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HxNA: a Bridged Nucleic Acid with a Perhydro-1,2-oxazin-3-one Ring

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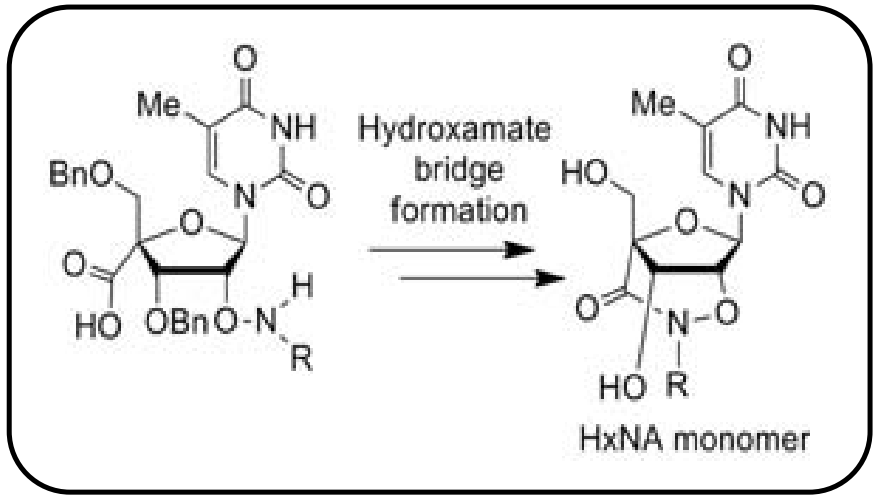
[Objective] As a novel modification of 2',4'-Bridged Nucleic Acid/Locked Nucleic Acid, a bridged nucleic acid containing six-membered perhydro-1,2-oxazin-3-one ring was designed and synthesized, termed as Hydroxamate bridged Nucleic Acid (HxNA).[1] The presence of a carbonyl function along with an N-O linkage in the bridge is the unique feature of the structure. The carbonyl function would restrict the flexibility of the sugar moiety by its trigonal planarity, which is expected to improve the properties of the modification.

[Result] The target HxNA monomers were successfully synthesized in 14 and 16 steps, starting from the common intermediate for 2',4'-BNA/LNA i.e. 3-*O*-benzyl-4-*C*-hydroxy methyl-1,2-*O*-isopropylidene-α-D-ribofuranose. The characteristic N-O linkage was introduced by S_N2-type substitution reaction at 2'-position of sugar moiety by *N*-hydroxylphthalimide. The ring of the bridged structure was cyclized by the condensation reaction between aminooxy group at 2'-position and carboxyl group at 4'-position, activated by carbodiimide. The synthesized HxNA-[NMe] monomer was incorporated into oligonucleotides and their properties were investigated and compared with the natural DNA oligonucleotide. The HxNA-modified oligonucleotides exhibited highly RNA selective binding affinity, along with an interesting nuclease resistance.



1. Shrestha, A. R.; Hari, Y.; Yahara, A.; Osawa, T.; Obika, S. *J. Org. Chem.* **2011** (In press) DOI: 10.1021/JO 201597E