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Design and Synthesis of A₃ Adenosine Receptor Ligands, 2'-Fluoro Analogues of CI-IB-MECA

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Design and Synthesis of A₃ 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 A₃ adenosine receptor are described.

Key Words: A₃ adenosine receptor; 2'-Deoxy-2'-fluoro-N⁶-substituted.

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Scheme I. Reagents: a) Ac₂O/pyridine, 84%; b) 90% aq. TFA, 77%; c) Ac₂O/Pyridine, 97%; d) silylated 2,6-dichloropurine, SnCl₄, 0°C, 85%; e) 3-iodobenzylamine, EtOH/TEA, 88%, then 1 M NaOMe (cal.), MeOH, 88%; f) 2 M MeNH2, THF, 87%; g) TBDPSCI, Et3N, then BzCl/pyridine, 68%; h) 1 M TBAF, AcOH, 92%; i) TPAP, NMO, 70%; j) Me2SO4, DBU, 85%; k) 80% TFA, 42%; l) Ac2O/pyridine, 95%; m) silylated 2-chloro-N⁶-iodobenzylamine, SnCl₄, 70%, o) MeNH₂, THF, 81%.

2'-Fluoro Analogues of Cl-IB-MECA

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 Darabinose 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 SnCl₄ 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'-carbox-amide 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 A₁ and A_{2A} and human A₃ adenosine receptors. Compounds **1a–1c** did not exhibit any binding affinity to human A₃ receptor up to 1 μ M of K_i unlike high binding affinity (K_i = 1.0 nM) of Cl-IB-MECA to A₃ 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 A₁ 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 A₁, A_{2A}, or A₃ adenosine receptors.

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REFERENCES

 Daly, J.W.; Jacobson, K.A. Adenosine receptors: Selective agonists and antagonists. In Adenosine and Adenine Nucleotides: From Molecular Biology to Integrative Physiology; Bellardinelli, L., Pelleg, A., Eds.; Kluwer: Norwell, MA, 1995; 157–166.

- 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 adenosine receptors. J. Med. Chem. **1994**, *37*, 3614–3621.
- Thomas, H.J.; Tiwari, K.N.; Clayton, S.J.; Secrest, III J.A.; Montgomery, J.A. Synthesis and biologic activity of purine 2'-deoxy-2'-fluoro-ribonucleosides. Nucleosides Nucleotides 1994, 13, 309–323.
- 4. Olah, M.E.; Gallo-Rodriguez, C.; Jacobson, K.A.; Stiles, G.L. ¹²⁵I-4-Aminobenzyl-5'-N-methylcarboxamideadenosine, A high affinity radioligand for the rat A₃ adenosine receptor. Mol. Pharmacol. **1994**, *45*, 978–982.
- Jarvis, M.F.; Schutz, R.; Hutchison, A.J.; Do, E.; Sills, M.A.; Williams, M. [³H]CGS 21680, A selective A₂ adenosine receptor agonist directly labels A₂ receptors in rat brain. J. Pharmacol. Exp. Ther. **1989**, *251*, 888–893.
- Schwabe, U.; Trost, T. Characterization of adenosine receptors in rat brain by (-)[³H]N⁶-phenylisopropyladenosine. Naunyn-Schmiedeberg's Arch. Pharmacol. **1980**, *313*, 179–187.

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