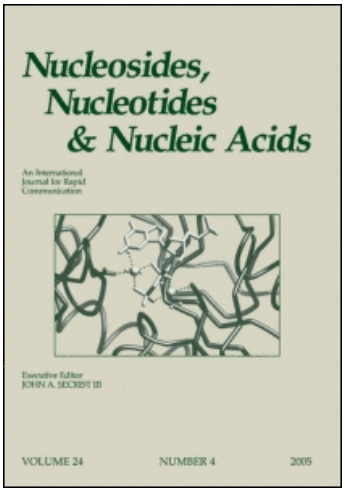

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Synthesis of N^6-Substituted 3'-Ureidoadenosine Derivatives as Highly Potent Agonists at the Mutant A_3 Adenosine Receptor

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SYNTHESIS OF N^6-SUBSTITUTED 3′-UREIDOADENOSINE DERIVATIVES AS HIGHLY POTENT AGONISTS AT THE MUTANT A_3 ADENOSINE RECEPTOR

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□ *Several N^6-substituted 3′-ureidoadenosine derivatives were efficiently synthesized starting from D-glucose for the development of H272E mutant A_3 adenosine receptor (AR) agonists. Among compounds tested, 3′-ureido-N^6-(3-iodobenzyl)adenosine (**2c**) exhibited the highest binding affinity ($K_i = 0.22\ \mu M$) at the H272E mutant A_3 AR without binding to the natural A_3 AR.*

Keywords Mutant A3 adenosine receptor; 3′ureidoadenosine derivatives; agonist; electrostatic; neoligand; neoceptor

INTRODUCTION

Selective A_3 adenosine receptor (AR) full agonists show high therapeutic potentials in the treatment of cardiac and cerebral ischemia[1] and cancer[2] but, the ubiquitous presence of adenosine receptors throughout the body hindered them from being developed as clinically useful agents. Thus, Jacobson et al.[3] have demonstrated a re-engineered G protein-coupled receptor, mutant A_3 AR in which the His residue (H272) of natural A_3 AR, strongly hydrogen-bonded to the 3′-hydroxyl group of adenosine,[4] was mutated to a negatively charged residue, Glu or Asp. This mutant A_3AR called neoceptor can recognize only a specifically designed A_3 agonist, but not the native A_3 agonist.

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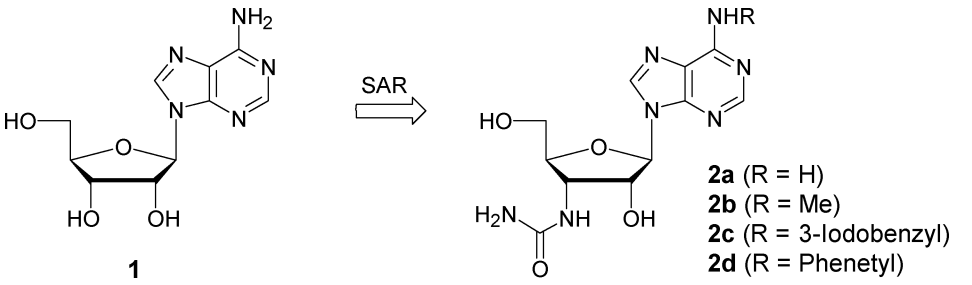
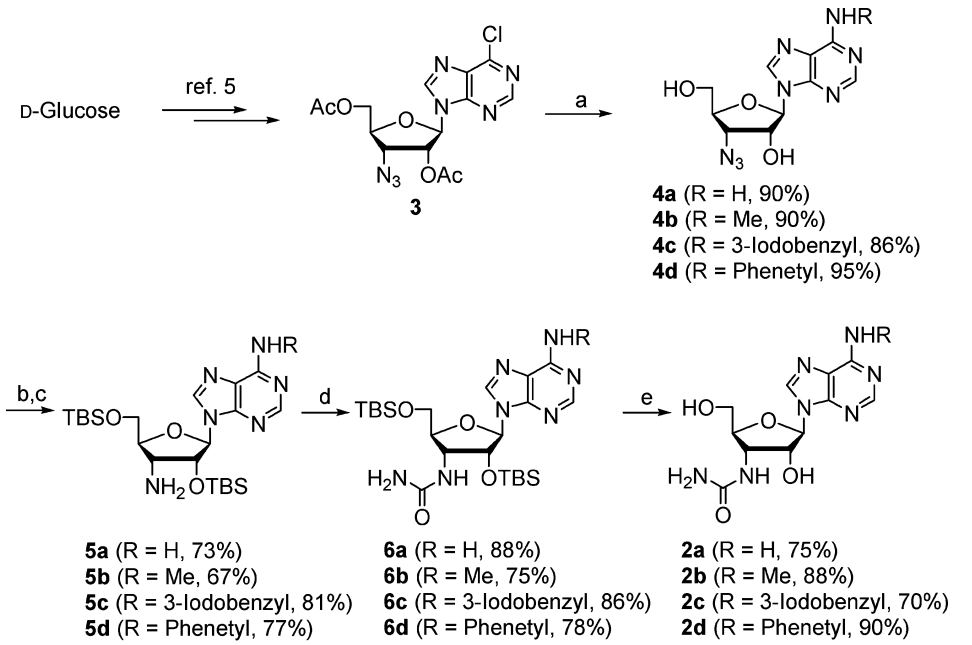


FIGURE 1 Rationale for the design of the desired nucleosides **2a–d**.

Thus, for the purpose of developing optimal agonists at the mutant A_3AR, we modified the 3′-hydroxyl group of adenosine (**1**) to the 3′-ureido group, because the 3′-ureido group is able to form highly favorable electrostatic interaction with the Glu residue of H272E mutant A_3 adenosine



Reagents and Conditions: (a) NH_4OH, 1,4-dioxane, rt or $MeNH_2$, 1,4-dioxane, rt or 3-iodobenzylamine-HCl or phenetylamine-HCl , Et_3N, EtOH, 50 °C, then NaOMe, MeOH, rt; (b) TBSCl, imidazole, DMF, rt; (c) Ph_3P, NH_4OH/H_2O, THF, rt; (d) chloroacetyl isocyanate, DMF, 0 °C, then NaOMe, MeOH, rt; (e) TBAF, THF, rt.

SCHEME 1 Reagents and conditions: (a) NH_4OH, 1,4-dioxane, rt or $MeNH_2$, 1,4-dioxane, rt or 3-iodobenzylamine-HCl or phenetylamine-HCl, Et_3N, EtOH, 50°C, then NaOMe, MeOH, rt; (b) TBSCl, imidazole, DMF, rt; (c) Ph_3P, NH_4OH/H_2O, THF, rt; (d) chloroacetyl isocyanate, DMF, 0°C, then NaOMe, MeOH, rt; (e) TBAF, THF, rt.

receptor. Herein, we report the synthesis of 3′-ureidoadenosine derivatives and their binding affinity at the mutant A_3 adenosine receptor (Figure 1).

RESULTS AND DISCUSSION

Synthesis of the target nucleosides **2a–d** started from the known intermediate **3**[5] which was derived from D-glucose, as depicted in Scheme 1.

Treatment of **3** with various appropriate amines followed by deacetylation with sodium methoxide gave the 3′-azido-N^6-substituted adenosine derivatives **4a–d** in high yields. Protection of two hydroxyl groups in **4a–d** with *t*-butyldimethylsilyl (TBS) group followed by catalytic hydrogenation of azido group with triphenylphosphine in aqueous ammonium hydroxide afforded the 3′-amino derivatives **5a–d**, respectively. Conversion of 3′-amino group into 3′-ureido group was accomplished by treating **5a–d** with chloroacetyl isocyanate followed by reacting with sodium methoxide to give the 3′-ureido compounds **6a–d**, respectively. Removal of TBS groups in **6a–d** with TBAF yielded the final nucleosides **2a–d**, respectively.

Binding affinities of all synthesized 3′-ureido derivatives at the wild-type A_3 AR as well as H272E mutant A_3 AR were measured using a radioligand binding assay. All compounds did not show any significant binding affinities to all subtypes of wild-type adenosine receptors. However, compound **2c** had no effect on the WT A_3AR but bound to the H272E mutant receptor with a K_i value of 0.22 μM.

In summary, we have synthesized the 3′-ureidoadenosine derivatives, among which compound **2c** formed a favorable electrostatic interaction only at the H272E mutant A_3 AR (neoceptor), not at the WT A_3AR. This selective ligand (neoligand)-neoceptor approach will expedite the development of clinically useful organ-specific compounds.

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