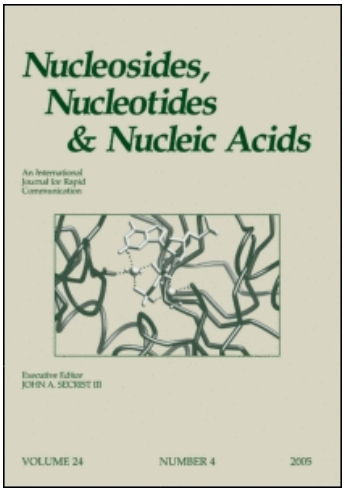
This article was downloaded by:
On: *26 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



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

Computer Aided Design of Triplet Forming Artificial Nucleobases

R. Fenyõ[a]; Z. Timár[a]; I. Pálinkó[b]; B. Penke[a]
[a] Department of Medical Chemistry, Albert Szent-Györgyi Medical University, Szeged, Hungary [b] Department of Organic Chemistry, Attila József University, Szeged, Hungary

To cite this Article Fenyõ, R. , Timár, Z. , Pálinkó, I. and Penke, B.(1999) 'Computer Aided Design of Triplet Forming Artificial Nucleobases', Nucleosides, Nucleotides and Nucleic Acids, 18: 4, 1127 — 1129
To link to this Article: DOI: 10.1080/15257779908041667
URL: http://dx.doi.org/10.1080/15257779908041667

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.

NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 1127–1129 (1999)

COMPUTER AIDED DESIGN OF TRIPLET FORMING ARTIFICIAL NUCLEOBASES

R. Fenyõ[1*], Z. Timár[1], I. Pálinkó[2], B. Penke[1]

Albert Szent-Györgyi Medical University, Department of Medical Chemistry, Dóm tér 8., Szeged, Hungary H-6720 ; [2]Attila József University, Department of Organic Chemistry, Dóm tér 8., Szeged, Hungary H-6720

*To whom correspondence should be addressed.

Tel.: +36 62 455145; Fax: +36 62 313833; e-mail: robi@ovlev1.mdche.u-szeged.hu

Downloaded At: 14:18 26 January 2011

ABSTRACT : Triplex forming oligonucleotides could prevent genetic transcription at the level of genes. Nucleotide bases with the capability of specific H-bonding interactions with base pairs in the major groove of DNA have been designed. Calculations by semiempirical methods lead to four compounds as possible triplet forming nucleobases.

RESULTS AND DISCUSSION

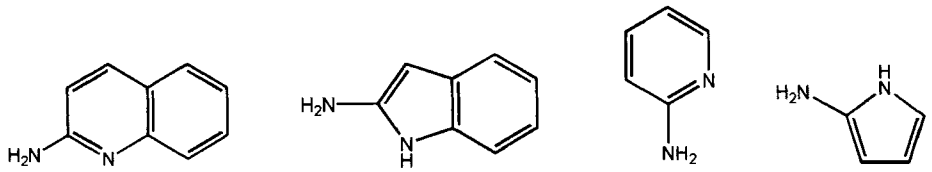
Since it is known that the fundamental organizing role in duplex as well as in triplex formation is hydrogen bonding, studying interactions of this type on simpler but analogues systems may lead to a better understanding of the laws of superstructure formation in DNA aggregates. During the procedure several factors were taken into account: the molecule should contain substructure capable of Hoogsteen H-bonding with the purine base of the Watson-Crick doublet, should be cyclic and planar, for practical purposes it should be chemically stable and the triplet should be stable too.

The A(denine)-T(hymine) and G(uanine)-C(ytosine) base pairs were built and optimized using Biosym Insight II molecular graphics program. A methyl group was placed on each base at the deoxyribose binding site to provide some resemblance to the real thing. Two fragments of the novel molecule were docked to two adjacent hydrogen bonding sites of guanine or adenine. The other parts were appended to meet criteria

Copyright © 1999 by Marcel Dekker, Inc. www.dekker.com

mentioned above. Semiempirical MNDO method was applied for studying planarity of the newly designed molecules and both AM1 and PM3 methods for geometric optimization of the triplets, providing with enthalpies of formation, hydrogen bond energies and hydrogen bond distances. Computational procedures were performed on a SGI Indy R5000 graphic workstation and an IBM RS6000 computer using either the Spartan or the QCPE MOPAC 7.0 program package.

Trying to meet geometric and chemical criteria we ended up with four compounds having possible triplex forming ability: quinolin-2-ylamin (**1**), indol-2-ylamin (**2**), pyridin-2-ylamin (**3**) and 2-aminopyrrol (**4**) (Fig. 1).



1 2 3 4

Figure 1.

Calculated values of enthalpies of formation and hydrogen bond energy of base triplets can be seen in Table 1.

Table 1. Enthalpies of formation and hydrogen bond energy of base triplets (A - adenine, T - thymine, G - guanine, C - cytosine)

Triplet	Method	ΔH^f/kcalmol^{-1}	H-bond energy /kcalmol^{-1}
1-A-T	AM1	81.523	-2.585
	PM3	15.171	-1.363
3-A-T	AM1	61.488	-2.664
	PM3	-2.086	-4.375
2-G-C	AM1	97.829	-4.337
	PM3	18.672	-1.154
4-G-C	AM1	85.041	-2.731
	PM3	9.284	2.664

Downloaded At: 14:18 26 January 2011

Aromatic π-π stacking interaction is as important in stabilization of DNA helices as hydrogen bonding is. It also works with triplex DNA as well, however, theoretical investigation is computationally very expensive. Basically, this is the reason why we limited ourselves to studying base triplets only.

Oligonucleotides containing nucleosides derived from pyridin-2-ylamin, one of our designed compounds, was synthesized by Cassidy and co-workers and their triple helix forming abilities were studied by various experimental methods. Measurements verified that this compound does have triplex forming ability. We are continouing to study our lead compounds using *ab initio* calculations and also planning to verify the capability of specific H-bonding interactions of designed nucleobases by physical chemical methods.

ACKNOWLEDGEMENTS

This work was supported by grants from the Hungarian Research Foundation (OTKA T 022551).

Downloaded At: 14:18 26 January 2011

REFERENCES

1 Thuong, N.T., Héléne, C. *Angew. Chem. Int Ed.*, **1993,** *32,* 666.

2 Cassidy, S.A.; Slickers, P.; Trent, J.O.; Capaldi, D.C.; Roselt, P.D.; Reese, C.B.; Neidle, S.; Fox, K.R. *Nucl. Ac. Res.*, **1997,** *25,* 4891.

3 Kool, E.T. *Chem. Rev.*, **1997,** *97,* 1473.

4 Griffin, L.C.; Kiesling, L.L.; Beal, P.A.; Gillespie, P.; Dervan, P.B. *J. Am. Chem. Soc.*, **1992,** *114,* 7976.

5 INSIGHT II (release 97.0), Molecular Simulation Inc., 9685 Scranton Road, San Diego, USA

6 SPARTAN 4.1.1 (SGI version) Wavefunction, Inc., 18401 von Karman Ave. #370, Irvine CA 92715 USA