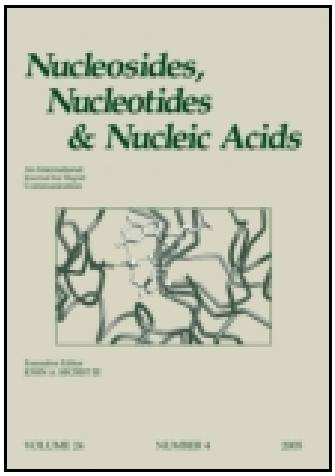


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn20

D-4′-THIOADENOSINE DERIVATIVES AS HIGHLY POTENT AND SELECTIVE AGONISTS AT THE HUMAN A_3 ADENOSINE RECEPTOR

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

[a] Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul, Korea

[b] Molecular Recognition Section, Laboratory of Bioorganic Chemistry, NIDDK, NIH, Bethesda, Maryland, USA

[c] College of Pharmacy, Seoul National University, Seoul, Korea

Published online: 28 Jul 2006.

To cite this article: Hyouk Woo Lee, Dae Hong Shin, Ji Young Jung, Hea Ok Kim, Moon Woo Chun, N. Melman, Z.-G. Gao, Kenneth A. Jacobson & Lak Shin Jeong (2005) D-4′-THIOADENOSINE DERIVATIVES AS HIGHLY POTENT AND SELECTIVE AGONISTS AT THE HUMAN A_3 ADENOSINE RECEPTOR, Nucleosides, Nucleotides and Nucleic Acids, 24:5-7, 607-609, DOI: 10.1081/NCN-200061827

To link to this article: http://dx.doi.org/10.1081/NCN-200061827

Nucleosides, Nucleotides, and Nucleic Acids, 24 (5–7):607–609, (2005)

ISSN: 1525-7770 print/ 1532-2335 online
DOI: 10.1081/NCN-200061827

D-4′-THIOADENOSINE DERIVATIVES AS HIGHLY POTENT AND SELECTIVE AGONISTS AT THE HUMAN A_3 ADENOSINE RECEPTOR

Hyouk 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_3 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^6-methyladenosine-5′-methyluronamide showed the most potent and selective binding affinity (K_i = 0.28 ± 0.09 nM) at the human A_3 adenosine receptor.*

INTRODUCTION

A number of ligands have been synthesized and tested for binding affinity at the A_3 versus A_1 and A_{2A} receptors. Among these ligands, IB-MECA (1) was found to be a highly potent rat A_3 agonist (K_i=1.1 nM), which is 50-fold selective for rat brain A_3 versus either A_1 or A_2 receptors.[1] Introduction of chlorine at the 2-position of IB-MECA, resulting in the formation of Cl-IB-MECA (**2**),[1,2] dramatically increased binding affinity and selectivity (Figure 1).

This work was supported by the grant from the Korea Health R & D Project, Ministry of Health & Welfare, Korea (03-PJ2-PG4-BD02-0001).

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

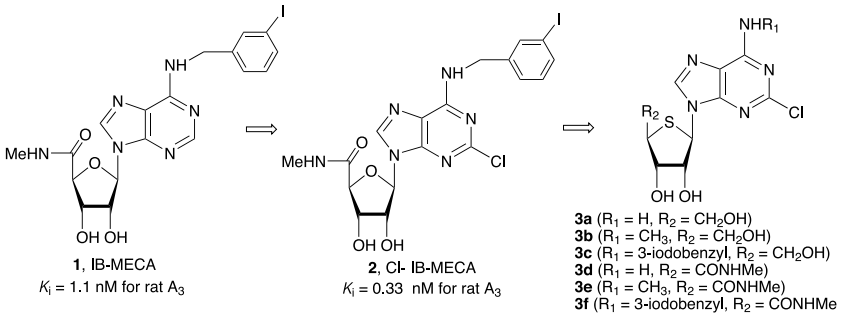
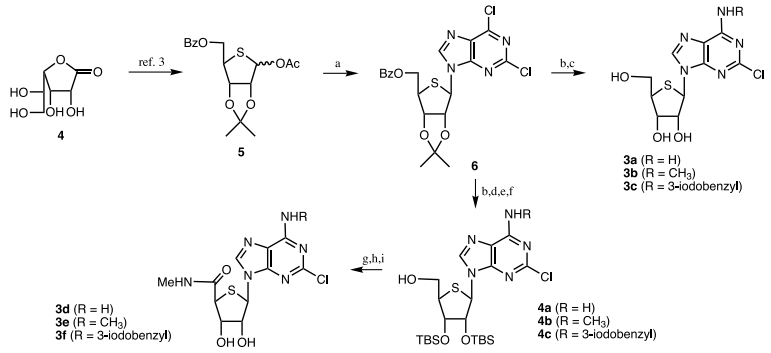


FIGURE 1 The rationale for the design of the desired 4′-thionucleosides.

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-γ-lactone (**4**) via D-thioribosyl acetate **5**[3] 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[a]: a) silylated 2,6-dichloropurine, TMSOTf; b) RNH_2; c) i. 80% AcOH; ii. NaOMe, MeOH; d) 80% AcOH; e) TBSCI, DMF; f) NaOMe, MeOH; g) i. PDC, DMF, ii. K_2CO_3, MeI; h) 40% $MeNH_2$, MeOH; i) n-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*-buylammonium fluoride.

All synthesized 4′-thionucleosides exhibited higher binding affinity to the human A_3 adenosine receptor than Cl-IB-MECA, among which the 2-chloro-N^6-methyladenosine-5′-methyluronamide showed the most potent binding affinity ($K_i = 0.28 \pm 0.09$ nM). It was selective for A_3 vs rat A_1 and rat A_{2A} receptors by 700- and 23,000-fold, respectively and for A_3 vs. human A_1 and human A_{2A} receptors by 4,800- and 36,000-fold, respectively.

In summary, we have discovered ultrapotent and selective A_3 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.

REFERENCES

1. Kim, H.O.; Ji, X.-D.; Siddiqi, S.M.; Olah, M.E.; Stiles, G.L.; Jacobson, K.A. 2-Substitution of N^6-benzyladenosine-5′-uronamides enhances selectivity for A_3-adenosine receptors. J. Med. Chem. **1994**, *37*, 3614–3621.
2. Jacobson, K.A.; Knutsen, L.J.S. P1 and P2 purine and pyrimidine receptors. In *Purinergic and Pyrimidinergic Signalling I*; Abbracchio, M.P., Williams, M., Eds.; Handbook of Experimental Pharmacology, Springer-Verlag: Berlin, Germany, 2001; Vol. 151/I, 129–175.
3. Jeong, L.S.; Yoo, S.J.; Lee, K.M.; Koo, M.J.; Choi, W.J.; Kim, H.O.; Moon, H.R.; Lee, M.Y.; Park, J.G.; Lee, S.K.; Chun, M.W. Design, synthesis and biological evaluation of fluoro-neplanocin A as the novel mechanism-based inhibitor of S-adenosylhomocysteine hydrolase. J. Med. Chem. **2003**, *46*(2), 201–203.