Synthesis of novel hetero-fused 7-deazapurine nucleosides and nucleotides with potential biological activity or for modifications of DNA and RNA

In medicinal chemistry, 7-deazapurine ribonucleosides are important analogues to purine nucleosides and represent a privileged scaffold in the research for new treatments against cancer, leukemia, and diseases caused by viruses. This thesis discusses the synthesis of new heteroaryl-fused 7-deazapurine ribonucleosides and reports on the biological activity of the target nucleosides against different cancer cell lines and viruses *in vitro*.

In the first part of the thesis, the focus lies on the comparison of strategies for the synthesis of different methylpyrazolo-fused 7-deazapurine ribonucleosides. The tricyclic nucleobase was furnished by (i) a six-step classical heterocyclization approach starting from 5-chloro-1-methyl-4-nitropyrazole, and by (ii) a three-step cross-coupling and cyclization approach starting from the zincated 4,6-dichloropyrimidine and 5-iodo-1-methylpyrazole. Both strategies resulted in comparable yields overall. Then, three different glycosylation methods were explored to give the *β*-anomeric nucleoside intermediate. Only the Vorbrüggen glycosylation yielded the intermediate as a pure *β*-anomer. Derivatization and deprotection gave a series of eight different pyrazolo-fused deazapurine ribonucleosides, some of which were weakly fluorescent. Methyl, amino, and methylsulfanyl derivatives exerted submicromolar cytotoxic effects *in vitro* against a panel of cancer and leukemia cell lines as well as antiviral effects against the Hepatitis C virus in the replicon assay.

In the second part of the thesis, the focus lies on the systematic study of the C-H functionalization of 5-membered heterocycles through the formation of different sulfonium salts and their use as an alternative substrate to heteroaryl iodides in the Negishi cross-coupling reaction with zincated 4,6-dichloropyrimidine. Twelve different 5-membered heterocycles bearing one or two heteroatoms were subjected to thianthrenation and dibenzothiophenation with thianthrene *S*-oxide (TT=O) and dibenzothiophene *S*-oxide (DBT=O), respectively. For both sulfoxides, only the corresponding aryl sulfonium salts with pyrrole, 1-methylpyrrole, thiophene, and 1-methylpyrazole were formed. The Negishi cross-coupling between the methylpyrazol-4-yl-thianthrenium salt and zincated 4,6-dichloropyrimidine did not yield the desired pyrazolyl pyrimidine cross-coupling product. The same reaction was performed also with the dibenzothiophenium salts but only the corresponding thiophene derivative gave the desired cross-coupling product.

In the third part of the thesis, the focus lies on the synthesis of different quinolino-fused 7-deazapurine ribonucleosides and their application in biochemistry. The synthesis of the tetracyclic nucleobase was based on the cross-coupling and cyclization approach. Different cyclization methods were explored and compared. The Vorbrüggen glycosylation gave the desired nucleoside intermediate as pure *β*-anomer. Derivatization and deprotection gave a series of seven different quinolino-fused ribonucleosides which showed moderate to weak cytotoxic activity against cancer cell lines and fluorescent properties. The amino derivative was then triphosphorylated and, as an ATP analogue, successfully incorporated into RNA using *in vitro* transcription with T7 RNA polymerase.