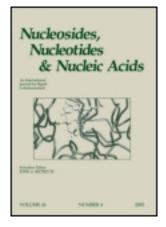
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Design and Synthesis of A₃ Adenosine Receptor Ligands, 3'-Fluoro Analogues of CI-IB-MECA

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Design and Synthesis of A₃ 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 A₃ 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 A₃ 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 ($K_i = 1.0 \text{ nM}$).^[2] On the basis of its high binding affinity

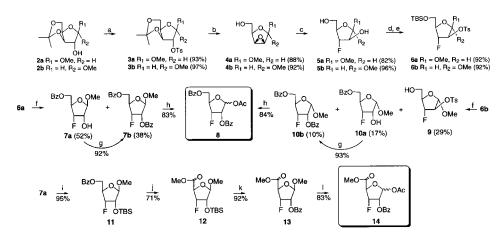
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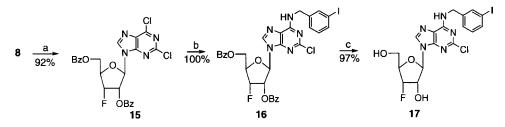


Scheme 1. Reagents and conditions: (a) TsCl; (b) i. 80% AcOH, ii. NaOMe, MeOH; (c) KHF₂, NaF, 1,2-ethylene glycol, reflux; (d) TBSCl; (e) TsCl, pyridine; (f) NaOBz, 18-crown-6, DMSO, reflux; (g) BzCl; (h) Ac₂O, AcOH, H₂SO₄; (i) TBSCl; (j) i. NaOMe, ii. RuCl₃, NalO₄, MeCN/CCl₄/H₂O (1/1/1.5), iii. DCC, DMAP, MeOH; (k) i. TBAF/AcOH, THF, ii. BzCl; (l) Ac₂O, AcOH, H₂SO₄.

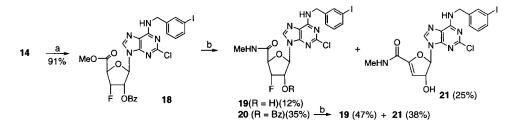
to adenosine A_3 receptor, we wanted to determine whether 2'- or 3'-hydroxyl group of 2-Cl-IB-MECA is compatible with bioisosteric fluorine for the binding affinity to adenosine A_3 receptor. Herein, we report the synthesis of the new ligands, 3'-fluoro analogues to substitute the 3'-hydroxyl group of 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 A₁ and A_{2A} and human A₃ adenosine receptors. Compared to the high binding affinity ($K_i = 1.0$ nM) of Cl-IB-MECA to the A₃ adenosine receptor, binding affinities ($K_i = 75$ nM and 406 nM) of compounds **17** and **19** to A₃ receptor



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



Scheme 3. Reagents and conditions: (a) silylated 2-chloro- N^6 -(3-iodobenzyl)adenine, TMSOTf; (b) 2 M MeNH₂.

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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REFERENCES

- Jacobson, K.A.; van Galen, P.J.M.; Williams, M. Adenosine receptors: pharmacology, structure-activity relationships, and therapeutic potential. J. Med. Chem. 1992, 35, 407–422.
- 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.
- Mikhailopulo, I.A.; Poopeiko, N.E.; Prikota, T.I.; Sivets, G.G.; Kvasyuk, E.I.; Balzarini, J.; De Clercq, E. Synthesis and antiviral and cytostatic properties of 3'-deoxy-3'-fluoro- and 2'-azido-3'-fluoro-2',3'-dideoxy-D-ribofuranosides of natural heterocyclic bases. J. Med. Chem. 1991, 34, 2195–2202.
- Olah, M.E.; Gallo-Rodriguez, C.; Jacobson, K.A.; Stiles, G.L. ¹²⁵I-4-aminobenzyl-5'-N-methylcarboxamidoadenosine, a high affinity radioligand for the rat A₃ adenosine receptor. Mol. Pharmacol. **1994**, *45*, 978–982.
- Jarvis, M.; 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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