



Synthetic Analogs of Diphosphoinositol Polyphosphates

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Diphosphoinositol Polyphosphates (InsP₇, InsP₈) are water-soluble second messengers derived from the *myo*-inositol scaffold. In contrast to inositol polyphosphates they harbor one or multiple high-energy P-anhydride bonds. Due to this special feature, they are difficult synthetic targets. Moreover, since they only occur in low concentrations in nature, their study has been significantly hampered by a lack of readily available material.

InsP₇ and InsP₈ have been shown to play roles in diverse cellular functions, such as vesicle trafficking, apoptosis, regulation of cell energy homeostasis and regulation of PH domains. Especially InsP₇ mediated inhibition of Akt signaling by downregulation of Akt phosphorylation has received significant attention, since IP6K1 KO mice displayed a lean phenotype on high-fat diet. In order to study the function of InsP₇ and InsP₈ in more detail, chemical tools are in high demand. It is conceivable, that similar tools as already available for inositol polyphosphate or phosphatidyl inositol polyphosphate studies will be helpful in understanding the function of InsP₇ and InsP₈.

In this study, we will present novel chemical tools derived from our total synthesis program. These tools include photocaged InsP₇, permeabilized InsP₇ and heavy isotope labeled analogs. Initial biological evaluations will be presented in order to showcase the utility of these compounds.

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References:

1. T. Wundenberg, G. W. Mayr (2012), *Biol Chem* 393: 979-998
 2. C. J. Barker, P-O. Berggren (2013), *Pharmacol Rev* 65:641-669
 3. A. Chakraborty, M. A. Koldobskiy, N. T. Bello, M. Maxwell, J. J. Potter, K. R. Juluri, D. Maag, S. Kim, A. S. Huang, M. J. Dailey, M. Saleh, A. M. Snowman, T. H. Moran, E. Mezey, S. H. Snyder (2010) *Cell* 143: 897-910
 4. H. Wang, J. R. Falck, T. M. T. Hall, S. B. Shears (2012) *Nat Chem Biol* 8: 111-116.
 5. S. Capolicchio, D. T. Thakor, A. Linden, H. J. Jessen (2013) *Angew. Chem. Int. Ed.* 52: 6912-6916
 6. S. S. Capolicchio, H. Wang, D. T. Thakor, S. B. Shears, H. J. Jessen (2014) *Angew. Chem. Int. Ed.*
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