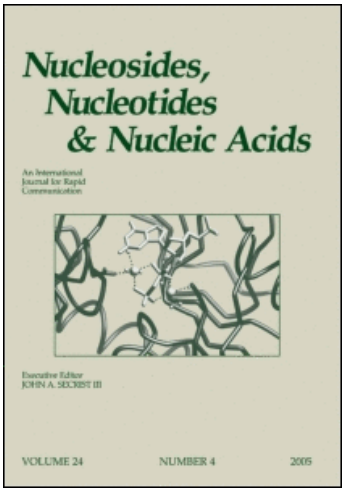

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PARALLEL DNA CONTAINING PYRAZOLO[3,4-D]PYRIMIDINE ANALOGUES OF ISOGUANINE

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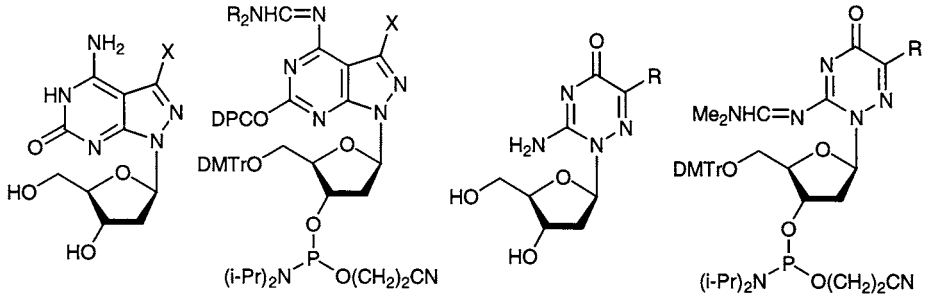
ABSTRACT

The phosphoramidites of 8-aza-7-deaza-2′-deoxyisoguanosine (**1a**) and its bromo derivative **1b** as well as of 6-aza-2′-deoxyisocytidine and its 5-methyl derivative (**3a**,**b**) were synthesized. Parallel-stranded duplexes containing the nucleosides **1a**,**b** show a significantly enhanced duplex stability compared to those containing 2′-deoxyisoguanosine.

Parallel-stranded (ps) DNA is formed when the guanine-cytosine base pair is replaced by isoguanine-cytosine and/or guanine-isocytosine pairs. This work reports on the adjustment of the lower stability of parallel DNA to that with antiparallel chain orientation and on the replacement of the acid-labile 2′-deoxyisoguanosine (5) and 2′-deoxyisocytidine (6) by nucleoside analogues. For this purpose the nucleosides **1a**,**b** and **3a**,**b** were synthesized. They were converted in their phosphoramidites **2a**,**b** and **4a**,**b**. Compounds **2a**,**b** were employed in solid-phase synthesis.

The nucleoside **1b** was prepared by selective deamination of 2-amino-7-bromo-8-aza-7-deaza-2′-deoxyadenosine (1) (7) with sodium nitrite/acetic acid. Compound **1a** – and even more **1b** – are acid stable surrogates of 2′-deoxyisoguanosine (5). The latter shows a rather low glycosylic bond stability (2–4). The

*Corresponding author.



1a: X = H
1b: X = Br

2a: X = H, R = n-Bu
2b: X = Br, R = Me

3a: R = H
3b: R = Me

4a: R = H
4b: R = Me

Scheme 1.

2′-deoxyisocytidine (6) and its 5-methyl derivative are also acid labile; thus 6-aza-2′-deoxyisocytidine (**3a**) and its 5-methyl derivative (**3b**) were synthesized as well (5–9). The glycosylic bond stability of the nucleosides is shown in Table 1.

Oligonucleotides containing compounds **1a**,**b** were synthesized using phosphoramidite chemistry. The N,N-dimethylaminomethylidene group was used for the protection of the amino group of **1a** (→ **8**), the 2-oxo group was protected with the diphenylcarbamoyl residue (→ **9**). Tritylation and phosphitylation furnished the phosphoramidite **2b**. The building blocks of **4a**,**b** were prepared in a similar way. Solid-phase synthesis of oligonucleotides was performed on 1-μmole scale using the phosphoramidites **2a**,**b**. The coupling yield was always higher than 97%.

According to Table 2 the replacement of dG by compound **1b** results in a significant enhancement of the T_m-values of self-complementary oligonucleotides with overhanging nucleoside residues (4°C/modification). The effect on the non self-complementary duplexes is smaller (Table 2). In the case of the alternating structures roughly 1/3 of the T_m-enhancement can be traced back to the overhangs while the incorporation of the bromo derivative **1b** contributes the other 2/3.

In the case of non self-complementary duplexes a smaller T_m increase (1.5°C/-modification) is observed. Obviously, bulky halogen atoms are well accommodated

Table 1. Half Lifes of 2′-Deoxyisoguanosine and 2′-Deoxyisocytidine Analogues

Compound	0.1 N HCl	0.5 N HCl	τ [min]
iG_d	25°C	—	14
$c^7z^8iG_d$ (**1a**)	—	25°C	13
$Br^7c^7z^8iG_d$ (**1b**)	—	40°C	46
z^6iC_d (**3a**)	40°C	—	75
$m^5z^6iC_d$ (**3b**)	40°C	—	250

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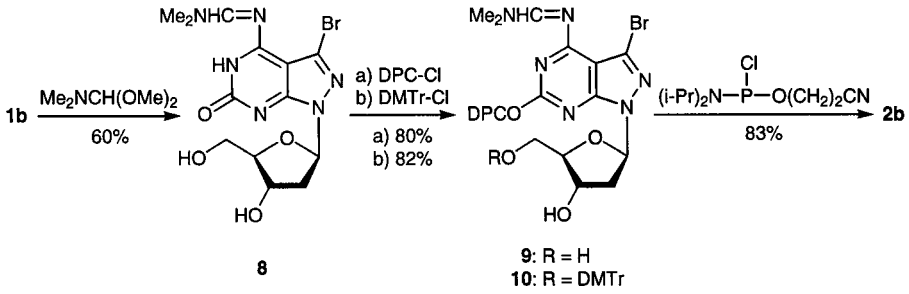


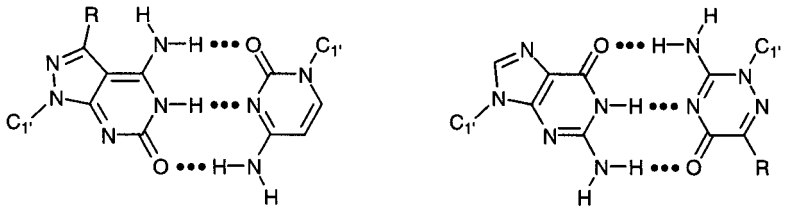
Scheme 2.

Table 2. T_m-Values and Thermodynamic Data of Parallel-stranded Duplexes

Duplex	T_m [°C]	ΔH° [kcal/mol]	ΔS° [cal/molK]	ΔG° [kcal/mol]
5′-d(**1b**-C-**1b**-C-**1b**-C) **11**	57	−60	−162	−10.5
5′-d(**1b**-C-**1b**-C-**1b**-C) **11**				
5′-d(**1a**-C-**1a**-C-**1a**-C) **12**[10]	41	−47	−128	−7.8
5′-d(**1a**-C-**1a**-C-**1a**-C) **12**				
5′-d(**5**-C-**5**-C-**5**-C) **13**[10]	33	−34	−88	−6.2
5′-d(**5**-C-**5**-C-**5**-C) **13**				
5′-d(T-iC-A-T-A-A-iC-T-5-5-A-T) **14**[11]	44	−85	−242	−10.3
5′-d(A-G-T-A-T-T-G-A-C-C-T-A) **15**				
5′-d(T-iC-A-T-A-A-iC-T-**1a**-**1a**-A-T) **16**	43	−78	−209	−9.0
5′-d(A-G-T-A-T-T-G-A-C-C-T-A) **15**				
5′-d(T-iC-A-T-A-A-iC-T-**1b**-**1b**-A-T) **17**	47	−82	−231	−10.4
5′-d(A-G-T-A-T-T-G-A-C-C-T-A) **15**				

[a]) Measured in 1 M NaCl, 0.1 M $MgCl_2$, 60 mM sodiumcacodylate buffer, pH 7.0.
[b]) $iC_d = m^5iC_d$.

in the grooves of parallel-stranded DNA which show an almost identical size. The base pairs of 8-aza-7-deazaisoguanine-containing duplexes are represented by the tridentate motifs I and II. Currently, we are investigating duplexes containing the base pair motifs III and IV.



MOTIFS I-IV

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6. NMR-Data of 3a: δ_H [D_6(DMSO)] 2.07, 2.57 (2 H, 2 m, 2′-H); 3.44 (2 H, m, 5′-H); 3.74 (1 H, m, 4′-H); 4.27 (1 H, m, 3′-H); 4.86 (1 H, t, J 5.4, 5′-OH); 5.26 (1 H, d, J 4.4, 3′-OH); 6.06 (1 H, t, J 6.3, 1′-H); 7.34 (1 H, s, 5-H); 7.46 (2 H, s, NH2).
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12. NMR-Data of 8: δ_H[D_6(DMSO)] 2.31, 2.77 (2 H, 2 m, 2′-H); 3.04 (2 H, m, 5′-H); 3.22, 3.27 (6 H, 2 m, 2 × NCH_3); 3.68 (6 H, 2 m, 2 × CH_3O); 3.93 (1 H, m, 4′-H); 4.50 (1 H, t, J 4.9, 3′-H); 5.35 (1 H, d, J 4.9, 3′-OH-C(3′)); 6.51 (1 H, m, 1′-H); 6.49 − 7.45 (23 H, m, DPC + DMT); 8.87 (1 H, s, HC=N).

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