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# Nucleosides, Nucleotides and Nucleic Acids

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# 7-Deazapurin-2,6-Diamine and 7-Deazaguanine: Synthesis and Property of 7-Substituted Nucleosides and Oligonucleotides

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# 7-DEAZAPURIN-2,6-DIAMINE AND 7-DEAZAGUANINE: SYNTHESIS AND PROPERTY OF 7-SUBSTITUTED NUCLEOSIDES AND OLIGONUCLEOTIDES

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<sup>-</sup> The synthesis of 7-substituted 7-deazaguanine and 7-deazaguanine ribonucleosides 1-2, the incorporation of 3a-d into oligonucleotides, and the stability of the corresponding duplexes and base discrimination are described. The  $pK_a$  values of 3-4 are determined.

**Keywords** 7-Deazapurine, 7-Substituents, Nucleosides, Oligonucleotides, Base-Pairing

#### INTRODUCTION

The frequent occurrence and unusual biological properties of 7-deazapurine nucleosides have promoted studies towards the synthesis, biological activity and incorporation into oligonucleotides of their chemically designed analogs. <sup>[1]</sup> Earlier, the 7-halogenated 7-deazapurin-nucleosides related to dA or dG were described and their base-pairing properties in oligonucleotides were studied. It was shown that the 7-halogeno substituents enhance the DNA-duplex stability compared to the unmodified counterparts. <sup>[2,3]</sup> Also, the 7-substituted nucleosides **1–4** as well as the phosphoramidites **5a–d** and **6b–c** were synthesized. <sup>[4,5]</sup> Now, the synthesis of **1b–g** and **2e–g** is described, oligonucleotides containing **3a–d** were prepared and their stability was studied in duplex DNA (Schemes 1 and 2).

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**SCHEME 1** Structure of nucleosides 1-6.

SCHEME 2 Synthesis of guanosine analogs 1b-d.

1d 
$$\xrightarrow{\text{Pd}(\text{PPh}_3)_4, \text{ Cul}}$$
  $\xrightarrow{\text{Pd}(\text{PPh}_3)_4, \text{ Cul}}$   $\xrightarrow{\text{Pd}(\text{PPh}_3)_4, \text{ C$ 

**SCHEME 3** Palladium-catalyzed Sonogashira cross coupling reaction.

## **RESULTS AND DISCUSSION**

Nucleobase-anion glycosylation reaction  $^{[6,7]}$  was employed for the synthesis of 7-halogenated 7-deazaguanosines  $\bf 1b-d$ . The 7-halogenated nucleobases  $\bf 7a-c$  served as starting materials  $^{[5]}$  Glycosylation of  $\bf 7a-c$  with halogenose  $\bf 8$  gave 7-halogenated 7-deazapurine ribonucleosides  $\bf 9a-c$  in 58-62% yield, which were deprotected and treated with 2N NaOH to yield guanosine analogs  $\bf 1b-d$ . The

TABLE 1	$T_{\mathrm{m}}$	Values of	Oligonucleo	tides Con	taining $3\mathbf{a} - \mathbf{d}^a$
---------	------------------	-----------	-------------	-----------	--------------------------------------

Duplex	$T_{\mathrm{m}}$ (°C)
5'-d(TAGGTCAATACT)-3'(11)	47
3'-d(ATCCAGTTATGA)-5'(12)	
5'-d(TAGGTC <b>3a</b> ATACT)-3'( <b>13</b> )	47
3'-d(ATCC <b>3a</b> GTT <b>3a</b> TGA)-5'( <b>14</b> )	
5'-d(TAGGTC <b>3b</b> ATACT)-3'( <b>15</b> )	55
3'-d(ATCC <b>3b</b> GTT <b>3b</b> TGA)-5'( <b>16</b> )	
5'-d(TAGGTC <b>3c</b> ATACT)-3'( <b>17</b> )	56
3'-d(ATCC <b>3c</b> GTT <b>3c</b> TGA)-5'( <b>18</b> )	
5'-d(TAGGTC <b>3d</b> ATACT)-3'( <b>19</b> )	54
3'-d(ATCC <b>3d</b> GTT <b>3d</b> TGA)-5'( <b>20</b> )	

<sup>a</sup>Measured in 0.1 M NaCl, 10 mM MgCl<sub>2</sub>, and 10 mM Nacacodylate buffer, pH 7.0, with 5  $\mu$ M + 5  $\mu$ M single-strand concentration.

synthesis of 7-alkynyl-7-deazapurine nucleosides 1e-g and 2e-g was accomplished by palladium-catalyzed Sonogashira cross coupling reaction using the 7iodo-nucleoside **1d** or **2d**<sup>[8]</sup> as precursors (Scheme 3).

The synthesis of oligonucleotides containing 7-deazapurin-2,6-diamine nucleosides 3a-d using the protocol of phosphoramidite chemistry was performed on an ABI 392-08 synthesizer. The phosphoramidites **5a-d** were used, which were prepared as described. [5] The replacement of the dA residues by non-functionalized nucleoside 3a has no influence on the duplex stability, while the incorporation of the 7-halogenated derivatives  $3\mathbf{b} - \mathbf{d}$  causes a significant increase of the  $T_{\rm m}$ -values (duplexes  $15 \cdot 16$ ,  $17 \cdot 18$  and  $19 \cdot 20$ ) (Table 1). For the standard duplex  $11 \cdot 12$ compounds  $3\mathbf{b} - \mathbf{d}$  show a similar stabilizing effect. The  $T_{\rm m}$  increase corresponds to 2.3-2.7°C per modification. A tridentate base pair is suggested for the **3a-d**/dT pair (motif I) (see Figure 1).

Hybridization experiments of oligonucleotides having **3a-d** incorporated opposite to the four canonical nucleosides show that nucleoside 3a forms rather stable base pairs with dC and dG (duplexes 21 · 14 and 22 · 14) (Table 2), [9] while the incorporation of 7-halogenated analogs **3b-d** enhance the base discrimination. A bidentate base pair motif II is suggested for the mismatches **3a-d**/dC (see Figure 1).

a: R = H; b: R = Cl; c: R = Cl; d: R = I

FIGURE 1 Base-pair motifs related to dA-dT and mismatches dA-dC.