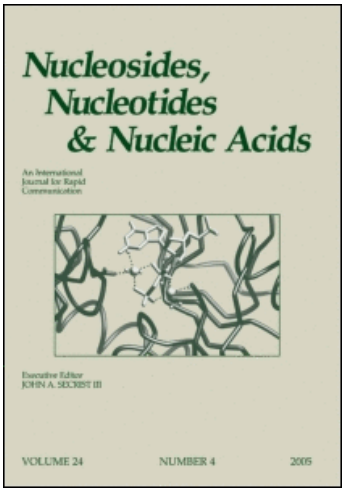

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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

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To cite this Article Seela, Frank , Peng, Xiaohua and Ming, Xin(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, 839 — 841
To link to this Article: DOI: 10.1081/NCN-200060319
URL: http://dx.doi.org/10.1081/NCN-200060319

Nucleosides, Nucleotides, and Nucleic Acids, 24 (5–7):839–841, (2005)

ISSN: 1525-7770 print/ 1532-2335 online
DOI: 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.[1] 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.[2,3] Also, the 7-substituted nucleosides **1–4** as well as the phosphoramidites **5a–d** and **6b–c** were synthesized.[4,5] 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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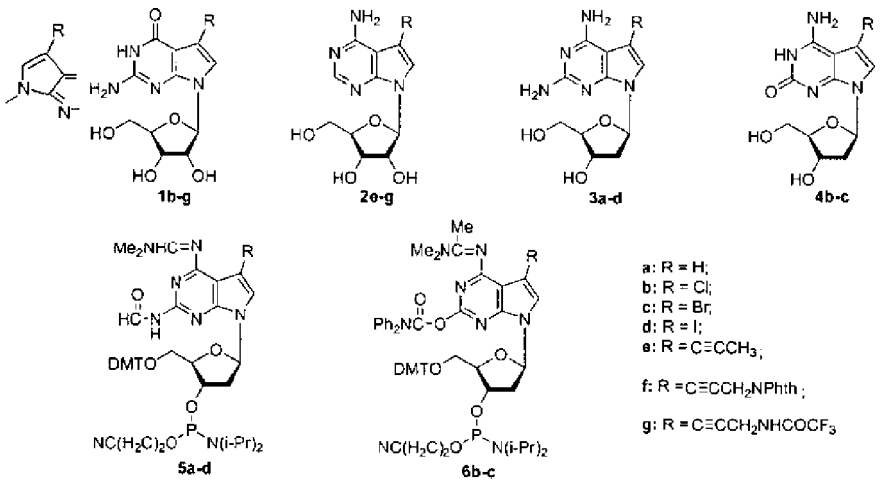
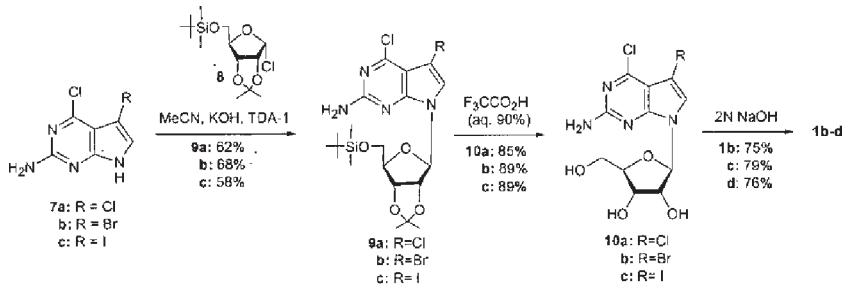
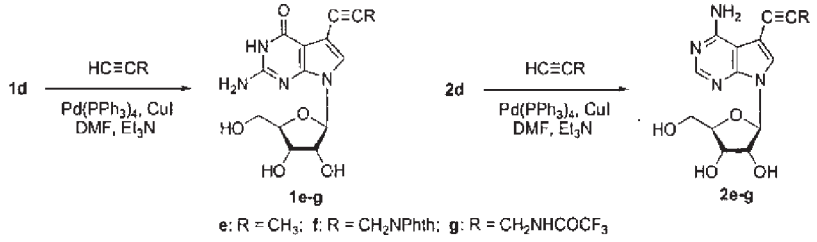


SCHEME 1 Structure of nucleosides **1–6**.



SCHEME 2 Synthesis of guanosine analogs **1b–d**.



SCHEME 3 Palladium-catalyzed Sonogashira cross coupling reaction.

RESULTS AND DISCUSSION

Nucleobase-anion glycosylation reaction[6,7] was employed for the synthesis of 7-halogenated 7-deazaguanosines **1b–d**. The 7-halogenated nucleobases **7a–c** served as starting materials[5] 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**[a]

Duplex	T_m (°C)
5′-d(TAGGTCAATACT)-3′(**11**)	47
3′-d(ATCCAGTTATGA)-5′(**12**)	
5′-d(TAGGTC**3a**ATACT)-3′(**13**)	47
3′-d(ATCC**3a**GTT**3a**TGA)-5′(**14**)	
5′-d(TAGGTC**3b**ATACT)-3′(**15**)	55
3′-d(ATCC**3b**GTT**3b**TGA)-5′(**16**)	
5′-d(TAGGTC**3c**ATACT)-3′(**17**)	56
3′-d(ATCC**3c**GTT**3c**TGA)-5′(**18**)	
5′-d(TAGGTC**3d**ATACT)-3′(**19**)	54
3′-d(ATCC**3d**GTT**3d**TGA)-5′(**20**)	

[a]Measured in 0.1 M NaCl, 10 mM $MgCl_2$, 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**[8] 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 **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),[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).

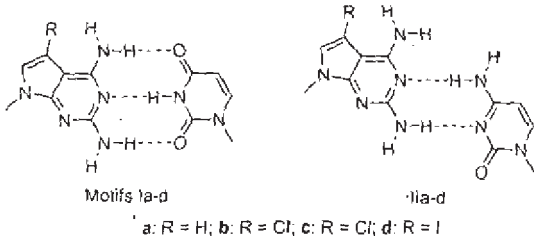


FIGURE 1 Base-pair motifs related to dA-dT and mismatches dA-dC.