

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>

### 2-5A-PNA Complexes: A Novel Class of Antisense Compounds

J. C. Verheijen<sup>a</sup>; S. F. Bayly<sup>b</sup>; M. R. Player<sup>b</sup>; P. F. Torrence<sup>b</sup>; G. A. van der Marel<sup>a</sup>; J. H. Van Boom<sup>a</sup>

<sup>a</sup> Leiden Institute of Chemistry, RA Leiden, the Netherlands <sup>b</sup> Section on Biomedical Chemistry, Bethesda, Maryland, USA

**To cite this Article** Verheijen, J. C. , Bayly, S. F. , Player, M. R. , Torrence, P. F. , van der Marel, G. A. and Van Boom, J. H.(1999) '2-5A-PNA Complexes: A Novel Class of Antisense Compounds', *Nucleosides, Nucleotides and Nucleic Acids*, 18: 6, 1485 – 1486

**To link to this Article:** DOI: 10.1080/07328319908044761

**URL:** <http://dx.doi.org/10.1080/07328319908044761>

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.

## 2-5A-PNA COMPLEXES: A NOVEL CLASS OF ANTISENSE COMPOUNDS

J.C. Verheijen<sup>1</sup>, S.F. Bayly<sup>2</sup>, M.R. Player<sup>2</sup>, P.F. Torrence<sup>2</sup>, G.A. van der Marel<sup>1</sup>  
and J.H. van Boom<sup>\*1</sup>

<sup>1</sup>Leiden Institute of Chemistry, PO Box 9502, 2300 RA Leiden, the Netherlands.

<sup>2</sup>Section on Biomedical Chemistry, NIDDK, NIH, Bethesda, Maryland 20982, USA.

**ABSTRACT:** This paper presents the fully automated solid phase synthesis of 2-5A-PNA hybrids. These stable antisense probes cause RNase L mediated hydrolysis of target RNA sequences.

### INTRODUCTION

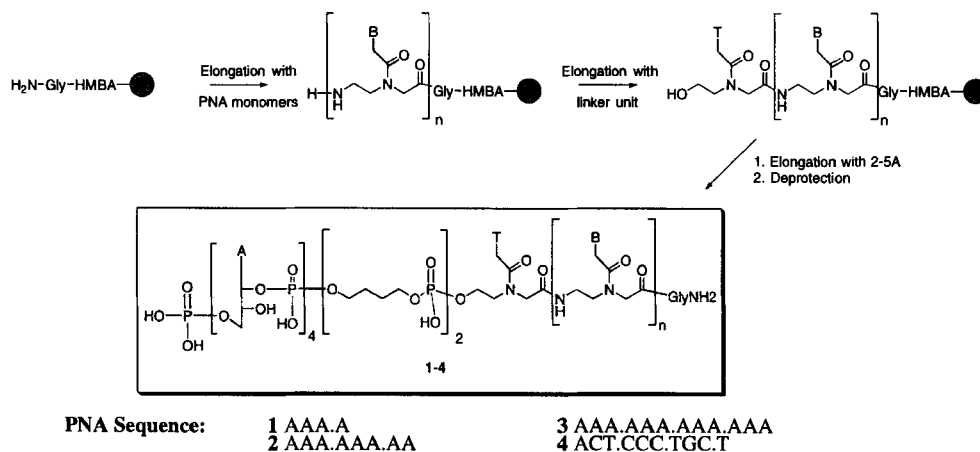
Despite their resistance to enzymatic degradation and favorable hybridization properties, the application of Peptide Nucleic Acids (PNAs)<sup>1</sup> as antisense agents is limited because PNA•RNA duplexes are not recognized by RNase H. Therefore hybridization of PNA to RNA does not result in the hydrolytic breakdown of the target sequence. It occurred to us that this drawback could be overcome by linking p(S'A2'p)<sub>3</sub>A, so-called 2-5A<sup>2</sup>, to the aminoterminal of PNA. This would lead to stable antisense probes with the ability to cleave target RNA *via* activation of RNase L.

We here report the synthesis of 2-5A-PNA complexes (**1-4**, Scheme 1) as well as a preliminary evaluation of their antisense activity.

### RESULTS AND DISCUSSION

The 2-5A-PNA complexes were obtained following the solid phase synthesis protocol presented in scheme 1: First, the PNA part was synthesized on a fully automated DNA synthesizer with MMTr/acyl protected PNA building blocks<sup>3</sup> using HATU as the coupling agent. The last cycle of the PNA synthesis was followed by the introduction of the *N*-thymine-1-ylacetyl hydroxyethylglycine linker.<sup>4</sup> Next, the 2-5A part could be appended using standard phosphoramidite chemistry.

## SCHEME 1



Preliminary biological evaluation revealed that the thus obtained 2-5A-PNA hybrids lead to the hydrolysis of complementary mRNA through activation of RNase L with comparable activity as 2-5A-DNAs.

In conclusion, the results presented here show that 2-5A-PNA hybrids form an interesting novel class of antisense agents which may be of great importance for the future development of pharmaceuticals. A full report on the synthesis and biological properties of 2-5A-PNAs will be published in due course.

## ACKNOWLEDGEMENT

The work described in this paper was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific research (NWO). We wish to thank Nico Meeuwenoord and Hanneke Stuivenberg for their technical assistance.

## REFERENCES

- 1) Nielsen, P. E.; Egholm, M.; Berg, R. H.; Buchardt, O. *Science*, **1991**, 254, 1497-1500.
- 2) Maran, A.; Maitra, R. K.; Kumar, A.; Dong, B.; Xiao, W.; Li, G.; Williams, B. R. G.; Torrence, P. F.; Silverman, R. H. *Science*, **1994**, 265, 789-792.
- 3) Will, D. W.; Breipohl, G.; Langner, D.; Knolle, J.; Uhlmann, E. *Tetrahedron*, **1995**, 51, 12069-12082.
- 4) Van der Laan, A. C.; Brill, R.; Kruimelis, R. G.; Kuyl-Yeheskiely, E.; Van Boom, J. H.; Andrus, A.; Vinayak, R. *Tetrahedron*, **1997**, 38, 2249-2252.