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Extended Abstract

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

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Cyclic ADP-ribose (cADPR, **1**, Figure 1) is a naturally occurring metabolite of NAD^+ capable of mobilizing Ca^{2+} ions from intracellular stores. It was firstly isolated from sea urchin egg 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, by 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 variation in the Ca^{2+} concentration, such as synaptic homeostasis in neurons as well as fertilization and cellular proliferation. This cyclic nucleotide, characterized by a very labile glycosidic bond at N1, is also rapidly hydrolysed in neutral aqueous solutions to inactive ADP-ribose. Matsuda and co-workers [1] were the first to synthesize new analogues of cADPR in which the adenine base is 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. Many 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 [2–7]. 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 is 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.

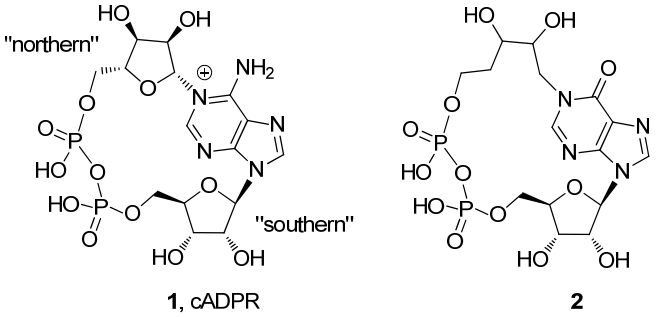

Figure 1. The structures of cADPR (**1**) and of the novel analogue **2**.

Supplementary Materials: The following are available online at https://www.mdpi.com/2504-3900/83/1/5/s1.

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Informed Consent Statement: Not applicable.

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References

1. Fukuoka, M.; Shuto, S.; Minakawa, N.; Ueno, Y.; Matsuda, A. An Efficient Synthesis of Cyclic IDP-and Cyclic 8-Bromo-IDP-Carbocyclic-Riboses Using a Modified Hata Condensation Method To Form an Intramolecular Pyrophosphate Linkage as a Key Step. An Entry to a General Method for the Chemical Synthesis of Cyclic ADP-Ribose Analogues. *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. Synthesis of cyclic N1-pentylinosine phosphate, a new structurally reduced cADPR analogue with calcium-mobilizing activity on PC12 cells. *Beilstein J. Org. Chem*. **2015**, *11*, 2689.
3. Oliviero, G.; Amato, J.; Borbone, N.; D'Errico, S.; Piccialli, G.; Mayol, L. Synthesis of N-1 and ribose modified inosine analogues on solid support. *Tetrahedron Lett*. **2007**, *48*, 397.
4. Oliviero, G.; Amato, J.; Borbone, N.; D'Errico, S.; Piccialli, G.; Bucci, E.; Piccialli, V.; Mayol, L. Synthesis of 4-N-alkyl and ribose-modified AICAR analogues on solid support. *Tetrahedron* **2008**, *64*, 6475.
5. D'Errico, S.; Oliviero, G.; Borbone, N.; Amato, J.; Piccialli, V.; Varra, M.; Mayol, L.; Piccialli, G. Solid-phase synthesis of a new diphosphate 5-aminoimidazole-4-carboxamide riboside (AICAR) derivative and studies toward cyclic AICAR diphosphate ribose. *Molecules* **2011**, *16*, 8110.
6. D'Errico, S.; Borbone, N.; Catalanotti, B.; Secondo, A.; Petrozziello, T.; Piccialli, I.; Pannaccione, A.; Costantino, V.; Mayol, L.; Piccialli, G.; Oliviero, G. Synthesis and Biological Evaluation of a New Structural Simplified Analogue of cADPR, a Calcium-Mobilizing Secondary Messenger Firstly Isolated from Sea Urchin Eggs. *Mar. Drugs* **2018**, *16*, 89.
7. D'Errico, S.; Basso, E.; Falanga, A. P.; Marzano, M.; Pozzan, T.; Piccialli, V.; Piccialli, G.; Oliviero, G.; Borbone, N. New linear precursors of cIDPR derivatives as stable analogs of cADPR: A potent second messenger with Ca2+-Modulating activity isolated from sea urchin eggs. *Mar. Drugs* **2019**, *17*, 476.