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cADPR Analagues as Probes for the Cellular Ca^{2+} Ions Signaling

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Cyclic ADP-ribose (cADPR) is a natural occurring metabolite of NAD^+ capable of mobilizing Ca^{2+} ions from intracellular stores. It was firstly isolated from sea urchin eggs extract, but it was later established that it is also produced in many other mammalian cells, including pancreatic β-cells, T-lymphocytes, smooth and cardiac muscle cells and cerebellar neurons, acting as a Ca^{2+}-mobilizing agent. For this activity, cADPR has been classified as a second messenger that, activating the ryanodine receptors of the sarcoplasmatic reticulum, is able to mobilize the calcium ions from intracellular stores. cADPR is involved in many physiological processes related to the variation of the Ca^{2+} concentration, such as the synaptic homeostasis in neurons, as well as fertilization and cellular proliferation. The chemical instability of cADPR N1 glycosidic bond at physiological pH together with its low ability to cross membranes for the presence of the strong negative charge at the pyrophosphate moiety pushed chemists to develop semi-synthetic and/or synthetic methodologies to obtain novel non-hydrolysable and cell permeant cADPR analogues. In the last years, we reported on the syntheses of several cIDPR analogues, focusing our attention on derivatives containing alkyl chains in place of the "northern" or "southern" riboses. We found promising Ca^{2+} releasing activities in neuronal PC12 cells for the cpIDP derivative with the "northern" ribose replaced by a pentyl chain.[1] With cpIDP in hand, we asked if it would be possible to obtain more potent analogues by tuning its molecular polarity. Herein, we report on the preliminary Ca^{2+} mobilizing activities of the novel cpIPP,[2] containing the pentyl chain and the unprecedented phosphono-phospate moiety in the place of the "northern" ribose and pyrophosphate respectively.

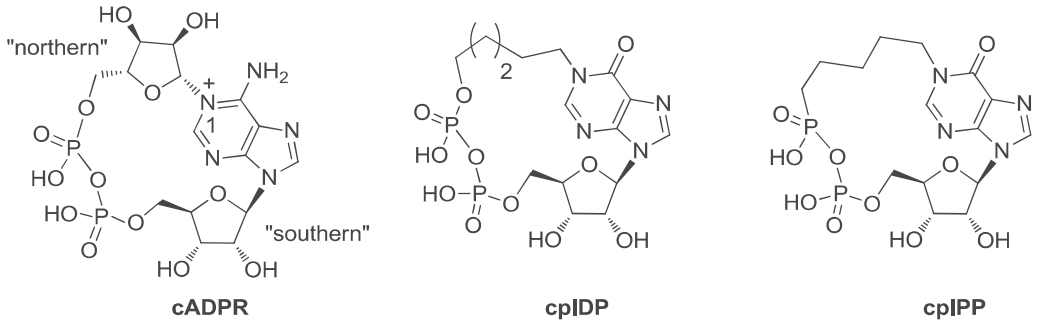

Figure 1: cADPR analogues

References:

[1] A. Mahal, S. D'Errico et al., *Beilstein J. Org. Chem.* **2015**, *11*, 2689 – 2695.

[2] S. D'Errico, G. Oliviero et al., *Mar. Drugs* **2018**, *16*, 89 – 102.