KL01 Modified and Decorated Adenosines Targeted at ATP/NAD Recognition Motifs

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In each cell, proteins with many different functions use adenosine and its derivatives as ligands. Of course, adenosine is present in nucleic acids such as leucyl-tRNA. The economy by which a single active site of leucyl-tRNA synthetase accommodates two distinct substrates in a proof reading process is critical to the fidelity of protein synthesis. In this respect, synthetic analogues of labile pre- and post-transfer editing substrates proved to be valuable molecular tools for the investigation of mechanistic aspects [1]. Related stabilized 2′-amido-2′-deoxyadenosine nucleotides might find use as molecular probes for the investigation of adenylyl cyclases [2]. Moreover, the adenosine scaffold might be regarded as a privileged structure in drug discovery. Recently, adenosine derivatives have been reported to interact with novel and highly relevant drug targets such as poly(ADP-ribose) polymerase-1 and adenylation enzymes required for siderophore biosynthesis of the mycobactins. Ribose-modified N^6-substituted nucleosides are under investigation as ribonucleotide reductase inhibitors. The endogenous occurrence and cytokinin activity of N^6-(2,4-dimethoxybenzyl)adenosine, first described by our group in 2002, meanwhile has been elucidated. Due to the fact that adenosine-binding motifs are found in many ATP-, CoA-, NAD-, NADP- and FAD-dependent proteins; modified and decorated adenosines are prone to exert multiple interactions. Because pathogenic protozoa such as *P. falciparum* and *T. brucei ssp.* rely heavily on the salvage of purine nucleosides from the bloodstream of their host, such compounds are of interest as antiplasmodial and antitrypanosomal agents with numerous molecular targets [3, 4]. The aminopurine nucleoside cordycepin is a potent trypanocide in vitro. The uptake of cordycepin is mediated by protozoal purine transporters (P1 and P2), thus an elegant strategy to attain selective toxicity even in case of interaction with multiple adenosine related targets might be achievable. Nevertheless, cordycepin only shows trypanocidal activity in vivo when coadministered with an adenosine deaminase inhibitor. Thus, the development of bioactive and metabolically stable adenosine analogues is an attractive research goal.

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