H_{30}N_4O_4$	C,H,N
7b	Pr−MeOEt−POM	78	H	oil	$C_{22}H_{28}N_4O_2$	C,H,N
7c	Pr−2FPr−POM	39	H	oil	$C_{22}H_{33}FN_4O_4$	C,H,N
7d	Pr−3FPr−POM	46	H	105	$C_{22}H_{33}FN_4O_4$	C,H,N
7e	Pr−TBSP−POM	95	DCM	oil	$C_{34}H_{58}SnN_4O_4$	C,H,N
7f	Pr−IP−POM	92	LC H−E, 4:1	oil	$C_{22}H_{31}IN_4O_4$	C,H,N
7g	Pr−HOEt−POM	72	H	oil	$C_{25}H_{32}N_4O_5$	C,H,N
7h	Pr−2OHPr−POM	88	M	114	$C_{22}H_{34}N_4O_5$	C,H,N
7i	Pr−3OHPr−POM	67	H	89	$C_{22}H_{34}N_4O_5$	C,H,N
7j	Pr−propyn−POM	73	M	158−60	$C_{22}H_{30}N_4O_4$	C,H,N
8a	Pr−Me−H	92	M	182−4	$C_{14}H_{20}N_4O_2$	C,H,N
8b	Pr−MeOEt−H	88	M−H	173−5	$C_{16}H_{24}N_4O_3$	C,H,N
8c	Pr−2FPr−H	93	H	206−8	$C_{16}H_{23}FN_4O_2$	C,H,N
8d	Pr−3FPr−H	82	H	190−3	$C_{16}H_{23}FN_4O_2$	C,H,N
8e	Pr−TBSP−H	92	LC H−E, 3:2	69−71	$C_{28}H_{48}SnN4O_2$	C,H,N
8f	Pr−IP−H	91	M−H	211−2	$C_{16}H_{21}IN_4O_2$	C,H,N
8g	Pr−HOEt−H	78	M−H	104−5	$C_{21}H_{32}N_4O_5$	C,H,N
8h	Pr−2OHPr−H	85	H	106−7	$C_{22}H_{34}N_4O_5$	C,H,N
8i	Pr−3OHPr−H	89	H	88−9	$C_{22}H_{34}N_4O_5$	C,H,N
9	H−Bz−POM	94	M	142	$C_{23}H_{28}N_4O_4$	C,H,N
10a	Me−Bz−POM	91	Et_2O	146	$C_{24}H_{30}N_4O_4$	C,H,N
10b	MeOEt−Bz−POM	78	M−W	121	$C_{24}H_{34}N_4O_5$	C,H,N
10c	2FP−Bz−POM	84	M	116	$C_{26}H_{33}FN_4O_4$	C,H,N
10d	3FP−Bz−POM	76	E	124	$C_{26}H_{33}FN_4O_4$	C,H,N
10e	HOEt−Bz−POM	79	E	oil	$C_{25}H_{32}N_4O_5$	C,H,N
10f	2O═Pr−Bz−POM	87	M	126	$C_{26}H_{32}N_4O_5$	C,H,N
10g	3OHPr−Bz−POM	72	E	oil	$C_{26}H_{34}N_4O_5$	C,H,N
11a	Me−H−POM	95	M	196	$C_{17}H_{24}N_4O_4$	C,H,N
11b	MeOEt−H−POM	89	M−W	121	$C_{19}H_{28}N_4O_5$	C,H,N
11c	2FPr−H−POM	93	M−W	144	$C_{19}H_{27}FN_4O_4$	C,H,N
11d	3FPr−H−POM	86	M	159	$C_{19}H_{27}FN_4O_4$	C,H,N
11e	HOEt−H−POM	91	M−H	69	$C_{18}H_{26}N_4O_5$	C,H,N
11f	2OHPr−H−POM	91	M−W	97	$C_{19}N_{28}N_4O_5$	C,H,N
11g	3OHPr−H−POM	86	M	oil	$C_{19}H_{28}N_4O_5$	C,H,N
12a	Me−Pr−POM	86	M−W	97	$C_{20}H_{30}N_4O_4$	C,H,N
12b	MeOEt−Pr−POM	82	M−W	63	$C_{22}H_{24}N_4O_5$	C,H,N
12c	2FPr−Pr−POM	76	E	oil	$C_{22}H_{33}FN_4O_4$	C,H,N
12d	3FPr−Pr−POM	69	E	oil	$C_{22}H_{33}FN_4O_4$	C,H,N
12e	HOEt−Pr−POM	75	E	oil	$C_{21}H_{32}N_4O_5$	C,H,N
12f	2OHPr−Pr−POM	82	E	oil	$C_{22}H_{34}N_4O_5$	C,H,N
12g	3OHPr−Pr−POM	76	E	oil	$C_{22}H_{34}N_4O_5$	C,H,N
13a	Me−Pr−H	94	M	197	$C_{14}H_{20}N_4O_2$	C,H,N
13b	MeOEt−Pr−H	87	M	188	$C_{16}H_{24}N_4O_2$	C,H,N
13c	2FP−Pr−H	67	DMSO−W	oil	$C_{16}H_{23}NFN_4O_2$	C,H,N
13d	3FP−Pr−H	91	EE	212	$C_{16}H_{23}FN_4O_2$	C,H,N
13e	HOEt−Pr−H	84	M	198	$C_{15}H_{24}N_4O_3$	C,H,N
13f	2OHPr−Pr−H	82	DMSO−W	oil	$C_{16}H_{26}N_4O_3$	C,H,N
13g	3OHPr−Pr−H	89	DMSO−W	218	$C_{16}H_{26}N_4O_3$	C,H,N

[a] Solvents for crystallization or liquid chromatography. Abbreviations are: DCM, dichloromethane; DMSO, methyl sulfoxide; Et, ethanol; E, ethyl acetate; EC, tetrachloroethane; H, hexane, LC, liquid chromatography; PE, petroleum ether, and W, water. [b] Analyses for C, H and N agreed with calculated composition by ± 0.4%. [c] Based on the 6-aminouracil starting material.

A suspension of the green diaminouracil in dry CH_2Cl_2 was treated with cyclopentanecarbonyl chloride, freshly prepared from cyclopentanecarboxylic acid (15.4 g, 124 mmol) and $SOCl_2$ (16.2 g, 136 mmol). The addition of the acid chloride turned the suspension a deep red. The mixture was stirred overnight; a white solid was filtered off and boiled for 12 h in 2 N NaOH (100 mL). The clear solution was brought to pH 5 with concentrated HCl, which precipitated a solid that was filtered off, washed with water, and crystallized. ^{1}H NMR (DMSO-d_6) δ: 1.35−2.20 (m, 8H, cyclopentyl CH_2), 2.85−3.5 (br m, 1H, cyclopentyl *H*-1), 5.08 (s, 2H, $C_6H_5CH_2$), 7.30 (m, 5H, C_6H_5), 11.00 (s, 1H, N^1*H*), 13.08 (s, 1H, N^7*H*).

Table 2. Antagonism of Binding of [^{3}H]CPX to Bovine Brain Cortex Membranes



no.	R_1−R_3−R_7[a]	K_i, nM	95% confidence limits
6	Pr−H−Me	149	132−166
8a	Pr−Me−H	0.310	0.269−0.356
8b	Pr−MeOEt−H	0.493	0.377−0.644
8c	Pr−2FPr−H	0.094	0.085−0.103
8d	Pr−3FPr−H	0.183	0.163−0.207
8f	Pr−Ipren−H	0.237	0.217−0.258
CPX[b]	Pr−Pr−H	0.170	0.161−0.180
13a	Me−Pr−H	0.526	0.420−0.659
13b	MeOEt−Pr−H	0.286	0.259−0.315
13c	2FPr−Pr−H	1.23	1.08−1.40
13d	3FPr−H	0.216	0.181−0.257
CPX[c]	Pr−Pr−H	0.155	0.127−0.180

[a] Abbreviations: Me, methyl; Et, ethyl; Pr, propyl; 2FPr, 2-fluoropropyl; 3FPr, 3-fluoropropyl; Ipren, (*E*)-3-iodoprop-2-en-1-yl. [b] Standard for comparison of **8a**−**d**,**f**. [c] Standard for comparison of **13a**−**d**.

3-Benzyl-7-*(tert*-butoxycarbonyl)-8-cyclopentyl-1-propylxanthine (3a). A solution of **1** (14.0 g, 39.3 mmol) and triethylamine (4.0 g, 39.5 mmol) in dry CH_2Cl_2 (50 mL) was stirred during the portionwise addition of di-*tert*-butyl pyrocarbonate (8.6 g, 39.4 mmol). When gas evolution ceased the clear solution was filtered through a 1- × 3-cm column of silica gel to remove a polar impurity, and the filtrate was evaporated. A solution of the residue in CH_2Cl_2 was washed with water (100 mL), 1 N NaOH (3 × 100 mL), and water (100 mL). Drying over $MgSO_4$ and evaporation gave 18 g (100%) of product as an off-white solid. ^{1}H NMR ($CDCl_3$) δ: 0.91 (t, 3H, $CH_2CH_2CH_3$), 1.40−2.25 (m, 19H, $CH_2CH_2CH_3$, cyclopentyl CH_2 and $C(CH_3)_3$), 3.55 (t, 1H, cyclopentyl *H*-1), 3.95 (m, 2H, $CH_2CH_2CH_3$), 5.25 (s, 2H, $PhCH_2$), 7.30 (m, 5H, C_6H_5).

3-Benzyl-8-cyclopentyl-7-(methoxymethyl)-1-propylxanthine (3b). A suspension of **1** (103 mg, 0.4 mmol) in hexamethyldisilazane (10 mL) containing a catalytic amount of ammonium sulfate was refluxed for 90 min. During that time the mixture became homogeneous. Evaporation gave a liquid residue that was treated with methyl bromomethyl ether (MOM-Br; 350 μL, 4 mmol) in dry THF (4 mL). After stirring for 20 h at room temperature the reaction mixture was treated with methanol (20 mL) and stirred for 30 min. The solution was concentrated nearly to dryness and was treated with 33% ammonia (2 mL) and acetone (25 mL). Crystals of NH_4Br were filtered off, and the filtrate was evaporated to dryness. The residue was taken up in ethyl acetate, washed with water, dried over Na_2SO_4, and evaporated to yield a yellow oil. Crystallization from petroleum ether gave fluffy white needles. ^{1}H NMR ($CDCl_3$) δ: 0.95 (t, 3H, $CH_2CH_2CH_3$), 1.45−2.27 (m, 10H, $CH_2CH_2CH_3$ and cyclopentyl CH_2), 3.0−3.3 (m, 1H, cyclopentyl *H*-1), 3.40 (s, 3H, OCH_3), 3.95 (t, 2H, $CH_2CH_2CH_3$), 5.75 (s, 2H, N^7CH_2O).

3-Benzyl-8-cyclopentyl-7-(pivaloyloxymethyl)-1-propylxanthine (3c). A mixture of **1** (20.6 g, 58.5 mmol), chloromethyl pivalate (POM-Cl; 17.7 mL, 122.6 mmol), and anhydrous Na_2CO_3 (13.0 g, 122.6 mmol) in anhydrous DMF (150 mL) was stirred overnight at 50 °C. TLC (solvent A) showed complete conversion of the starting material ($R_f = 0.68$) to a less polar product ($R_f = 0.91$). Evaporation in vacuo gave a gummy residue that was taken up in CH_2Cl_2, washed with water, dried over Na_2SO_4, and evaporated. Crystallization gave 25.1 g (92%) of product. ^{1}H NMR ($CDCl_3$) δ: 0.95 (t, 3H, $CH_2CH_2CH_3$), 1.20 (s, 9H, $C(CH_3)_3$), 1.40−2.20 (m, 10H, $CH_2CH_2CH_3$ and cyclopentyl CH_2), 3.05−3.45 (m, 1H, cyclopentyl *H*-1), 3.97 (t, 2H, $CH_2CH_2CH_3$), 5.25 (s, 2H, $C_6H_5CH_2$), 6.25 (s, 2H, N^7CH_2OPOM), 7.2−7.7 (m, 5H, C_6H_5).

8-Cyclopentyl-1-propylxanthine (4). For CTH a 500-mL flask was flushed with argon and charged with **2** (5.2 g, 16.8 mmol), 10% Pd−C (5.2 g), dry ammonium formate (10.6 g, 168 mmol), and absolute methanol (250 mL). The contents were stirred in an oil bath heated to 140 °C. After 4 h TLC (solvent A) showed the reaction was complete. Filtration through sea sand removed the catalyst, and methanol was evaporated. The filter cake was washed three times with 1 N NaOH (3 × 80 mL), and the washings and residue from the evaporation were combined. Adding crushed ice to the alkaline solution followed by careful acidification to pH 3−4 with dilute HCl precipitated crude product. Dissolution in alkali and reprecipitation gave 3.7 g (83%) of essentially pure product. Crystallization from methanol gave an analytical sample. ^{1}H NMR (DMSO-d_6) δ: 0.88 (t, 3H, $CH_2CH_2CH_3$), 1.2−2.3 (m, 10H, $CH_2CH_2CH_3$ and cyclopentyl CH_2), 2.90−3.35 (m, 1H, cyclopentyl *H*-1), 3.85 (t, 2H, $CH_2CH_2CH_3$), 12.51 (s, 1H, N^3H), 13.54 (s, 1H, N^7H).

8-Cyclopentyl-7-(pivaloyloxymethyl)-1-propylxanthine (5a). The debenzylation of **3c** (10 g, 2.15 mmol) followed the general method for CTH. Workup consisted of removal of catalyst by filtration, washing the filter cake with $CHCl_3$ (3 × 100 mL), and evaporation of the filtrate and washings to a yellowish oil that solidified on standing. Two crystallizations from methanol gave 7.4 g (92%) of white crystals, mp 127 °C. ^{1}H NMR ($CDCl_3$) δ: 0.95 (t, 3H, $CH_2CH_2CH_3$), 1.20 (s, 9H, $C(CH_3)_3$), 1.4−2.2 (m, 10H, $CH_2CH_2CH_3$ and cyclopentyl CH_2), 3.05−3.45 (m, 1H, cyclopentyl *H*-1), 3.98 (t, 2H, $CH_2CH_2CH_3$), 6.25 (s, 2H, N^7CH_2OPOM), 11.7 (br s, 1H, N^3H).

Reaction of 4 with Pivaloyloxymethyl Chloride. 8-Cyclopentyl-3-(pivaloyloxymethyl)-1-propylxanthine (5b) and 3,7-Bis(pivaloyloxymethyl)-8-cyclopentyl-1-propylxanthine (5c). A suspension of **4** (1.56 g, 6.0 mmol) and anhydrous Na_2CO_3 (630 mg, 5.94 mmol) in anhydrous DMF (40 mL) was stirred during the dropwise addition of POM-Cl (1.0 g, 6.6 mmol) in dry DMF (10 mL). Stirring continued for 16 h at room temperature. The suspension was filtered, the filtrate was evaporated, and the residue was taken up in acetone. The insoluble educt was filtered off, and the filtrate was taken to dryness. MPLC on a 1.2- × 23-cm column of silica gel eluted with solvent A gave two products. The fraction eluting between 30 and 50 mL contained **5c** (1 g, 35%). ^{1}H NMR ($CDCl_3$) δ: 0.99 (m, 3H, $CH_2CH_2CH_3$), 1.2 (br s, 18H, 2 × $C(CH_3)_3$), 1.15−2.10 (m, 10H, $CH_2CH_2CH_3$ and cyclopentyl CH_2), 3.05−3.42 (m, 1H, cyclopentyl *H*-1), 3.97 (t, 2H, $CH_2CH_2CH_3$), 6.10 (s, 2H, N^3CH_2OPOM), 6.23 (s, 2H, N^7CH_2OPOM). The second fraction eluting between 60 and 95 mL contained **5b** (0.27 g, 12%). ^{1}H NMR ($CDCl_3$) δ: 1.0 (t, 3H, $CH_2CH_2CH_3$), 1.20 (s, 9H, $C(CH_3)_3$), 1.48−2.25 (m, 10H, $CH_2CH_2CH_3$ and cyclopentyl CH_2), 3.05−3.46 (m, 1H, cyclopentyl H-1), 4.05 (t, 2H, $CH_2CH_2CH_3$), 6.15 (s, 2H, N^3CH_2OPOM), 13.5 (br s, 1H, N^7H).

8-Cyclopentyl-7-methyl-3-(pivaloyloxymethyl)-1-propylxanthine (6a). General Method A. A mixture of **5b** (376 mg, 1 mmol), Na_2CO_3 (106 mg, 1 mmol), and iodomethane (125 μL, 2 mmol) in dry DMF (4 mL) was stirred for 1 h at room temperature. Workup began with dilution with water (10 mL), acidification with 2 N HCl, and extraction with CH_2Cl_2 (4 × 25 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated to give a semisolid residue that was crystallized from an appropriate solvent (Table 1). Yield 355 mg, 91%. ^{1}H NMR ($CDCl_3$) δ: 0.98 (t, 3H, $CH_2CH_2CH_3$), 1.20 (s, 9H, $C(CH_3)_3$), 1.48−2.31 (m, 10H, $CH_2CH_2CH_3$ and cyclopentyl CH_2), 3.05−3.49 (m, 1H, cyclopentyl *H*-1), 3.84 (s, 3H, N^7CH_3), 4.07(t, 2H, $CH_2CH_2CH_3$), 6.13 (s, 2H, N^3CH_2OPOM).

8-Cyclopentyl-7-methyl-1-propylxanthine (6b). A suspension of **6a** in 4 N aqueous NaOH (4 mL, 16 mmol) was stirred at reflux for 6 h. Cooling and acidification to pH 3 precipitated a yellowish solid that was dried over P_4O_{10}. Crystallization gave white crystals. Yield 107 mg, 77%. ^{1}H NMR ($CDCl_3$) δ: 0.93 (t, 3H, $CH_2CH_2CH_3$), 1.50−2.36 (m, 10H, $CH_2CH_2CH_3$ and cyclopentyl CH_2), 3.06−3.50 (m, 1H, cyclopentyl *H*-1), 3.81 (s, 3H, N^7CH_3), 4.02 (t, 2H, $CH_2CH_2CH_3$), 9.79 (s, 1H, N^3H).

8-Cyclopentyl-3-methyl-7-(pivaloyloxymethyl)-1-propylxanthine (7a). Alkylation by general method A employed iodomethane as the alkylating reagent and a reaction time of 24 h at 80 °C. Yield 363 mg, 93%, white crystals.

8-Cyclopentyl-3-(methoxyethyl)-7-(pivaloyloxymethyl)-1-propylxanthine (7b). General method A employed 2-chloroethyl methyl ether (182 μL, 2 mmol) as the alkylation reagent and a reaction time of 24 h at 80 °C. Yield 338 mg, 78%, colorless oil.

8-Cyclopentyl-3-(2-fluoropropyl)-7-(pivaloyloxymethyl)-1-propylxanthine (7c). General method A employed 1-bromo-2-fluoropropane (282 mg, 2 mmol) as the alkylation reagent and a reaction time of 24 h at 80 °C. Yield 170 mg, 39%, colorless oil.

8-Cyclopentyl-3-(3-fluoropropyl)-7-(pivaloyloxymethyl)-1-propylxanthine (7d). General method A employed 1-bromo-3-fluoropropane (282 mg, 2 mmol) as the alkylation reagent and a reaction time of 24 h at 60 °C. Yield 201 mg, 46%, white crystals.

8-Cyclopentyl-3-[(*E*)-3-(tri-*n*-butylstannyl)prop-2-en-1-yl]-7-(pivaloyloxymethyl)-1-propylxanthine (7e). A suspension of **5a** (545 mg, 1.5 mmol) and K_2CO_3 (249 mg, 1.8 mmol) in dry DMF (15 mL) was stirred for 5 min at room temperature before the addition of (*E*)-3-(tri-*n*-butylstannyl)-prop-2-en-1-yl tosylate[23,24] (867 mg, 1.8 mmol). Stirring continued at room temperature for 3 h. Acidification of the reaction mixture with 2 N HCl, extraction with CH_2Cl_2 (3 × 25 mL), drying of the combined organic phases over Na_2SO_4, and evaporation of the solvent yielded 1.12 g (95%) of **7e** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 0.5−1.0 (m, 12H, CH_3 of POM and $CH_2CH_2CH_3$), 1.1−1.75 (m, 28H, CH_2-Bu and cyclopentyl CH_2 and $CH_2CH_2CH_3$), 1.20 (s, 9H, C(CH_3)$_3$), 3.0−3.50 (m, 1H, cyclopentyl *H*-1), 3.88−4.15 (q, 2 H, $CH_3CH_2CH_2$), 4.62−4.75 (q, 2H, CH_2-propenyl), 5.97−6.17 (m, 2H, C*H*═C*H*), 6.25 (s, 2H, N^{7}CH_2OPOM).

8-Cyclopentyl-3-[(*E*)-3-iodoprop-2-enyl]-7-(pivaloyloxymethyl)-1-propylxanthine (7f). A solution of I_2 (127 mg, 0.5 mmol) in CH_2Cl_2 (7.5 mL) was added dropwise to a solution of **7e** (350 mg, 0.5 mmol) in CH_2Cl_2 (5 mL). After the addition of a stochiometric amount of iodine the color of iodine persisted. Evaporation of the solvent left an oily residue for purification by MPLC (silica gel 60, 25- × 1.5-cm, eluted with hexanes−ethyl acetate, 80:20; flow 15 mL/min; UV detection at 254 nm). Evaporation of effluent collected between 6:40 and 9:25 min yielded a colorless oil (246 mg, 92%). ^{1}H NMR ($CDCl_3$) δ: 0.95 (t, 3H, $CH_2CH_2CH_3$), 1.20 (s, 9H, C(CH_3)$_3$), 1.28−2.15 (m, 12H, cyclopentyl CH_2 and $CH_3CH_2CH_2$), 3.05−3.47 (m, 1H, cyclopentyl *H*-1), 3.85−4.15 (q, 2H, $CH_3CH_2CH_2$-), 4.5−4.65 (t, 2H, CH_2-propenyl), 6.25 (s, 2H, N^{7}CH_2OPOM), 6.35−6.83 (m, 2H, C*H*═C*H*).

8-Cyclopentyl-3-(2-hydroxyethyl)-7-(pivaloyloxymethyl)-1-propylxanthine (7g). General method A employed 2-chloroethanol (134 μL, 2 mmol) as the alkylation reagent and a reaction time of 24 h at 80 °C. Yield 310 mg, 72%, colorless oil.

8-Cyclopentyl-3-(2-hydroxypropyl)-7-(pivaloyloxymethyl)-1-propylxanthine (7h). General method A employed chloroacetone (160 μL, 2 mmol) as the alkylation reagent and a reaction time of 24 h at 60 °C. Workup yielded a yellowish solid (415 mg, 96%, >95% pure as shown by TLC), which underwent CTH in dry methanol (5 mL) at a bath temperature of 140 °C for 10 min. Filtration of the catalyst, washing the filter cake three times with hot methanol (3 × 10 mL), and evaporation of the solvent gave a solid residue which was recrystallized from methanol. Yield 382 mg, 88%, white crystals.

8-Cyclopentyl-3-(3-hydroxypropyl)-7-(pivaloyloxymethyl)-1-propylxanthine (7i). General method A employed 3-bromo-1-propanol (278 mg, 2 mmol) as the alkylation reagent and a reaction time of 24 h at 80 °C. Yield 291 mg, 67%, white crystals.

8-Cyclopentyl-7-(pivaloyloxymethyl)-3-(1-propyn-3-yl)xanthine (7j). A solution of **5a** (720 mg, 2 mmol) in dry DMF (10 mL) containing Na_2CO_3 (212 mg, 2 mmol) was stirred for 5 min at room temperature. Propargyl chloride (145 mg, 2 mmol) was added via syringe, and the reaction mixture was stirred for 6 h at 85 °C. After cooling and addition of water (30 mL), the mixture was extracted with chloroform (3 × 50 mL). The combined organic phases were washed with water (2 × 25 mL), dried over Na_2SO_4, filtered, and evaporated, and the yellowish solid was recrystallized from methanol to yield 583 mg (73%) of **7j** as white crystals. ^{1}H NMR ($CDCl_3$) δ: 0.95 (t, 3H, $CH_2CH_2CH_3$), 1.20 (s, 9H, C(CH_3)$_3$), 1.45−2.18 (m, 10H, $CH_2CH_2CH_3$ and cyclopentyl CH_2), 2.47 (t, 1H, $CH_2C{\equiv}CH$), 3.0−3.50 (m, 1H, cyclopentyl *H*-1), 3.97 (t, 2H, C$H_2CH_2CH_3$), 4.85 (d, 2H, CH_2C≡CH), 6.25 (s, 2H, N^{7}CH_2OPOM).

8-Cyclopentyl-3-methyl-1-propylxanthine (8a). General Method B. To 1 mmole of **7a**−**d** dissolved in DMSO (5−10 mL/mmol), was added 4 N aqueous NaOH (4 mL, 16 mmol). The solution was stirred at room temperature for 30 min. Slow dilution with water precipitated the 7-H xanthine. Recrystallization from an appropriate solvent yielded the analytically pure compound. Yield 254 mg, 92%. ^{1}H NMR ($CDCl_3$) δ: 1.00 (t, 3H, $CH_2CH_2CH_3$), 1.50−2.38 (m, 10H, $CH_2CH_2CH_3$ and cyclopentyl CH_2), 3.09−3.53 (m, 1H, cyclopentyl *H*-1), 3.61 (s, 3H, N^{3}CH_3), 4.05 (t, 2H, C$H_2CH_2CH_3$), 12.76 (s, 1H, N^7*H*).

8-Cyclopentyl-3-(methoxyethyl)-1-propylxanthine (8b). Yield 282 mg, 88%; mp 173−175 °C (MeOH−hexane), white crystals.

8-Cyclopentyl-3-(2-fluoropropyl)-1-propylxanthine (8c). Yield 300 mg, 93%; mp 206−208 °C (hexane), white crystals.

8-Cyclopentyl-3-(3-fluoropropyl)-1-propylxanthine (8d). Yield 264 mg, 82%; mp 190−193 °C (hexane), white crystals.

8-Cyclopentyl-3-[(*E*)-3-(tri-*n*-butylstannyl)prop-2-en-1-yl]-1-propylxanthine (8e). A solution of the POM tin compound **7e** (175 mg, 0.25 mmol) in DMSO (10 mL) containing 4 N NaOH (3 mL) was stirred for 5 min at room temperature. After dilution with water (100 mL) the aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the combined organic phases were dried over Na_2SO_4. The resulting oily residue was purified by MPLC, on a 1.5- × 25-cm column of silica gel 60, eluted with hexanes−ethyl acetate, 60:40, at 20 mL/min, UV detection at 254 nm. Evaporation of the fraction eluted from 2:5 to 4:1 min yielded 544 mg (92%) of a colorless oil which solidified upon standing, mp 69−71 °C. ^{1}H NMR ($CDCl_3$) δ: 0.68−0.98 (m, 12H, C(CH_3)$_3$ and CH_3-CH_2CH_2), 1.0−1.53 (m, 18H, CH_2-C(CH_3)$_3$), 1.54−2.36 (m, 10H, cyclopentyl CH_2 and CH_3CH_2-CH_2), 3.05−3.48 (m, 1H, cyclopentyl *H*-1), 3.85−4.26 (t, 2H, C$H_2CH_2CH_3$), 4.75 (d, 2H, CH_2-propenyl), 5.97−6.17 (m, 2H, C*H*═C*H*), 12.63 (br s, 1H, N^7*H*).

8-Cyclopentyl-3-[(*E*)-3-iodoprop-2-enyl]-1-propylxanthine (8f). Compound **7f** (108 mg, 0.2 mmol) was stirred in 2 N NaOH (5 mL) for 12 h at 100 °C. Acidification with 6 N HCl, extraction with CH_2Cl_2 (3 × 20 mL), drying of the combined organic phases over Na_2SO_4, and rotary evaporation of the solvent yielded a solid residue which was recrystallized from methanol−hexane. Yield 80 mg, 91%. ^{1}H NMR ($CDCl_3$) δ: 0.95 (t, 3H, C$H_3CH_2CH_2$), 1.25−2.3 (m, 10H, cyclopentyl CH_2 and $CH_3CH_2CH_2$), 3.05−3.45 (m, 1H, cyclopentyl *H*-1), 3.75−4.15 (t, 2H, C$H_2CH_2CH_3$), 4.55−4.75 (d, 2H, CH_2-propenyl), 6.45−6.95 (m, 2H, C*H*═C*H*), 12.6 (br s, 1H, N^7*H*).

8-Cyclopentyl-3-(2-hydroxyethyl)-1-propylxanthine (8g). Yield 239 mg, 78%, white crystals.

8-Cyclopentyl-3-(2-hydroxypropyl)-1-propylxanthine (8h). Yield 272 mg, 85%, white crystals.

8-Cyclopentyl-3-(3-hydroxypropyl)-1-propylxanthine (8i). Yield 285 mg, 89%, white crystals.

3-Benzyl-8-cyclopentyl-7-(pivaloyloxymethyl)xanthine (9). A mixture of **2** (15.5 g, 50 mmol), anhydrous Na_2CO_3 (10.6 g, 100 mmol), and pivaloyl chloromethyl ester (15 g, 100 mmol) in dry DMF (100 mL) was stirred overnight at room temperature, diluted with water (200 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with water and brine, dried over Na_2SO_4, and evaporated. Product crystallized from a solution of the residue in methanol. Yield 20 g, 94%. ^{1}H NMR (DMSO-d_6) δ: 1.10 (s, 9H, C(CH_3)$_3$), 1.40−2.20 (m, 8H, cyclopentyl CH_2), 3.40 (br s, 1H, cyclopentyl

H-1), 5.1 (s, 2H, $CH_2C_6H_5$), 6.20 (s, 2H, N^7CH_2OPOM), 7.30 (m, 5H, C_6H_5), 11.2 (s, 1H, N^1H).

3-Benzyl-8-cyclopentyl-1-methyl-7-(pivaloyloxymethyl)-xanthine(10a). General Method C. A solution of **9** (412 mg, 1 mmol) in dry DMF (5 mL) was treated with K_2CO_3 (138 mg, 1 mmol) and iodomethane (125 μL, 2 mmol). After stirring for 4 h at room temperature, the mixture was concentrated in vacuo (bath temperature < 70 °C), the residue taken up in ethyl acetate (50 mL), the organic phase washed with water (6 × 30 mL), dried over Na_2SO_4, and filtered, and the solvent evaporated. The residue was recrystallized from an appropriate solvent. Yield 384 mg, 91%, white crystals. ^{1}H NMR ($CDCl_3$) δ: 1.16 (s, 9H, $C(CH_3)_3$), 1.50−2.27 (m, 8H, cyclopentyl CH_2), 3.05−3.47 (m, 1H, cyclopentyl *H*-1), 3.35 (s, 3H, CH_3), 5.25 (s, 2H, $CH_2C_6H_5$), 6.25 (s, 2H, N^7CH_2OPOM), 7.17−7.65 (m, 5H, C_6H_5).

3-Benzyl-8-cyclopentyl-1-(2-methoxyethyl)-7-(pivaloyloxymethyl)xanthine (10b). Alkylation with 1-chloroethyl methyl ether proceeded for 24 h at 80 °C. Yield 364 mg, 78%; mp 121 °C (MeOH−H_2O).

3-Benzyl-8-cyclopentyl-1-(2-fluoropropyl)-7-(pivaloyloxymethyl)xanthine (10c). Alkylation with 1-bromo-2-fluoropropane proceeded for 48 h at 80 °C. Yield 394 mg, 84%, white crystals; mp 116 °C (MeOH).

3-Benzyl-8-cyclopentyl-1-(3-fluoropropyl)-7-(pivaloyloxymethyl)xanthine (10d). Alkylation with 1-bromo-3-fluoropropane proceeded for 24 h at 80 °C. Yield 357 mg, 76%, white crystals; mp 123.9 °C (EtOH).

3-Benzyl-8-cyclopentyl-1-(2-hydroxyethyl)-7-(pivaloyloxymethyl)xanthine (10e). Alkylation with 2-chloroethanol proceeded for 24 h at 80 °C. Yield 351 mg, 79%, yellowish oil.

3-Benzyl-8-cyclopentyl-1-(2-oxopropyl)-7-(pivaloyloxymethyl)xanthine (10f). Alkylation with chloroacetone proceeded for 24 h at 60 °C. Yield 404 mg, 87%, white crystals; mp 126.1 °C (MeOH).

3-Benzyl-8-cyclopentyl-1-(3-hydroxypropyl)-7-(pivaloyloxymethyl)xanthine (10g). Alkylation with 1-bromo-3-hydroxypropane proceeded for 24 h at 80 °C. Yield 387 mg, 72%, colorless oil.

8-Cyclopentyl-1-methyl-7-(pivaloyloxymethyl)xanthine (11a). General Method D. A mixture of 1 mmol of **10a**−**g**, 10% Pd−C (0.5 g/g of benzyl compound), and dry ammonium formate (0.94 g, 20 mmol) in dry methanol (10 mL) was stirred in an oil bath for 4 h at 140 °C. After cooling the mixture was filtered through sea sand, the filter cake was washed three times with warm methanol (3 × 25 mL), and the combined filtrates were evaporated. The resulting residue was recrystallized from an appropriate solvent. Yield 331 mg, 95%, white crystals. ^{1}H NMR ($CDCl_3$) δ: 1.20 (s, 9H, $C(CH_3)_3$), 1.65−2.00 (m, 8H, cyclopentyl CH_2), 3.00−3.60 (br s, 1H, cyclopentyl *H*-1), 3.63 (s, 3H, CH_3), 6.25 (s, 2H, N^7CH_2OPOM), 9.20 (s, 1H, N^3H).

8-Cyclopentyl-1-(2-methoxyeth-1-yl)-7-(pivaloyloxymethyl)xanthine (11b). Yield 349 mg, 89%, white crystals.

8-Cyclopentyl-1-(2-fluoropropyl)-7-(pivaloyloxymethyl)xanthine (11c). Yield 361 mg, 93%, white crystals.

8-Cyclopentyl-1-(3-fluoropropyl)-7-(pivaloyloxymethyl)xanthine (11d). Yield 339 mg, 86%, white crystals.

8-Cyclopentyl-1-(2-hydroxyethyl)-7-(pivaloyloxymethyl)xanthine (11e). Yield 334 mg, 91%, white crystals.

8-Cyclopentyl-1-(2-hydroxypropyl)-7-(pivaloyloxymethyl)xanthine (11f). Yield 351 mg, 91%, white crystals.

8-Cyclopentyl-1-(3-hydroxypropyl)-7-(pivaloyloxymethyl)xanthine (11g). Yield 338 mg, 86%, yellowish oil.

8-Cyclopentyl-1-methyl-7-(pivaloyloxymethyl)-3-propylxanthine (12a) General Method E. A solution of **11a** (348 mg, 1 mmol) in dry DMF (5 mL) was treated with K_2CO_3 (138 mg, 1 mmol) and 1-iodopropane (195 μL, 2 mmol). The mixture was stirred for 12 h at room temperature and then concentrated in vacuo (bath temperature < 70 °C). A solution of the residue in ethyl acetate (50 mL) was washed with water (6 × 30 mL) to remove DMF, dried over Na_2SO_4, and filtered and the solvent evaporated. The residue was recrystallized. Yield 336 mg, 86%, white crystals. ^{1}H NMR ($CDCl_3$) δ: 0.95 (t, 3H, $CH_3CH_2CH_2$), 1.21 (s, 9H, $C(CH_3)_3$), 1.45−2.20 (m, 10H, $CH_3CH_2CH_2$ and cyclopentyl CH_2), 3.00−3.50 (m, 1H, cyclopentyl *H*-1), 3.40 (s, 3H, CH_3), 4.07 (t, 2H, $CH_3CH_2CH_2$), 6.25 (s, 2H, N^7CH_2OPOM).

8-Cyclopentyl-1-(2-methoxyeth-1-yl)-7-(pivaloyloxymethyl)-3-propylxanthine (12b). Yield 356 mg, 82%, white crystals.

8-Cyclopentyl-1-(2-fluoropropyl)-7-(pivaloyloxymethyl)-3-propylxanthine (12c). Yield 334 mg, 76%, colorless oil.

8-Cyclopentyl-1-(3-fluoropropyl)-7-(pivaloyloxymethyl)-3-propylxanthine (12d). Yield 301 mg, 69%, colorless oil.

8-Cyclopentyl-1-(2-hydroxyethyl)-7-(pivaloyloxymethyl)-3-propylxanthine (12e). Yield 315 mg, 75%, colorless oil.

8-Cyclopentyl-1-(2-hydroxypropyl)-7-(pivaloyloxymethyl)-3-propylxanthine (12f). Yield 359 mg, 82%, colorless oil.

8-Cyclopentyl-1-(3-hydroxypropyl)-7-(pivaloyloxymethyl)-3-propylxanthine (12g). Yield 330 mg, 76%, colorless oil.

8-Cyclopentyl-1-methyl-3-propylxanthine (13a). General method B served for the deprotection of **13a**−**g**. The yield of **13a** was 260 mg, 94%, white crystals. ^{1}H NMR ($CDCl_3$) δ: 0.98 (t, 3H, $CH_3CH_2CH_2$), 1.45−2.30 (m, 10H, $CH_3CH_2CH_2$ and cyclopentyl CH_2), 3.05−3.60 (m, 1H, cyclopentyl *H*-1), 3.45 (s, 3H, CH_3), 4.10 (t, 2H, $CH_3CH_2CH_2$), 12.63 (br s, 1H, N^7H).

8-Cyclopentyl-1-(2-methoxyethyl)-3-propylxanthine (13b). Yield 219 mg, 87%, white crystals.

8-Cyclopentyl-1-(2-fluoropropyl)-3-propylxanthine (13c). Yield 214 mg, 67%, colorless oil.

8-Cyclopentyl-1-(3-fluoropropyl)-3-propylxanthine (13d). Yield 293 mg, 91%, white crystals.

8-Cyclopentyl-1-(2-hydroxyethyl)-3-propylxanthine (13e). Yield 251 mg, 84%, white crystals.

8-Cyclopentyl-1-(2-hydroxypropyl)-3-propylxanthine (13f). Yield 262 mg, 82%, colorless oil.

8-Cyclopentyl-1-(3-hydroxypropyl)-3-propylxanthine (13g). Yield 285 mg, 89%, white crystals.

Radioligand Binding Studies. Competitive radioligand binding assays were performed at room temperature in a total volume of 250 μL in 50 mM Tris·HCl, 0.02% CHAPS, pH 7.4, containing 0.2 nM [^{3}H]CPX (4 Gbq/μmol; New England Nuclear, Bad Homburg, Germany), 25 μg of bovine cerebral cortex membranes, 0.2 U/mL adenosine deaminase, and a CPX analogue. Binding was initiated by the addition of the cerebral cortex membranes. Incubations were terminated after 2 h by filtration of a 200-μL aliquot through Whatman GF/B glass fiber filters, and filter-bound radioactivity was determined by liquid scintillation counting. Binding in the presence of 10 μM (*R*)-PIA (N^6-(1*R*)-methyl-2-phenethyladenosine) defined unspecific binding. Equilibrium binding data were analyzed by nonlinear curve fitting using the program SCTFIT described by De Lean et al.[33] Reported values of K_i represent the geometric means and 95% confidence limits of 3−5 independent experiments performed on duplicate samples.

Supporting Information Available: Additional NMR data for compounds mentioned in the text (8 pages). Ordering information is given on any current masthead page.

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