ABSTRACT

Modificated nucleosides, nucleotides and nucleobases have attracted special interest among many research groups. The main reason for this is that large number of such compounds are currently undergoing evaluation as antiviral and anticancer agents with wide biological activity. Unfortunately such activity could also cause many undesirable side effects. For this reason it is still a challenge to develop analogues that can be used as therapeutic drugs while minimizing side effects. In general such modifications can assist in several ways, including modification of the heterocyclic base and changes at the furanose ring. It has been shown that structural changes in such analogues could be fulfill in both simple and more complex transformations. Undoubtedly 1,3-dipolar cycloaddition which is a general and widely applied method for the preparation of five-membered heterocycles, could be applied in synthetic route of nucleosides analogues preparation. The formation of a five-membered isoxazolidine ring as a result of cycloaddition between nitrones and dipolarophile double bond was the basis of the synthetic part in herein doctoral dissertation. *N,O*-nucleosides possessing an isoxazolidinyl moiety which mimics ribofuranose, have recently attracted much attention. These compounds have displayed potent antitumoral, cytotoxic and anti-HIV activity and they exert this bioactivity by complete reversible inhibition of reverse transcriptase, acting as viral DNA chain terminators or acting as antimetabolites. Moreover the introduction of fluorine atom or fluorinated group into biologically active compounds often induces strong modifications in their chemical and biological properties by increasing lipophilicity and metabolic stability of modified molecules.

Therefore first research goal of herein doctoral project was to synthesize new trifluoromethyl-substituted isoxazolidynyl derivatives of nucleobases in which trifluoromethyl group was introduced to the target structure thru two separate synthetic strategies. In first approach *N*-fluorovinyl derivatives of adenine react with *N*-alkilomethylenenitrones and in second approach *N*-vinylnucleobases react with prochiral *N*-alkyltrifluorometylnitrones. Isoxazolidines derived from fluorinated *N*-vinyladenine **1** (figure 1) were obtained with coplete regioselectivity and the reactions proceeded with full transfer of the dipolarophile geometry to the cycloadduct. In case of cycloaddition reactions between *N*-alkyltrifluomethylnitrones with *N*-vinyl adenine obtained isoxazolidynyl products **2** (figure 1) show very high

diastereoselectivity to mixtures of stereoisomers *cis* and *trans*. It also has been shown that mentioned diastereoselectivity was strongly determined by steric factor and definitely was depend on the character of *N*-alkyl substituent of nitrone molecule. Due to biological activity is often dependent of the intramolecular phosphorylation ability of the nucleoside analogue, further investigations on the synthesis of fluorinated derivatives, possessing also hydroxymethyl or phosphonate groups in the isoxazolidynyl moiety were taken. Unfortunately all attempts to phosponate derivatives synthesis were unsuccessful, so the scope of the study has been extended to successful synthesis of $C^{2'}$-functionalized fluorinated homonucleoside analogues **3** and **4** (figure 1) and their ester precursors **5**, **6** and **7** (figure 1).

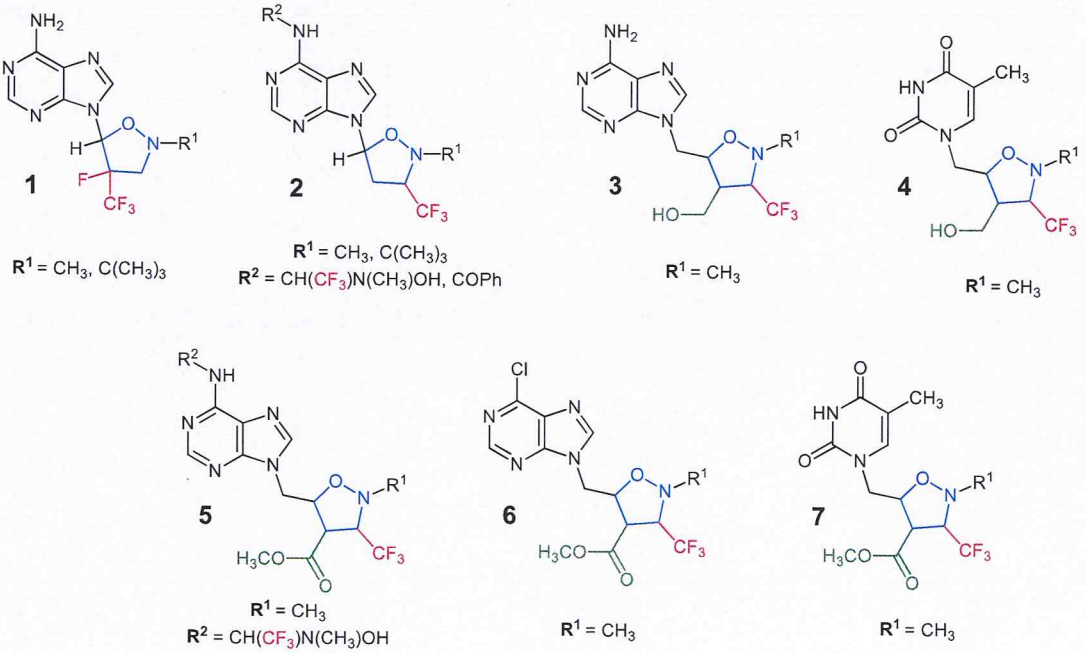

Figure 1. Structures of obtained fluorinated isoxazolidinyl nucleoside and homonucleoside derivatives

As a result of further research work on 1,3-dipolar cycloaddition of nitrones to fluorinated *N*-vinyl pyrimidine nucleobases, a series of new fused isoxazolidines were additionally prepared from reactions between 1,3-dimethyluracil derivatives with *N*-alkylmethylenenitrones **8** (figure 2). NMR analysis of obtained compounds performed in TFA-*d* and in $CDCl_3$ over a wide range of temperatures indicates the slow nitrogen inversion process, which was revealed by presence of two invertomers for all isoxazolidines in NMR spectra.

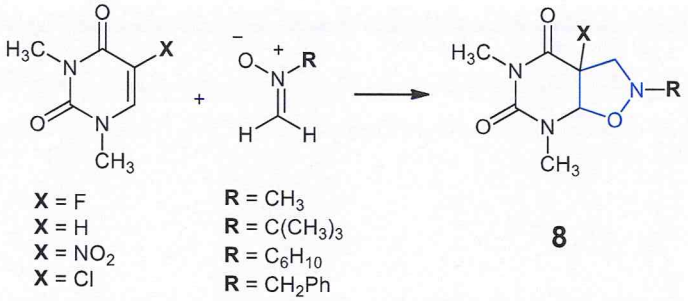

Figure 2. Synthesis of fused isoxazolidynyl derivatives of substituded uracil

In order to rationalize the presence of two invertomers, the theoretical studies of the possible structures of *N*-methyl and *N-tert*-butyl derivatives were carried out. Calculations were aimed to find an optimized geometry of two invertomers and consequently a TS structure between them in order to compare the theoretical energy barrier of nitrogen inversion in studied systems, to similar literature examples. As it has beed shown, the proper inversion of nitrogen proceeds at more complex path that was originally assumed, involving the conformational factors of fused isoxazolidine ring.