Tailoring Peptide Nucleic Acid backbones towards enhanced PNA-based circuitry

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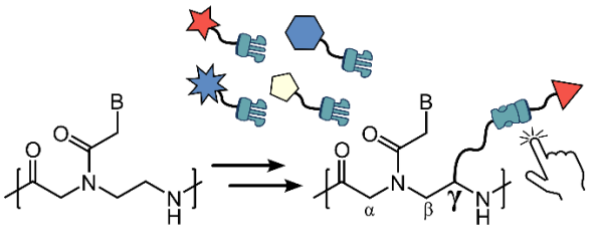
Peptide nucleic acids (PNAs) emerged as one of the most promising classes of nucleic acid mimics. Their remarkable hybridization capabilities, together with their straightforward synthesis, have established these artificial nucleic acids as valuable tools in diagnostics, therapeutics, and supramolecular engineering. Numerous modifications to the PNA backbone have been investigated to fine-tune their physicochemical properties and enable the attachment of functional molecules.[1]

We developed a universal γ-propargyl PNA backbone derived from Serine, followed by its acylation with the four canonical DNA nucleobases.[2] Because Serine is available in both D- and L-enantiomeric forms, this platform offers straightforward access to PNA oligomers suited for hybridization with natural oligonucleotides or for use in orthogonal hybridization circuits. We demonstrated that late-stage conjugation can be used to tune the physicochemical properties. This strategy is particularly attractive due to its orthogonality to Fmoc-SPPS, its flexibility, and its compatibility with introducing structural diversity through on or off-resin copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC). We examined how the nature of the attached groups (neutral, negatively charged, or positively charged) affects the hybridization kinetics and thermal stabilities of these PNAs when forming duplexes with either DNA or PNA.[3] Moreover, the utility of these new monomers was further illustrated through their application in PNA-based hybridization chain reactions (HCRs).



References:

(1) - E. E. Watson, *Org. Biomol. Chem.,* **2025**, 23, 9797-9814
(2) - M. López-Tena, E. E. Watson , P. Romanens and N. Winssinger, *Helvetica Chimica Acta*, **2023**, 106 , e202300110
(3) - M. López-Tena and N. Winssinger, *Org. Biomol. Chem.*, **2024**, 22, 5759-5767