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

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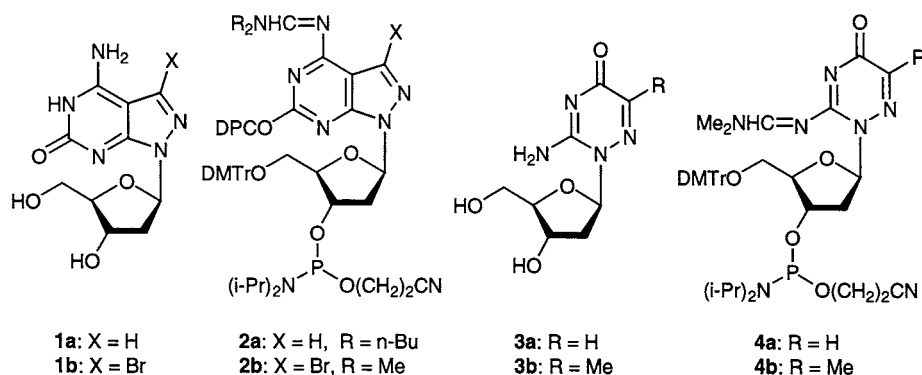
ABSTRACT

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

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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** (\rightarrow **8**), the 2-oxo group was protected with the diphenylcarbamoyl residue (\rightarrow **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- μ mole scale using the phosphoramidites **2a,b**. The coupling yield was always higher than 97%.

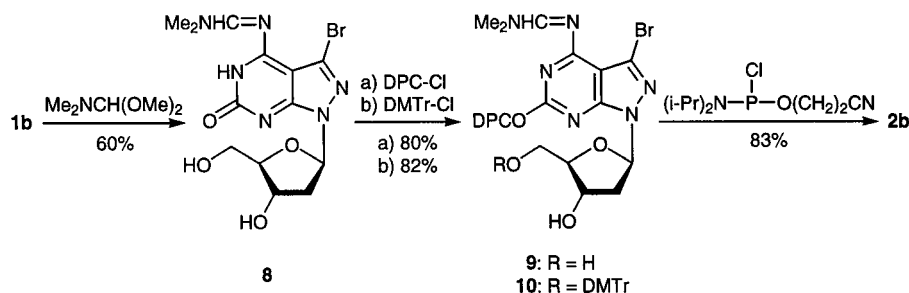
According to Table 2 the replacement of dG by compound **1b** results in a significant enhancement of the T_m -values of self-complementary oligonucleotides with overhanging nucleoside residues (4°C/modification). The effect on the non self-complementary duplexes is smaller (Table 2). In the case of 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 ⁷ z ⁸ iG _d (1a)	—	25°C	13
Br ⁷ c ⁷ z ⁸ iG _d (1b)	—	40°C	46
z ⁶ iC _d (3a)	40°C	—	75
m ⁵ z ⁶ iC _d (3b)	40°C	—	250





Scheme 2.

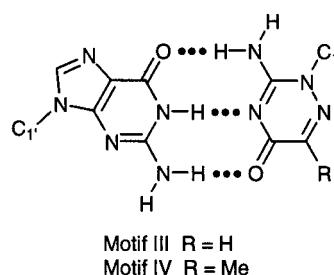
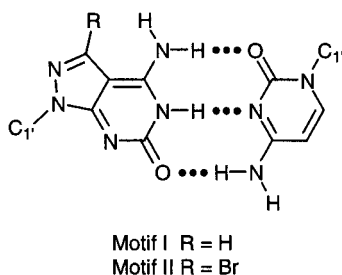
Table 2. T_m -Values and Thermodynamic Data of Parallel-stranded Duplexes

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 MgCl₂, 60 mM sodiumcacodylate buffer, pH 7.0.

b) $iC_d = m^5 iC_d$.

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} [$\text{D}_6(\text{DMSO})$] 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} [$\text{D}_6(\text{DMSO})$] 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 \times NCH₃); 3.68 (6 H, 2 m, 2 \times CH₃O); 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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