# Abstract

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Organic And Bioorganic Chemistry

Candidate: Jana Sedláková

Supervisors: Dr. Fabrizio Pertusati

doc. PharmDr. Jaroslav Roh, Ph.D.

Title of diploma thesis: Synthesis of phosphoramidate prodrugs „ProTides“ as novel potential therapeutic agents for the treatment of congenital disorders of glycosylation and mitochondrial DNA depletion syndrome

At the present time, no effective treatment is available neither for the most of the congenital disorders of glycosylation (CDGs) nor the mitochondrial DNA depletion syndrome (MDS). Regarding the CDG therapy, D-mannose-1-phosphate (Man-1-P) offers considerable pharmacological potential to improve the pathological patterns in patients affected by phosphomannomutase 2 deficiency (PMM2-CDG), similarly as *N*-acetyl-D-mannosamine-6-phosphate (ManNAc-6-P) in case of GNE myopathy (GNEM). Administration of selected deoxyribonucleotides was proposed as a potential pharmacological strategy for the treatment of MDS. Unfortunately, the problematic membrane penetration of such polar molecules reduces their effect and limits their clinical application. Hydrophobic, membrane permeable derivatives of the sugar monophosphates and nucleotides, might represent more efficient potential therapeutics for CDGs and MDS, respectively.

In this work, various phosphoramidate prodrugs (ProTides) of Man-1-P, ManNAc-6-P and their peracetylated derivatives were synthesized. Two different synthetic approaches were used: a) coupling of the desired substrate with previously prepared phosphorochloridate in the presence of *t*BuMgCl, b) coupling of the appropriate substrate with the phosphorochloridate using *N*-methylimidazole (NMI). The ProTides were successfully prepared via the Grignard methodology, nevertheless, the NMI method did not provide the desired phosphoramidates even after several attempts to improve the reaction conditions.

In order to investigate the bioactivation of ProTides, an enzymatic experiment was carried out with one of the phosphoramidate derivatives synthesised.

The ProTide approach was also applied to 6-methoxyguanosine monophosphate with the aim to prepare potentially effective prodrugs for MDS treatment. Two derivatives were fruitfully synthetized via the nucleoside coupling with various (aryl) (*p*-nitrophenyl) phosphoramidates in the presence of *t*BuMgCl.