2-(1,2,3-TRIAZOL-1-YL) N^6-CH_3-SUBSTITUTED ADENOSINE DERIVATIVES: HIGHLY POTENT AND SELECTIVE A_3 RECEPTOR LIGANDS

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A series of 2-substituted N^6-methyl derivatives of adenosine has been synthesized and evaluated for its affinity and selectivity at the human A_3 adenosine receptor (A_3AR). All these 2-alkynyl (**1**–**3**) and 2-(1,2,3)-triazol-1-yl (**5**–**13**) derivatives showed A_3AR affinity in the low nanomolar range and a very high A_{2A}/A_3 and a moderate to high A_1/A_3 selectivity ratio.

INTRODUCTION

Adenosine receptors (AR) are G-protein coupled receptors. Among the four AR-subtypes, i.e. A_1, A_{2A}, A_{2B} and A_3AR, the A_3AR is the most recently identified[1]. Many cells express several AR subtypes, although in different densities. In humans the highest A_3AR densities are found in lung, liver and cells of the immune system (neutrophils, eosinophils, T-lymphocytes)[2]. The A_3ARs are coupled to G_i proteins and, therefore, inhibit adenylate cyclase leading to a decrease in intracellular levels of cAMP. A_3AR agonists also act as cardio- and neuroprotective agents and attenuate ischemic damage[2]. A_3AR antagonists might be useful for the treatment of glaucoma[2]. Cristalli et al. discovered that introducing a methyl group at the N^6 position of 2-alkynyl adenosine derivatives increases the affinity for the human A_3AR and enhances the A_3AR selectivity significantly[3]. Zablocki et al. have shown that introduction of a methyl group at the N^6 position of A_{2A}AR selective 2-(1*H*-pyrazol-1-yl)adenosine analogues induces an increase in the affinity and selectivity for the human A_3AR [4]. Based on these results, the goal of this study was to continue the exploration of the 2-alkynyl adenosine derivatives and to investigate the affinity and selectivity of 4-substituted 2-(1,2,3-triazol-1-yl)adenosine derivatives.

RESULTS AND DISCUSSION

The 2-alkynylated derivatives (**1**–**3**) were prepared according to Cristalli et al.[3] The triazole derivatives were prepared by click chemistry (Scheme 1)[5]. The use of a water/butanol mixture as a solvent for the 1,3-cycloaddition

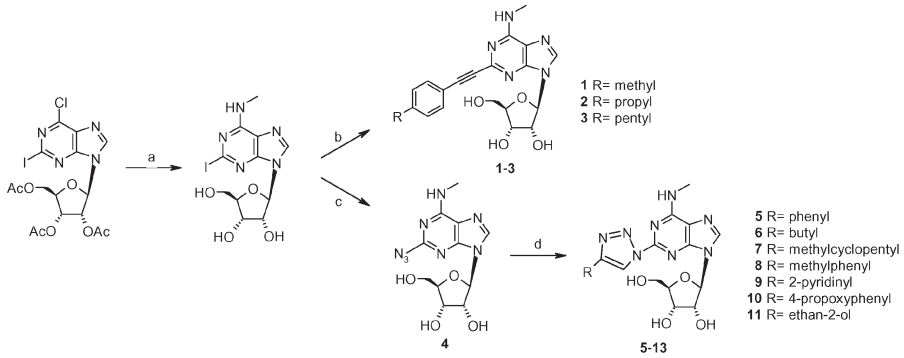
reaction allowed simple isolation of the desired compounds, which (generally) precipitated from this reaction medium.

Cristalli et al.[3] showed that N^6-methyl-2-phenylethynyladenosine has an A_3AR affinity in the low nanomolar range (K_i = 3.4 nM). From this study it is possible to conclude that a slightly higher affinity (K_i = 2.3 nM) is obtained when a methyl group (**1**) is introduced in *para*-position of the phenyl ring. Extending the size of the alkyl chain resulted in a decrease in affinity (**2**–**3**).

To our surprise, the azide precursor **4** showed a very good A_3AR binding affinity (K_i = 8.0 nM). ^{1}H and ^{13}C NMR in DMSO-d_6 proved the presence of a tautomeric form (17%) of the 2-azido adenosine derivative **4** due to a spontaneous cyclization resulting in a fused tetrazole ring.

All triazole compounds showed A_3AR affinity in the low nanomolar range (e.g. **7** has a K_i = 2 nM) and a very high A_{2A}/A_3 and a moderate to high A_1/A_3 selectivity ratio.

These 2-(1,2,3-triazol-1-yl)-N^6-methyl adenosine analogues constitute a new class of highly potent and selective A_3AR ligands and might be useful as pharmacological tools.



SCHEME 1

a) i: $CH_3NH_3^+Cl^-$, Et_3N, EtOH, ii: 7N NH_3 in MeOH; b) CuI, $(Ph_3P)_2PdCl_2$, alkyne, Et_3N, DMF; c) $CuSO_4 \cdot 5H_2O$, sodium ascorbate, L-proline, Na_2CO_3, H_2O:tBuOH 1:1, 60 °C; d) $CuSO_4 \cdot 5H_2O$, sodium ascorbate, alkyne, H_2O:tBuOH 3:1, rt

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