

This article was downloaded by:

On: 26 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



## Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

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

Natalia Dyatkina<sup>a</sup>; Alexander Khorlin<sup>a</sup>; Yuri Khrlin<sup>a</sup>; Kyoichi A. Watanabe<sup>a</sup>

<sup>a</sup> CODON Pharmaceuticals, Inc., Gaithersburg, Maryland, USA

**To cite this Article** Dyatkina, Natalia , Khorlin, Alexander , Khrlin, Yuri and Watanabe, Kyoichi A.(1999) 'Synthesis of Novel Pyrene-Bearing C-Nucleoside and Its Incorporation into Oligonucleotides', *Nucleosides, Nucleotides and Nucleic Acids*, 18: 4, 621 – 622

**To link to this Article:** DOI: 10.1080/15257779908041518

**URL:** <http://dx.doi.org/10.1080/15257779908041518>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

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

Natalia Dyatkina, Alexander Khorlin, Yuri Khripin, and Kyoichi A. Watanabe

CODON Pharmaceuticals, Inc. 200 Perry Parkway., Gaithersburg,  
Maryland, 20877, USA

**Abstract:** Phosphoramidite of (1,2,4-triazol-1-yl)-4-[(4-pyren-1-ylbutyl)amino]-5-(2-O-methyl-5-dimethoxytrityl- $\beta$ -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<sup>1-3</sup>. 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  $\psi$ -cytidine derivatives from  $\psi$ -uridine.

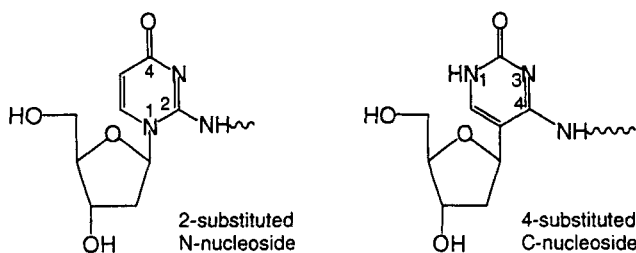
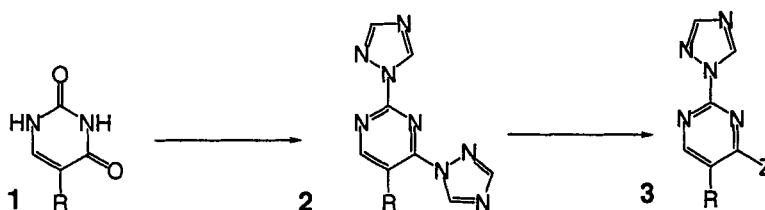


Fig.1

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

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<sub>3</sub> **b:** R= 5'-O-Dimethoxytrityl-2'-O-methyl-3'-O-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl

**3 a:** R=CH<sub>3</sub>, Z=NH<sub>2</sub>; **b:** R=CH<sub>3</sub>, 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**<sup>5</sup> 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.

## REFERENCES

1. MacMillan, A.; Verdine, G.L. *Tetrahedron*, 1991, **47**, 2603-2616
2. Xu, Y-Z., Zheng, Q., Swann, P.F J. *Org. Chem.*, 1992, **57**, 3839-3835.
3. Ganesh, K.N., Rajeev, K.G., Pallan, P.S., Rana, V.S., Barawkar, D.A., Kumar, V.A. *Nucleosides & Nucleotides*, 1997, **16**, 1271-1278.
4. Miah, A., Reese, C.B., Song, Q. *Nucleosides & Nucleotides*, 1997, **16**, 53-65.
5. Ono, A., Ts'O, P.O.P., Kan, L. *J. Org. Chem.*, 1992, **57**, 3225-3230.