Mimetics of ADP-Ribosylated Histidine through Copper(I)-Catalyzed Click Chemistry

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ABSTRACT: A convergent synthesis provided nearly perfect τ-ADP-ribosylated histidine isosteres (His*-τ-ADPr) via a copper(I)-catalyzed cycloaddition between an azido-ADP-ribosyl analogue and an oligopeptide carrying a propargyl glycine. Both α- and β-configured azido-ADP-ribosyl analogues have been synthesized. The former required participation of the C-2 ester functionality during glycosylation, while the latter was obtained in high stereoselectivity from an imidate donor with a nonparticipating para-methoxy benzyl ether. Four His*-τ-ADPr peptides were screened against a library of human ADP-ribosyl hydrolases.

Among the different acceptor residues, serine has emerged as the primary target in DNA damage-induced ADP-ribosylation. Recent proteomic studies have also drawn attention toward the occurrence of lower-frequency modifications at tyrosine and histidine sites. The identification of these new flavors of stress-induced ADP-ribosylation is suggestive of a specialized control mechanism for subprocesses within the DNA-damage response (DDR). For an identification and characterization of the responsible “writers”, “readers”, and “erasers” as well as an examination of their cellular function, well-defined molecular tools are indispensable.

To generate tools to study histidine ADP-ribosylation, we reasoned that click chemistry could be exploited to create a nearly perfect isostere of ADP-ribosylated histidine (Figure 1A). Although the exact structure of ADP-ribosylated histidine (His-ADPr) has not yet been determined, we hypothesize here that ADPr is introduced at the τ-position of the imidazole functionality, most likely via an α-configured linkage. This hypothesis is based on the isolation of ribosylated and ADP-ribosyl histidine metabolites combined with the known stereospecificity of PARP enzymes. The suspected 1,4-substitution pattern can be mimicked via a Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC), known for its high regioselectivity, with an azido-ADPr analogue and an oligopeptide carrying a propargyl click handle at a specific

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The use of CuAAC has been successfully implemented before in the synthesis of ADP-ribosylated oligopeptides and proteins.24-26 Here, the convergent syntheses of both α- and β-configured ADP-ribosylated histidine mimetics 1-4 (Figure 1B) are described. The target oligopeptides 1-4 are based on two potential His-ADPr sites, located on histone PARylation factor 1 (HPF1) and PARP1, respectively, that have been identified in recent proteomic studies.27 We aimed to assemble the peptides by a late-stage click reaction between the fully deprotected propargyl-glycine containing peptides and the α- and β-ADP-ribosyl azides 22 and 25, which in turn can be obtained from the two anomeric azido ribose 5-phosphates (9 and 17) and known adenosine phosphoramidite 20 using our P(III)−P(V) coupling method.28

Synthesis of the β-configured 5-phosphorylribofuranoside 9 started with commercially available ribofuranose tetraacetate (Scheme 1). Owing to neighboring group participation of the C-2-O-acetyl, the desired β-azide was acquired with excellent stereoselectivity (α/β = 14:1, Scheme 1B). Removal of the PMB protecting groups proved difficult at this point using either oxidative or acidic conditions, which resulted in the formation of 2,3-O-p-methoxybenzylidene products or degradation of the compound, respectively. We therefore decided to postpone the removal of the PMB ethers to a later stage and first removed the C-5-O-silyl group in 15 with HF-pyridine as a fluorine source. Then, phosphitylation and subsequent oxidation, as described above for β-ribosyl azide 9, provided α-azido-5-phosphorylribofuranoside 17.

The pyrophosphate linkage in the target α- and β-azido ADP-ribose building blocks was installed using our P(III)−P(V) coupling method (Scheme 3).28 The required adenosine donor 14 with trimethylsilyl triflate at −60 °C in the presence of trimethylsilyl azide provided ribosyl azide 15 with excellent stereoselectivity (α/β = 14:1, Scheme 1B). Removal of the PMB protecting groups proved difficult at this point using either oxidative or acidic conditions, which resulted in the formation of 2,3-O-p-methoxybenzylidene products or degradation of the compound, respectively. We therefore decided to postpone the removal of the PMB ethers to a later stage and first removed the C-5-O-silyl group in 15 with HF-pyridine as a fluorine source. Then, phosphitylation and subsequent oxidation, as described above for β-ribosyl azide 9, provided α-azido-5-phosphorylribofuranoside 17.

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phosphoramidite 20 was synthesized from adenosine in 6 steps according to a previously reported method (Scheme S3). First, the phosphates in 9 and 17 were liberated by removal of the PMB-groups with triethylamine. Next, the phosphates 21 and 23 were coupled with adenosine amide 20 upon activation with dicyanoimidazole (DCI). Subsequent t-BuOOH mediated oxidation of the P(III)−P(V) intermediate provided the partially protected pyrophosphates. Deprotection of these building blocks started with the removal of the cyanoethyl groups with DBU, after which treatment with aqueous ammonia provided the fully deprotected β-azido-ADPr 22 and α-azido-ADPr 24, carrying the two PMB ethers. β-Azido-ADPr 22 could be purified by size exclusion chromatography (SEC) and was isolated as the ammonium salt. On the contrary, due to hydrophobic interactions of the C-2- and C-3-O-PMB groups of α-azido-ADPr 25, SEC was not efficient, and preparative reversed-phase high-performance liquid chromatography (RP-HPLC) was required to obtain the pure compound. Final removal of the PMB groups was executed using a catalytic amount of HCl in hexafluoro-2-propanol to yield 25 as triethylammonium salt after workup and lyophilization.

The required peptides 26 and 27 were synthesized using Fmoc-based solid phase peptide synthesis (SPPS), incorporating propargyl glycine at the positions that are to carry the His-type ADPr modification. Both peptides were obtained in good yield and purity after RP-HPLC purification using an NH₄OAC buffered eluent system.

For the final Cu(I)-catalyzed conjugation, a 1.5-fold molar excess of the azido-ADPr analogue (22 or 25) was added to an aqueous solution of the oligopeptide (26 or 27) after which the solution was degassed with argon (Scheme 4). In parallel, a fresh “click mixture” was prepared for every reaction by adding an aqueous solution of sodium ascorbate to CuSO₄ directly followed by tris(3-hydroxypropyltriazolylmethyl)amine (THPTA). After addition of this mixture to the solution of the azide and the alkyne, the conversion of the oligopeptide was monitored with liquid chromatography−mass spectrometry (LC-MS). Upon complete conversion, the crude products were desalted by SEC and subsequently purified by preparative HPLC. Unfortunately, this tandem purification method provided the desired products in moderate yields. Direct preparative RP-HPLC proved to be more efficient and provided the desired products in high purity.

Having obtained the triazole mimetics of ADP-ribosylated histidine peptides, we set out to investigate the enzymatic turnover of this modification (Figure 2A). Peptides 1−4 were incubated in the presence of different human (ADP-ribosyl)-hydrolases and nudix hydrolase 5 (NudT5) for 1 h at 30 °C. The former may catalyze the breakage of the N-glycosidic bond of the ribosyltriazole, while the latter converts the released ADP into adenosine monophosphate (AMP), which was quantified using the AMP-Glo assay. As a positive control, the samples were incubated in the presence of NudT16, which in contrast to NudT5 can hydrolyze ADPr that is conjugated to a peptide. Although most human hydrolases were unable to remove ADP from the peptides, we observed a consistent minor turnover (−8.2%) for the HPF1-α peptide 4, indicating that our developed isostere is indeed a functional mimic of ADP-ribosylated histidine. Interestingly, ARH3 appeared unable to convert PARP1-α (2), which could suggest that the removal of His-ADPr modifications is sequence-dependent. These findings were substantiated in a time-course experiment (Figure 2B), which showed the steady enzymatic conversion of 4 and the resistance of 2 toward enzymatic turnover.

In conclusion, we have described the synthesis of both α- and β-configured ADPr-azole analogues that were successfully used to prepare mimetics of ADP-ribosylated histidine using CuAAC. Initial screening of the peptides against a collection of human ADPr hydrolases revealed that ARH3 is able to hydrolyze the N-glycosidic triazole-ribose linkage of HPF1-α 4, while PARP1-α 2 remained unscathed. Not only do these
results suggest that ARH3 is likely able to remove the ADPribosylation from histidine residues in the right sequential context,35 but it also demonstrates that the peptides presented here provide useful tools for the further study of the interactions of the His-ADPr modification with either binders or hydrolases. Our current efforts in the synthesis of peptides with native ADP-ribosylated histidine will hopefully further elucidate the process of His-ADPr demodification in the near future.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01300.

Syntheses of β-configured ribose 5-phosphate 9, α-configured ribose 5-phosphate 17, and phosphoramidate 20; procedures for pyrophosphate construction, final CuAAC conjugation, solid-phase peptide synthesis of 26 and 27, plasmid expression, protein purification, and (ADP-ribosyl)hydrolase activity screening; general experimental procedures; and copies of IR and NMR spectra (PDF)

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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