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Synthesis and Antimalarial Activity of Novel *N*⁶-Substituted Adenosine Derivatives

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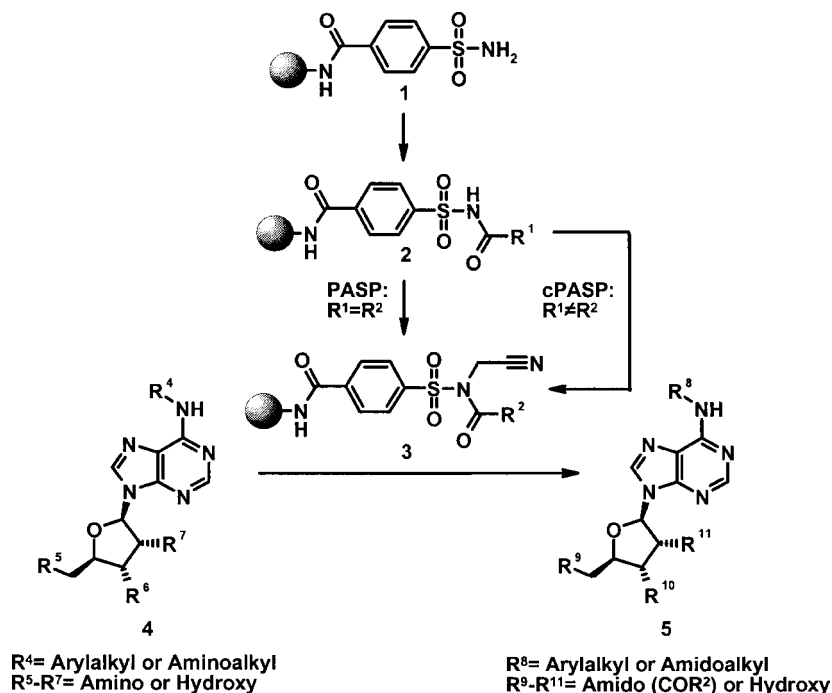
Substituted adenosine analogues were previously obtained as hits in a screening program focussed on the identification of novel drug leads for antimalarial chemotherapy.^[1]

Continuing these efforts, we have investigated the in vitro antimalarial activity of a new series of adenosine derivatives **5** combining available information on favourable substitution patterns.

The results show that e.g., *N*⁶-(1-naphthylmethyl)-5'-deoxy-5'-(amido)-adenosines as well as *N*⁶-(4-phenylbenzyl)-5'-deoxy-5'-(amido)adenosines display significant activity against the malaria causing parasites, with the sterically demanding bisubstituted species reported being active in most cases in the low-micro molar range.

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Scheme 1. Scaffold derivatization yielding a library of adenosine derivatives **5**.

The novel compounds were obtained applying an efficient convergent polymer-assisted solution phase (cPASP) synthesis protocol. The nucleoside building blocks were assembled in solution via multi-step synthesis and treated with an excess of polymer-supported carboxylic acid equivalents in parallel leading to chemoselective, practically quantitative conversion of the amines to the desired amides, as described.^[2,3]

Work-up consisted of filtration and removal of the solvent, yielding the target compounds in sufficient purity, ready for biological evaluation.

In addition to amino deoxy modification of the ribose moiety, *N*⁶-alkylamino functionalised derivatives could be shown to be distinctly suited for the introduction of diversity elements into the molecular regions of interest.

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