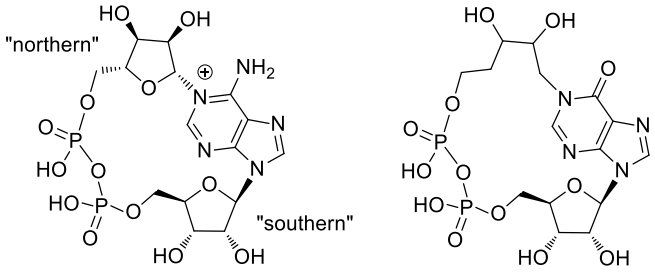
Design and Synthesis of a cADPR Mimic as a Novel Tool for Monitoring the Intracellular Ca^{2+} concentration

Stefano D'Errico,[1] Nicola Borbone,[1] Andrea Patrizia Falanga,[2] Maria Marzano,[1] Monica Terracciano,[1] Francesca Greco,[1] Gennaro Piccialli,[1] Giorgia Oliviero[2]

[1]Dipartimento di Farmacia, Università degli Studi di Napoli 'Federico II', via D. Montesano, 49 – 80131 Napoli
[2]Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università degli Studi di Napoli 'Federico II', via S. Pansini, 5 – 80131 Napoli

e-mail: stefano.derrico@unina.it

Cyclic ADP-ribose (cADPR, **1**) 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. This cyclic nucleotide, characterized by a very labile glycosidic bond at the N1, is rapidly hydrolysed also in neutral aqueous solutions to the inactive ADP-ribose. Matsuda and co-workers[1] were the first who synthesized new analogues of the cADPR in which the adenine base was replaced by a hypoxanthine ring. This kind of modification produced the cyclic inosine diphosphate ribose (cIDPR) which proved to be stable in hydrolytic physiological conditions and showed significant Ca^{2+} mobilizing activity. A lot of modifications regarding the northern and southern ribose, as well as the purine base of cADPR, have been proposed so far. In our laboratories we have synthesized several analogues of cIDPR.[2,3] In particular, the analogue with the northern ribose replaced by a pentyl chain (cpIDP) showed interesting Ca^{2+} mobilizing activity on the neuronal PC12 cell line.[2] Starting from these results, we report here the synthesis of the novel analogue **2**, in which the "northern" ribose of cIDPR was replaced by a 2",3"-dihydroxy pentyl chain. The effect of the presence of the diol moiety on the intracellular Ca^{2+} release will be assessed in due course.



1, cADPR **2**

1. Fukuoka, M.; Shuto, S.; Minakawa, N.; Ueno, Y.; Matsuda, A. *J. Org. Chem*. **2000**, *65*, 5238.
2. Mahal, A.; D'Errico, S.; Borbone, N.; Pinto, B.; Secondo, A.; Costantino, V.; Tedeschi, V.; Oliviero, G.; Piccialli, V.; Piccialli, G. *Beilstein J. Org. Chem*. **2015**, *11*, 2689.
3. D'Errico S.; Borbone, N.; Catalanotti, B.; Secondo A.; Petrozziello, T.; Piccialli, I.; Pannaccione, A.; Costantino, V.; Mayol, L.; Piccialli, G.; Oliviero, G. *Marine Drugs* **2018**, *16*, 89.