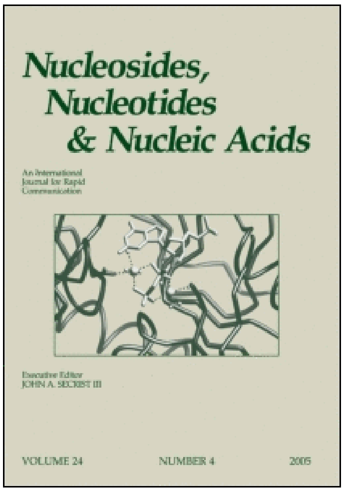

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Synthesis of Novel Pyrene-Bearing C-Nucleoside and Its Incorporation into Oligonucleotides

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SYNTHESIS OF NOVEL PYRENE-BEARING C-NUCLEOSIDE AND ITS INCORPORATION INTO OLIGONUCLEOTIDES

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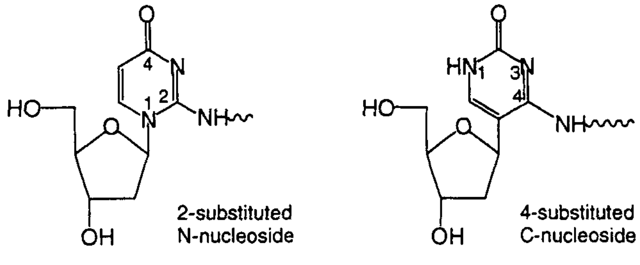
Abstract: Phosphoramidite of (1,2,4-triazol-1-yl)-4-[(4-pyren-1-ylbutyl)amino]-5-(2-O-methyl-5-dimethoxytrityl-β-D-ribofuranosyl)pyrimidine has been synthesized, incorporated into polypyrimidine oligonucleotides, and studied for thier triplex forming capacity.

There is an increasing interest in chemical synthesis of oligonucleotides containing modified bases. A variety of N4-substituted pyrimidine nucleosides have been reported as monomeric units for oligonucleotide synthesis[1-3]. We are interested in preparation of oligonucleotides containing C2-modified nucleotides. To our best knowledge, no convenient methods have been developed to prepare C2 substituted pyrimidine N-nucleosides. However, geometrical shapes of C2 substituted pyrimidine N-nucleosides is quite similar to that of C4 substituted C-nucleosides (Fig.1). We, thus, embarked on the synthesis of N4-substituted ψ-cytidine derivatives from ψ-uridine.



2-substituted N-nucleoside

4-substituted C-nucleoside

Fig.1

Treatment of thymine (**1a**) with phosphoro-*tris*-(1,2,4-triazolide)[4] was found to lead to 2,4-ditriazolyl-derivatives (**2a**), which were isolated in good yield after column

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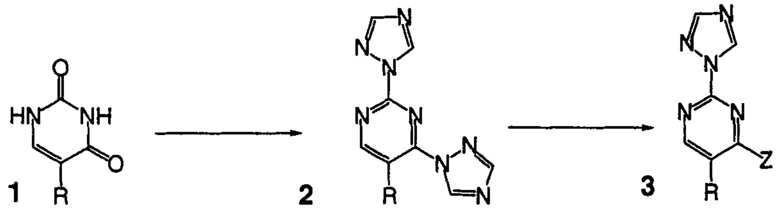
chromatography (Scheme 1). The triazolyl groups in derivatives **2a** exhibited completely different reactivity. Upon treatment of **2a** (65°C, 25 h) with large excess of nucleophilic agents such as ammonia or aminobutylpyrene only the triazolyl group at C4 was substituted, leaving the triazole at C2 intact (**3a** and **3b**, respectively). The structure of all new compounds was confirmed with NMR and FAB-mass spectra. The regiochemistry of substitution was established based on NOEDS for compounds **3b**. Thus, we have developed a method which selectively modify the C4 position of thymine.

Scheme 1



1-2 a: R=CH_3 **b**: R= 5'-O-Dimethoxytrityl-2'-O-methyl-3'-O-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl
3 a: R=CH_3, Z=NH_2; **b**: R=CH_3, Z= (4-pyren-1-yl)butylamino **c**: R= 5'-O-Dimethoxytrityl-2'-O-methyl-β-D-ribofuranosyl; Z= (4-pyren-1-yl)butylamino

We applied the same approach to ψ-uridine derivative **1b**[5] and successfully synthesized the C-nucleoside **3c** bearing an intercalator at C4 position. Phosphoramidite prepared from **3c** was compatible for DNA synthesis. The coupling time for the amidite was 5 min, and the coupling was repeated twice to achieve the coupling yield of 97%. Incorporation of the intact modified bases and the integrity of the resulting oligonucleotides were confirmed by MALDI-TOF mass spectrometry. Triplex-forming capacity of the synthesized oligomers was tested in a pyrimidine parallel motif. Base **3c** demonstrated CG-, GC- and TA-specificity, and no AT-binding was determined.

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