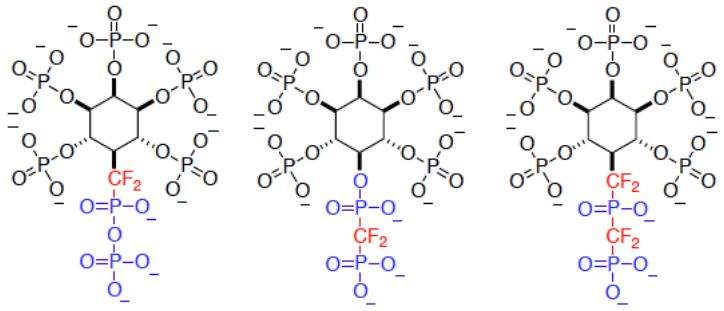
Development of Non-Hydrolysable Analogs of Phosphoinositol Polyphosphates

Igor Pavlović[a], Henning Jessen[b]
[a] [b]University of Zurich, Winterthurerstrasse 190, 8057 Zürich; Switzerland
***Email**: igor.pavlovic@uzh.ch - **web page**: www.uzh.ch*

In the last years the secondary messengers inositol polyphosphates moved into sharp focus of research as their importance in different cellular processes like apoptosis, cytoskeleton dynamics or telomere length regulation became obvious.

5-PP-InsPx has recently been identified as a competitive binder of the PH-domain (Pleckstrin Homology) of Akt (Protein Kinase B) with nanomolar affinity.[1] The binding prevents recruitment of Akt to the membrane and thus leads to inhibition of the PI3K/Akt/mTOR signaling pathway, which is linked to different types of cancer but also to diabetes and obesity. PP-InsPx are rapidly synthesized from the intracellular pool of inositol-hexakisphosphate (InsP6) and are at the same time rapidly degraded by diphosphoinositol polyphosphate phosphohydrolases (DIPP) of the Nudix family (**nu**cleoside **di**phosphate linked to **x**) with multiple turnovers per hour. [2]

We want to examine the possibility of synthesizing non-hydrolysable analogs of densely phosphorylated PP-InsPx. To this end, replacement of the bridging phosphoanhydride oxygen with a CF_2 group is envisaged. These analogs would be stable to dephosphorylation catalyzed by DIPPs and should still be capable of binding to the PH domain of Akt with high affinity and persistence.



As no biological probes of PP-InsPx are available to date[3], the introduction of difluoromethylene phosphonates (DFM phosphonates[4]) would be a significant advance both regarding the chemical syntheses of these complex molecules as well as the potential biological use in Akt and DIPP inhibition. Possible synthetic approaches to these structures can rely both on nucleophilic or electrophilic displacements as well as radical chemistry and transition metal mediated hydrophosphonylations.[5] Although this chemistry is available for simple substrates, it has never been applied in the synthesis of such complex and challenging structures. Thus, we are additionally aiming at significant improvements of the current methodologies.

1. A. Prasad et al. Nature Immunology 2011, 12, 752–760; A. Chakraborty et al. *Cell* **2010**, 143, 897.
2. C. Azvedo, Z. Szijgyarto, A. Saiardi, *Advances in Enzyme Regulation*, **2011**, 51, 74.
3. M. D. Best, H. Zhang, G. D. Prestwich, *Natural Product Reports* **2010**, 27, 1403.
4. C. E. McKenna, P. D. Shen, *Journal of Organic Chemistry* **1981**, 46, 4573.
5. P. Merino, E. Marquéz-Lopez, R. P. Herrera, *Advanced Synthesis & Catalysis* **2008**, 350, 1195.