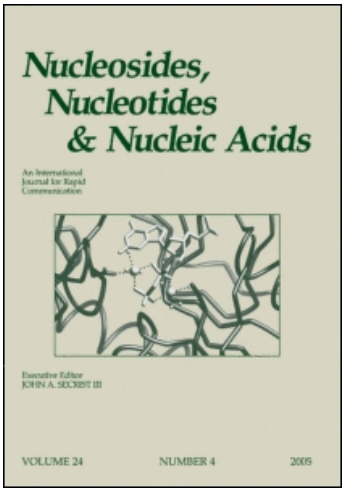

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SYNTHESIS OF 3′-UREIDOADENOSINE ANALOGUES AND THEIR BINDING AFFINITY TO THE A_3 ADENOSINE RECEPTOR

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▫ *Novel 3′-ureidoadenosine analogues were synthesized from 1,2:5,6-di-O-isopropylidene-D-glucose in order to lead to stronger hydrogen bonding at the A_3 adenosine receptor than the corresponding 3′-aminoadenosine derivatives. However, all synthesized 3′-ureidoadenosine analogues have lost their binding affinities to the all subtypes of adenosine receptors, indicating that bulky 3′-urea moiety led to conformational distortion.*

INTRODUCTION

Among many N^6-and/or 2-substituted adenosine derivatives with A_3 adenosine receptor agonistic activity, N^6-(3-iodobenzyl)-5′-*N*-methylcarbamoyladenosine (IB-MECA) and 2-chloro-N^6-(3-iodobenzyl)-5′-*N*-methylcarbamoyladenosine (Cl-IB-MECA) were found to be highly selective full agonists with high binding affinities (K_i = 1.8 ± 0.7 nM, 1.4 ± 0.3 nM, respectively) at the human A_3 adenosine receptor.[1,2] On the basis of high binding affinity of Cl-IB-MECA, we

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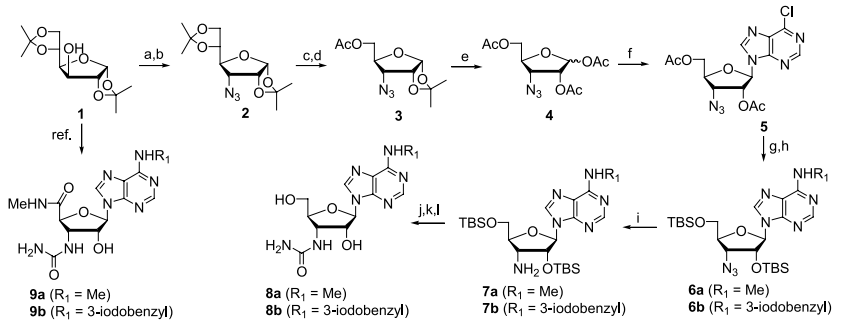
have recently reported the role of 3′-hydroxyl group of Cl-IB-MECA as a hydrogen bonding donor, not a hydrogen bonding acceptor by comparing its binding affinity with 3′-fluoro analogue of Cl-IB-MECA.[3] More recently, 3′-aminoadenosine analogues[4] exhibited potent agonistic activity at the human A_3 adenosine receptor, indicating that 3′-amino group served as a hydrogen bonding donor at the binding site of the human A_3 adenosine receptor.

Thus, as our continuing efforts to search for potent and selective A_3 adenosine receptor agonists, it was of great interest to design 3′-ureidoadenosine analogues since 3′-ureido moiety may form stronger hydrogen bond in the binding site than the corresponding 3′-amino-or 3′-hydroxy-substituted nucleosides.

RESULTS AND DISCUSSION

The target nucleosides **8a,b** and **9a,b** were synthesized from 1,2:5,6-di-*O*-isopropylidene-D-glucose as shown in Scheme 1.

Treatment of 1,2:5,6-di-*O*-isopropylidene-D-glucose (**1**) with triflic anhydride in pyridine followed by treating with sodium azide in DMF produced azido sugar **2**. Selective hydrolysis of **2** with 75% aqueous acetic acid followed by successive treatments with $NaIO_4$ and $NaBH_4$ afforded a 4-hydroxylmethyl derivative, which was acetylated to give **3**. Hydrolysis of **3** using 85% formic acid followed by acetylation of the resulting diol with acetic anhydride in pyridine afforded the key intermediate **4**. The glycosyl donor **4** was condensed with silylated 6-chloropurine in the presence of TMSOTf as a Lewis acid catalyst afforded the protected nucleoside **5**. Compound **5** was treated with methylamine and 3-iodobenzylamine to give the N^6-substituted nucleosides, **6a** and **6b**, respectively. The acetyl protecting groups of **12a** and **12b** were removed and protected again as TBS ethers **6a** and **6b**, respectively, because of the facile migration of a 2′-acetyl group to the 3′-ureido group. Reduction of azido group of **6a** and **6b** with



Reagents and Conditions: a) Tf_2O, pyridine, 0°C; b) NaN_3, DMF, rt; c) i. 75% AcOH, 55°C; ii. $NaIO_4/H_2O$, EtOH, 20 min, then $NaBH_4$; d) Ac_2O, pyridine, rt; e) i. 85% HCO_2H, 60°C; ii. Ac_2O, pyridine; f) silylated 6-chloropurine, TMSOTf, $C_2H_4Cl_2$, 0°C to 60°C; g) $MeNH_2$, 1,4-dioxane, rt or 3-iodobezylamine hydrochloride, Et_3N, EtOH, then NaOMe, MeOH; h) TBSCl, imidazole, DMF; i) Ph_3P, NH_4OH/H_2O, THF; j) Chloroacetyl isocyanate, DMF; k) NaOMe, MeOH; l) TBAF, THF, rt, 4 h.

SCHEME 1

triphenylphosphine and ammonium hydroxide in aqueous solution yielded 3′-amino derivatives, **7a** and **7b**, respectively. For the introduction of urea moiety to the 3′-position, the amino derivatives, **7a** and **7b** was treated with chloroacetyl isocyanate in DMF followed by treating with sodium methoxide to give the 3′-ureido derivatives, **8a** and **8b**, respectively after desilylation with tetra-*n*-butylammonium fluoride. The 5′-uronamide derivatives **9a** and **9b** were synthesized from 1,2:5,6-di-*O*-isopropylidene-D-glucose (**1**), according to our previous procedure.[5]

Binding affinity of the synthesized nucleosides, **8a,b** and **9a,b** were measured using radioligand binding assays. Unfortunately, all tested compounds were totally devoid of their binding affinities at all subtypes of adenosine receptors, indicating that 3′-urea moiety might cause steric repulsion at the binding site of the receptor, leading to conformational distortion, although it might potentially serve as stronger hydrogen bonding donor than hydroxyl or amino group.

In summary, novel 3′-ureidoadenosine derivatives were synthesized from 1,2:5,6-di-*O*-ispropylidene-D-glucose. The key 3′-urea moiety was introduced from reacting 3′-amino derivative with chloroacetylurea followed by treating with sodium methoxide. Although 3′-ureidoadenosine derivatives did not exhibit potent A_3 adenosine receptor agonistic activity, our results will give valuable information about the identification of the binding site of the A_3 adenosine receptor.

REFERENCES

1. Gao, Z.-G.; Blaustein, J.B.; Gross, A.S.; Melman, N.; Jacobson, K.A. N^6-Substituted adenosine derivatives: selectivity, efficacy, and species differences at A_3 adenosine receptors. Biochem. Pharmacol. **2003**, *65*(10), 1675–1684.
2. Kim, H.O.; Ji, X.-d.; Siddiqi, S.M.; Olah, M.E.; Stiles, G.L.; Jacobson, K.A. 2-substitution of N6-benzyladenosine-5′-uronamides enhances selectivity for A3 receptors. J. Med. Chem. **1994**, *37*(21), 3614–3621.
3. Lim, M.H.; Kim, H.O.; Moon, H.R.; Lee, S.J.; Chun, M.W.; Gao, Z.-G.; Melman, N.; Jacobson, K.A.; Kim, J.H.; Jeong, L.S. Synthesis and binding affinity of 3′-fluoro analogues of Cl-IB-MECA as adenosine A_3 receptor ligands. Bioorg. Med. Chem. Lett. **2003**, *13*(5), 817–820.
4. DeNinno, M.P.; Masamune, H.; Chenard, L.K.; DiRico, K.; Eller, C.; Etienne, J.B.; Tickner, J.E.; Kennedy, S.P.; Knight, D.R.; Kong, J.; Oleynek, J.J.; Tracey, W.R.; Hill, R.J. 3′-aminoadenosine-5′-uronamides: discovery of the first highly selective agonist at the human adenosine A3 receptor. J. Med. Chem. **2003**, *46*(3), 353–355.
5. Jeong, L.S.; Kim, M.J.; Kim, H.O.; Gao, Z.-G.; Kim, S.-K.; Jacobson, K.A.; Chun, M.W. Design and synthesis of 3′-ureidoadenosine-5′-uronamides: effects of the 3′-ureido group on binding to the A_3 adenosine receptor. Bioorg. Med. Chem. Lett. **2004**, *14*(19), 4851–4854.