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SYNTHESIS OF 3'-UREIDOADENOSINE ANALOGUES AND THEIR BINDING AFFINITY TO THE A₃ ADENOSINE RECEPTOR

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SYNTHESIS OF 3'-UREIDOADENOSINE ANALOGUES AND THEIR BINDING AFFINITY TO THE A₃ 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 A₃ 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 N⁶-and/or 2-substituted adenosine derivatives with A₃ adenosine receptor agonistic activity, N⁶-(3-iodobenzyl)-5'-N-methylcarbamoyladenosine (IB-MECA) and 2-chloro-N⁶-(3-iodobenzyl)-5'-N-methylcarbamoyladenosine (Cl-IB-MECA) were found to be highly selective full agonists with high binding affinities ($K_i = 1.8 \pm 0.7$ nM, 1.4 ± 0.3 nM, respectively) at the human A₃ adenosine receptor.^[1,2] On the basis of high binding affinity of Cl-IB-MECA, we

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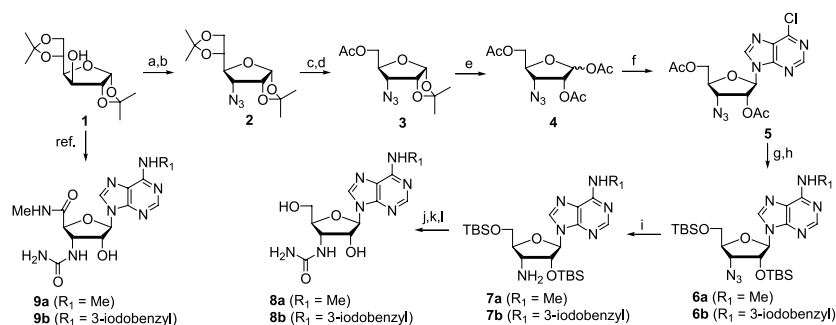
have recently reported the role of 3'-hydroxyl group of ClIB-MECA as a hydrogen bonding donor, not a hydrogen bonding acceptor by comparing its binding affinity with 3'-fluoro analogue of ClIB-MECA.^[3] More recently, 3'-aminoadenosine analogues^[4] exhibited potent agonistic activity at the human A₃ adenosine receptor, indicating that 3'-amino group served as a hydrogen bonding donor at the binding site of the human A₃ adenosine receptor.

Thus, as our continuing efforts to search for potent and selective A₃ 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 NaIO₄ and NaBH₄ afforded a 4-hydroxymethyl 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) Tf₂O, pyridine, 0°C; b) NaN₃, DMF, rt; c) i. 75% AcOH, 55°C; ii. NaIO₄/H₂O, EtOH, 20 min, then NaBH₄; d) Ac₂O, pyridine, rt; e) i. 85% HCO₂H, 60°C; ii. Ac₂O, pyridine; f) silylated 6-chloropurine, TMSOTf, C₂H₄Cl₂, 0°C to 60°C; g) MeNH₂, 1,4-dioxane, rt or 3-iodobenzylamine hydrochloride, Et₃N, EtOH, then NaOMe, MeOH; h) TBSCl, imidazole, DMF; i) Ph₃P, NH₄OH/H₂O, 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*-isopropylidene-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 A₃ adenosine receptor agonistic activity, our results will give valuable information about the identification of the binding site of the A₃ adenosine receptor.

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