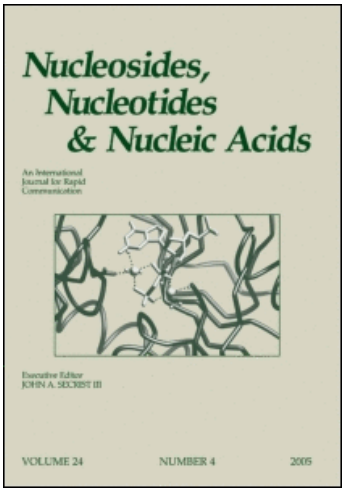

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SYNTHESIS OF A NEW RIBOSE MODIFIED ANALOGUE OF CYCLIC INOSINE DIPHOSPHATE RIBOSE

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□ *A new analogue of cyclic inosine diphosphate ribose (cIDPR), in which the N-1 and N-9 ribosyl moieties were substituted by an alkyl moiety and an hydroxy-alkyl chain, has been synthesized and characterized.*

Keywords cADPR; cIDPR; IP3; Ca^{2+}

INTRODUCTION

Cyclic ADP-ribose is an endogenous metabolite synthesized from NAD^+ by ADP-ribosyl cyclase in cells.[1] In recent years cADPR has been attracting much attention because of its potent calcium-mobilizing activities as well as for its important role as a potent second messenger in cellular Ca^{2+} homeostasis, insulin secretion, and T-lymphocites activation.[2,3] It is also known to mobilize intracellular Ca^{+2} more actively than inositol-1,4,5-triphosphate (IP3) by a mechanism completely IP3 independent. Since Ca^{+2} ion regulate diverse cell functions, the cADPR signalling pathway may become a valuable target for pharmaceutical intervention.

cADPR is characterized by a very labile *N-1* glycosidic bond which is rapidly hydrolyzed, both enzymatically or not, to give ADP-ribose even in neutral aqueous solution. This biological and chemical instability can hinder the studies on cADPR aimed at elucidating its physiological role. Many nonhydrolyzable mimics of cADPR which retained a similar calcium release profile to that of cADPR are reported.[4] Some structural modifications on cADPR adenine moiety make the mimic more potent than its parent—e.g. the 3-deaza-cADPR is 70-fold more potent than cADPR.[5] Additional structural modification includes the pyrophosphate

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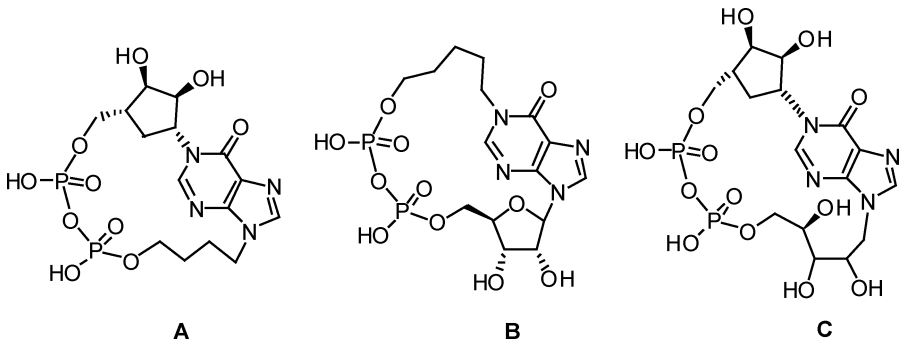
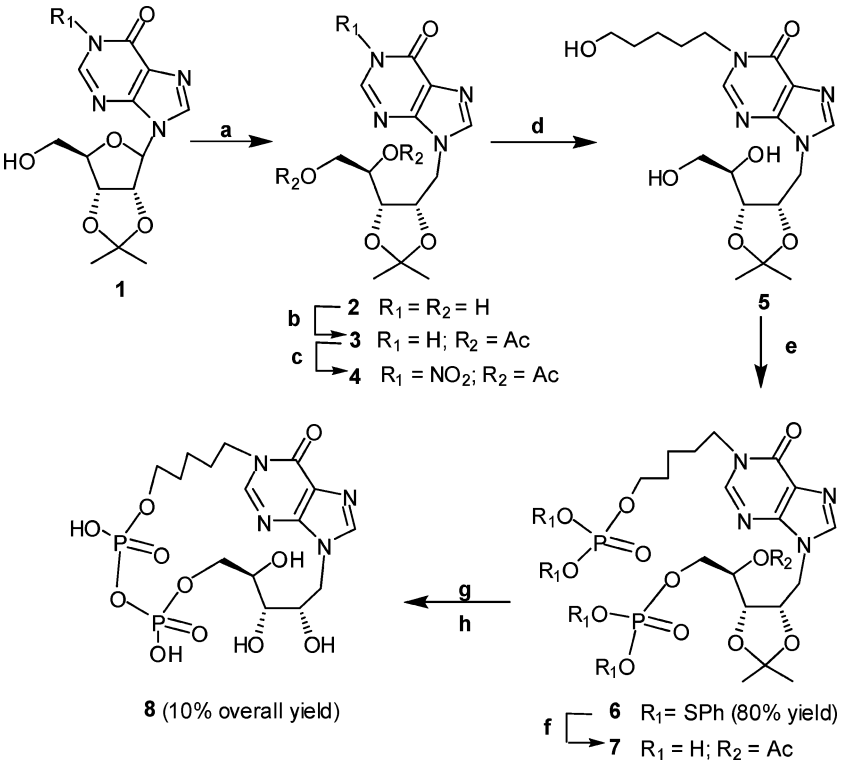


FIGURE 1 *N-1* and/or *N-9* modified analogues of cIDPR.

moiety. Cyclic adenosine triphosphate ribose was more potent in inducing Ca^{2+} release as compared to cADPR.[6] Furthermore, *N-1* deribosylated derivatives of cIDPR (methoxyethyl-8-substituted inosine) are found to be novel membrane permeant cADPR mimics causing the release of Ca^{2+} in human Jurkat T-lymphocytes.[7] Recently we have proposed the syntheses of several analogues of cIDPR in which the *N-1* or the *N-9* ribosyl moiety has been replaced by an alkyl[8,9] or hydroxyalkyl chain[10] (products **A–C** Figure 1). To collect more information on the role of the *N-1* and *N-9* ribosyl moieties into Ca^{2+} release activity, we synthesized the new cIDPR analogue **8** (Scheme 1) containing a penthyl and an hydroxyalkyl chain at *N-1* and *N-9* hypoxanthine base positions, respectively.

The synthetic strategy adopted for **8** is shown in Scheme 1. The *N-9* acyclic ribose inosine derivative **2** was obtained by reaction of the 2′,3′-*O*-isopropilidene-inosine **1** with DIBALH.[11] After protection of the alcoholic functions of **2** the *N-1* nitro derivative **4** was obtained in good yield by reacting the diacetyl derivative **3** with ammonium nitrate and trifluoroacetic anhydride.[12] The reaction of **4** with 5-amino-penthan-1-ol furnished the derivative **5** which in turn was converted into the bis-phosphorylated compound **6** (80%) by treatment with *S,S*-diphenyl-phosphorodithioate (cycloesilammonium salt) in the presence of 2,4,6-triisopropylbenzen-sulfonylchloride (TPSCl) and tetrazole in pyridine. In this reaction we observed the formation of the corresponding triphosphate derivative in 20% yield. **6** was acetylated at secondary alcoholic function and then treated with silver acetate to remove the phosphate protecting group.[13] The obtained product **7** was purified by HPLC (RP18) before the cyclization step which was performed as previously described,[10] thus obtaining **8** (10% overall yield starting from **1**), whose structure was confirmed by ^{1}H-NMR, ^{31}P-NMR, and MS data. Studies on the biological activity of **8** are currently in progress.



SCHEME 1 Reagents and conditions: **a**) DIBALH, THF; **b)** Ac_2O, pyridine, r.t., **c)** NH_4NO_3, TFA, CH_2Cl_2; **d)** 5-aminopenthanol, DMF, r.t. 8 hours; **e)** S,S-diphenylphosphorodithioate, TPSCl, pyridine, r.t., 8 hours; **f)** Ac_2O, AgAc, pyridine/H_2O; **g)** EDC, NMP, r.t.; 60 hours; **h)** aq. HCO_2H, r.t., 3.5 hours.

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