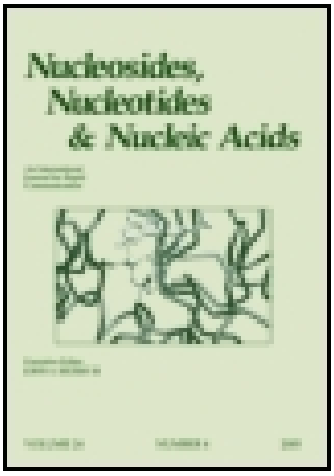

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Duplex Stability of Oligonucleotides Containing 7-Substituted 7-Deaza- and 8-Aza-7-Deazapurine Nucleosides

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DUPLEX STABILITY OF OLIGONUCLEOTIDES CONTAINING 7-SUBSTITUTED 7-DEAZA- AND 8-AZA-7-DEAZAPURINE NUCLEOSIDES

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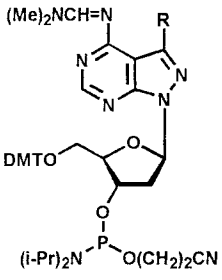
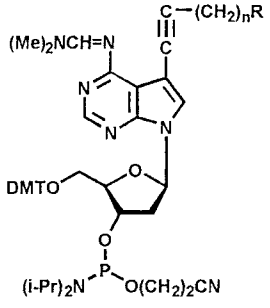
ABSTRACT.- The synthesis of 7-substituted 7-deaza- and 8-aza-7-deazapurine 2'-deoxyribonucleosides, their incorporation into oligonucleotides, and the stability of corresponding duplexes is described.

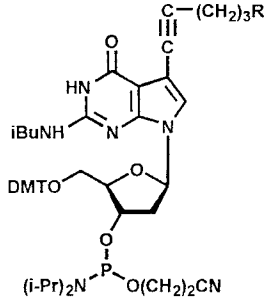
The presence of methyl, as well as halogeno substituents in position 7 of a series of 7-deazapurine-containing oligonucleotides leads to duplex stabilization with retention of the B-DNA structure.[1,2] In continuation of our investigations on the properties of base-modified oligodeoxynucleotides we now report on the synthesis of the phosphoramidites **1-3** of 7-substituted 8-aza-7-deaza-2'-deoxyadenosine, as well as 7-deazapurine 2'-deoxyribonucleosides. They are employed in solid-phase synthesis of oligonucleotides which are then investigated with regard to duplex stability.



1 a R = I
b R = Br

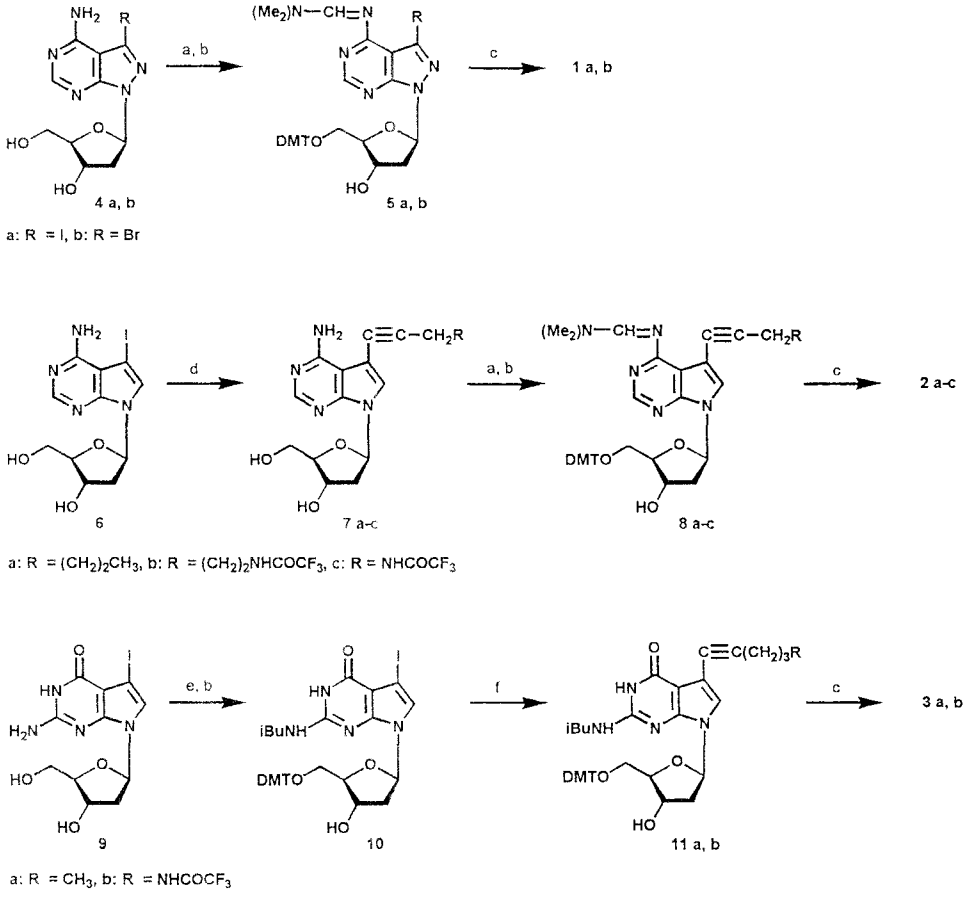


2 a R = CH_3, n = 3
b R = $NHCOCF_3$, n = 3
c R = $NHCOCF_3$, n = 1



3 a R = CH_3
b R = $NHCOCF_3$

Compounds **4a,b**[3], **6**[4], and **9**[5] served as precursors for the synthesis of the protected nucleosides **5a,b**, **8a-c** and **11a,b** (Scheme 1), which were then converted into



(a): $HC(OMe)_2NMe_2$, MeOH; (b): DMT-Cl / pyr.; (c): $NC(CH_2)_2OP(Cl)N(i\text{-}Pr)_2$, $EtN(i\text{-}Pr)_2$, CH_2Cl_2 ; (d): $Pd(PPh_3)_4$, CuI, DMF, Et_3N; (e): TMS-Cl, iBu_2O, pyr.; (f): $Pd(PPh_3)_4$, CuI, CH_3CN, Et_3N

Scheme 1

phosphoramidites. The ω-(trifluoroacetyl)aminoalkynyl- and hexynyl nucleosides **7a-c**, and **11a,b** were prepared using the palladium-catalyzed cross-coupling reaction[6]. All compounds were characterized by ^1H-[7], ^{13}C-, and ^{31}P-NMR spectra as well as by elemental analyses.

The oligonucleotides containing 7-bromo or 7-iodo-7-deazapurine 2'-deoxyribonucleosides exhibit significantly higher T_m-values than those containing 2'-deoxyadenosine or -guanosine (Table 1).

TABLE 1. T_m-Values of 7-deazapurine-containing oligonucleotides.

Oligonucleotide	T_m [°C][a]	Oligonucleotide	T_m [°C][b]
d(A -T)$_6$	33	d(G -C)$_4$	60
d(c^{7}A - T)$_6$	36	d(c^{7}G - C)$_4$	53
d(c^{7}I^{7}A - T)$_6$	60	d(c^{7}I^{7}G - C)$_4$	70
d(c^{7}Br^{7}A - T)$_6$	55	d(c^{7}Br^{7}G - C)$_4$	67
d(c^{7}Me^{7}A - T)$_6$	41	d(c^{7}Me^{7}G - C)$_4$	58
d(c^{7}Hex^{7}A - T)$_6$	50	d(c^{7}Hex^{7}G - C)$_4$	58
d(c^{7}X^{7}A - T)$_6$[c]	50		
d(c^{7}z^{8}Br^{7}A - T)$_6$	52		
d(c^{7}z^{8}I^{7}A - T)$_6$	56		
d(c^{7}z^{8}A - T)$_6$	36		

[a] 8 µM Oligomer conc., 60 mM Na-cacodylate, pH 7.1, 100 mM $MgCl_2$, 1 M NaCl; [b] 10 µM oligomer conc., 10 mM Na-cacodylate, pH 7, 10 mM $MgCl_2$, 100 mM NaCl; [c] X = $C{\equiv}CCH_2NH_3^{\oplus}$.

Although, 7-deaza-2'-deoxyguanosine destabilizes the duplex structure [d(c^{7}G-C)$_4$] compared to the parent oligonucleotide containing 2'-deoxyguanosine [d(G-C)$_4$], the replacement of the 7-hydrogen by a methyl [d(c^{7}Me^{7}G-C)$_4$] or a hexynyl group [d(c^{7}Hex^{7}G-C)$_4$] increases the stability of the duplex strongly.

On the other hand, the duplex d(c^{7}A-T)$_6$ is slightly more stable than d(A-T)$_6$. The replacement of the 7-hydrogen by a methyl [d(c^{7}Me^{7}A-T)$_6$], a hexynyl [d(c^{7}Hex^{7}A-T)$_6$], as well as a 7-(3-aminopropynyl) group [d(c^{7}X^{7}A-T)$_6$] leads to further stabilization of the duplexes (Table 1). In the case of 8-aza-7-deaza-2'-deoxyadenosines the introduction of bromo or iodo substituents in position 7 (**1a**,**1b**) shows the same tendency of duplex stabilization as 7-deaza-2'-deoxyadenosines.

Table 1 indicates that substituents in the 7-position of 7- deazapurines have considerable steric freedom within the major groove of DNA and may carry bulky substituents without significantly interfering overall binding. Therefore, the 7-position of 7-deazapurines is an ideal position for the functionalization of DNA with reporter groups.

References and Notes

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7. **5a**: ^{1}H-NMR (d_6-DMSO): δ, 2.30 (1H, m, H-2'), 2.84 (1H, m, H-2'), 3.06 (2H, m, 2H-5'), 3.76, 3.78 (6H,2s, NMe_2), 3.71, 3.72 (6H, 2s, 2 OMe), 3.95 (1H, m, H-4'), 4.51 (1H, m, H-3'), 5.30 (1H, d, 3'-OH), 6.58 (1H, t, H-1'), 6.76-7.37 (13H, m, arom. H), 8.47 (1H, s, H-6), 8.98 (1H, s, CH).

   8b: ^{1}H-NMR (d_6-DMSO): δ, 1.74 (2H, m, CH_2), 2.23 (1H, m, H-2'), 2.46 - 2.48 (3H, m, CH_2, H-2'), 3.11, 3.15 (6H, 2s, NMe_2), 3.13 (2H, m, 2H-5'), 3.33 (2H, m, CH_2), 3.74 (6H, s, OCH_3), 3.91 (1H, m, H-4'), 4.34 (1H, m, H-3'), 5.29 (1H, d, 3'-OH), 6.54 (1H, t, H-1'), 6.82-7.36 (13H, m, arom. H), 7.56 (1H, s, H-6), 8.29 (1H, s, H-2), 8.73 (1H, s, CH), 9.43 (1H, s, NH).

   11b: ^{1}H-NMR (d_6-DMSO): δ, 1.12 (6H, m, 2 Me), 1.74 (2H, m, CH_2), 2.23 (1H, m, H-2'), 2.41 (2H, m, CH_2), 2.76 (1H, m, CH), 3.11 (2H, m, 2H-5'), 3.30 (2H, m, CH_2), 3.72 (6H, s, 2 OCH_3), 3.90 (1H, m, H-4'), 4.32 (1H, m, H-3'), 5.27 (1H, d, 3'-OH), 6.39 (1H, t, H-1'), 6.85-7.37 (14H, m, arom.H, H-6), 9.47 (1H, t, $NHCOCF_3$), 11,53 (1H, s, NH), 11.81 (1H, s, NH).