Design and synthesis of alkynylated pyridone nucleosides toward selective unnatural base pairing

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The development of unnatural base pairs (UBPs) is considered as one of the most promising methods to expand the functionality as well as genetic information of DNA.[1] Over the past decades, researchers have reported different types of UBPs which exhibit orthogonality in base pairing and enzymatic replication in the presence of canonical A-T and G-C base pairs. In our own effort to expand design repertoire of UBP, we have very recently created a new type of UBPs, named alkynylated purine-pyridazine pairs, bearing additional hydrogen bonding modules (pseudo-nucleobases) in the major groove (Fig. 1a).[2] These unnatural nucleosides formed stable base pair when the hydrogen-bonding pattern of pseudo-nucleobases is complementary to each other. Furthermore, both alkynylated purines and pyridazines exhibited a good selectivity against the canonical nucleobases; however, the alkynylated pyridazine showed moderate affinity toward adenine.

In this work, we designed new derivatives of ^{O}Pz and ^{N}Pz (Fig. 1b; ^{O}Pc, ^{N}Pc) in which the pyridazine core was replaced by 2-pyridone. We envisioned that the base pairing selectivity could be enhanced by potential Van der Waals interaction between C-H and alkyne. To test the hypothesis, ^{O}Pc and ^{N}Pc nucleosides were synthesized and incorporated into oligonucleotides, and their pairing stability and selectivity were investigated by UV denaturing temperature measurement. We will report the details of the molecular design, synthesis, and base pairing properties in the presentation.

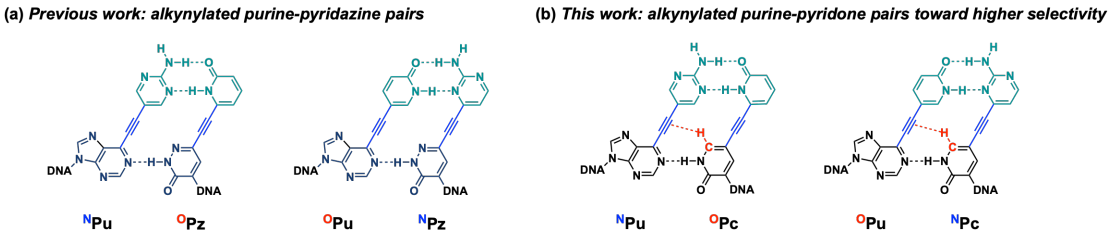

Figure 1 (a) Structures of alkynylated purine-pyridazine base pairs. (b) Design of the alkynylated pyridone derivatives.

1) M. Kimoto, I. Hirao, *Chem. Soc. Rev.* **2020**, *49*, 7602-7626.

2) H. Okamura, G. H. Trinh, Z. Dong, Y. Masaki, K. Seio, F. Nagatsugi, *Nucleic Acids Res.* **2022**, *50*, 3042-3055.