



## Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

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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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Published online: 15 Nov 2011.

To cite this article: Frank Seela, Xiaohua Peng & Xin Ming (2005) 7-DEAZAPURIN-2,6-DIAMINE AND 7-DEAZAGUANINE: SYNTHESIS AND PROPERTY OF 7-SUBSTITUTED NUCLEOSIDES AND OLIGONUCLEOTIDES, *Nucleosides, Nucleotides and Nucleic Acids*, 24:5-7, 839-841, DOI: [10.1081/NCN-200060319](https://doi.org/10.1081/NCN-200060319)

To link to this article: <http://dx.doi.org/10.1081/NCN-200060319>

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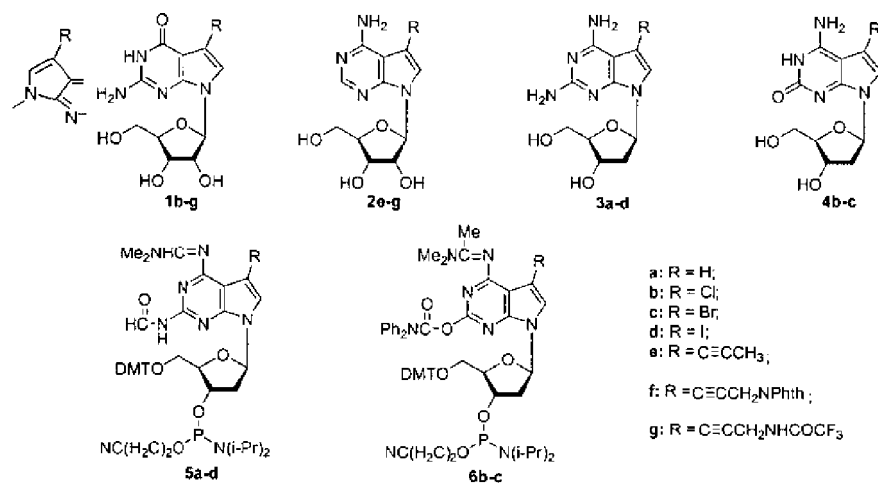
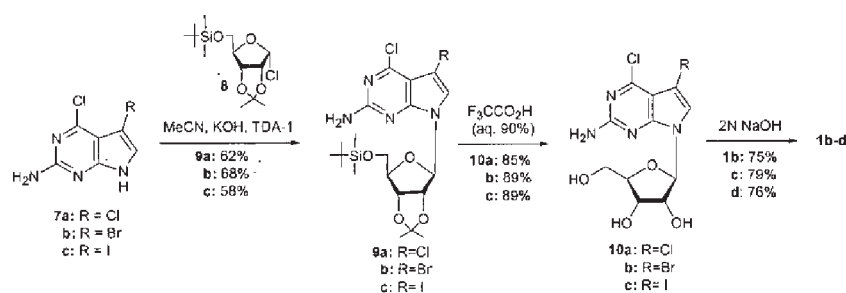
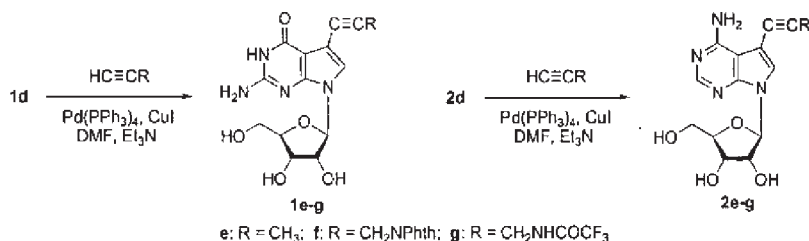
□ *The synthesis of 7-substituted 7-deazaguanine and 7-deazaadenine ribonucleosides 1–2, the incorporation of 3a–d into oligonucleotides, and the stability of the corresponding duplexes and base discrimination are described. The  $pK_a$  values of 3–4 are determined.*

**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**.

SCHEME 3 Palladium-catalyzed Sonogashira cross coupling reaction.

## RESULTS AND DISCUSSION

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

**TABLE 1**  $T_m$  Values of Oligonucleotides Containing **3a–d**<sup>a</sup>

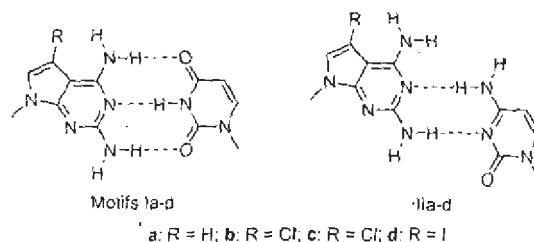
Duplex	$T_m$ (°C)
5'-d(TAGGTCAATACT)-3'( <b>11</b> )	47
3'-d(ATCCAGTTATGA)-5'( <b>12</b> )	
5'-d(TAGGTC <b>3a</b> ATACT)-3'( <b>13</b> )	47
3'-d(ATCC <b>3a</b> GTT <b>3a</b> TGA)-5'( <b>14</b> )	
5'-d(TAGGTC <b>3b</b> ATACT)-3'( <b>15</b> )	55
3'-d(ATCC <b>3b</b> GTT <b>3b</b> TGA)-5'( <b>16</b> )	
5'-d(TAGGTC <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 Na-cacodylate buffer, pH 7.0, with 5 μM + 5 μM 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 7-iodo-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.<sup>[5]</sup> 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 **3b–d** causes a significant increase of the  $T_m$ -values (duplexes **15·16**, **17·18** and **19·20**) (Table 1). For the standard duplex **11·12** compounds **3b–d** show a similar stabilizing effect. The  $T_m$  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),<sup>[9]</sup> 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).

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