

Nucleosides and Nucleotides

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/Incn19>

8-Aza-7-deazapurine DNA: Synthesis and Duplex Stability of Oligonucleotides Containing 7-Substituted Bases

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Published online: 04 Oct 2006.

To cite this article: F. Seela, G. Becher & M. Zulauf (1999) 8-Aza-7-deazapurine DNA: Synthesis and Duplex Stability of Oligonucleotides Containing 7-Substituted Bases, *Nucleosides and Nucleotides*, 18:6-7, 1399-1400, DOI: [10.1080/07328319908044730](https://doi.org/10.1080/07328319908044730)

To link to this article: <http://dx.doi.org/10.1080/07328319908044730>

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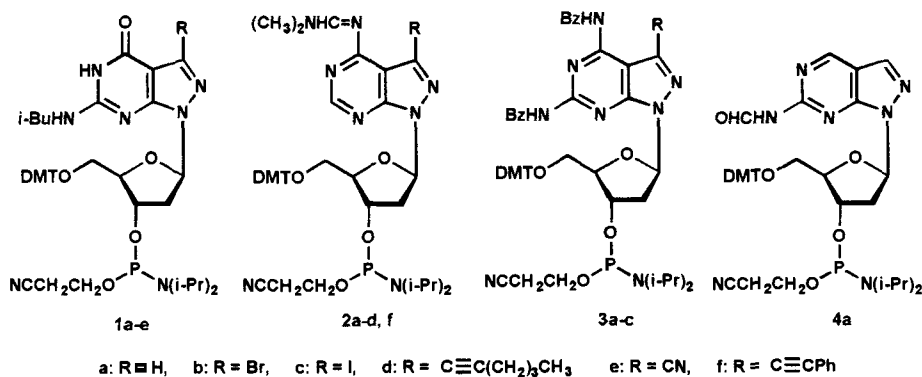
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8-AZA-7-DEAZAPURINE DNA: SYNTHESIS AND DUPLEX STABILITY OF OLIGONUCLEOTIDES CONTAINING 7-SUBSTITUTED BASES

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ABSTRACT: The 7-substituted 8-aza-7-deazapurine phosphoramidites **1a - 3c** as well as the phosphoramidite **4a** were synthesized. In comparison to the parent purine oligonucleotide duplexes, the 7-substituted 8-aza-7-deazapurine residues lead to a significant duplex stabilization.



For the synthesis of the corresponding 8-aza-7-deazapurine nucleosides related to **1a - c**, **1e** and **2a - c** see [1-3]. The nucleosides related to **1d**, **2d** and **2f** were obtained by the cross-coupling reaction on the 7-iodo precursor compounds with either hex-1-yne or phenylacetylene. According to the Table 8-aza-7-deazaguanine (\rightarrow **1a**) already stabilizes the duplex compared to the parent guanine, whereas 8-aza-7-deazaadenine (\rightarrow **2a**) does

Table. T_m -Values of Oligonucleotides ^{a,b)}

Oligodeoxynucleotide	T_m [°C]	Oligodeoxynucleotid	T_m [°C]
5'-d(TAGGTCAATACT)		5'-d(T2aGGTC2a2aT2aCT)	
d(ATCCAGTTATGA)- 5'	46	d(ATCC2aGTT2aTGA)- 5'	47
5'-d(TA1a1aTCAATACT)		5'-d(T2bGGTC2b2bT2bCT)	
d(ATCCA1aTTAT1aA)- 5'	51	d(ATCC2bGTT2bTGA)- 5'	57
5'-d(TA1b1bTCAATACT)		5'-d(T2cGGTC2c2cT2cCT)	
d(ATCCA1bTTAT1bA)- 5'	55	d(ATCC2cGTT2cTGA)- 5'	58
5'-d(TA1c1cTCAATACT)		5'-d(T2dGGTC2d2dT2dCT)	
d(ATCCA1cTTAT1cA)- 5'	55	d(ATCC2dGTT2dTGA)- 5'	58
5'-d(TA1d1dTCAATACT)		5'-d(T3aGGTC3a3aT3aCT)	
d(ATCCA1dTTAT1dA)- 5'	53	d(ATCC3aGTT3aTGA)- 5'	57
5'-d(TA1e1eTCAATACT)		5'-d(T4aGGTC4a4aT4aCT)	
d(ATCCA1eTTAT1eA)- 5'	60	d(ATCC4aGTT4aTGA)- 5'	41

^{a)} 10 mM Na-cacodylate, 10 mM MgCl₂, 0.1 M NaCl, pH 7. ^{b)} The numbers refer to the phosphoramidites used in the oligonucleotide synthesis.

not show this stabilization. Halogeno-, alkynyl-, and alkyl- [4-6] substituents in position 7 increase the T_m -value of oligonucleotides significantly. Incorporation of **1b** - **e** and **2b** - **d**, **f** enhance the T_m by about 2°C per residue [5,6]. The strongest increase was found for the derivative **1e** (4°C per residue). When **3a-c** were employed the T_m -value was raised by 2 - 4°C per residue. The phosphoramidite **4a** leads to duplexes which are destabilized. The B-DNA structure is retained in the case of the duplexes, which is shown by CD-spectroscopy. The nucleosides of **2f** and **4a** show strong fluorescence, while those of **1a** - **e**, **2a** - **d**, and **3a** - **c** are only minimal fluorescent. Treatment of the parent nucleosides of **3a** - **c** with adenosine deaminase converted only **3a** into the guanine derivative, while the halogeno-substituted compounds are resistant.

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