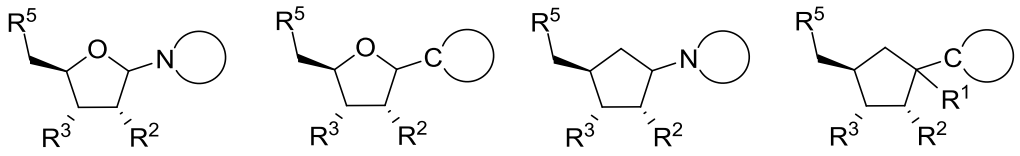
Synthesis of new carbocyclic C-nucleoside analogs

Prashant Khirsariya[*1, 2], Lukáš Maier[1, 2] and Kamil Paruch[1, 2]

[1]*Masaryk University, Faculty of Science, Department of Chemistry, Kamenice 5/A8, 623 00 Brno, Czech Republic*
[2]*International Clinical Research Center, St. Anne's University Hospital Brno, Pekarska 53, 656 91 Brno, Czech Republic*
**prashant@mail.muni.cz*

The chemical modification of nucleosides has been – and will continue to remain – a major research topic in medicinal chemistry. Classical nucleoside analogs (**A**) constitute an important class of biologically active compounds, which has promising antiviral and anticancer properties[1]. Since they possess labile hemiaminal motif, extensive effort has been invested into the identification of more stable substances while preserving the biological activity, e.g. C-nucleosides (**B**) or carbocyclic N-nucleosides (**C**).



It is conceivable that, at least in some cases, carbocyclic C-nucleosides (**D**) might be even more robust versions of nucleoside analogs **B** and **C.** In addition, installation of certain substituents (e.g. R^1 = OH) is meaningful only in this class as this would lead to chemically unstable ketals and aminals in the series **A**, **B** and **C**. However, analogs **D** are quite rare and most published syntheses only produced single target compounds[2].

Our recently developed flexible synthesis of compounds **D** enables selective manipulation of individual positions around the cyclopentane ring, including highly diastereoselective installation of carbo - and heterocyclic substituents at position 1´, orthogonal functionalization of position 5´, and efficient inversion of stereochemistry at position 2´, which are important for subsequent SAR development. Some of the newly prepared carbocyclic C-nucleosides inhibit human DNA glycosylases.

References:

1 a) *Modified Nucleosides in Biochemistry*, *Biotechnology and Medicine*; Ed.: P. Herdewijn, Wiley-VCH, **2008**. (b) *Chemical Synthesis of Nucleoside Analogues*; Ed.: P. Merino, Wiley, **2013**.

2 a) Just, G.; Reader, G. *Tetrahedron Lett.* **1973**, *14*, 1524. b) Just, G.; Kim, S. *Tetrahedron Lett.* **1976**, *17*, 1063. c) Just, G.; Ouellet, R. *Can. J. Chem.* **1976**, *54*, 2925. d) Chun, B. K.; Song, G. Y.; Chu, Ch. K. *J. Org. Chem.* **2001**, *66*, 4852. e) Rao, R. J.; Schinazi, R. F.; Chu, Ch. K. *Bioorg. Med. Chem.* **2007**, *15*, 839. f) Maier, L.; Hylse, O.; Nečas, M.; Trbušek, M.; Arne, M. Y.; Dalhus, B.; Bjoras, M.; Paruch, K. *Tetrahedron Lett*., **2014**, *55*, 3713.