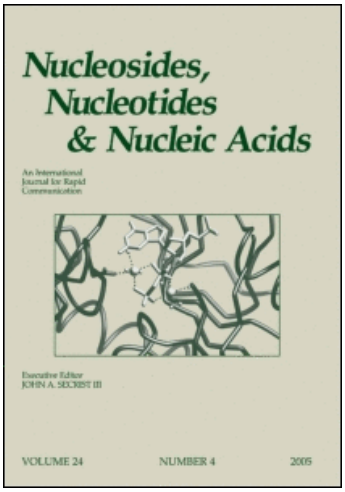


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Properties of Some Morpholino Oligonucleotide Analogues

O. Chakhmakhcheva[a]; M. Andrianov[a]; A. Buryakova[a]; M. Choob[a]; V. Efimov[a]
[a] Shemyakin & Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Moscow, Russia

To cite this Article Chakhmakhcheva, O. , Andrianov, M. , Buryakova, A. , Choob, M. and Efimov, V.(1999) 'Synthesis and Properties of Some Morpholino Oligonucleotide Analogues', Nucleosides, Nucleotides and Nucleic Acids, 18: 6, 1427 — 1428
To link to this Article: DOI: 10.1080/07328319908044742
URL: http://dx.doi.org/10.1080/07328319908044742

NUCLEOSIDES & NUCLEOTIDES, 18(6&7), 1427–1428 (1999)

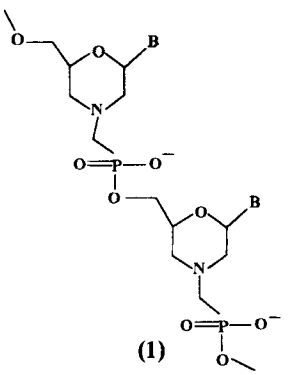
SYNTHESIS AND PROPERTIES OF SOME MORPHOLINO OLIGONUCLEOTIDE ANALOGUES

O. Chakhmakhcheva*, M. Andrianov, A. Buryakova, M. Choob and V. Efimov

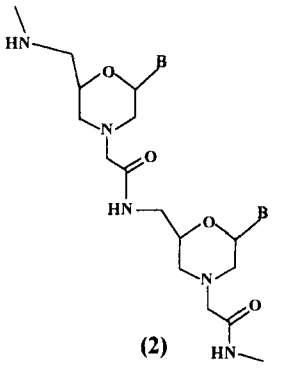
Shemyakin & Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, ul.Miklukho-Maklaya 16/10, Moscow 117871, Russia.

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

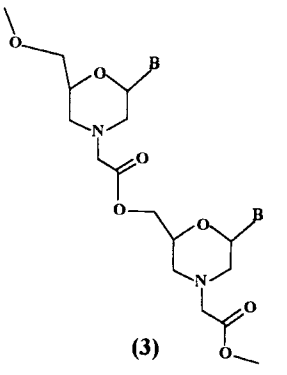
Recently, morpholido antisense oligomers have been reported as nucleic acids analogues having very high efficacy and specificity, immunity to nucleases, good water solubility and low production costs[1]. To continue our investigations on the design and synthesis of modified nucleic acid fragments as 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 previously[3]. The synthesis of polyester analogues (3) was performed starting from monomers (7) on an alkylsulfonylethyl-CPG support, which was functionalized with p-chlorophenyl ester of 5'-dimethoxytrityldeoxynucleoside 3'-phosphate[5]. 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



(1)



(2)



(3)

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

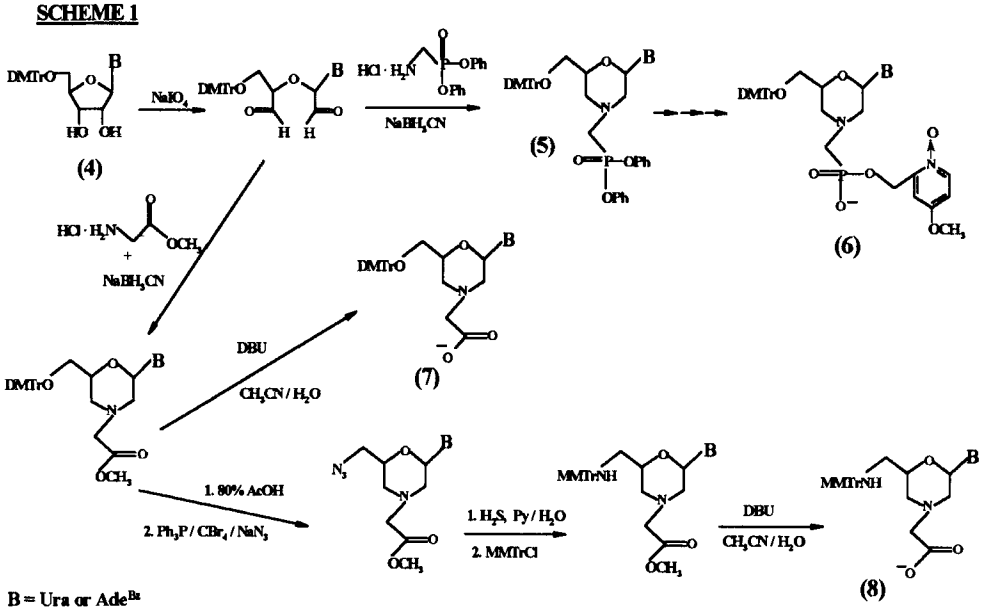


TABLE 1. Melting temperatures of complexes formed by morpholino-analogues (3 μM) with the complementary oligomers in 0.15 M NaCl / 10 mM Tris-HCl / 1 mM $MgCl_2$ (pH 7). The values were measured at 260 nm by heating from 2°C to 80°C (0.5°C/min).

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)

REFERENCES AND NOTES

1. Summerton, J.; Weller, D. *Antisense Nucleic Acid Drug Dev.*, **1997.** *7*, 187-195.
2. Efimov, V.; Choob, M.; Kalinkina, A.; Chakhmakhcheva, O. *Nucleosides & Nucleotides*, **1997,** *16*, 1475-1480.
3. Efimov, V.; Buryakova, A.; Chakhmakhcheva, O. *Bio. Med. Lett.*, **1998,** *8*, 1013-1018.
4. 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].
5. 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), TPSCl (0.15 M) and MeIm (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.