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Purine and Pyrazolopyrimidine Derivatives
Design and Synthesis of Chemical Tools for Biological Applications

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Abstract

Purines can be found in a multitude of naturally occurring compounds with a range of functions. This thesis describes the design and synthesis of purines and structurally related pyrazolopyrimidine derivatives intended for biological applications.

Pyrazolopyrimidines are structurally related to purines and are used as scaffolds for ATP-competitive protein kinase inhibitors. A pyrazolopyrimidine based selective inhibitor of receptor tyrosine kinase REarranged during Transfection (RET), a protein kinase involved in cell development, was modified with a photolabile protecting group. The modification allowed for photocontrolled release of the inhibitor. Photodependent inhibition of RET was demonstrated in both a biochemical assay and in a cell based RET-assay. The utility of the caged inhibitor was demonstrated in transgenic zebrafish embryos by demonstrating the effect of photocontrolled RET-inhibition on motoneuron development. In addition, it was shown that the timing of irradiation was critical for motoneuron development.

The purine structure is a key constituent of aminoacyl-adenosine monophosphate (aa-AMP), an intermediate in protein biosynthesis. Stable mimics of aa-AMP could have potential as inhibitors of protein biosynthesis, a mechanism identified as a target for antiinfectives. A series of 8-(triazolyl)purines was synthesized as aa-AMP mimics. In addition, their photophysical properties were studied to evaluate their potential as fluorescent probes. Unexpectedly, these compounds displayed very low quantum yields in contrast to previous data for similar structures.

Protein-protein interactions (PPIs) are ubiquitously present in cells, have a central role in cell signaling and have been identified as interesting drug targets. The α-helix secondary structure has been identified as a central element in many PPIs. In this project, 2,6,9-substituted 8-(triazolyl)purines were evaluated as α-helix mimetics and inhibitors of the p53/MDM2 PPI. A series of compounds were synthesized and two of the compounds exhibited micromolar activity against MDM2. In addition, a bromination procedure for 8-bromination of purines was developed. Bromination with pyridinium tribromide at room temperature resulted in high yields for electron rich 2,6,9-substituted purines. The procedure is a convenient alternative to elemental bromine for this transformation. The fluorescent properties of the compounds were also measured. One of the compounds showed a high quantum yield of 51% and several compounds had quantum yields between 5-10%. The fluorescent properties could be useful for example to study intracellular localization of bioactive compounds.

Keywords: Purine, Pyrazolopyrimidine, Photoactivation, Caged compounds, Protein kinases, Protein-protein interactions, Inhibitors, Fluorescence.