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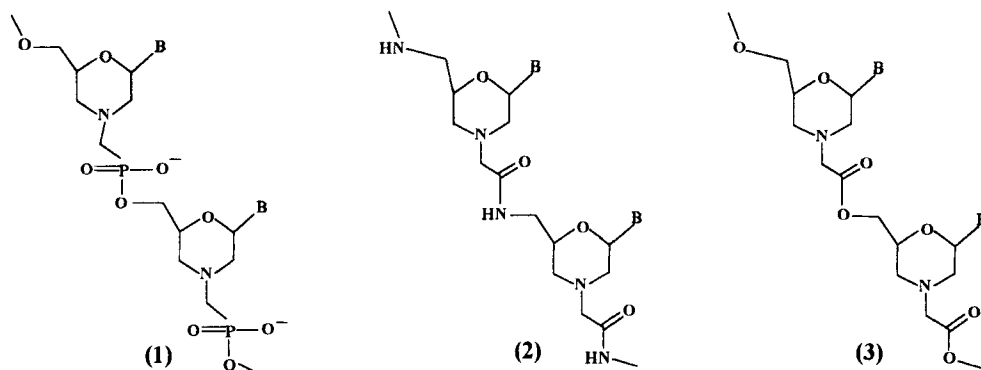
SYNTHESIS AND PROPERTIES OF SOME MORPHOLINO OLIGONUCLEOTIDE ANALOGUES

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ABSTRACT. The solid phase synthesis of the three types of morpholino analogues of nucleic acids has been accomplished and their hybridization properties were evaluated.

Recently, morpholino antisense oligomers have been reported as nucleic acids analogues having very high efficacy and specificity, immunity to nucleases, good water solubility and low production costs¹. To continue our investigations on the design and synthesis of modified nucleic acid fragments as potential therapeutics agents and diagnostic tools^{2, 3}, we have accomplished the synthesis of a set of novel morpholino analogues of oligonucleotides with phosphonate ester (1), amide (2) or ester (3) linkages between morpholino-nucleoside residues. Procedures to obtain uracil and adenine containing monomer units (6-8) starting from the corresponding ribonucleosides (4) were developed (Scheme 1)⁴. The solid phase synthesis of oligomers of type (1, 2) was accomplished using the protocols, which were developed for the formation of phosphonate ester and amide internucleoside linkages previously³. The synthesis of polyester analogues (3) was performed starting from monomers (7) on an alkylsulfonyl ethyl-CPG support, which was functionalized with p-chlorophenyl ester of 5'-dimethoxytrityldeoxynucleoside 3'-phosphate⁵. After the removal of blocking groups, oligomers were isolated by anion-exchange or reversed-phase chromatography, and their purity and identity was confirmed by MALDI-TOF MS. Preliminary evaluation of



hybridization properties has revealed that analogues (1-3) are able to form complexes with complementary RNA and DNA fragments as well as with the complementary sequences of morpholino-analogues of the same type. Some of the results obtained are shown in Table 1.

SCHEME 1

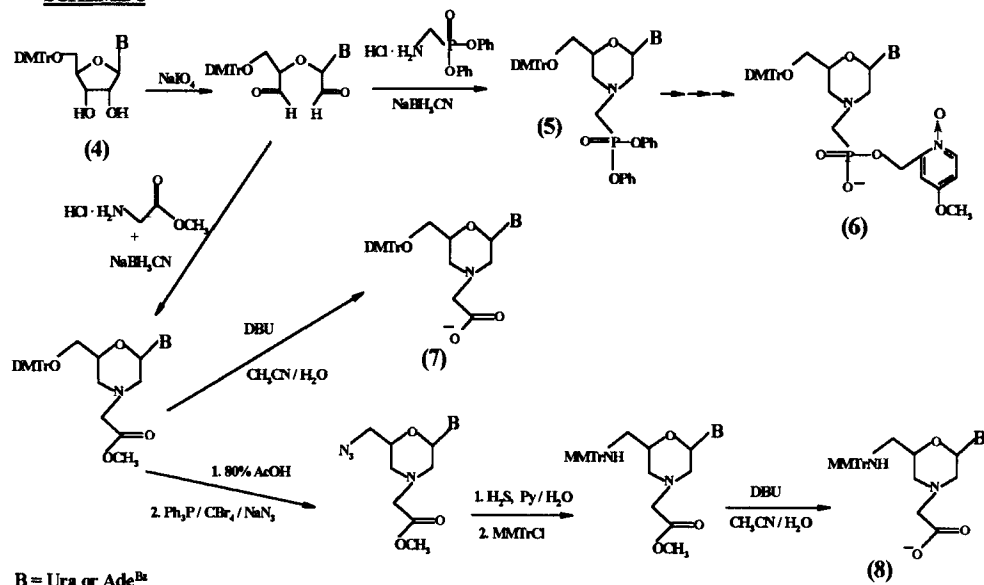


TABLE 1. Melting temperatures of complexes formed by morpholino-analogues (3 μ M) with the complementary oligomers in 0.15 M NaCl / 10 mM Tris-HCl / 1 mM MgCl₂ (pH 7). The values were measured at 260 nm by heating from 2°C to 80°C (0.5°C/min).

| Oligomer type | Sequence | Complementary target | T _m , (Δ T _m) °C |
|---------------|----------------------|----------------------|---|
| DNA | dT ₁₅ | dA ₁₅ | 42 |
| DNA | dT ₁₀ | dA ₁₀ | 25 |
| Morph-1 | U ₁₄ -dT | dA ₁₅ | <10 (>-32) |
| Morph-2 | U ₁₀ -dT | dA ₁₀ | 31 (+6) |
| Morph-3 | U ₁₄ -dTp | dA ₁₅ | 48 (+6) |
| Morph-1 | A ₁₄ -dA | dT ₁₅ | 12 (-30) |
| Morph-2 | A ₁₀ -dA | dT ₁₀ | 22 (-3) |
| Morph-1 | U ₁₄ -dT | Morph-1-A | 34 (-8) |

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- The synthetic protocols for monomers (6-8) will be published elsewhere. The conversion of compound (5) into monomer (6) was performed in 3 steps essentially as described earlier^{2,3}.
- Efimov, V.; Buryakova, A.; Reverdatto, S.; Chakhmakhcheva, O.; Ovchinnikov, Yu. *Nucleic Acids Res.*, **1983**, *11*, 8369-8387. The condensations during the chain elongation were performed for 10 min in acetonitrile - pyridine (2:1, v/v) using monomers (7) (0.05 M), TPSCI (0.15 M) and Melm (0.3 M). The target oligomer was cleaved from the support by the action of *tert*-butylamine - dioxane (1:1, v/v) for 2 hrs at 20°C.