Short Note

O6-[(2″,3″-*O*-Isopropylidene-5″-*O*-*t*butyldimethylsilyl)pentyl]-5′-*O*-*t*butyldiphenylsilyl-2′,3′-*O*-isopropylideneinosine

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Abstract: Cyclic adenosine diphosphate ribose (cADPR) is a cyclic nucleotide involved in the Ca^{2+} homeostasis. In its structure, the northern ribose, bonded to adenosine through an N1 glycosidic bond, is connected to the southern ribose through a pyrophosphate bridge. Due to the chemical instability at the N1 glycosidic bond, new bioactive cADPR derivatives have been synthesized. One of the most interesting analogues is the cyclic inosine diphosphate ribose (cIDPR), in which the hypoxanthine replaced adenosine. The efforts for synthesizing new linear and cyclic northern ribose modified cIDPR analogues led us to study in detail the inosine N1 alkylation reaction. In the last few years, we have produced new flexible cIDPR analogues, where the northern ribose has been replaced by alkyl chains. With the aim to obtain the closest flexible cIDPR analogue, we have attached to the inosine N1 position a 2″,3″-dihydroxypentyl chain, possessing the two OH groups in a ribose-like fashion. The inosine alkylation reaction afforded also the O6-alkylated regioisomer, which could be a useful intermediate for the construction of new kinds of cADPR mimics.

Keywords: cADPR; nucleosides; nucleotides; inosine; alkylation; calcium mobilization; ryanodine receptor; primary cortical neurons

1. Introduction

The design and synthesis of new nucleoside and nucleotide analogues is a frontier theme in light of the current SARS-CoV-2 pandemic that the world is facing [1]. However, apart from being employed in medicinal chemistry both as antiviral [2] and antitumor drugs [3], nucleosides, nucleotides, and their analogues can be also used as probes in the signaling pathways [4–6]. Cyclic nucleotides are important second messengers involved in signal transduction [7,8]. Among them, cADPR (**1**, Figure 1), an 18-membered cyclic nucleotide firstly isolated from sea urchin egg extracts [9], elicits Ca^{2+} ions from the endoplasmic reticulum (ER) to cytosol through the ryanodine receptor (RyR) in several cellular systems [10]. Alterations in the cADPR biosynthesis and calcium homeostasis can play pathological roles in diabetes, airway hyper-responsiveness and autism [11]. Unfortunately, the chemical instability at the N1 glycosidic bond in physiological conditions

hampered the definition of cADPR molecular mechanism of action [12]. In this frame, efforts have been devoted to the synthesis of stable cADPR analogues [13–16]. In particular, the replacement of the adenine with hypoxanthine generated the very stable cIDPR analogue **2**, which retained the same Ca^{2+} mobilizing activity of the endogenous metabolite [17]. In the last few years, we have produced both in solution [18–21] and on solid phase [22,23] some cIDPR analogues with alkyl chains in the place of the northern ribose (**3–7**). As we have found a promising Ca^{2+} mobilizing activity in the derivative with a pentyl chain (**6**, *n* = 4) in a neuronal cellular model [18], we have recently prepared a new flexible cIDPR analogue (**8**), with a 2″,3″-dihydroxypentyl chain replacing the northern ribose [21].
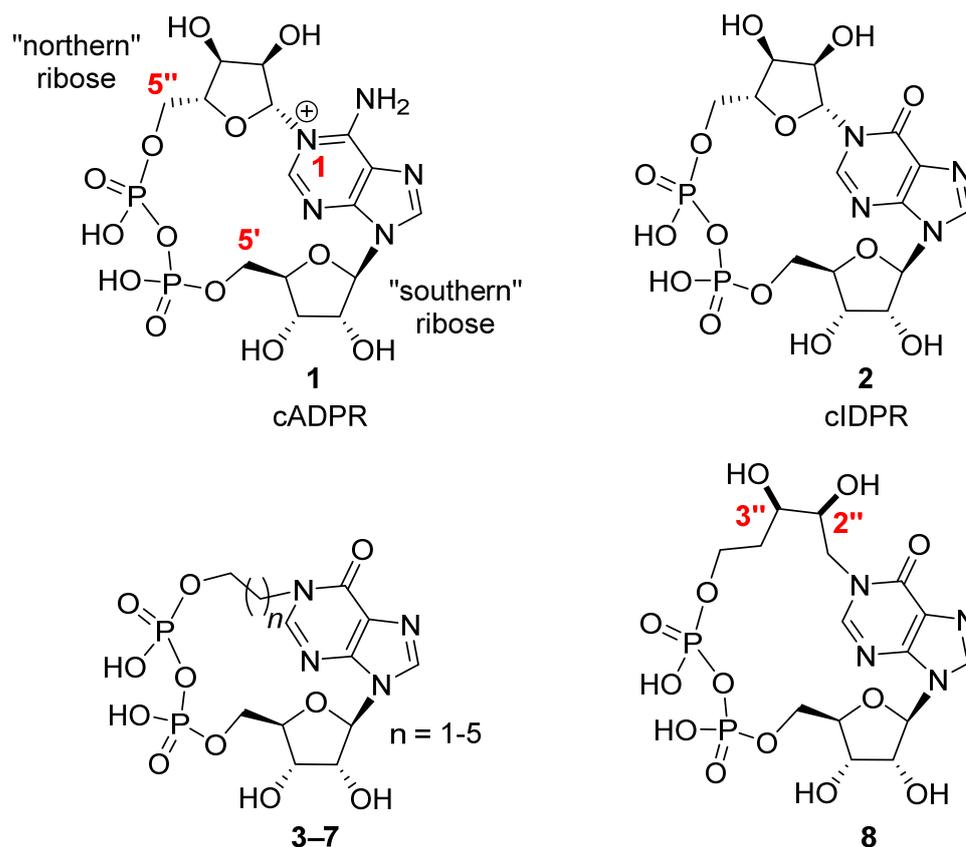

Figure 1. The structures of cADPR (**1**), cIDPR (**2**) and their analogues (**3–8**).

As the last mimic possesses the two OH groups in a ribose-like fashion, it may be considered the closest cIDPR flexible analogue. Interestingly, the cyclic compound **8** induced a concentration-dependent increase in $[Ca^{2+}]_i$ when perfused to primary cortical neurons as efficiently as cADPR.

Since 6-substituted purine nucleosides displayed interesting biological activities [24–26], herein we report on the synthesis and characterization of the O6-alkylated compound **9**, obtained as a side product during the coupling reaction of the protected inosine **10** and the tosylate **11** (Scheme 1). That reaction was revealed to be fundamental for the construction of the new cyclic analogue (**8**) scaffold.
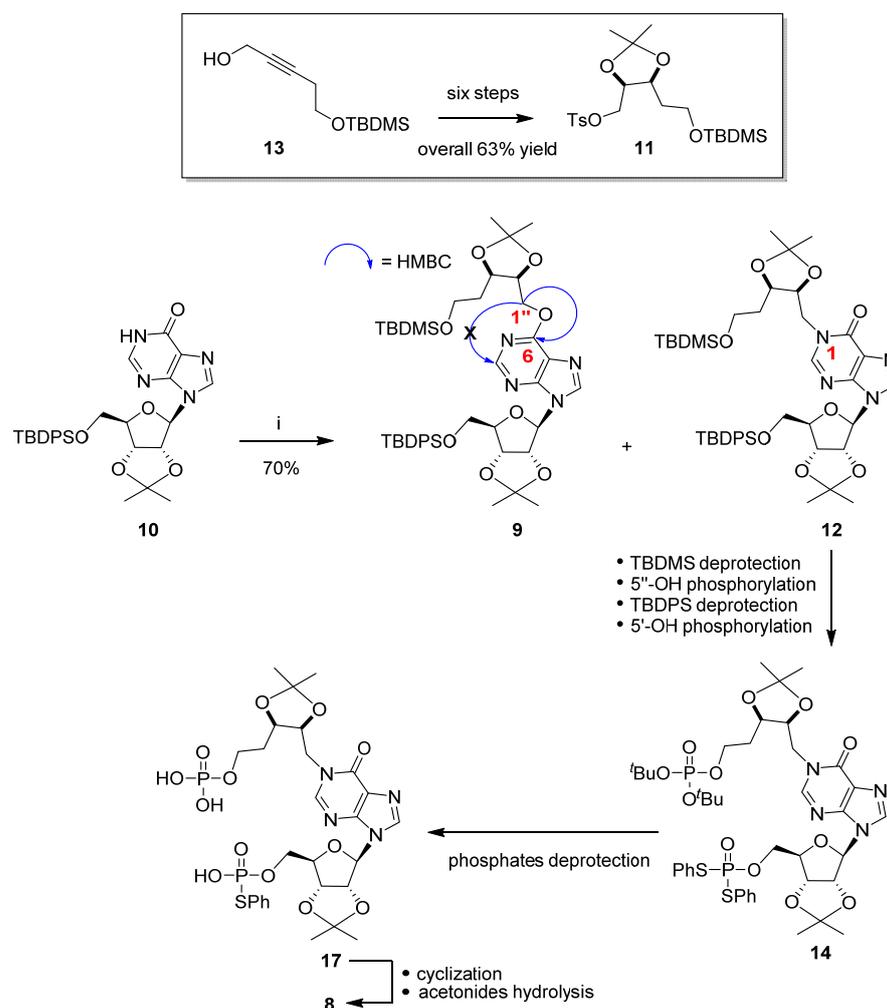
Scheme 1. Reagents and conditions: (i) **11**, DBU, DMF, 80 °C, 12 h (entry 6, Table 1).

Table 1. Optimization of the reaction between **10** and **11** [1].

Entry	Base	Equivalents [2]	Temperature (°C)	Yield (%)	9:12
1	K$_2$CO$_3$	1 or 3	r.t.	No reaction	-
2	K$_2$CO$_3$	3	80	10	20:80
3	Triethylamine	1 or 3	r.t.	No reaction	-
4	Triethylamine	3	80	No reaction	-
5	DBU	1 or 3	r.t.	No reaction	-
6	DBU	3	80	70	30:70
7	DBU	3	120	30	60:40

[1] All the reactions were carried out in anhydrous *N,N*-dimethylformamide (DMF) as solvent. [2] Calculated from **10**.

2. Results and Discussion

Scheme 1 shows the convergent synthetic approach that we have used for the preparation of the cyclic compound **8**. The ribose-protected inosine **10**, after reaction with the tosylate **11**, afforded as the main product the N1-alkylated derivative **12**. The electrophile **11** was prepared as a racemic mixture starting from the commercially available propargyl alcohol **13** with an overall 63% yield [21].

To obtain the target compound **8**, we used the well-known Hata protocol, which required an I$_2$ mediated cyclopyrophosphorylation reaction among a phosphomonoester and a phosphorothioate [14]. As a TBDMS group could be selectively removed in the presence of a TBDPS group [27], we followed the synthetic sequence reported in Scheme 1,

and compound **14** was readily obtained. The two phosphates in **14** were then deprotected to give the key intermediate **17**. The pyrophosphate bond formation was carried out by adding compound **17** through a syringe pump to a very diluted solution of I_2. The cyclic compound was isolated from a complex reaction mixture and finally deprotected from both the acetonides, affording the new cADPR analogue **8** with an overall 1% yield.

The reaction between the protected inosine **10** with the electrophile **11** has been studied in detail. In principle, as hypoxanthine is an ambient nucleophile [28] at the N1 and O6 purine positions [29,30], the two regioisomers **12** and **9** could be expected. In our studies focused on the inosine N1 functionalization, we discovered that the Mitsunobu reaction was not a good method to regioselectivity obtain the N1-alkylated isomer. In fact, the reaction of inosine with di-*tert*-butyl (5-hydroxypentyl)phosphonate in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (PPh_3) afforded mainly the O6-alkylated regioisomer. We attributed the observed regioselectivity to the hard–hard interaction between the alkoxy-phosphonium cation intermediate and the nucleobase O6 atom [19]. On the other hand, previous findings demonstrated that inosine could be efficiently alkylated at the N1 purine position at room temperature (r.t.) when a soft electrophile was used [31]. Unfortunately, all the attempts to transform both the tosylate **11** and its primary alcohol precursor into the iodide derivative proceeded with very unsatisfactory yields [21]. As literature data reported on the efficient nucleophilic mediated displacement of a tosylate flanked by an isopropylidene under mild conditions [32,33], we reacted the inosine derivative **10** with the electrophile **11** at r.t. in the presence of some bases (Table 1); unfortunately, no reaction took place. By increasing the temperature, we noted on TLC (petroleum ether/AcOEt, 6:4) the formation of two spots. 1D/2D NMR analyses of the purified compounds (see Supplementary Materials) allowed to assign the N1-alkylated inosine **12** to the spot with Rf = 0.10, whereas the O6-alkylated inosine **9** to that with Rf = 0.50. In detail, in the ^{1}H NMR spectrum of compound **12** the two 1"-H protons resonated as two doublets of doublets centered at 4.70 and 4.66 ppm and correlated with their carbon atom resonating around 47.7 ppm. The HMBC correlation between the purine 2-H and the C1" carbon atom supported the structure **12** [21]. Conversely, in the ^{1}H NMR spectrum of compound **9** (Figure S1, Supplementary Materials) the 1"-H protons resonated in the range 4.68–4.54 ppm and correlated with their carbon atom resonating at 65.6 ppm (Figure S4). The HMBC correlation between the two 1"-H protons and the C6 purine carbon atom resonating at 160.3 ppm and the absence of HMBC correlation between the purine 2-H (8.43 ppm) and the C1" carbon atom supported the structure **9** (Figure S5).

Careful tuning of the reaction conditions allowed to recover the N1-alkylated regioisomer **12** as the main product. In particular, 3.0 equiv. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 80 °C for 12 h were the best conditions to recover the N1 and O6 regioisomers with a good 70% yield in a 7:3 ratio. (Scheme 2 and Table 1) Higher temperatures were detrimental to the reaction yield and increased the ratio **9:12**. The last experimental evidence could be explained assuming that compound **9** is the thermodynamic regioisomer.
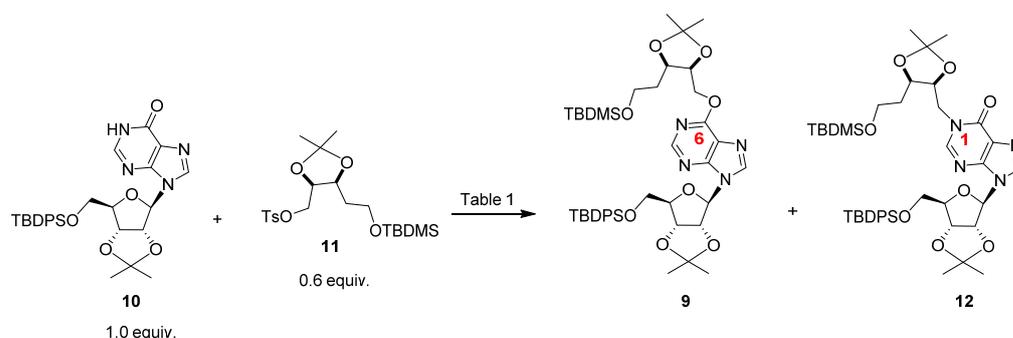
Scheme 2. The reaction of the nucleoside **10** with the tosylate **11**.

3. Materials and Methods

All the reagents and solvents were commercially available and used without further purification. ^{1}H- and ^{13}C-NMR spectra were acquired on the Bruker Avance 600 MHz spectrometer (Bruker-Biospin, Billerica, MA, USA) using CDCl$_3$ as solvent. NMR chemical shifts are reported in parts per million (δ) relative to residual solvents signals: CHCl$_3$ 7.26 for ^{1}H-NMR and CDCl$_3$ 77.0, for ^{13}C-NMR. The ^{1}H NMR chemical shifts were assigned through 2D NMR experiments. The NMR spectra were processed with the MestReNova (Mestrelab Research, Santiago de Compostela, Spain) suite. The HRESI-MS spectra were acquired on a Thermo Orbitrap XL mass spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). Column chromatography was carried out on silica gel-60 (Merck, Readington Township, NJ, USA, 0.063–0.200 mm). TLC analyses were carried out on F$_{254}$ silica gel plates (0.2 mm thick, Merck). TLC spots were detected under UV light (254 nm).

O6-[(2″,3″-*O*-isopropylidene-5″-*O*-*tert*-butyldimethylsilyl)pentyl]-5′-*O*-*tert*-butyldiphenylsilyl-2′,3′-*O*-isopropylideneinosine **9**. To a stirred solution of compound **10** (0.10 g, 0.18 mmol) in anhydrous DMF (2.0 mL), DBU (80 μL, 0.55 mmol) was added. After 20 min. the tosylate **11** (49 mg, 0.11 mmol) was added and reaction warmed to 80 °C for 12 h (TLC monitoring: petroleum ether/AcOEt, 6:4). The mixture was cooled, and the solvents removed under reduced pressure. The crude product was purified over a silica gel column eluted with increasing amounts of AcOEt in petroleum ether (up to 20%), giving the pure **9** as a 1:1 mixture of diastereomers (Rf = 0.50). Colorless syrup (21% yield). ^{1}H NMR (600 MHz, CD$_3$Cl) δ 8.43 (s, 1H, 2-H), 8.42 (s, 1H, 2-H), 8.07 (s, 1H, 8-H), 8.07 (s, 1H, 8-H), 7.62−7.54 (complex signal, 8H, arom.), 7.43−7.25 (complex signal, 12H, arom.), 6.15 (d, *J* = 1.7 Hz, 2H, 2 × 1′-H), 5.32−5.28 (m, 2H, 2 × 2′-H), 4.98−4.95 (m, 2H, 2 × 3′-H), 4.68−4.62 (m, 2H, 2 × 1″-H$_a$), 4.61−4.54 (complex signal, 4H, 2 × 1″-H$_b$ and 2 × 2″-H), 4.49−4.43 (m, 2H, 2 × 3″-H), 4.42−4.38 (m, 2H, 2 × 4′-H), 3.92−3.85 (m, 2H, 2 × 5′-H$_a$), 3.83−3.74 (complex signal, 6H, 2 × 5′-H$_b$ and 2 × 5″-H$_{a,b}$), 1.97−1.89 (m, 2H, 2 × 4″-H$_a$), 1.85−1.75 (m, 2H, 2 × 4″-H$_b$), 1.62 (s, 6H, 2 × CH$_3$ acetonide), 1.48 (s, 6H, 2 × CH$_3$ acetonide), 1.37 (two overlapped singlets, 12H, 4 × CH$_3$ acetonide), 1.01 (two overlapped singlets, 18H, 2 × ^{t}Bu), 0.88 (s, 18H, 2 × ^{t}Bu), 0.04 (s, 6H, 2 × SiCH$_3$), 0.05 (s, 6H, 2 × SiCH$_3$). ^{13}C NMR (151 MHz, CDCl$_3$) δ 160.32 (2 × C6), 152.10 (C2), 152.08 (C2), 151.45 (C4), 151.44 (C4), 141.01 (C8), 140.98 (C8), 135.49, 135.47, 132.82, 132.80, 132.69, 129.85, 127.74, 127.69, 127.62, 122.05 (2 × C5), 114.34 (C$_q$ ribose acetonide) 114.33 (C$_q$ ribose acetonide), 108.37 (2 × C$_q$ acetonide), 91.19 (C1′), 91.17 (C1′), 87.02 (C4′), 86.97 (C4′), 84.40 (C2′), 84.36 (C2′), 81.36 (C3′), 81.35 (C3′), 75.14 (C2″), 75.12 (C2″), 73.71 (C3″), 73.70 (C3″), 65.60 (2 × C1″), 63.85 (2 × C5′), 60.02 (C5″), 60.00 (C5″), 32.16 (C4″), 32.14 (C4″), 29.66, 28.19, 28.17, 27.19, 26.81, 25.91, 25.86, 25.58, 25.35, 19.15, 18.30, −5.39, −5.44. HRESI-MS *m/z* 819.4184, ([M + H]$^+$ calcd. for C$_{43}$H$_{63}$N$_4$O$_8$Si$_2$ 819.4191).

4. Conclusions

Purine bases and nucleosides carrying O-, N- and C-substituents at the C6 position represent an important class of compounds endowed with important biological activities. These compounds are generally prepared by nucleophilic aromatic (S$_N$Ar) substitutions, [34] metal-mediated cross-coupling reactions [35,36] and by Grignard's reagents addition [26] to 6-halopurine ribosides. In our search of new cADPR analogues, we have obtained the O6-alkylated inosine **9** as a side product during the S$_N$2 reaction between the nucleoside **10** and the tosylate **11**. The O6 reactivity of the ambident nucleophile hypoxanthine in **10** was a consequence of the high temperature necessary to perform the coupling reaction. Product **9** is an interesting intermediate that will be exploited for the synthesis of unprecedented O6-substituted cADPR derivatives.

Supplementary Materials: The following are available online. Figures S1–S6: copies of ^{1}H-, ^{13}C-NMR, COSY, HSQC, HMBC and HRESI-MS spectra of compound **9**.

Author Contributions: S.D. conceived and designed the experiments; V.P. performed the synthetic experiments; M.M. performed the spectroscopic experiments; M.T. and A.M. analyzed the data; R.N. finalized the draft; S.D. wrote the paper. All authors have read and agreed to the published version of the manuscript.

References

1. Borbone, N.; Piccialli, G.; Roviello, G.N.; Oliviero, G. Nucleoside analogues and nucleoside precursors as drugs in the fight against SARS-CoV-2 and other coronaviruses. *Molecules* **2021**, *26*, 986. [CrossRef] [PubMed]

2. Yates, M.K.; Seley-Radtke, K.L. The evolution of antiviral nucleoside analogues: A review for chemists and non-chemists. Part II: Complex modifications to the nucleoside scaffold. *Antivir. Res.* **2019**, *162*, 5–21. [CrossRef]

3. Guinan, M.; Benckendor, C.; Smith, M.; Miller, G.J.; Way, S.; Derek, J.; Mcphee, J. Evaluation Analogues Evaluation of Anticancer Anticancer Nucleoside. *Molecules* **2020**, *25*, 2050. [CrossRef]

4. Giuliani, A.L.; Sarti, A.C.; Di Virgilio, F. Extracellular nucleotides and nucleosides as signalling molecules. *Immunol. Lett.* **2019**, *205*, 16–24. [CrossRef] [PubMed]

5. Ewald, B.; Sampath, D.; Plunkett, W. Nucleoside analogues: Molecular mechanisms signaling cell death. *Oncogene* **2008**, *27*, 6522–6537. [CrossRef] [PubMed]

6. Zarrilli, F.; Amato, F.; Morgillo, C.M.C.M.; Pinto, B.; Santarpia, G.; Borbone, N.; D'Errico, S.; Catalanotti, B.; Piccialli, G.; Castaldo, G.; et al. Peptide nucleic acids as miRNA target protectors for the treatment of cystic fibrosis. *Molecules* **2017**, *22*, 1144. [CrossRef] [PubMed]

7. Poppe, H.; Rybalkin, S.D.; Rehmann, H.; Hinds, T.R.; Tang, X.B.; Christensen, A.E.; Schwede, F.; Genieser, H.G.; Bos, J.L.; Doskeland, S.O.; et al. Cyclic nucleotide analogues as probes of signaling pathways. *Nat. Methods* **2008**, *5*, 277–278. [CrossRef] [PubMed]

8. Fajardo, A.M.; Piazza, G.A.; Tinsley, H.N. The role of cyclic nucleotide signaling pathways in cancer: Targets for prevention and treatment. *Cancers* **2014**, *6*, 436–458. [CrossRef] [PubMed]

9. Clapper, D.L.; Walseth, T.F.; Dargie, P.J.; Lee, H.C. Pyridine nucleotide metabolites stimulate calcium release from sea urchin egg microsomes desensitized to inositol trisphosphate. *J. Biol. Chem.* **1987**, *262*, 9561–9568. [CrossRef]

10. Guse, A.H. Calcium mobilizing second messengers derived from NAD. *Biochim. Biophys. Acta* **2015**, *1854*, 1132–1137. [CrossRef]

11. Gul, R.; Park, J.H.; Kim, S.Y.; Jang, K.Y.; Chae, J.K.; Ko, J.K.; Kim, U.H. Inhibition of ADP-ribosyl cyclase attenuates angiotensin II-induced cardiac hypertrophy. *Cardiovasc. Res.* **2009**, *81*, 582–591. [CrossRef] [PubMed]

12. Potter, B.V.L.; Walseth, T.F. Medicinal chemistry and pharmacology of cyclic ADP-ribose. *Curr. Mol. Med.* **2004**, *4*, 303–311. [CrossRef] [PubMed]

13. Takano, S.; Tsuzuki, T.; Murayama, T.; Kameda, T.; Kumaki, Y.; Sakurai, T.; Fukuda, H.; Watanabe, M.; Arisawa, M.; Shuto, S. Synthesis of 8-Substituted Analogues of Cyclic ADP-4-Thioribose and Their Unexpected Identification as Ca^{2+}-Mobilizing Full Agonists. *J. Med. Chem.* **2017**, *60*, 5868–5875. [CrossRef]

14. Watt, J.M.; Graeff, R.; Thomas, M.P.; Potter, B.V.L. Second messenger analogues highlight unexpected substrate sensitivity of CD38: Total synthesis of the hybrid "l-cyclic inosine 5′-diphosphate ribose". *Sci. Rep.* **2017**, *7*, 16100. [CrossRef]

15. Sato, T.; Watanabe, M.; Tsuzuki, T.; Takano, S.; Murayama, T.; Sakurai, T.; Kameda, T.; Fukuda, H.; Arisawa, M.; Shuto, S. Design, Synthesis, and Identification of 4″α-Azidoethyl-cyclic ADP-Carbocyclic-ribose as a Highly Potent Analogue of Cyclic ADP-Ribose, a Ca^{2+}-Mobilizing Second Messenger. *J. Med. Chem.* **2016**, *59*, 7282–7286. [CrossRef] [PubMed]

16. Galeone, A.; Mayol, L.; Oliviero, G.; Piccialli, G.; Varra, M. Synthesis of a novel N-1 carbocyclic, N-9 butyl analogue of cyclic ADP ribose (cADPR). *Tetrahedron* **2002**, *58*, 363–368. [CrossRef]

17. Wagner, G.K.; Guse, A.H.; Potter, B.V.L. Rapid synthetic route toward structurally modified derivatives of cyclic adenosine 5′-diphosphate ribose. *J. Org. Chem.* **2005**, *70*, 4810–4819. [CrossRef] [PubMed]

18. Mahal, A.; D'Errico, S.; Borbone, N.; Pinto, B.; Secondo, A.; Costantino, V.; Tedeschi, V.; Oliviero, G.; Piccialli, V.; Piccialli, G. Synthesis of cyclic N^1-pentylinosine phosphate, a new structurally reduced cADPR analogue with calcium-mobilizing activity on PC12 cells. *Beilstein J. Org. Chem.* **2015**, *11*, 2689–2695. [CrossRef]

19. D'Errico, S.; Borbone, N.; Catalanotti, B.; Secondo, A.; Petrozziello, T.; Piccialli, I.; Pannaccione, A.; Costantino, V.; Mayol, L.; Piccialli, G.; et al. 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. [CrossRef]

20. D'Errico, S.; Basso, E.; Falanga, A.P.A.P.; Marzano, M.; Pozzan, T.; Piccialli, V.; Piccialli, G.; Oliviero, G.; Borbone, N. New linear precursors of cIDPR derivatives as stable analogues of cADPR: A potent second messenger with Ca^{2+}-Modulating activity isolated from sea urchin eggs. *Mar. Drugs* **2019**, *17*, 476. [CrossRef]

21. D'Errico, S.; Greco, F.; Patrizia Falanga, A.; Tedeschi, V.; Piccialli, I.; Marzano, M.; Terracciano, M.; Secondo, A.; Roviello, G.N.; Oliviero, G.; et al. Probing the Ca^{2+} mobilizing properties on primary cortical neurons of a new stable cADPR mimic. *Bioorg. Chem.* **2021**, *117*, 105401. [CrossRef]

22. Oliviero, G.; D'Errico, S.; Borbone, N.; Amato, J.; Piccialli, V.; Varra, M.; Piccialli, G.; Mayol, L. A solid-phase approach to the synthesis of N-1-alkyl analogues of cyclic inosine-diphosphate-ribose (cIDPR). *Tetrahedron* **2010**, *66*, 1931–1936. [CrossRef]

23. 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*, 8110–8118. [CrossRef]

24. Bonnac, L.F.; Dreis, C.D.; Geraghty, R.J. Structure activity relationship, 6-modified purine riboside analogues to activate hSTING, stimulator of interferon genes. *Bioorgan. Med. Chem. Lett.* **2019**, 126819. [CrossRef] [PubMed]

25. Hulpia, F.; Bouton, J.; Campagnaro, G.D.; Alfayez, I.A.; Mabille, D.; Maes, L.; de Koning, H.P.; Caljon, G.; Van Calenbergh, S. C6–O-alkylated 7-deazainosine nucleoside analogues: Discovery of potent and selective anti-sleeping sickness agents. *Eur. J. Med. Chem.* **2020**, *188*, 112018. [CrossRef] [PubMed]

26. D'Errico, S.; Oliviero, G.; Amato, J.; Borbone, N.; Cerullo, V.; Hemminki, A.; Piccialli, V.; Zaccaria, S.; Mayol, L.; Piccialli, G. Synthesis and biological evaluation of unprecedented ring-expanded nucleosides (RENs) containing the imidazo[4,5-d][1,2,6]oxadiazepine ring system. *Chem. Commun.* **2012**, *48*, 9310–9312. [CrossRef] [PubMed]

27. Prakash, C.; Saleh, S.; Blair, I.A. Selective Deprotection of Silyl Ethers. *Tetrahedron Lett.* **1989**, *30*, 19–22. [CrossRef]

28. Leškovskis, K.; Zaķis, J.M.; Novosjolova, I.; Turks, M. Applications of Purine Ring Opening in the Synthesis of Imidazole, Pyrimidine, and New Purine Derivatives. *Eur. J. Org. Chem.* **2021**, *2021*, 5027–5052. [CrossRef]

29. Shuto, S.; Shirato, M.; Sumita, Y.; Ueno, Y.; Matsuda, A. Nucleosides and Nucleotides. 173. Synthesis of Cyclic IDP-carbocyclic-ribose, a Stable Mimic of Cyclic ADP-Ribose. Significant Facilitation of the Intramolecular Condensation Reaction of N-1-(Carbocyclic-ribosyl)inosine 5″, 6″-Diphosphate Derivatives by an 8-Bromo-Sustitution at the Hypoxanthine Moiety. *J. Org. Chem.* **1998**, *63*, 1986–1994.

30. De Napoli, L.; Di Fabio, G.; Messere, A.; Montesarchio, D.; Piccialli, G.; Varra, M. Synthetic studies on the glycosylation of the base residues of inosine and uridine. *J. Chem. Soc. Perkin Trans.* **1999**, *1*, 3489–3493. [CrossRef]

31. Hyde, R.M.; Broom, A.D.; Buckheit, R.W. Antiviral amphipathic oligo- and polyribonucleotides: Analogue development and biological studies. *J. Med. Chem.* **2003**, *46*, 1878–1885. [CrossRef] [PubMed]

32. Karnekanti, R.; Hanumaiah, M.; Sharma, G.V.M. Stereoselective Total Synthesis of (+)-Anamarine and 8-epi-(-)-Anamarine from D-Mannitol. *Synthesis* **2015**, *47*, 2997–3008. [CrossRef]

33. Lanier, M.L.; Park, H.; Mukherjee, P.; Timmerman, J.C.; Ribeiro, A.A.; Widenhoefer, R.A.; Hong, J. Formal Synthesis of (+)-Laurencin by Gold(I)-Catalyzed Intramolecular Dehydrative Alkoxylation. *Chem.-A Eur. J.* **2017**, *23*, 7180–7184. [CrossRef] [PubMed]

34. Véliz, E.A.; Beal, P.A. 6-Bromopurine nucleosides as reagents for nucleoside analogue synthesis. *J. Org. Chem.* **2001**, *66*, 8592–8598. [CrossRef] [PubMed]

35. Buchanan, H.S.; Pauff, S.M.; Kosmidis, T.D.; Taladriz-Sender, A.; Rutherford, O.I.; Hatit, M.Z.C.; Fenner, S.; Watson, A.J.B.; Burley, G.A. Modular, Step-Efficient Palladium-Catalyzed Cross-Coupling Strategy to Access C6-Heteroaryl 2-Aminopurine Ribonucleosides. *Org. Lett.* **2017**, *19*, 3759–3762. [CrossRef] [PubMed]

36. Perkins, J.J.; Shurtleff, V.W.; Johnson, A.M.; El Marrouni, A. Synthesis of C6-Substituted Purine Nucleoside Analogues via Late-Stage Photoredox/Nickel Dual Catalytic Cross-Coupling. *ACS Med. Chem. Lett.* **2021**, *12*, 662–666. [CrossRef] [PubMed]