

Investigation of on-column Sonogashira coupling for structural optimization of alkynylated purine-pyridazine base pairs

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Synthetic unnatural base pairs (UBPs) have been proved to be attractive tools for developing DNA-based biotechnology. To date, several research groups have reported sets of unnatural bases which form orthogonal pairing without interacting with natural ones, yet active in replication, transcription and translation.¹⁾ Recently, we have developed a new type of UBP system with alkynylated purine and pyridazine nucleosides bearing additional hydrogen bonding units (pseudo-nucleobases). We have envisioned that the selectivity against the canonical bases can be acquired by pseudo-nucleobases forming hydrogen bonds at a distant position from Watson-Crick base pairs (Fig. 1). The thermal stability assays have shown that the alkynylated purine-pyridazine pairs exhibit the selective and stable interaction in the duplex DNAs through the formation of complementary hydrogen bonds in the major groove.²⁾

In this study, we aimed to modify the structures of pseudo-nucleobase units in order to gain deeper insight into the molecular interaction in the major groove as well as to improve the pairing ability of the alkynylated base pairs. To this end, we attempted a post-synthetic method *via* on-column Sonogashira reaction to prepare various alkynylated purine analogs on oligonucleotides in a convenient and systematic way (Fig. 2). The oligonucleotide bearing a halogenated purine analog (**1**) was synthesized by solid phase DNA synthesis and reacted with various ethynyl pseudo-nucleobases to construct the desired nucleosides within the strand. We studied the conditions for on-column Sonogashira reaction and succeeded in introducing pseudo-nucleobases with different chemical structures. Details of the reaction as well as properties of the synthesized nucleoside analogs will be reported in this presentation.

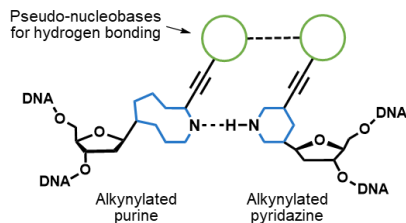


Figure 1. Schematic of alkynylated purine-pyridazine pair

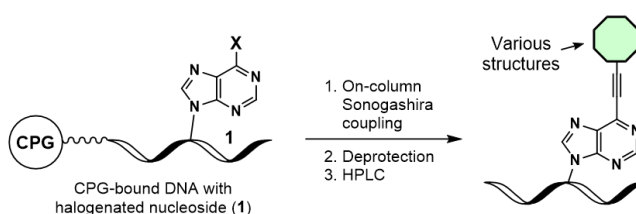


Figure 2. On-column Sonogashira coupling for preparing purine derivatives

- 1) S. Hoshika, *et al.*, *Science*, **2019**, 363, 884; V. T. Dien, *et al.*, *J. Am. Chem. Soc.*, **2018**, 140, 16115; M. Kimoto, *et al.*, *Nat. Biotechnol.*, **2013**, 31, 453.
- 2) Manuscript under preparation.