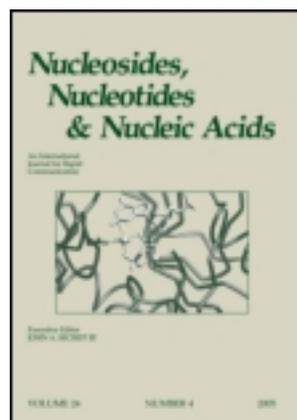


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SYNTHESIS AND BIOLOGICAL ACTIVITY OF CYCLIC ADP-CARBOCYCLIC-RIBOSE ANALOGS: STRUCTURE-ACTIVITY RELATIONSHIP AND CONFORMATIONAL ANALYSIS OF N-1-CARBOCYCLIC-RIBOSE MOIETY

Takashi Kudoh^a, Masayoshi Fukuoka^a, Satoshi Shuto^a & Akira Matsuda^a

^a Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF CYCLIC ADP-CARBOCYCLIC-RIBOSE ANALOGS: STRUCTURE-ACTIVITY RELATIONSHIP AND CONFORMATIONAL ANALYSIS OF *N*-1-CARBOCYCLIC-RIBOSE MOIETY

Takashi Kudoh, Masayoshi Fukuoka, Satoshi Shuto, and Akira Matsuda

□ Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

□ Several cyclic ADP-carbocyclic-ribose analogs **3–10** modified in the *N*-1-carbocyclic-ribose moiety were synthesized. Their Ca^{2+} -releasing activity was estimated in sea urchin eggs to show that the 3'-deoxy analog **6** shows 5 times more potent activity than cADPcR, but the 2'',3''-didieoxy-2'',3''-unsaturated analog **3** has very weak activity. We also calculated their stable conformation and found that **3** and **6** were significantly different in their stable conformation.

Keywords Cyclic ADP-Carbocyclic-Ribose, Ca^{2+} -Releasing Activity, Conformational Analysis

INTRODUCTION

Cyclic ADP-carbocyclic-ribose (cADPcR, **1**) was designed as a stable mimic of cyclic ADP-ribose (cADPR, **2**), an intracellular Ca^{2+} -mobilizing second messenger.^[1] cADPcR has a carbocyclic-ribose bound to *N*-1 position of adenine moiety instead of D-ribose in cADPR, the synthesis of which had previously been completed using effective formation of the pyrophosphate linkage.^[2] cADPcR is actually very stable under chemical and biological conditions and exhibits 3 times more potent Ca^{2+} -releasing activity than cADPR in sea urchin egg homogenates.

In this study, we focused on SAR of the *N*-1-carbocyclic-ribose moiety of cADPcR. Only a few analogs modified in this moiety have been synthesized, because of the difficulty in their synthesis by the classical enzymatic method.^[3–5] So we designed and synthesized the eight cADPcR analogs **3–10** modified in the *N*-1-carbocyclic-ribose moiety (Figure 1). We estimated their Ca^{2+} -releasing activity and analyzed their stable conformation.

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Address correspondence to Satoshi Shuto, Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan.

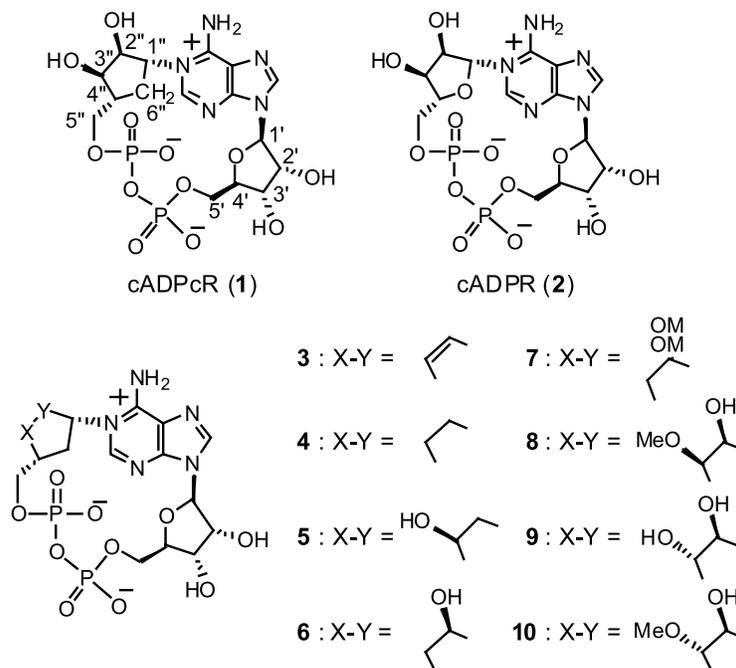


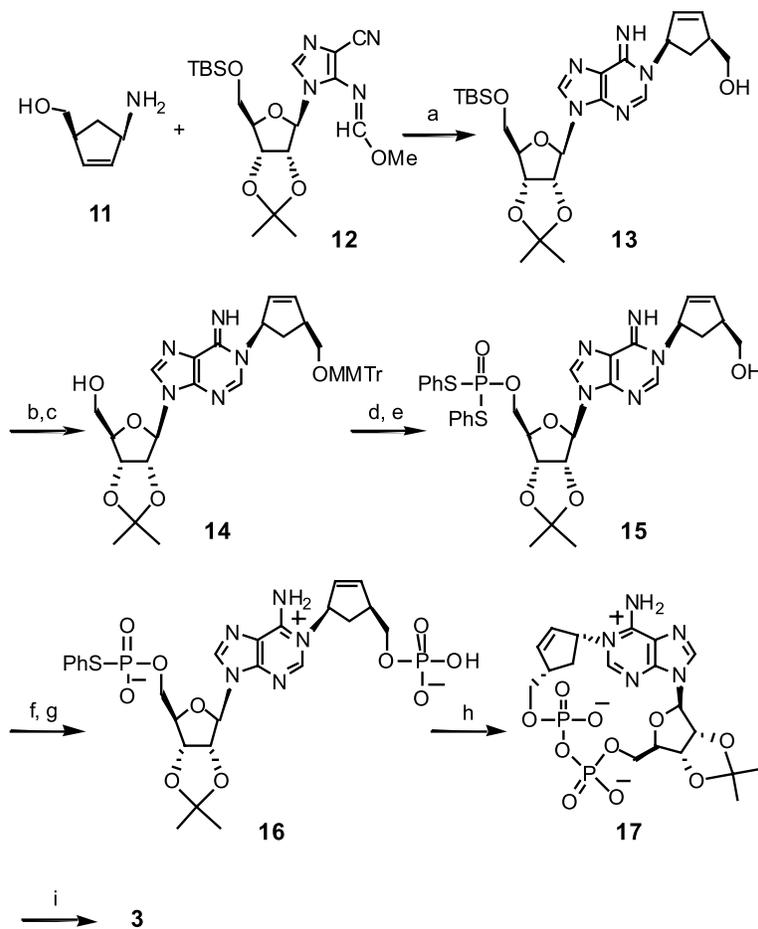
FIGURE 1

SYNTHESIS

Scheme 1 shows the synthetic route of the cADPcR analog **3**. The optically active cyclopentenylamine units **11**, corresponding to the carbocyclic-ribose moiety, were condensed with imidazole nucleoside **12** to construct the *N*-1-cyclopentenyladenosine derivative **13**. The 5''-hydroxy group of **13** was protected by MMTTr group, and 5'-*O*-TBS protection was removed to give **14**. Bisphenylthiophosphate group was introduced to the 5'-position of **14** with *S,S'*-diphenylphosphorodithioate (PSS) and TPSCl, and then the 5''-*O*-MMTTr group was removed to give **15**. The 5''-hydroxy group of **15** was phosphorylated by Yoshikawa's method, and one phenylthio group was removed by hypophosphorous acid to give the cyclization substrate **16**. The intramolecular condensation of two phosphates group was successfully proceeded by a silver nitrate/MS3A/pyridine systems to give the cyclic product **17**. Finally, remaining isopropylidene protection of hydroxy groups was removed by aqueous formic acid to complete the synthesis of **3**. Similarly, the other analogs **4**–**10** were synthesized using the corresponding optically active cyclopentylamine derivatives.

BIOLOGICAL ACTIVITY

We estimated Ca^{2+} -releasing activity of these analogs in sea urchin egg homogenates. The EC_{50} values of analogs were summarized in Figure 2. In this



SCHEME 1 (a) K_2CO_3 , MeOH, 82%; (b) MMTTrCl, pyridine, 84%; (c) TBAF, AcOH, THF, 96%; (d) PSS, TPSCl, pyridine, 54%; (e) 80% AcOH aq., 77%; (f) $POCl_3$, $(EtO)_3 PO$, $0^\circ C$; (g) H_3PO_2 , Et_3N , *N*-methylmaleimide, pyridine, $0^\circ C \rightarrow r.t.$, 2 steps 64%; (h) $AgNO_3$, Et_3N , MS3A, pyridine, 84%; (i) 60% HCOOH aq., quant.

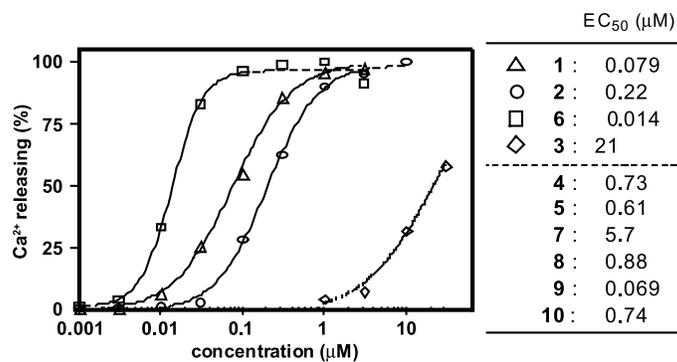


FIGURE 2 Ca^{2+} releasing activity in sea urchin egg homogenates. Maximum Ca^{2+} releasing by cADPR is 100%.

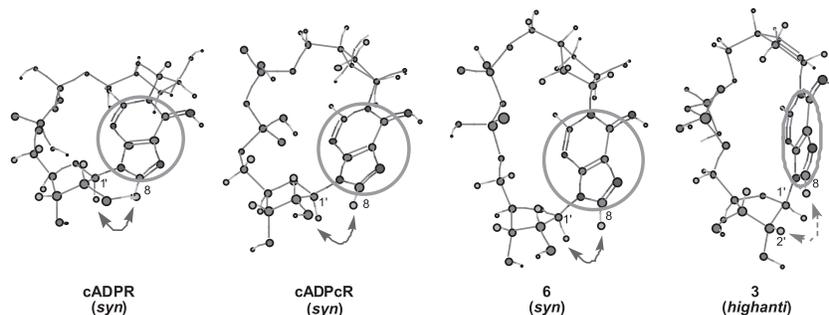


FIGURE 3 Conformational analysis by molecular dynamics: simulated annealing with NOESY constraints.

system, the EC_{50} value of cADPR was $0.22 \mu\text{M}$, and cADPcR was $0.079 \mu\text{M}$. As a result, 3''-deoxy-cADPcR (**6**) showed 5 times more potent activity than cADPcR. Xylose type analog **9** had potent activity equal as cADPcR, and 2'',3''-dideoxy (**4**), 3''-*O*-methyl (**8,10**) analogs showed moderate activity. However, the unsaturated analog **3** showed very weak activity.

CONFORMATIONAL ANALYSIS

We calculated the stable conformation of cADPR, cADPcR and the cADPcR analogs **6** and **3** by molecular dynamics with a simulated annealing method, based on the NOE constraints of the intramolecular proton pairs measured in D_2O . Analogues with strong Ca^{2+} -mobilizing activity, such as cADPR, cADPcR, and **6** had similar *syn* conformations around *N*-9-glycosidic linkage, while the almost inactive analog **3** showed *highanti* conformation (Figure 3).

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