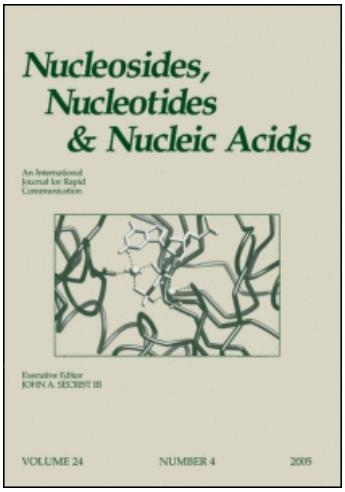

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Design and Synthesis of A_3 Adenosine Receptor Ligands, 2′-Fluoro Analogues of Cl-IB-MECA

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ABSTRACT

Synthesis of 2′-deoxy-2′-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; 2′-Deoxy-2′-fluoro-N^6-substituted.

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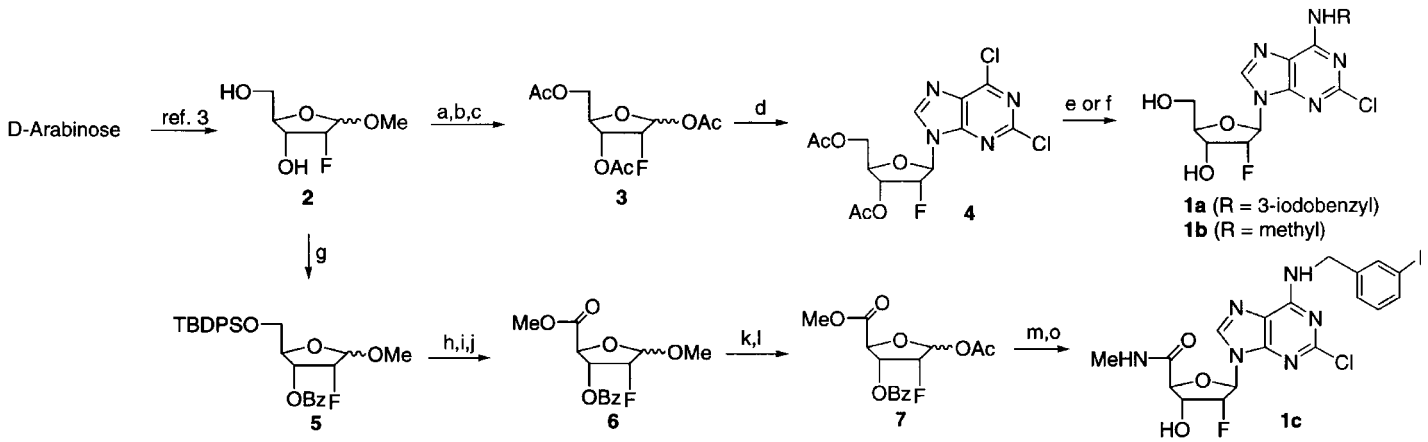

Scheme 1. Reagents: a) Ac_2O/pyridine, 84%; b) 90% aq. TFA, 77%; c) Ac_2O/Pyridine, 97%; d) silylated 2,6-dichloropurine, $SnCl_4$, 0°C, 85%; e) 3-iodobenzylamine, EtOH/TEA, 88%, then 1 M NaOMe (cal.), MeOH, 88%; f) 2 M $MeNH_2$, THF, 87%; g) TBDPSCl, Et_3N, then BzCl/pyridine, 68%; h) 1 M TBAF, AcOH, 92%; i) TPAP, NMO, 70%; j) Me_2SO_4, DBU, 85%; k) 80% TFA, 42%; l) Ac_2O/pyridine, 95%; m) silylated 2-chloro-N^6-iodobenzylamine, $SnCl_4$, 70%; o) $MeNH_2$, THF, 81%.

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Since adenosine A_3 receptor[1] was cloned from rat brain, a number of compounds have been synthesized and evaluated for their binding affinity to this receptor. Among these, 2-chloro-N^6-(3-iodobenzyl)-adenosine-5′-methylcarboxamide (Cl-IB-MECA)[2] has been found to be one of the most selective agonists (K_i = 1.0 nM) for rat adenosine A_3 receptor. Based on this high binding affinity of Cl-IB-MECA to adenosine A_3 receptor, we wanted to synthesize the 2′-deoxy-2′-fluoroadenosine analogues to determine if the 2′-hydroxyl group of Cl-IB-MECA is compatible with fluorine atom, based on the bioisosteric rationale and to compare their binding affinities with those of Cl-IB-MECA. In the present paper, we report the synthesis of the new ligands, 2′-deoxy-2′-fluoroadenosine analogues from D-arabinose and their binding affinities to different adenosine receptors.

The synthesis of the 2′-deoxy-2′-fluoroadenosine analogues, **1a**–**1c** of Cl-IB-MECA started from D-arabinose as shown in Sch. 1. D-Arabinose was converted to 2-deoxy-2-fluororibose derivative **2** according to the known procedure.[3] Compound **2** was converted to the glycosyl donor **3** by acetylation, acid-catalyzed hydrolysis and acetylation. Condensation of **3** with silylated 2,6-dichloropurine in the presence of $SnCl_4$ afforded the desired nucleoside **4** which was converted to the final deprotected congeners **1a** and **1b**, by treating with 3-iodobenzyl amine followed by sodium methoxide or with methylamine, respectively. For the synthesis of 4′-carboxamide derivative **1c**, compound **2** was successively treated with TBDPSCl and benzoyl chloride to give **5**. Silyl deprotection of **5** followed by conversion of the resulting alcohol to the methyl ester produced **6**. Treatment of **6** with 80% trifluoroacetic acid followed by acetylation produced another glycosyl donor **7**, which was converted to the final 4-carboxamide **1c** using the similar method used above.

The final nucleosides **1a**–**1c** were evaluated in radioligand binding assays[4–6] for affinity at rat brain A_1 and A_{2A} and human A_3 adenosine receptors. Compounds **1a**–**1c** did not exhibit any binding affinity to human A_3 receptor up to 1 μM of K_i unlike high binding affinity (K_i = 1.0 nM) of Cl-IB-MECA to A_3 adenosine receptor, indicating that 2′-hydroxyl group of Cl-IB-MECA is essential for binding to the receptor. Binding affinities of compounds **1a**–**1c** to rat A_1 and A_{2A} receptors were also remarkably decreased, emphasizing the importance of the 2′-hydroxyl group to these receptors. This biological result indicates that the bioisosteric fluorine can not substitute for the 2′-hydroxyl group in binding to either A_1, A_{2A}, or A_3 adenosine receptors.

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