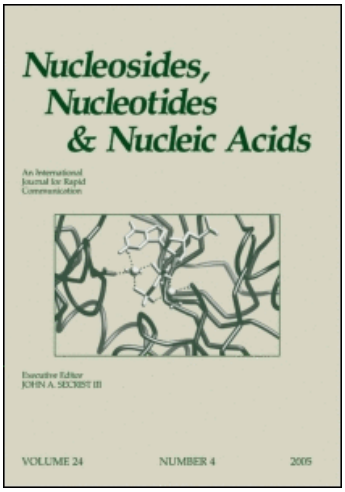

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DESIGN, SYNTHESIS, AND ANTI-TUMOR ACTIVITY OF 4′-THIONUCLEOSIDES AS POTENT AND SELECTIVE AGONISTS AT THE HUMAN A_3 ADENOSINE RECEPTOR

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□ *On the basis of potent and selective binding affinity of Cl-IB-MECA to the human A_3 adenosine receptor, its 4′-thioadenosine derivatives were efficiently synthesized starting from D-gulonic γ-lactone. Among compounds tested, 2-chloro-N^6-(3-iodobenzyl)- and 2-chloro-N^6-methyl-4′-thioadenosine-5′-methyluronamides (***7a*** and ***7b***) exhibited nanomolar range of binding affinity (K_i = 0.38 nM and 0.28 nM, respectively) at the human A_3AR. These compounds showed anti-growth effects on HL-60 leukemia cell, which resulted from the inhibition of Wnt signaling pathway.*

Keywords Bioisosteric; 4′-thionucleosides; A3 adenosine receptor agonist; anti-proliferative effect

INTRODUCTION

Adenosine is endogenous material and regulates many physiological functions in the body through adenosine receptors.[1] Thus, adenosine receptors have been good therapeutic targets for the development of clinically useful drugs.[2] On the basis of the structure of a natural ligand, adenosine, many nucleoside derivatives largely modified on N^6- and/or

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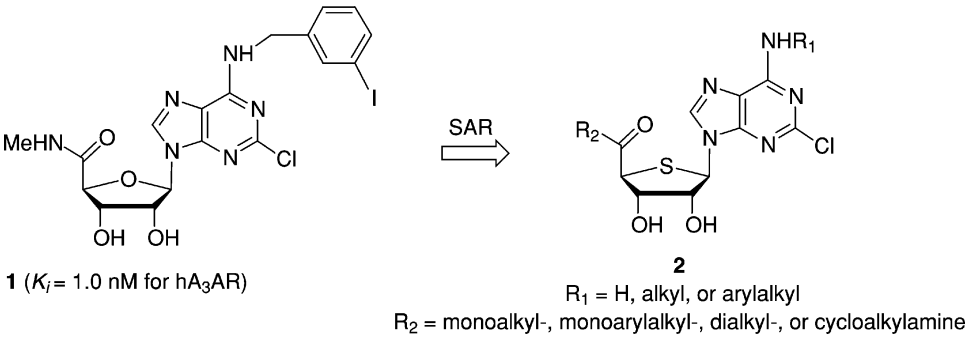


1 (K_i = 1.0 nM for hA_3AR)

2

R_1 = H, alkyl, or arylalkyl

R_2 = monoalkyl-, monoarylalkyl-, dialkyl-, or cycloalkylamine

FIGURE 1 Design of the 4′-thionucleosides **2** based on bioisosteric rationale.

4′-position of adenosine have been synthesized as potent adenosine receptor ligands.[3] Among these, 2-chloro-N^6-(3-iodobenzyl)-adenosine-5′-methyluronamide (**1**, Cl-IB-MECA)[4] was discovered as potent and selective agonist (K_i = 1.0 nM) at the human A_3 adenosine receptor (AR) and is being developed as anticancer agent. Therefore, on the basis of potent and selective binding affinity to the human A_3AR, we designed and synthesized 4′-thioadenosine derivatives which are in biosiosteric relationships with compound **1** (Figure 1).

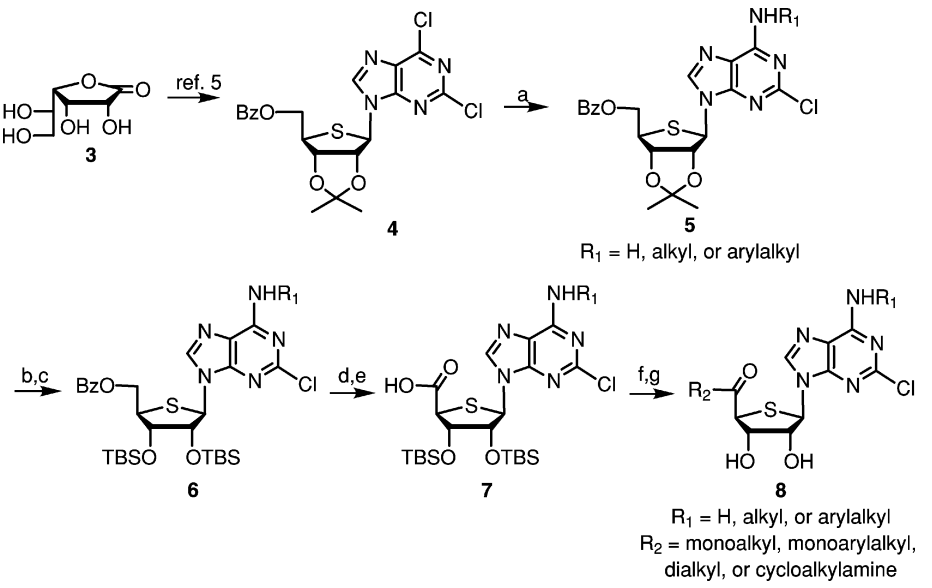
Herein, we report the synthesis, binding affinity at the A_3AR, and *in vitro* anti-proliferative effects in human cancer cell lines of 4′-thioadenosine derivatives.

RESULTS AND DISCUSSION

Synthesis of the target nucleosides **8** started from the known intermediate **3** which was derived from D-gulonic γ-lactone (**3**), as shown in Scheme 1.[5]

Treatment of **4** with various alkyl- and arylalkyl amines in EtOH produced N^6-alkyl- or arylalkylamino-4′-thioadenosine derivatives **5**. Because removal of the isopropylidene group under acidic conditions at the final step resulted in deglycosylation, the isopropylidene group in **5** was changed to di-*O*-TBS ether **6**. Deprotection of the benzoyl group of **6** followed by oxidation of the primary alcohol to the acid with PDC gave the acid derivative **7**. Conversion of the acid **7** to the various amides **8** was accomplished by coupling with various amines in the presence of EDC and HOBT.

Binding affinities of all synthesized 4′-thioadenosine derivatives at the A_3 AR were measured using a radioligand binding assay.[5] From this study, 2-chloro-N^6-methyl- and 2-chloro-N^6-(3-iodobenzyl)-4′-thioadenosine-5′-methyluronamides (K_i = 0.28 ± 0.09 nM and K_i = 0.38 ± 0.07 nM, respectively) were discovered as highly potent and selective agonists at the human A_3AR. It was also found that 5′-monoalkyl amide



SCHEME 1 Reagents and conditions: a) R_1NH_2, Et_3N; b) 80% AcOH; c) TBSOTf, pyridine; d) NaOMe, MeOH; e) PDC, DMF; f) amines, EDC, HOBT, DIPEA, CH_2Cl_2; g) TBAF, THF.

showed better binding affinity than the corresponding 5′-dialkyl amide, indicating that at least one hydrogen forms a hydrogen bond within the binding site.[6] The 4′-thionucleosides generally showed higher binding affinity to the A_3AR than the corresponding 4′-oxonucleosides.

2-Chloro-N^6-(3-iodobenzyl)-4′-thioadenosine-5′-methyluronamide showing high binding affinity to the A_3AR was tested for anti-proliferative effects in human cancer cell lines such as A549, Col2, HL-60 cells. This compound exhibited concentration-dependent anti-proliferative effects. A further study indicated that anti-growth effect of this agonist resulted from the inhibition of Wnt signalling pathway by lowering the levels of β-catenine, phosphorylated-Akt, and phosphorylated-GSK 3β.[7]

In summary, we carried out the systematic structure-activity relationships of 4′-thioadenosine derivatives, among which 2-chloro-N^6-(3-iodobenzyl)-4′-thioadenosine-5′-methyluronamide emerged as potent and selective A_3AR agonist. In vitro anti-growth effects and novel mechanism of action of this agonist guarantees it has a high potential to be a good anticancer agent.

REFERENCES

1. Olah, M.E.; Stiles, G.L. The role of receptor structure in determining adenosine receptor activity. *Pharmacol. Ther.* **2000**, 85, 55–75.
2. Jacobson, K.A.; Gao. Z.-G. Adenosine receptors as therapeutic targets. *Nature Rev. Drug Dis.* **2006**, 5, 247–264.

3. Baraldi, P.G.; Cacciari, B.; Romagnoli, R.; Merighi, S.; Varani, K.; Borea, P.A.; Spalluto, G. A_3 Adenosine receptor ligands: History and perspectives. *Med. Res. Rev.* **2000**, 20, 103–128.
4. 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.
5. Jeong, L.S.; Lee, H.W.; Jacobson, K.A.; Kim, H.O.; Shin, D.H.; Lee, J.A.; Gao, Z.-G.; Lu, C.; Duong, H.T.; Gunaga, P.; Lee, S.K.; Jin, D.Z.; Chun, M.W.; Moon, H.R. Structure-activity relationship of 2-chloro-N^6-substituted-4′-thioadenosine-5′-uronamides as highly potent and selective agonists at the human A_3 adenosine receptor. *J. Med.Chem.* **2006**, 49, 273–281.
6. Gao, Z.-G.; Joshi, B.V.; Klutz, A.M.; Kim, S.K.; Lee, H.W.; Kim, H.O.; Jeong, L.S.; Jacobson, K.A. Conversion of A_3 adenosine receptor agonists into selective antagonists by modification of the 5′-ribofuran-uronamide moiety. *Bioorg. Med. Chem. Lett.* **2006**, 16, 596–601.
7. Lee, E.J.; Min, H.Y.; Chung, H.J.; Park, E.J.; Shin, D.H.; Jeong, L.S.; Lee, S.K. A novel adenosine analog, thio-Cl-IB-MECA, induces G_0/G_1 cell cycle arrest and apoptosis in human promyelocytic leukemia HL-60 cells. *Biochem. Pharmacol.* **2005**, 70, 918–924.