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### D-4'-THIOADENOSINE DERIVATIVES AS HIGHLY POTENT AND SELECTIVE AGONISTS AT THE HUMAN A<sub>3</sub> ADENOSINE RECEPTOR

Hyouk Woo Lee<sup>a</sup>, Dae Hong Shin<sup>b</sup>, Ji Young Jung<sup>b</sup>, Hea Ok Kim<sup>c</sup>, Moon Woo Chun<sup>a</sup>, N. Melman<sup>c</sup>, Z.-G. Gao<sup>c</sup>, Kenneth A. Jacobson<sup>c</sup> & Lak Shin Jeong<sup>b</sup>

<sup>a</sup> Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul, Korea

<sup>b</sup> Molecular Recognition Section, Laboratory of Bioorganic Chemistry, NIDDK, NIH, Bethesda, Maryland, USA

<sup>c</sup> College of Pharmacy, Seoul National University, Seoul, Korea

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## D-4'-THIOADENOSINE DERIVATIVES AS HIGHLY POTENT AND SELECTIVE AGONISTS AT THE HUMAN A<sub>3</sub> ADENOSINE RECEPTOR

**Hyoun Woo Lee** □ *Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul, Korea*

**Dae Hong Shin and Ji Young Jeong** □ *Molecular Recognition Section, Laboratory of Bioorganic Chemistry, NIDDK, NIH, Bethesda, Maryland, USA*

**Hea Ok Kim** □ *College of Pharmacy, Seoul National University, Seoul, Korea*

**Moon Woo Chun** □ *Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul, Korea*

**N. Melman, Z.-G. Gao, and Kenneth A. Jacobson** □ *College of Pharmacy, Seoul National University, Seoul, Korea*

**Lak Shin Jeong** □ *Molecular Recognition Section, Laboratory of Bioorganic Chemistry, NIDDK, NIH, Bethesda, Maryland, USA*

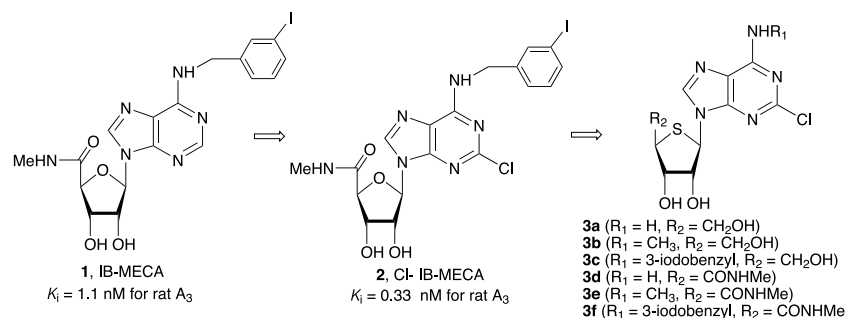
□ *4'-Thionucleoside derivatives as potent and selective A<sub>3</sub> adenosine receptor agonists were synthesized, starting from D-gulono-γ-lactone via D-thioribosyl acetate as a key intermediate, among which the 2-chloro-N<sup>6</sup>-methyladenosine-5'-methyluronamide showed the most potent and selective binding affinity ( $K_i = 0.28 \pm 0.09$  nM) at the human A<sub>3</sub> adenosine receptor.*

### INTRODUCTION

A number of ligands have been synthesized and tested for binding affinity at the A<sub>3</sub> versus A<sub>1</sub> and A<sub>2A</sub> receptors. Among these ligands, IB-MECA (1) was found to be a highly potent rat A<sub>3</sub> agonist ( $K_i=1.1$  nM), which is 50-fold selective for rat brain A<sub>3</sub> versus either A<sub>1</sub> or A<sub>2</sub> receptors.<sup>[1]</sup> Introduction of chlorine at the 2-position of IB-MECA, resulting in the formation of Cl-IB-MECA (2),<sup>[1,2]</sup> dramatically increased binding affinity and selectivity (Figure 1).

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Address correspondence to Hyoun Woo Lee, Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea.

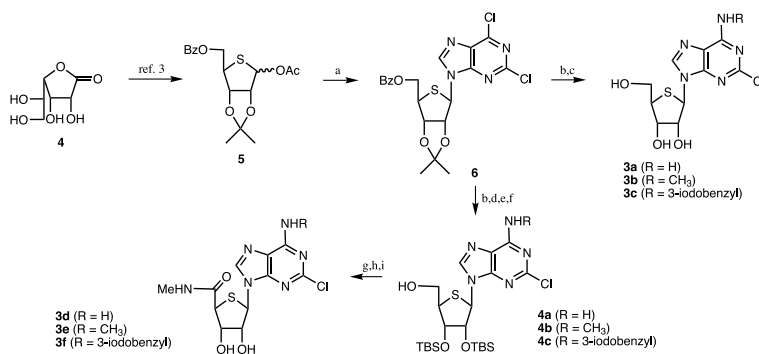


**FIGURE 1** The rationale for the design of the desired 4'-thionucleosides.

It has been reported to display a  $K_i$  value of 0.33 nM and showed 2500- and 1400-fold rat  $A_3$  receptor selectivity versus  $A_1$  and  $A_{2A}$  receptors, respectively. Thus, on the basis of the high binding affinity and selectivity of Cl-IB-MECA on  $A_3$  adenosine receptors, we designed and synthesized the 4'-thionucleoside analogues, **3a–f** of Cl-IB-MECA, since a sulfur atom is well known as a bioisostere of an oxygen atom.

## RESULTS AND DISCUSSION

The target nucleosides were synthesized, starting from D-gulono- $\gamma$ -lactone (**4**) via D-thioribosyl acetate **5**<sup>[3]</sup> as a key intermediate (Scheme 1). The glycosyl donor **5** was condensed with silylated 2,6-dichloropurine to give the protected nucleoside **6**. Compound **6** was treated with ammonia, methylamine, and 3-iodobenzylamine followed by removal of the protecting groups to give 2-chloro-4'-thioadenosine (**3a**), 2-chloro- $N^6$ -methyl-4'-thioadenosine (**3b**), and  $N^6$ -(3-iodobenzyl)-4'-thioadenosine (**3c**), respectively.



**SCHEME 1** Reagents<sup>a</sup>: a) silylated 2,6-dichloropurine, TMSOTf; b)  $RNH_2$ ; c) i. 80% AcOH; ii. NaOMe, MeOH; d) 80% AcOH; e) TBSCl, DMF; f) NaOMe, MeOH; g) i. PDC, DMF, ii.  $K_2CO_3$ , MeI; h) 40%  $MeNH_2$ , MeOH; i)  $n\text{-Bu}_4NF$ , THF.

For the synthesis of 4'-uronamide derivatives **3d–e**, treatment of **6** with ammonia, methylamine, and 3-iodobenzylamine followed by removal of the isopropylidene group, protection of the resulting diol to TBS ether, and final removal of the benzoyl group afforded **4a–c**, respectively. Oxidation of **4a–c** with PDC in DMF followed by methylation gave their corresponding methyl esters, which were converted to the final 4'-uronamide derivatives **3d–e**, respectively, after the successive treatments of methyl amine and tetra-*n*-butylammonium fluoride.

All synthesized 4'-thionucleosides exhibited higher binding affinity to the human A<sub>3</sub> adenosine receptor than Cl-IB-MECA, among which the 2-chloro-*N*<sup>6</sup>-methyladenosine-5'-methyluronamide showed the most potent binding affinity ( $K_i = 0.28 \pm 0.09$  nM). It was selective for A<sub>3</sub> vs rat A<sub>1</sub> and rat A<sub>2A</sub> receptors by 700- and 23,000-fold, respectively and for A<sub>3</sub> vs. human A<sub>1</sub> and human A<sub>2A</sub> receptors by 4,800- and 36,000-fold, respectively.

In summary, we have discovered ultrapotent and selective A<sub>3</sub> adenosine receptor agonist by the simple change of furanose to thiofuranose. These nucleosides may be useful as pharmacological tools and also are of interest for the development of therapeutic agents.

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