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Synthesis and Hybridization Properties of Oligodeoxynucleotides Containing 3'-Deoxy-3'-C-methyleneuridine

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ABSTRACT

3'-Deoxy-3'-C-methyleneuridine nucleoside 1¹ has been incorporated into oligodeoxynucleotides. Relative to the unmodified references, oligomers containing nucleoside 1 displayed reduced binding affinities towards complementary DNA and RNA with a tendency towards RNA-selective hybridization.

Key Words: Oligonucleotides; Oligodeoxynucleotides; 3'-Methyleneuridine; Hybridization.

We have studied the effect of incorporating 3'-deoxy-3'-C-methyleneuridine (1)¹ into oligodeoxynucleotides. Nucleoside 1 was synthesized by a convergent strategy starting from 1,2-O-isopropylidene-α-D-xylofuranose (Sch. 1).^[1-3] Coupling between the tri-O-acyl furanose derivative and uracil by the Vorbrüggen method followed by deactylation afforded nucleoside 1. The corresponding phosphoramidite 2 was obtained and used for automated synthesis of oligomers B, D and E (Table 1).

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Scheme 1. a) Ref. 2–3; b) Uracil, BSA, TMS-triflate, CH₃CN; c) MeONa, MeOH (48%, two steps); d) DMTCl, DMAP, pyridine; e) NCCH₂CH₂OP(Cl)N(*i*-Pr)₂, EtN(*i*-Pr)₂, CH₂Cl₂ (52%, two steps).

Table 1. Hybridization data.^a

| | Complementary ssDNA | | Compleme | Complementary ssRNA | |
|---|----------------------------|------------------------|-----------------|------------------------|--|
| Oligonucleotide | $T_{\rm m}/^{\circ}{ m C}$ | $\Delta T_m/^{\circ}C$ | $T_m/^{\circ}C$ | $\Delta T_m/^{\circ}C$ | |
| A: 5'-GTGATATGC | 28.0 | Ref. | 26.0 | Ref. | |
| B: 5'-GTGAXATGC | 21.0 | -7.0 | 24.0 | -2.0 | |
| C: 5'-T ₁₄ | 32.5 | Ref. | 29.0 | Ref. | |
| D : $5'$ - T_7 X T_6 | 24.0 | -8.5 | 25.0 | -4.0 | |
| E: $5'$ - T_5 X ₄ T_5 | < 5.0 | | 15.0 | -3.5 | |

^aA₂₆₀ as a function of temperature was recorded in a medium salt buffer (100 mM sodium chloride, 10 mM sodium phosphate, 0.1 mM EDTA, pH = 7.0) with 1.5 μM concentration of each of the two complementary strands. X = 2',5'-linked nucleotide monomer derived from 1.

The possibility of forming an allylic carbocation during the iodine oxidation of a standard oligonucleotide synthesis cycle made us replace the usual oxidation reagent, iodine/water/pyridine, with tert-butyl hydroperoxide.^[4] The cyanoethyl group was selectively deprotected with diisopropylamine to limit the cleavage of internucleotide bonds known to be a problem for similar compounds. [5]

Due to the presence of the exocyclic double bond, the furanose ring of nucleoside 1¹ is restricted into a C1'-exo type furanose conformation as shown by molecular modeling. However, hybridization studies towards complementary DNA and RNA showed reduced melting temperatures for oligomers B, D and E compared to the oligodeoxynucleotide references A and C (Table 1). As for oligonucleotides containing 2',5'-linked RNA, [6,7] a selectivity towards complementary RNA was found.

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REFERENCES

- 1. Samano, V.; Robins, M.J. Nucleic acid related compounds. 62. Stereoselective addition of a Wittig reagent to give at single nucleoside oxaphosphetane diastereoisomer. Synthesis of 2'(and 3')-deoxy-2'(and 3')-methyleneuridine (and cytidine) derivatives from uridine ketonucleosides. Synthesis 1991, 283 pp.
- 2. Johnson, C.R.; Bhumralkar, D.R. 3'-C-Trifluoromethyl ribonucleosides. Nucleosides Nucleotides 1995, 14, 185 pp.
- 3. Giradet, J.; Gunic, E.; Esler, C.; Cieslak, D.; Pietzkowski, Z.; Wang, G. Synthesis and cytotoxicity of 4-amino-5-oxopyrido[2,3-d]pyrimidine nucleosides. Phosphoramidites derived from tertiary alcohols. Why do they sometimes couple with low efficiency? J. Med. Chem. **2000**, *43*, 3704 pp.
- 4. Scheuer-Larsen, C.; Dahl, B.M.; Wengel, J.; Dahl, O. Synthesis and properties of some (2',5') linked dinucleoside monophosphates modified with 3'-difluoromethylene groups. Tetrahedron Lett. **1998**, *39*, 8361 pp.
- 5. Brown, C.A.; Barnes, C.L.; Serafinowski, P.J. Oligoribonucleotides containing 2',5'-phosphodiester linkages exhibit binding selectivity for 3',5'-RNA over 3',5'-ssDNA. Nucleosides Nucleotides 1999, 18, 1249 pp.
- 6. Giannaris, P.A.; Dahma, M.J. Oligoribonucleotides containing 2',5'-phosphordiester linkages exhibit binding selectivity for 3',5'-RNA over 3',5'-ssDNA. Nucleic Acids Res. **1993**, 21, 4742 pp.
- 7. Kandimalla, E.R.; Manning, A.; Zhao, Q.; Shaw, D.R.; Byrn, R.A.; Sasisekharan, V.; Agrawal, S. Mixed backbone antisense oligonucleotides: design, biochemical and biological properties of oligonucleotides containing 2'-5'-ribo- and 3'-5'-deoxyribonucleotide segments. Nucleic Acids Res. 1997, 25, 370 pp.