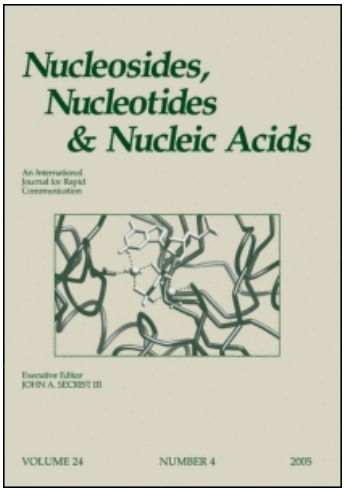

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Lead Optimization of N^6-Cyclopentyl-3'-amido-3'-deoxyxylofuranosyladenines as Adenosine A_1 Receptor Antagonists

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LEAD OPTIMIZATION OF N^6-CYCLOPENTYL-3'-AMIDO-3'-DEOXY-XYLOFURANOSYLADENINES AS ADENOSINE A_1 RECEPTOR ANTAGONISTS

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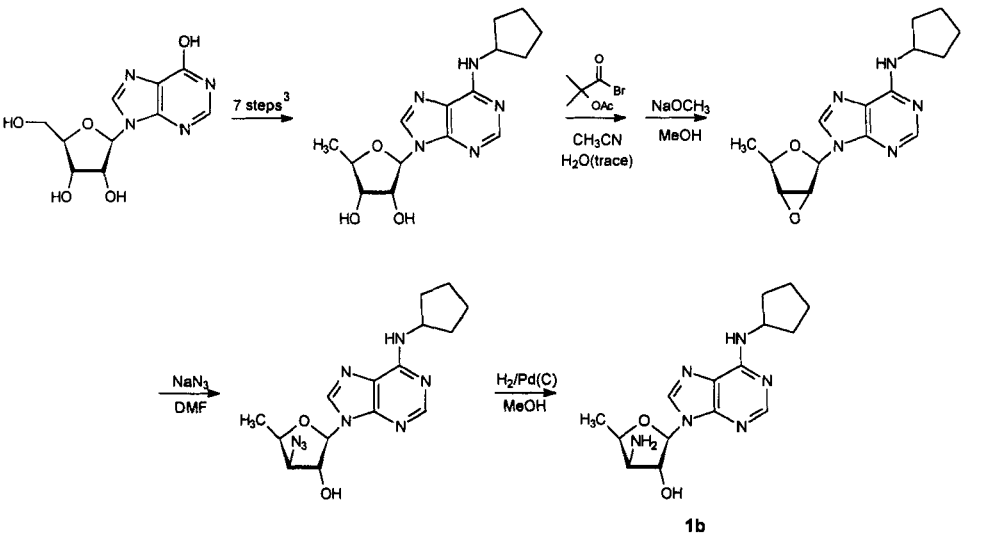
ABSTRACT : Strategies toward the further lead optimization of N^6-cyclopentyl-3'-amido-3'-deoxyxylofuranosyladenosines as adenosine A_1 receptor antagonists including the synthesis of the 5'-deoxy-analogues and a practical method for parallel amidation are presented.

The effects of numerous modifications of the adenosine scaffold on affinity and intrinsic activity towards adenosine A_1 receptors are well documented. Most modifications at the 2' and 3' positions of the sugar ring or inversion of chiral centers at these positions are found to abolish A_1 receptor binding.

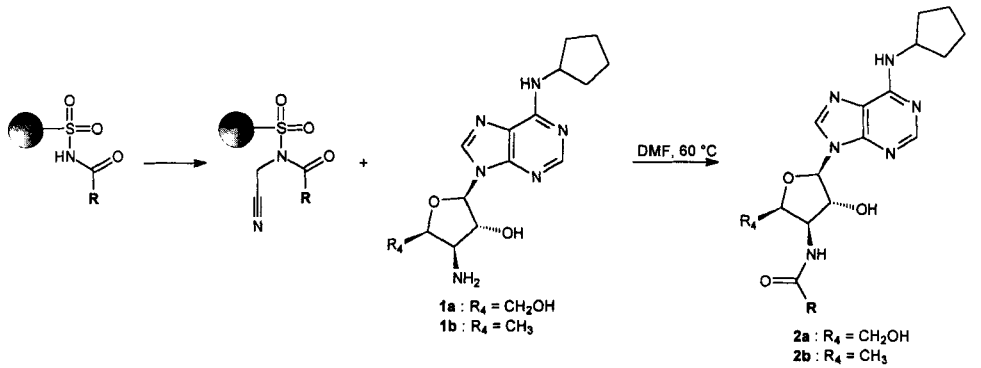
Recently we demonstrated that substitution of the ribofuranosyl moiety of N^6-cyclopentyladenosine (CPA) for a 3'-amido-3'-deoxyxylofuranosyl moiety results in potent and selective A_1 receptor antagonists.[1]

Here we describe our efforts towards further lead optimization. First we developed a route to prepare the 5'-deoxy analogue of the amine synthon of **1**. Such modification should avoid our new analogues to be susceptible to phosphorylation and incorporation into DNA. It was achieved in 4 steps from N^6-cyclopentyl-5'-deoxyadenosine (see Scheme 1). Subsequently, we set up a solid-phase assisted synthesis designed for the acylation of the weakly nucleophilic 3'-amino group of 9-(3'-amino-3'-deoxyxylofuranosyl)-N^6-cyclopentyladenine[1] (**1a**) and its 5'-deoxy analogue (**1b**). This was achieved by coupling the selected acids to the Kenner safety catch linker improved by Ellman et al. using standard amide bond forming procedures.[2] Cyanomethylation of

the linker resulted in highly reactive polymer bound acids that could easily be coupled with the aforementioned amines (see Scheme 2).



Scheme 1 △, Scheme 2 ▽



Filtration of the beads and removal of the solvent afforded 3'-amido-3'(,5')-(*di*)deoxyxylofuranosyl CPA analogues (**2a,b**) in high yield ready for biological testing.

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