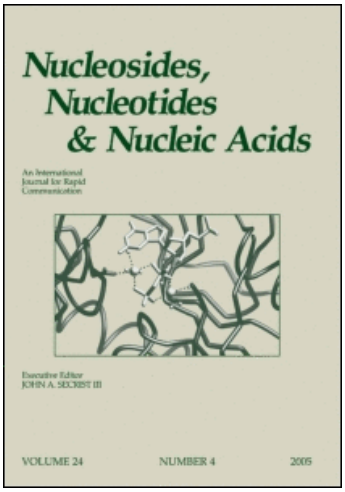

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Triplex Formation of α-Oligodeoxynucleotides Containing 5-Me-α-dC(N-4-Spermine)

A. Meyer[a]; F. Morvan[a]; B. Rayner[a]; J. L. Imbach[a]
[a] Laboratoire de Chimie Bio-Organique, Montpellier Cedex, (France)

To cite this Article Meyer, A. , Morvan, F. , Rayner, B. and Imbach, J. L.(1999) 'Triplex Formation of α-Oligodeoxynucleotides Containing 5-Me-α-dC(N-4-Spermine)', Nucleosides, Nucleotides and Nucleic Acids, 18: 6, 1631 — 1632
To link to this Article: DOI: 10.1080/07328319908044805
URL: http://dx.doi.org/10.1080/07328319908044805

NUCLEOSIDES & NUCLEOTIDES, 18(6&7), 1631–1632 (1999)

TRIPLEX FORMATION OF α-OLIGODEOXYNUCLEOTIDES CONTAINING 5-Me-α-dC(N-4-SPERMINE)

A. Meyer, F. Morvan*, B. Rayner and J.-L. Imbach

Laboratoire de Chimie Bio-Organique, UMR 5625, Université de Montpellier II, Place E. Bataillon 34095 Montpellier Cedex 5, (France)

ABSTRACT : Pyrimidine α-ODNs containing 5-Me-α-dC(N-4-spermine) at the 5'-end or in the sequence were synthesized. The corresponding αββ triple helices were strongly stabilized by Mg^{2+} cations. Unlike in β-series these triplexes were not stabilized at pH 7.

Triplex oligodeoxynucleotide (ODN) has therapeutic importance (1) and depends on Hoogsteen hydrogen bonds between a duplex DNA and a third DNA strand, T*A:T triplets are formed at neutral pH and C^+*G:C are favored at acidic pH. It was demonstrated that spermine conjugation at N-4 of 5-Methyl-deoxycytidine in ODNs lead to triplexes stable at physiological pH (2). However since natural ODNs are rapidly degraded by nucleases and nuclease resistant PS-ODNs exhibited poor triplex ability, we developed the same strategy with the nuclease resistant α-ODNs (3).

Di-*O*-3',5'-acetyl-α-thymidine was converted in three steps into *O*-4-(2,6-dimethylphenyl)-α-thymidine. After 5'-dimethoxytritylation the 2,6-dimethylphenyl group was then displaced by spermine to yield 5-methyl-α-deoxycytidine(N-4-spermine) derivative which was finally converted, after protection of their amino functions by trifluoroacetyl groups, into the desired phosphoramidite building block.

Pyrimidine α-ODNs (**Table**) containing 5-Me-α-dC(N-4-spermine) at the 5'-end or in the sequence were synthesized and the stability of the corresponding αββ triple helices were studied, by UV melting experiments, at pH 6 and 7 in absence and in presence of Mg^{2+}.

Table : Sequence of α-oligonucleotides third strand and ββ-target.

	α-oligonucleotides third strand
I	α-5'-TCTCTCTCTCTTTTT-3'
II	α-5'-T^{me}CT^{me}CT^{me}CT^{me}CT^{me}CTTTTT-3'
III	α-5'-T^{me}C^{Sper}TCTCTCTCTTTTT-3'
IV	α-5'-TCTCTCTCT^{me}C^{Sper}TTTTT-3'
V	α-5'-T^{me}C^{Sper}T^{me}CT^{me}CT^{me}CT^{me}CTTTTT-3'

	β-Double-Stranded DNA Target
VI	3'-GCT**AGAGAGAGAGAAAAA**TCG-5'
VII	5'-CGA**TCTCTCTCTCTTTTT**AGC-3'

The presence of 20mM Mg^{2+} strongly stabilized the triple helices at pH 6 and 7. As expected introduction of 5-methyl cytosine (II and V) increased the Tm values (ΔTm +9°C). In contrary to what was found in β-series introduction of spermine into α-ODNs (III and V) destabilized the resulting triplexes (ΔTm - 11°C). The destabilization was more pronounced (ΔTm - 20°C) when spermine was conjugated in the sequence of the ODN (IV) than at its 5'-end (III and V).

Furthermore we showed at pH 7 that α-ODNs have a propensity to form self-hybridization that competes with triplex formation.

At pH 7 no enhancement of triplexes stability was observed in contrary to what was found in β-series. This discrepancy may be due to the difference of sequence since the sequence reported in β-triplexes contained only three cytosines.

REFERENCES

1.Helene, C. *Anticancer Drug Des,* **1991,** *6*, 569-84.
2.Barawkar, D. A.; Rajeev, K. G.; Kumar, V. A.;Ganesh, K. N. *Nucleic Acids Res.*, **1996,** *24*, 1229-1237.
3.Morvan, F.; Porumb, H.; Degols, G.; Lefebvre, I.; Pompon, A.; Sproat, B. S.; Rayner, B.; Malvy, C.; Lebleu, B.;Imbach, J. L. *J. Med. Chem.*, **1993,** *36*, 280-287.