

# Xanthines with C<sup>8</sup> Chiral Substituents as Potent and Selective Adenosine A<sub>1</sub> Antagonists

Norton P. Peet,\* Nelsen L. Lentz, Mark W. Dudley, Ann Marie L. Ogden, Deborah R. McCarty, and Margaret M. Racke

Discovery Chemistry, Marion Merrell Dow Research Institute, 2110 East Galbraith Road, Cincinnati, Ohio 45215

Received June 24, 1993\*

Several 8-substituted 1,3-dipropylxanthines were synthesized, and their receptor binding affinities at adenosine A<sub>1</sub> and A<sub>2</sub> receptors were measured. When enantiomeric pairs of compounds were examined, the *R* enantiomers were significantly more potent than the corresponding *S* enantiomers. The most potent compound at the A<sub>1</sub> receptor was (*R*)-3,7-dihydro-8-(1-methyl-2-phenylethyl)-1,3-dipropyl-1*H*-purine-2,6-dione (**5a**; MDL 102,503), whose *K<sub>i</sub>* value at the A<sub>1</sub> receptor was 6.9 nM. However, a more selective compound was (*R*)-3,7-dihydro-8-(1-phenylpropyl)-1,3-dipropyl-1*H*-purine-2,6-dione (**5d**; MDL 102,234), which had a *K<sub>i</sub>* value of 23.2 nM at the A<sub>1</sub> receptor and an A<sub>2</sub>/A<sub>1</sub> ratio of 153.

## Introduction

The recognition of purinoceptors<sup>1</sup> in peripheral cell membranes, specifically the A<sub>1</sub> and A<sub>2</sub> receptors,<sup>2</sup> has stimulated a surge of activity in adenosine research.<sup>3</sup> The host of suggested therapeutic utilities for adenosine receptor ligands has prompted the design of potent and selective adenosine A<sub>1</sub> and A<sub>2</sub> antagonists and agonists. Indeed, there have been successes with three of these four targets. For example, several sets of 8-substituted 1,3-dipropylxanthines with selectivity and good potency for the A<sub>1</sub> receptor have been described.<sup>4-7</sup> Certain C<sup>6</sup> N-substituted adenosines are A<sub>1</sub>-selective agonists.<sup>8</sup> And adenosines and adenosine-5'-(N-substituted carboxamides) with alkylamino and aralkylamino substituents at the 2-position have shown potency and moderate selectivity as A<sub>2</sub> agonists.<sup>9,10</sup>

Certain substitution patterns have been found to favor A<sub>2</sub>-selectivity in xanthines. Very recently it has been shown that xanthines bearing an (*E*)-3,4-dimethoxystyryl or (*E*)-3,4,5-trimethoxystyryl group at the 8-position in combination with a methyl group at the 7-position were A<sub>2</sub>-selective antagonists.<sup>11</sup> Selectivity and potency of known adenosine receptor ligands, as well as a historical perspective on adenosine receptor research and potential areas of therapeutic intervention, are topics which have been recently and comprehensively reviewed.<sup>12</sup>

We have recently proposed a new binding mode for xanthines with respect to adenosine at adenosine receptors.<sup>13,14</sup> This new binding mode has recently been compared to other binding models and referred to as the "N<sup>6</sup>-C<sup>8</sup>" model.<sup>15</sup> To substantiate our model we prepared the optical isomers of 1,3-dipropyl-8-(phenylisopropyl)-xanthines and showed that the *R* enantiomer was substantially more potent than the *S* enantiomer at adenosine A<sub>1</sub> receptors, analogous to the enhanced potency of *N*<sup>6</sup>-(*R*)-1-methyl-2-phenylethyladenosine (*R*-PIA) with respect to *S*-PIA. This report describes additional xanthines with chiral substituents at the 8-position which also display a marked stereochemical requirement for receptor affinity, as well as related racemic 8-substituted xanthines which help define structure-activity relationships for potency at the A<sub>1</sub> receptor.

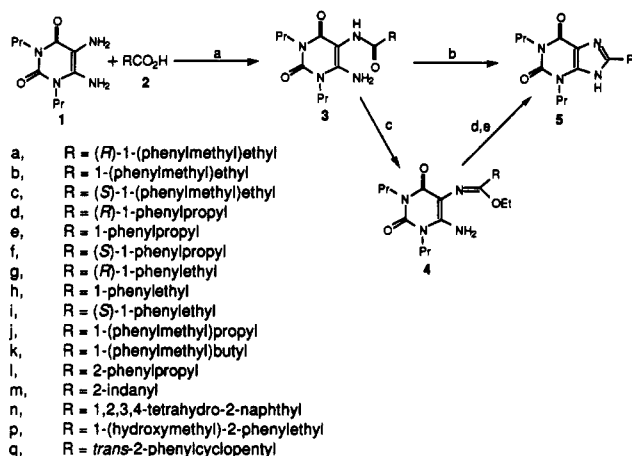
## Chemistry

The synthetic route which we employed for the preparation of both racemic chiral 8-substituted xanthines is shown in Scheme I. Treatment of 1,3-di-*n*-propyl-5,6-diaminouracil (**1**)<sup>16</sup> with the carboxylic acids gave 6-(acylamino)uracils **2**. For the preparation of racemic 8-substituted xanthines **4** we cyclized **2** with ethanolic potassium hydroxide.<sup>16,17</sup> The preparation of xanthines **4** bearing a chiral substituent at position 8 was achieved without the use of strong base. Thus, compounds **2** were treated with Meerwein's reagent to afford imino ethers **3**, which were thermally cyclized in benzene at reflux to afford xanthines **4**.<sup>13</sup> This conversion proceeds very cleanly and in good yield and can easily be monitored by thin-layer chromatography. Interestingly, this cyclization is formally a 5-*endo-trig*, anti-Baldwin closure.<sup>18,19</sup>

Table I lists the 8-substituted xanthines which were prepared using the routes shown in Scheme I. The racemic compounds were prepared directly from **3** by dehydrative cyclization with potassium hydroxide, while the chiral compounds were prepared by thermal cyclization of imino ethers **4**.<sup>13,20</sup>

Several carboxylic acids, both racemic and optically active, were required for this study. Phenylisobutyric acid **5** was prepared from propanoic acid by treating the dianion, which was made with 2 equiv of lithium diisopropylamide, with benzyl chloride. Enantiomers **5a** and **5c** were prepared using enzymatic resolution techniques as previously described.<sup>13,20</sup> Likewise, racemic homologs **5j**<sup>21</sup> and **5k**<sup>22</sup> were similarly prepared in yields of 77% and 87%, respectively. Carboxylic acids **5d-i**, **5l**, and **5n** were commercially available. Indan-2-carboxylic acid (**5m**) was prepared by alkylation of diethyl malonate with  $\alpha,\alpha'$ -dibromo-*o*-xylene, followed by hydrolysis and decarboxylation of the resulting diester.<sup>23,24</sup> *cis*-2-Chloro-6-phenylcyclohexanone<sup>25</sup> was prepared by treating 2-phenylcyclohexanone with sulfur chloride and subjected to Favorskii conditions to give *trans*-2-phenylcyclopentanecarboxylic acid (**5q**).<sup>26</sup> Scheme II describes the synthesis of a protected version of 2-benzyl-3-hydroxypropanoic acid (**5p**), 2-[(*tert*-butyldimethylsilyl)methyl]-3-phenylpropanoic acid (**10**), which initiated from  $\beta$ -propiolactone (**6**). Treatment of **6** with methanol and triethylamine gave 3-hydroxypropanoic acid methyl ester (**7**) which was alkylated with benzyl bromide to afford ester **8**. The *tert*-

\* Abstract published in *Advance ACS Abstracts*, November 1, 1993.

Scheme I. Synthesis of 8-Substituted Xanthines<sup>a</sup>

<sup>a</sup> Reagents: (a) *N*-methylmorpholine, isobutyl chloroformate, THF/DMF, -20 °C; (b) KOH, H<sub>2</sub>O-EtOH, reflux, 2 h; (c) triethylxonium tetrafluoroborate, benzene, 50 °C, 15 h; (d) silica gel chromatography; (e) dry benzene, reflux, 2 h.

butyldimethylsilyl ether of 8 (9) was treated with aqueous potassium hydroxide to hydrolyze the ester. The resulting ester 10 was used in the xanthine synthesis of Scheme I, during which the *tert*-butyldimethylsilyl group was removed.

## Structure-Activity Relationships

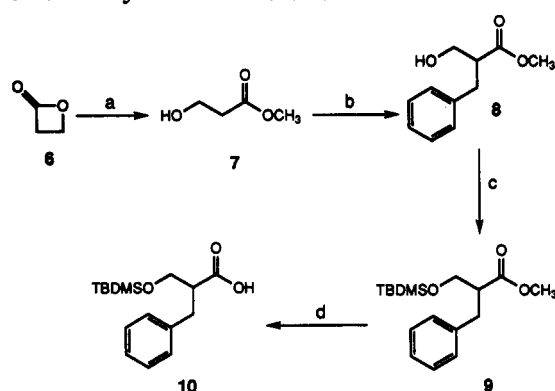
The (*R*)-phenylisopropyl group at the 8-position of the xanthine nucleus (compound 5a) confers the best potency at the A<sub>1</sub> adenosine receptor of the list of compounds in Table I. However, this chiral recognition unit does not provide much A<sub>1</sub> selectivity, with an A<sub>2</sub>/A<sub>1</sub> ratio of *ca.* 23. Compound 5d, which is isomeric with 5a, is about 3 times less potent at the A<sub>1</sub> receptor than 5a but is significantly more selective, with an A<sub>2</sub>/A<sub>1</sub> ratio of 153. Compound 5g, a close analog of 5d whose carbon skeleton in the chiral recognition unit is the same as 5d with the substitution of methyl for ethyl, has a binding profile very similar to that of 5d. Compounds 5h and 5i, the analogous racemate and *S* enantiomer, are also strictly analogous to their counterparts 5e and 5f. The significantly greater potencies of *R* enantiomers 5a, 5d, and 5g over their corresponding *S* enantiomers 5c, 5f, and 5i demonstrate the marked stereochemical requirement for receptor affinity of the substituent at position 8 on the xanthine antagonist. With all three pairs of enantiomers in Table I, the affinity and selectivity values for the racemates fall between those values registered for the enantiomers, which adds a checkpoint to the validity of the data.

Extension of methyl to ethyl and propyl in the phenylisopropyl group of 5b gave homologs 5j and 5k, respectively, which were less potent at the A<sub>1</sub> receptor and less A<sub>1</sub> selective. Addition of a hydroxy group to the methyl group of 5b gave compound 5p, which was markedly less potent at both A<sub>1</sub> and A<sub>2</sub> receptors. This addition of hydrophilicity suggests an unfavorable interaction with the receptors. In a model of the G-protein-coupled adenosine A<sub>1</sub> receptor which we recently described,<sup>27</sup> the proposed ligand binding site contains several hydrophobic amino acid residues in the pocket which accepts the xanthine substituent at the 8-position. Favorable interactions of a hydrophobic C<sup>8</sup> substituent with these residues, which are located on helices III, IV and VI, may be necessary for good binding affinity. Moving the methyl group of 5b to the β-position of the side chain (compound

Table I. Binding Constants for 8-Substituted Xanthines at A<sub>1</sub> and A<sub>2</sub> Adenosine Receptors

compd	R	stereo-chem	K <sub>i</sub> , nM		A <sub>2</sub> /A <sub>1</sub>
			A <sub>1</sub> receptor <sup>a</sup>	A <sub>2</sub> receptor <sup>b</sup>	
5a <sup>c</sup>		<i>R</i>	6.9 ± 1.6 <sup>d</sup>	157 ± 27 <sup>d</sup>	22.8
5b		racemic	32.6 ± 4.6 <sup>d</sup>	644 ± 209 <sup>d</sup>	19.8
5c		<i>S</i>	60.7 ± 5.3 <sup>d</sup>	848 ± 99 <sup>d</sup>	14.0
5d <sup>e</sup>		<i>R</i>	23.2 ± 3.5	3510 ± 250	153
5e		racemic	33.5 ± 1.6	3210 ± 1000	95
5f		<i>S</i>	136.1 ± 21.6	7500 ± 1600	55
5g		<i>R</i>	25.3 ± 1.45	4220 ± 590	160
5h		racemic	49.4 ± 5.3	4900 ± 2000	99
5i		<i>S</i>	174.7 ± 15.7	12900 ± 1500	74
5j		racemic	161.2 ± 27.2	1230 ± 330	8
5k		racemic	73.8 ± 8.7	610 ± 150	8
5l		racemic	94.3 ± 6.4	1740 ± 240	18
5m			64.3 ± 3.6	8350 ± 1500	129
5n		racemic	94.6 ± 17.2	10300 ± 2700	108
5p		racemic	1294 ± 10.7	12800 ± 1790	10
5q		racemic	164.3 ± 8.2	2720 ± 160	10

<sup>a</sup> Binding of [<sup>3</sup>H]CHA in whole rat brain membranes was measured at 25 °C. Values are geometric means ± standard error, *n* = 3 separate determinations. See: Goodman, R.; Cooper, M.; Gavish, M.; Snyder, S. *Mol. Pharmacol.* 1982, 21, 329. <sup>b</sup> Binding of [<sup>3</sup>H]NECA was measured in rat brain striatum at 25 °C. Values are geometric means ± standard error, *n* = 3 separate determinations. See: Bruns, R. R.; Lu, G. H.; Pugsley, T. A. *Mol. Pharmacol.* 1986, 29, 331. <sup>c</sup> MDL 102,503. <sup>d</sup> Reference 13. <sup>e</sup> MDL 102,234.

Scheme II. Synthesis of Acid 10<sup>a</sup>

<sup>a</sup> Reagents: (a) Et<sub>3</sub>N, CH<sub>3</sub>OH, 3 days; (b) LDA, -50 °C, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>Br, -20 °C; (c) TBDMSCl, imidazole, DMF, 1.5 h; (d) 30% KOH, 0 °C, 5 h.

5l) also reduced affinity, approximately 3-fold at both A<sub>1</sub> and A<sub>2</sub> receptors, without affecting selectivity.

Three conformationally restricted versions of the phenylisopropyl compound 5b were prepared, all of which were less potent than 5b. The indanyl-substituted xanthine 5m, in which the methyl group in the side chain of 5b is connected directly to the aromatic ring, was *ca.* 2-fold less potent than 5b at the A<sub>1</sub> receptor. However, 5m was more A<sub>1</sub> selective than 5b by a factor of 6. The tetrahydronaphthyl-substituted xanthine 5n, in which the methyl group of 5b is tethered to the aromatic group via a methylene spacer, was *ca.* 3-fold less potent at the A<sub>1</sub> receptor and similarly more selective. *trans*-2-Phenylcyclopentyl compound 5q, in which the methyl group in the side chain of 5b is tethered to the side chain methylene group via an ethylene spacer, was *ca.* 5-fold less potent than 5b at the A<sub>1</sub> receptor, with the same A<sub>1</sub> selectivity.

The restrictions that were imposed with compounds 5m, 5n, and 5q demonstrate that affinity at the A<sub>1</sub> receptor is better for the unrestricted 5b than for compounds wherein the methyl group is tethered to the substituent in three different ways. Certainly, additional conformational restrictions could be applied to 5b in an attempt to freeze a side-chain conformation which is precisely accommodated by the A<sub>1</sub> receptor pocket.

## Conclusion

Several 8-substituted 1,3-dipropylxanthines were prepared, and their binding affinities to adenosine A<sub>1</sub> and A<sub>2</sub> receptors were measured as shown in Table I. Three pairs of compounds were prepared where the first carbon of the substituent was chiral. In all three cases there was a *marked stereochemical requirement* for affinity, i.e., the *R* enantiomers were significantly more potent than the *S* enantiomers. The most potent compound of the series at the adenosine A<sub>1</sub> receptor was (*R*)-3,7-dihydro-8-(1-methyl-2-phenylethyl)-1,3-dipropyl-1*H*-purine-2,6-dione (5a; MDL 102,503), having a *K<sub>i</sub>* value of 6.9 nM. However, the A<sub>2</sub>/A<sub>1</sub> ratio for MDL 102,503 was only 23. An isomer of 5a, (*R*)-3,7-dihydro-8-(1-phenylpropyl)-1,3-dipropyl-1*H*-purine-2,6-dione (MDL 102,234, 5d), was less potent but more A<sub>1</sub> selective, with a *K<sub>i</sub>* value of 23.2 nM at the A<sub>1</sub> receptor and an A<sub>1</sub>/A<sub>2</sub> ratio of 153. Compound 5d (MDL 102,234) is currently undergoing evaluation in cognition enhancement studies.<sup>28</sup>

## Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer Model 727B spectropho-

tometer and NMR spectra with Varian Gemini 300 and Varian VXR-300 spectrometers; MS data were collected at 70 eV with a Finnigan TCQ GC/MS/MS instrument, and HRMS data were collected at 70 eV with a VG ZABZ-SE spectrometer, using computerized peak matching with perfluorokerosene as the reference and a resolution of 10 000. Chemical shifts for <sup>1</sup>H NMR signals are reported in ppm downfield from TMS (δ). TLC analyses were performed with Merck DC-F<sub>254</sub> on Analtech GHLF silica gel plates, with visualization by alkaline permanganate and UV irradiation. Gas chromatography was performed on an HP 5890A fitted with a 15-m × 0.321-mm DB-5 column. Optical rotations were determined on a JASCO DIP-360. Flash chromatography was performed using Merck silica gel, 230–400 mesh. A Model 7924T Chromatotron from Harrison Research was used for radial chromatography. All reactions were run under an atmosphere of nitrogen using commercially dried solvents.

Carboxylic acids used for the preparation of 8-substituted xanthines using the route shown in Scheme I were (i) prepared as previously described in the literature and referenced accordingly; (ii) prepared using new routes, as shown in Scheme II for 10 and as in refs 19 and 29 for 2a–c; or (iii) obtained commercially: (*R*)-, (*S*)-, and (±)-2-phenylbutanoic acids (2d, 2f, and 2e, respectively); (*R*)-, (*S*)-, and (±)-2-phenylpropanoic acids (2g, 2i, and 2h, respectively); 3-phenylbutanoic acid (21); and 1,2,3,4-tetrahydro-2-naphthoic acid (2n).

(*S*)-*N*-(6-Amino-1,2,3,4-tetrahydro-2,4-dioxo-1,3-dipropyl-5-pyrimidinyl)-α-methylbenzenepropanamide (3a). (*R*)-2-(Phenylmethyl)propanoic acid (2a)<sup>20,29</sup> (0.69 g, 4.6 mmol) was dissolved in 15 mL of THF and cooled to -20 °C. The solution was treated with *N*-methylmorpholine (0.46 mL, 4.6 mmol) followed by dropwise addition via syringe of isobutyl chloroformate (0.60 mL, 4.6 mmol). After the mixture was stirred at -20 °C for 30 min, 1,3-dipropyl-5,6-diaminouracil<sup>16</sup> (0.84 g, 3.8 mmol) in 5 mL of DMF was added. After being stirred for 4 h at -20 °C, the reaction mixture was allowed to warm to room temperature overnight. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (5% to 10% to 20% IPA/hexane) to give amide 3a (0.87 g, 64%) as a foam: [α]<sub>D</sub><sup>20</sup> -42.7° (*c* 0.82, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.40–7.18 (m, 6 H), 4.98 (s, 2 H), 3.83 (m, 4 H), 3.00 (m, 1 H), 2.80 (m, 2 H), 1.75–1.55 (m, 4 H), 1.28 (d, *J* = 6.7 Hz, 3 H), 0.96 (t, *J* = 8.6 Hz, 3 H), 0.90 (t, *J* = 3 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 373 (*M*<sup>+</sup> + 1), 401 (*M*<sup>+</sup> + 29), 413 (*M*<sup>+</sup> + 41); exact mass calcd for C<sub>20</sub>H<sub>28</sub>N<sub>4</sub>O<sub>3</sub> 372.2161, found 372.2163.

(*R*)-3,7-Dihydro-8-(1-methyl-2-phenylethyl)-1,3-dipropyl-1*H*-purine-2,6-dione (5a). Amide 3a (0.85 g, 2.28 mmol) was dissolved in 100 mL of benzene and treated with 1 M triethylxonium tetrafluoroborate in CH<sub>2</sub>Cl<sub>2</sub> (14.8 mL, 14.8 mmol) with stirring. The solution was heated to 50 °C for 15 h. After cooling, the solution was poured into 500 mL of Et<sub>2</sub>O, rinsed with 300 mL of 0.1 M phosphate buffer, and 200 mL of saturated NaCl, and dried over MgSO<sub>4</sub>. After filtering, the solvent was removed *in vacuo* and the residue purified by radial chromatography (2% to 5% methanol/CHCl<sub>3</sub>) to yield the unstable imino ether 4a (0.36 g, 39%), which was used immediately in the next step. Imino ether 4a (0.36 g, 0.9 mmol) was dissolved in 100 mL of benzene and heated at reflux for 3 h. The solvent was removed *in vacuo*, and the residue was purified by radial chromatography (50% ethyl acetate/hexane, 2-mm plate) to yield 5a (0.23 g). The solid was recrystallized from 20% Et<sub>2</sub>O/hexane and dried under high vacuum at 30 °C to yield pure 5a (187 mg, 59%) as a white solid: [α]<sub>D</sub><sup>20</sup> -42° (*c* 0.75, CHCl<sub>3</sub>); mp 141–142 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.29 (s, 1 H), 7.22–7.09 (m, 5 H), 4.11 (t, *J* = 7.3 Hz, 2 H), 4.03 (t, *J* = 7.8 Hz, 2 H), 3.39–3.20 (m, 2 H), 2.95 (dd, *J* = 13.7 Hz, *J* = 7.3 Hz, 1 H), 1.85–1.65 (m, 4 H), 1.41 (d, *J* = 7.0 Hz, 3 H), 0.98 (m, 6 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 355 (*M*<sup>+</sup> + 1), 383 (*M*<sup>+</sup> + 29), 395 (*M*<sup>+</sup> + 41). Anal. (C<sub>20</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

(±)-3,7-Dihydro-8-(1-phenylpropyl)-1,3-dipropyl-1*H*-purine-2,6-dione (5e). 2-Phenylbutanoic acid (2e; 1.1 g, 6.4 mmol) was dissolved in 15 mL of THF and treated with *N*-methylmorpholine (0.58 mL, 5.3 mmol). The solution was cooled to -20 °C, and isobutyl chloroformate (0.69 mL, 5.3 mmol) was added dropwise via syringe with stirring. After 20 min, 1,3-dipropyl-5,6-diaminouracil (1.2 g, 5.3 mmol) in 5 mL of DMF was added. After stirring at -20 °C for 4 h, the reaction mixture was allowed to warm to room temperature overnight. The mixture was then diluted with 500 mL of CHCl<sub>3</sub>, rinsed with 300 mL of saturated

NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum to yield crude **3a** (1.97 g). This intermediate was used immediately in the next step without further purification. The crude amide **3e** (1.97 g, 5.3 mmol) was dissolved in 40 mL of ethanol and 100 mL of 30% KOH, and the solution was heated at reflux for 2 h. The solution was then cooled to 0 °C and cautiously acidified with dilute HCl (42 mL of concentrated HCl in 300 mL of H<sub>2</sub>O). The mixture was extracted with CHCl<sub>3</sub> (3 × 200 mL), and the combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by radial chromatography (25% to 50% ethyl acetate/hexane, 4-mm plate) and triturated with 5% Et<sub>2</sub>O/hexane. The white solid was dried under high vacuum at 39 °C to yield **5e** (454 mg, 24%): mp 137–138 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.45 (s, 1 H), 7.42 (d, *J* = 8.6 Hz, 2 H), 7.38–7.20 (m, 3 H), 4.20–4.00 (m, 5 H), 2.38 (m, 1 H), 2.19 (m, 1 H), 1.90–1.70 (m, 4 H), 0.98 (m, 9 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 355 (M<sup>+</sup> + 1), 383 (M<sup>+</sup> + 29), 395 (M<sup>+</sup> + 41). Anal. (C<sub>20</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

The following racemic compounds were obtained using a method similar to the preparation of **5e**.

**3,7-Dihydro-8-(1-methyl-2-phenylethyl)-1,3-dipropyl-1H-purine-2,6-dione (5b)**. Compound **5b** (570 mg, 77%) was prepared from **1** and 2-methyl-3-phenylpropanoic acid and isolated as a white solid: mp 140–142 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.61 (s, 1 H), 7.22–7.09 (m, 5 H), 4.13 (t, *J* = 7.4 Hz, 2 H), 4.05 (t, *J* = 8.1 Hz, 2 H), 3.38 (dd, *J* = 14 Hz, *J* = 7.1 Hz, 1 H), 3.25 (dd, *J* = 7.6 Hz, 1 H), 2.96 (dd, *J* = 13.4 Hz, *J* = 7.4 Hz, 1 H), 1.85–1.65 (m, 4 H), 1.43 (d, *J* = 6.7 Hz, 3 H), 0.98 (m, 6 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 355 (M<sup>+</sup> + 1), 383 (M<sup>+</sup> + 29), 395 (M<sup>+</sup> + 41). Anal. (C<sub>20</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

**3,7-Dihydro-8-(1-phenylethyl)-1,3-dipropyl-1H-purine-2,6-dione (5h)**. Compound **5h** (584 mg, 65%) was prepared from **1** and 2-phenylpropanoic acid and isolated as a white solid: mp 148–150 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.81 (s, 1 H), 7.40–7.20 (m, 5 H), 4.35 (q, *J* = 7.0 Hz, 2 H), 4.11 (t, *J* = 7.7 Hz, 2 H), 4.00 (t, *J* = 7.8 Hz, 2 H), 1.90–1.60 (m, 4 H), 1.78 (d, *J* = 7.6 Hz, 3 H), 0.99 (t, *J* = 7.4 Hz, 3 H), 0.95 (t, *J* = 7.4 Hz, 3 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 341 (M<sup>+</sup> + 1), 369 (M<sup>+</sup> + 29), 381 (M<sup>+</sup> + 41). Anal. (C<sub>19</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

**3,7-Dihydro-8-[1-(phenylmethyl)propyl]-1,3-dipropyl-1H-purine-2,6-dione (5j)**. Compound **5j** (407 mg, 35%) was prepared from **1** and 1-(phenylmethyl)butanoic acid<sup>21</sup> and isolated as a white solid: mp 186–188 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.41 (s, 1 H), 7.20–7.03 (m, 5 H), 4.12 (t, *J* = 7.5 Hz, 2 H), 4.02 (t, *J* = 7.6 Hz, 2 H), 3.20–3.00 (m, 3 H), 1.95–1.65 (m, 6 H), 0.98 (m, 3 H), 0.96 (t, *J* = 7.6 Hz, 3 H), 0.89 (t, *J* = 7.5 Hz, 3 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 369 (M<sup>+</sup> + 1), 397 (M<sup>+</sup> + 29), 401 (M<sup>+</sup> + 41); exact mass calcd for C<sub>21</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub> 368.2212, found 368.2197.

**3,7-Dihydro-8-[1-(phenylmethyl)butyl]-1,3-dipropyl-1H-purine-2,6-dione (5k)**. Compound **5k** (217 mg, 41%) was prepared from **1** and 2-(phenylmethyl)pentanoic acid<sup>22</sup> and isolated as a white solid: mp 158–160 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.15 (s, 1 H), 7.20–7.00 (m, 5 H), 4.12 (t, *J* = 7.6 Hz, 2 H), 4.01 (t, *J* = 7.6 Hz, 2 H), 3.30–2.97 (m, 3 H), 1.98–1.65 (m, 6 H), 1.25 (m, 2 H), 0.97 (t, *J* = 7.3 Hz, 6 H), 0.88 (t, *J* = 7.1 Hz, 3 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 383 (M<sup>+</sup> + 1), 411 (M<sup>+</sup> + 29), 423 (M<sup>+</sup> + 41). Anal. (C<sub>22</sub>H<sub>30</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

**3,7-Dihydro-8-(2-phenylpropyl)-1,3-dipropyl-1H-purine-2,6-dione (5l)**. Compound **5l** (180 mg, 8%) was prepared from **1** and 3-phenylbutanoic acid and isolated as a white solid: mp 136–137 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.59 (s, 1 H), 7.25–7.10 (m, 5 H), 4.11 (t, *J* = 7.3 Hz, 2 H), 4.03 (t, *J* = 7.5 Hz, 2 H), 3.40 (m, 1 H), 3.20–3.00 (m, 2 H), 1.88–1.65 (m, 4 H), 1.34 (d, *J* = 7.2 Hz, 3 H), 0.98 (t, *J* = 7.3 Hz, 3 H), 0.95 (t, *J* = 7.3 Hz, 3 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 355 (M<sup>+</sup> + 1), 383 (M<sup>+</sup> + 29), 395 (M<sup>+</sup> + 41). Anal. (C<sub>20</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

**3,7-Dihydro-8-(2-indanyl)-1,3-dipropyl-1H-purine-2,6-dione (5m)**. Compound **5m** (1.10 g, 53%) was prepared from 2-indancarboxylic acid<sup>23,24</sup> and isolated as a white solid: mp 223–224 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.82 (s, 1 H), 7.30–7.18 (m, 4 H), 4.10 (t, *J* = 8.0 Hz, 2 H), 3.95 (quin, *J* = 9.0 Hz, 1 H), 3.81 (t, *J* = 7.5 Hz, 2 H), 3.50–3.38 (m, 4 H), 1.81 (m, 2 H), 1.58 (m, 2 H), 0.97 (t, *J* = 7.7 Hz, 3 H), 0.79 (t, *J* = 7.1 Hz, 3 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 353 (M<sup>+</sup> + 1), 381 (M<sup>+</sup> + 29), 393 (M<sup>+</sup> + 41). Anal. (C<sub>20</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

**3,7-Dihydro-1,3-dipropyl-8-(1,2,3,4-tetrahydro-2-naphthalenyl)-1H-purine-2,6-dione (5n)**. Compound **5n** (1.04 g, 55%)

was prepared from **1** and 1,2,3,4-tetrahydro-2-naphthoic acid and isolated as a white solid: mp 202–204 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.63 (s, 1 H), 7.15 (m, 4 H), 4.11 (t, *J* = 7.8 Hz, 2 H), 3.87 (t, *J* = 7.7 Hz, 2 H), 3.40–3.10 (m, 3 H), 2.95 (m, 2 H), 2.40–2.10 (m, 2 H), 1.82 (m, 2 H), 1.55 (m, 2 H), 0.98 (t, *J* = 7.7 Hz, 3 H), 0.68 (t, *J* = 7.7 Hz, 3 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 367 (M<sup>+</sup> + 1), 395 (M<sup>+</sup> + 29), 407 (M<sup>+</sup> + 41). Anal. (C<sub>21</sub>H<sub>26</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

**3,7-Dihydro-8-[1-(hydroxymethyl)-2-phenylethyl]-1,3-dipropyl-1H-purine-2,6-dione (5p)**. Compound **5p** (820 mg, 36%) was prepared from **1** and acid **10** and isolated as a white solid: mp 145–146 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.38 (s, 1 H), 7.25–7.10 (m, 5 H), 4.11 (t, *J* = 7.6 Hz, 2 H), 4.05–3.85 (m, 4 H), 3.58 (m, 1 H), 3.38 (m, 1 H), 3.22 (dd, *J* = 13.8 Hz, *J* = 7.4 Hz, 1 H), 3.10 (dd, *J* = 13.6 Hz, *J* = 8.8 Hz, 1 H), 1.82 (m, 2 H), 1.70 (m, 2 H), 0.99 (t, *J* = 7.6 Hz, 3 H), 0.93 (t, *J* = 7.8 Hz, 3 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 371 (M<sup>+</sup> + 1), 399 (M<sup>+</sup> + 29), 411 (M<sup>+</sup> + 41). Anal. (C<sub>20</sub>H<sub>28</sub>N<sub>4</sub>O<sub>3</sub>) C, H, N.

**trans-3,7-Dihydro-8-(2-phenylcyclopentyl)-1,3-dipropyl-1H-purine-2,6-dione (5q)**. Compound **5q** (63 mg, 45%) was prepared from **1** and *trans*-2-phenylcyclopentanecarboxylic acid (**2q**)<sup>25,26</sup> and isolated as a white solid: mp 152–153 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.95 (s, 1 H), 7.18–7.08 (m, 5 H), 4.09 (t, *J* = 7.4 Hz, 2 H), 3.98 (t, 7.6 Hz, 2 H), 3.54 (dd, *J* = 18.6 Hz, *J* = 9.3 Hz, 1 H), 3.33 (dd, *J* = 17.7 Hz, *J* = 10.2 Hz, 1 H), 2.30 (m, 2 H), 2.20–1.60 (m, 7 H), 0.98 (t, *J* = 7.6 Hz, 6 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 381 (M<sup>+</sup> + 1), 409 (M<sup>+</sup> + 29), 421 (M<sup>+</sup> + 41). Anal. (C<sub>22</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

The following chiral compounds were obtained using a method similar to the preparation of **5a**.

**(S)-3,7-Dihydro-8-(1-methyl-2-phenylethyl)-1,3-dipropyl-1H-purine-2,6-dione (5c)**. Compound **5c** (87 mg, 82%) was prepared from **1** and (*S*)-2-(phenylmethyl)propanoic acid (**2c**) and isolated as a white solid: [α]<sub>D</sub><sup>20</sup> +38.5° (c 0.69, CHCl<sub>3</sub>); mp 141–142 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.38 (s, 1 H), 7.22–7.09 (m, 5 H), 4.13 (t, *J* = 7 Hz, 2 H), 4.03 (t, *J* = 8 Hz, 2 H), 3.38 (m, 1 H), 3.23 (dd, *J* = 13 Hz, *J* = 8 Hz, 1 H), 2.98 (dd, *J* = 13 Hz, *J* = 7 Hz, 1 H), 1.85–1.65 (m, 4 H), 1.41 (d, *J* = 7 Hz, 3 H), 0.98 (m, 6 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 355 (M<sup>+</sup> + 1), 383 (M<sup>+</sup> + 29), 395 (M<sup>+</sup> + 41). Anal. (C<sub>20</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

**(R)-3,7-Dihydro-8-(1-phenylpropyl)-1,3-dipropyl-1H-purine-2,6-dione (5d)**. Compound **5d** (190 mg, 9%) was prepared from **1** and (*R*)-2-phenylbutanoic acid (**2d**) and isolated as a white solid: [α]<sub>D</sub><sup>20</sup> +4.4° (c 1.00, CHCl<sub>3</sub>); mp 128–130 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.41 (s, 1 H), 7.42 (d, *J* = 8.6 Hz, 2 H), 7.38–7.20 (m, 3 H), 4.20–4.00 (m, 5 H), 2.38 (m, 1 H), 2.19 (m, 1 H), 1.90–1.70 (m, 4 H), 0.98 (m, 9 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 355 (M<sup>+</sup> + 1), 383 (M<sup>+</sup> + 29), 395 (M<sup>+</sup> + 41). Anal. (C<sub>20</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

**(S)-3,7-Dihydro-8-(1-phenylpropyl)-1,3-dipropyl-1H-purine-2,6-dione (5f)**. Compound **5f** (547 mg, 28%) was prepared from **1** and (*S*)-2-phenylbutanoic acid (**2f**) and isolated as a white solid: [α]<sub>D</sub><sup>20</sup> –4.0° (c 1.07, CHCl<sub>3</sub>); mp 128–131 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.52 (s, 1 H), 7.42 (d, *J* = 8.6 Hz, 2 H), 7.38–7.20 (m, 3 H), 4.20–4.00 (m, 5 H), 2.38 (m, 1 H), 2.19 (m, 1 H), 1.90–1.70 (m, 4 H), 0.98 (m, 9 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 355 (M<sup>+</sup> + 1), 383 (M<sup>+</sup> + 29), 395 (M<sup>+</sup> + 41). Anal. (C<sub>20</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

**(R)-3,7-Dihydro-8-(1-phenylethyl)-1,3-dipropyl-1H-purine-2,6-dione (5g)**. Compound **5g** (374 mg, 65%) was prepared from **1** and (*R*)-2-phenylpropanoic acid (**2g**) and isolated as a white solid: [α]<sub>D</sub><sup>20</sup> –8.5° (c 1.00, CHCl<sub>3</sub>); mp 136–137 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.18 (s, 1 H), 7.40–7.20 (m, 5 H), 4.35 (q, *J* = 7.1 Hz, 1 H), 4.11 (t, *J* = 7.4 Hz, 2 H), 4.00 (t, *J* = 7.9 Hz, 2 H), 1.90–1.60 (m, 4 H), 1.78 (d, *J* = 7.3 Hz, 3 H), 0.98 (m, 6 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 341 (M<sup>+</sup> + 1), 369 (M<sup>+</sup> + 29), 381 (M<sup>+</sup> + 41). Anal. (C<sub>19</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

**(S)-3,7-Dihydro-8-(1-phenylethyl)-1,3-dipropyl-1H-purine-2,6-dione (5i)**. Compound **5i** (252 mg, 41%) was prepared from **1** and (*S*)-2-phenylpropanoic acid (**2i**) and isolated as a white solid: [α]<sub>D</sub><sup>20</sup> +8.5° (c 1.04, CHCl<sub>3</sub>); mp 134.5–136 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.05 (s, 1 H), 7.40–7.20 (m, 5 H), 4.37 (q, *J* = 7.1 Hz, 1 H), 4.10 (t, *J* = 7.0 Hz, 2 H), 4.01 (t, *J* = 7.8 Hz, 2 H), 1.90–1.60 (m, 4 H), 1.80 (d, *J* = 7.5 Hz, 3 H), 0.99 (t, *J* = 7.4 Hz, 3 H), 0.95 (t, *J* = 7.4 Hz, 3 H); MS (70 eV, CI, CH<sub>4</sub>) *m/z* 341 (M<sup>+</sup> + 1), 369 (M<sup>+</sup> + 29), 381 (M<sup>+</sup> + 41). Anal. (C<sub>19</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>) C, H, N.

**3-Hydroxypropanoic Acid Methyl Ester (7)**. β-Propiolactone (**6**) (5.5 g, 76 mmol) was dissolved in 100 mL of methanol. Triethylamine (10.8 mL, 76 mmol) was added with stirring at room temperature.<sup>31</sup> After 3 days, GC (40 °C/1.5 min → 40 °C/

min → 60 °C/3 min,  $t_R$  = 1.92 min) indicated completion of reaction. The solvent was removed under vacuum, and the residue was purified by flash chromatography (10% to 20% 2-propanol/hexane) to yield 7 (3.30 g, 42%) as an oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.88 (dt, 2 H), 3.72 (s, 3 H), 2.60 (broad triplet,  $J$  = 6.1 Hz, 3 H).

**2-(Hydroxymethyl)-3-phenylpropanoic Acid Methyl Ester (8).**<sup>31</sup> Compound 7 (3.23 g, 31 mmol) was dissolved in 100 mL of THF and cooled to -50 °C. Lithium diisopropylamide [prepared from 2.5 M *n*-BuLi (26.1 mL, 65 mmol) and diisopropylamine (9.1 mL, 65 mmol) in 100 mL of THF] was added slowly to produce the dianion. After 20 min at -50 °C, the reaction mixture was treated with benzyl bromide (3.68 mL, 31 mmol). The mixture was then warmed to -20 °C over 1 h and quenched with 500 mL of saturated NH<sub>4</sub>Cl. The aqueous mixture was extracted with diethyl ether (2 × 500 mL), and the combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (10% to 20% 2-propanol/hexane) to yield 8 (2.65 g, 44%) as an oil (GC conditions, 150 °C isotherm,  $t_R$  = 2.08 min): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.35–7.19 (m, 5 H), 3.80–3.65 (m, 2 H), 3.70 (s, 3 H), 3.03 (dd,  $J$  = 16.9 Hz,  $J$  = 9.2 Hz, 1 H), 2.88 (m, 2 H), 2.18 (t,  $J$  = 7.7 Hz, 1 H); MS (70 eV, CI, CH<sub>4</sub>)  $m/z$  195 ( $M^+$  + 1), 223 ( $M^+$  + 29); exact mass calcd for C<sub>11</sub>H<sub>15</sub>O<sub>3</sub> 195.1021, found 195.1019.

**2-[(*tert*-Butyldimethylsilyl)methyl]-3-phenylpropanoic Acid Methyl Ester (9).** Compound 8 (2.6 g, 13.4 mmol) was dissolved in 75 mL of DMF and treated with *tert*-butyldimethylsilyl chloride (2.2 g, 14.7 mmol) and imidazole (2.0 g, 29.4 mmol) with stirring. After 1.5 h, the reaction mixture was diluted with 500 mL of diethyl ether. The mixture was rinsed with 50% aqueous NaCl (3 × 200 mL), saturated NaCl (300 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (5% to 10% 2-propanol/hexane) to yield 9 (3.49 g, 85%) (GC conditions, 200 °C isotherm,  $t_R$  = 1.61 min): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.31–7.15 (m, 5 H), 3.75 (m, 2 H), 3.62 (s, 3 H), 2.89 (m, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H); MS (70 eV, CI, CH<sub>4</sub>)  $m/z$  309 ( $M^+$  + 1), 337 ( $M^+$  + 29), 349 ( $M^+$  + 41); exact mass calcd for C<sub>17</sub>H<sub>29</sub>O<sub>3</sub>Si 309.1885, found 309.1882.

**2-[(*tert*-Butyldimethylsilyl)methyl]-3-phenylpropanoic Acid (10).** Compound 9 (3.3 g, 10.7 mmol) was dissolved in 100 mL of methanol, cooled to 0 °C and treated with 50 mL of 30% KOH with vigorous stirring. The solution was allowed to warm to room temperature over 5 h, diluted with 200 mL of H<sub>2</sub>O, and rinsed with 200 mL of diethyl ether. The aqueous phase was cooled to 0–5 °C, and CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added. HCl (1 N; 260 mL) was added slowly with stirring. The layers were separated, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 200 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by radial chromatography (2% to 4% methanol/chloroform, 4-mm plate) to yield 10 (2.14 g, 68%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.35–7.18 (m, 5 H), 3.75 (m, 2 H), 3.00 (m, 1 H), 2.85 (m, 2 H), 0.90 (m, 9 H), 0.05 (s, 6 H); MS (70 eV, CI, CH<sub>4</sub>)  $m/z$  295 ( $M^+$  + 1), 277 ( $M^+$  + 1 - H<sub>2</sub>O), 237 ( $M^+$  + 1 - C<sub>4</sub>H<sub>9</sub>), 323 ( $M^+$  + 29), 335 ( $M^+$  + 41); exact mass calcd for C<sub>16</sub>H<sub>26</sub>O<sub>3</sub>Si 295.1729, found 295.1734.

## References

- Burnstock, G. In *Cell Membrane Receptors for Drugs and Hormones. A Multidisciplinary Approach*; Bolis, L., Straub, R. W., Eds.; Raven Press: New York, 1978; pp 107–118.
- Londos, C.; Cooper, D. M. F.; Wolff, J. Subclasses of External Adenosine Receptors. *Proc. Natl. Acad. Sci. U.S.A.* 1980, 77, 2551–2554.
- Daly, J. W. Adenosine Receptors: Targets for Future Drugs. *J. Med. Chem.* 1982, 25, 197–207.
- Williams, M. Adenosine Antagonists as Therapeutic Agents. *Med. Res. Rev.* 1989, 9, 219–243.
- Katsushima, T.; Nieves, L.; Wells, J. N. Structure-Activity Relationships of 8-Cycloalkyl-1,3-dipropylxanthines as Antagonists of Adenosine Receptors. *J. Med. Chem.* 1990, 33, 1906–1910.
- (a) Shimada, J.; Suzuki, F.; Nonaka, H.; Karasawa, A.; Mizumoto, H.; Ohno, T.; Kubo, K.; Ishii, A. 8-(Dicyclopropylmethyl)-1,3-dipropylxanthine: A Potent and Selective Adenosine A<sub>1</sub> Antagonist with Renal Protective and Diuretic Activities. *J. Med. Chem.* 1991, 34, 466–469. (b) Shimada, J.; Suzuki, F.; Nonaka, H.; Ishii, A. 8-Polycycloalkyl-1,3-dipropylxanthines as Potent and Selective Antagonists for A<sub>1</sub>-Adenosine Receptors. *J. Med. Chem.* 1992, 35, 924–930. (c) Suzuki, F.; Shimada, J.; Mizumoto, H.; Karasawa, A.; Kubo, K.; Nonaka, H.; Ishii, A.; Kawakita, T. Adenosine A<sub>1</sub> Antagonists. 2. Structure-Activity Relationships on Diuretic Activities and Protective Effects Against Acute Renal Failure. *J. Med. Chem.* 1992, 35, 3066–3075. (d) Suzuki, F.; Shimada, J.; Nonaka, H.; Ishii, A.; Shiozaki, S.; Ichikawa, S.; Ono, E. 7,8-Dihydro-8-ethyl-2-(3-noradamantyl)-4-propyl-1H-imidazo-[2,1-*i*]purin-5(4H)-one: A Potent and Water-Soluble Adenosine A<sub>1</sub> Antagonist. *J. Med. Chem.* 1992, 35, 3578–3581.
- Jacobson, K. A.; Kirk, K. L.; Padgett, W. L.; Daly, J. W. A Functionalized Congener Approach to Adenosine Receptor Antagonists: Amino Acid Conjugates of 1,3-Dipropylxanthine. *Mol. Pharmacol.* 1986, 29, 28–133.
- Trivedi, B. K.; Bridges, A. J.; Patt, W. C.; Priebe, S. R.; Bruns, R. F. N<sup>6</sup>-Bicycloalkyladenosines with Unusually High Potency and Selectivity for the Adenosine A<sub>1</sub> Receptor. *J. Med. Chem.* 1989, 32, 8–11.
- Francis, J. E.; Webb, R. L.; Ghai, G. R.; Hutchison, A. J.; Moskal, M. A.; deJesus, R.; Yokoyama, R.; Rovinski, S. L.; Contardo, N.; Dotson, R.; Barclay, B.; Stone, G. A.; Jarvis, M. F. Highly Selective Adenosine A<sub>2</sub> Receptor Agonists in a Series of N-Alkylated 2-Aminoadenosines. *J. Med. Chem.* 1991, 34, 2570–2579.
- Bridges, A. J.; Bruns, R. F.; Ortwin, D. F.; Priebe, S. R.; Szotek, D. L.; Trivedi, B. K. N<sup>6</sup>-[2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl]adenosine and Its Uronamide Derivatives. Novel Adenosine Agonists with Both High Affinity and High Selectivity for the Adenosine A<sub>2</sub> Receptor. *J. Med. Chem.* 1988, 31, 1282–1285.
- Shimada, J.; Suzuki, F.; Nonaka, H.; Ishii, A.; Ichikawa, S. (E)-1,3-Dialkyl-7-methyl-8-(3,4,5-trimethoxystyryl)xanthines: Potent and Selective Adenosine A<sub>2</sub> Antagonists. *J. Med. Chem.* 1992, 35, 2342–2345.
- (a) Williams, M. *Adenosine and Adenosine Receptors*; Humana Press: Clifton, NJ, 1990. (b) Jacobson, K. A.; van Galen, P. J. M.; Williams, M. Adenosine Receptors: Pharmacology, Structure Activity Relationships and Therapeutic Potential. *J. Med. Chem.* 1992, 35, 407–422.
- Peet, N. P.; Lentz, N. L.; Meng, E. C.; Dudley, M. W.; Ogden, A. M. L.; Demeter, D. A.; Weintraub, H. J. R.; Bey, P. A Novel Synthesis of Xanthines: Support for a New Binding Mode for Xanthines with Respect to Adenosine at Adenosine Receptors. *J. Med. Chem.* 1990, 33, 3127–3130.
- (a) Another superimposition of the theophylline and adenosine has recently been suggested. See: van Galen, P. J. M.; Vlijmen, H. W. T.; IJzerman, A. P.; Soudijn, W. A Model for the Antagonist Binding Site on the Adenosine A<sub>1</sub> Receptor, Based on Steric, Electrostatic, and Hydrophobic Properties. *J. Med. Chem.* 1990, 33, 1708–1713. (b) A recent superimposition of xanthines with respect to adenosine derivatives is termed the "three binding domain model" and is similar to the N<sup>6</sup>-C<sup>8</sup> model.<sup>13</sup> In this model the xanthine 8-substituent is close in space to the adenosine C<sup>8</sup> N-substituent, but the imidazopyrimidine rings are overlapped differently. See: Dooley, M. J.; Quinn, R. J. An Explanation of the Substituent Effect of 1,3,8-Trisubstituted Xanthines on Adenosine A<sub>1</sub>/A<sub>2</sub> Affinity. *Bioorg. Med. Chem. Lett.* 1992, 2, 1199–1200.
- van der Wenden, E. M.; IJzerman, A. P.; Soudijn, W. A Steric and Electrostatic Comparison of Three Models for the Agonist/Antagonist Binding Site on the Adenosine A<sub>1</sub> Receptor. *J. Med. Chem.* 1992, 35, 629–635.
- Daly, J. W.; Padgett, W. L.; Shamim, M. T.; Butts-Lamb, P.; Waters, J. 1,3-Dialkyl-8-(*p*-sulfophenyl)xanthines: Potent Water-Soluble Antagonists for A<sub>1</sub>- and A<sub>2</sub>-Adenosine Receptors. *J. Med. Chem.* 1985, 28, 487–492.
- Hamilton, H. W.; Ortwin, D. F.; Worth, D. F.; Badger, E. W.; Bristol, J. A.; Bruns, R. F.; Haleen, S. F.; Steffen, R. P. Synthesis of Xanthines as Adenosine Antagonists, A Practical Quantitative Structure-Activity Relationship Application. *J. Med. Chem.* 1985, 28, 1071–1079.
- Baldwin, J. E. Rules for Ring Closure. *J. Chem. Soc., Chem. Commun.* 1976, 734–736.
- Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. 5-Endo-Trigonal Reactions: A Disfavored Ring Closure. *J. Chem. Soc., Chem. Commun.* 1976, 736–738.
- Delinck, D. L.; Margolin, A. L. Synthesis of Chiral Building Blocks For Selective Adenosine Reagents. Lipase-Catalyzed Resolution of 2-Benzylpropanol and 2-Benzylpropionic Acid. *Tetrahedron Lett.* 1990, 31, 6707–6798.
- Galardy, R. E.; Kortylewicz, Z. P. Inhibition of Carboxypeptidase A by Aldehyde and Ketone Substrate Analogues. *Biochemistry* 1984, 23, 2083–2087.
- Bouisset, M.; Bousquet, A.; Heymes, A. Preparation of Genfibrozil and Valproic Acid by alpha-Alkylation of Metal Alkylcarboxylates. French Patent 2599737, 1987, Dec 11.
- Tomiyama, T.; Wakabayashi, S.; Yokota, M. Synthesis and Biological Activity of Novel Carbacyclins Having Bicyclic Substituents on the ω-Chain. *J. Med. Chem.* 1989, 32, 1988–1996.
- Carlson, G. L. B.; Quina, F. H.; Zarnegar, B. M.; Whitten, D. G. Excited State Interactions and Decay Routes in Bichromophoric Systems. Nonconjugated Phenyl Ketones. *J. Am. Chem. Soc.* 1975, 97, 347–354.

- (25) Berti, G.; Bottari, F.; Macchia, B.; Macchia, F. Stereochemistry of Some Derivatives of Phenylcyclohexanes. *Tetrahedron* 1966, 22, 189-197.
- (26) Bordwell, F. G.; Almy, J. Favorskii Rearrangements. VII. Formation of Amides from  $\alpha$ -Halo  $\alpha'$ -Aryl Ketones. *J. Org. Chem.* 1973, 38, 571-574.
- (27) Dudley, M. W.; Peet, N. P.; Demeter, D. A.; Weintraub, H. J. R.; Ijzerman, A. P.; Nordvall, G.; van Galen, P. J. M.; Jacobson, K. A. Adenosine A<sub>1</sub> Receptor and Ligand Molecular Modeling. *Drug Dev. Res.* 1993, 28, 237-243.
- (28) (a) Hitchcock, J. M.; Chaney, S. F.; Zwolschen, J. M.; Ketteler, H. J.; Peet, N. P.; Sorensen, S. M. Potential Cognition-Enhancing Activity of the Adenosine A<sub>1</sub> Receptor Antagonist MDL 102,234 in Spatial Learning and Hippocampal Long-Term Potentiation Models, October 25-30, 1992, Society for Neuroscience, Anaheim, California. (b) Dudley, M.; Racke, M.; Ogden, A. M.; Peet, N. P.; Secrest, R.; McDermott, R. MDL 102,234: A Selective Adenosine A<sub>1</sub> Receptor Antagonist Reflecting a New Binding Mode to the Receptor. October 25-30, 1992, Society for Neuroscience, Anaheim, CA. (c) Hitchcock, J. M.; Chaney, S. F.; Zwolschen, J. M.; Ketteler, H. J.; Peet, N. P.; Sorensen, S. M. Potential Cognition-Enhancing Activity of Adenosine A<sub>1</sub> Receptor Antagonists. December 14-18, 1992, ANCP Annual Meeting, Puerto Rico.
- (29) Lentz, N. L.; Peet, N. P. Synthesis of Chiral Adenosine Receptor Recognition Units via a Sharpless Asymmetric Epoxidation Procedure. *Tetrahedron Lett.* 1990, 31, 811-814.
- (30) Corey, E. J.; Clark, D. A.; Goto, G.; Marfat, A.; Mioskowski, C. Stereospecific Total Synthesis of a "Slow Reacting Substance" of Anaphylaxis, Leukotriene C-1. *J. Am. Chem. Soc.* 1980, 102, 1436-1439.
- (31) Compound 8 has been previously prepared in 2% yield by hydroformylation of 3-phenylpropanoic acid methyl ester. See: Okano, T.; Kobayashi, T.; Konishi, H.; Kiji, J. Hydroformylation of Olefins with Paraformaldehyde Catalyzed by Rhodium Complexes. *Tetrahedron Lett.* 1982, 23, 4967-4968.