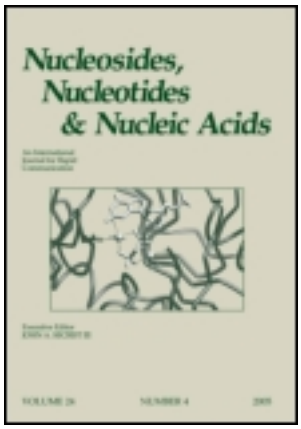

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Design and Synthesis of A_3 Adenosine Receptor Ligands, 3′-Fluoro Analogues of Cl-IB-MECA

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ABSTRACT

Synthesis of 3′-deoxy-3′-fluoro-N^6-substituted adenosines as bioisosteres of Cl-IB-MECA and their binding affinities to A_3 adenosine receptor are described.

Key Words: A_3 adenosine receptor; 3′-Deoxy-3′-fluoro-N^6-substituted adenosines.

From the structure-activity relationship study for N^6- and 5′-substituted adenosine derivatives as agonists at rat A_3 adenosine receptors,[1] 2-chloro-N^6-(3-iodobenzyl)-adenosine-5′-methylcarboxamide (Cl-IB-MECA) has been recognized to be one of the most selective agonists ($K_i = 1.0$ nM).[2] On the basis of its high binding affinity

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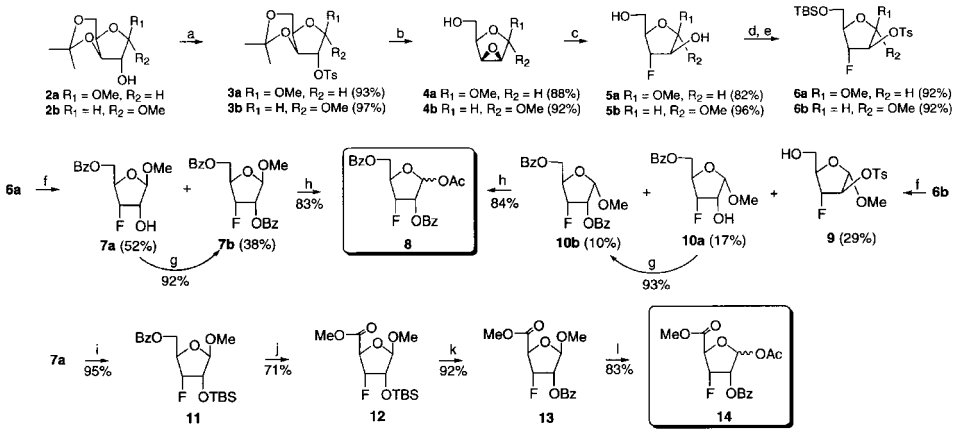
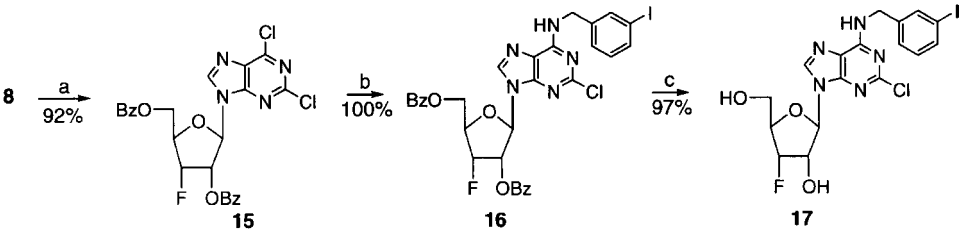


Scheme 1. Reagents and conditions: (a) TsCl; (b) i. 80% AcOH, ii. NaOMe, MeOH; (c) KHF_2, NaF, 1,2-ethylene glycol, reflux; (d) TBSCl; (e) TsCl, pyridine; (f) NaOBz, 18-crown-6, DMSO, reflux; (g) BzCl; (h) Ac_2O, AcOH, H_2SO_4; (i) TBSCI; (j) i. NaOMe, ii. $RuCl_3$, $NaIO_4$, $MeCN/CCl_4/H_2O$ (1/1/1.5), iii. DCC, DMAP, MeOH; (k) i. TBAF/AcOH, THF, ii. BzCl; (l) Ac_2O, AcOH, H_2SO_4.

to adenosine A_3 receptor, we wanted to determine whether 2′- or 3′-hydroxyl group of 2-Cl-IB-MECA is compatible with bioisosteric fluorine for the binding affinity to adenosine A_3 receptor. Herein, we report the synthesis of the new ligands, 3′-fluoro analogues to substitute the 3′-hydroxyl group of Cl-IB-MECA with bioisosteric fluorine and their evaluation for binding affinity to the adenosine A_3 receptor.

For the synthesis of 3′-fluoro analogues of Cl-IB-MECA, the glycosyl donors **8** and **14** were first synthesized according to Sch. 1, using regioselective opening[3] of **4a** and **4b** with fluoride anion as a key step.The synthesized glycosyl donors **8** and **14** were condensed with silylated 2,6-dichloropurine and silylated 2-chloro-N^6-(3-iodobenzyl) adenine and then transformed to the final nucleosides **17** and **19** according to Schs. 2 and 3, respectively.

The final nucleosides **17** and **19** were evaluated in radioligand binding assays[4–6] for affinity at rat brain A_1 and A_{2A} and human A_3 adenosine receptors. Compared to the high binding affinity ($K_i = 1.0$ nM) of Cl-IB-MECA to the A_3 adenosine receptor, binding affinities ($K_i = 75$ nM and 406 nM) of compounds **17** and **19** to A_3 receptor



Scheme 2. Reagents and conditions: (a) silylated 2,6-dichloropurine, TMSOTf; (b) 3-iodobenzylamine hydrochloride, EtOH; (c) NaOMe, MeOH.

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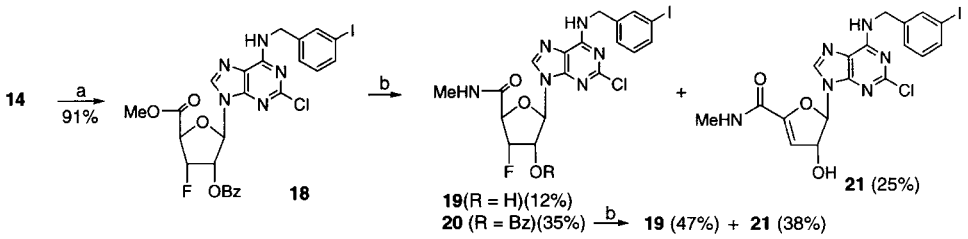

Scheme 3. Reagents and conditions: (a) silylated 2-chloro-N^6-(3-iodobenzyl)adenine, TMSOTf; (b) 2 M $MeNH_2$.

were remarkably decreased, but no binding affinity ($K_i > 10{,}000$ nM) to A_{2A} receptor and similar binding affinity to A_1 receptor were observed for both compounds. This biological result indicates that the bioisosteric fluorine can not substitute for the 3′-hydroxyl group in binding to A_3 and A_{2A} adenosine receptors, especially to A_{2A} receptor, but has little effect on binding to A_1 receptor.

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