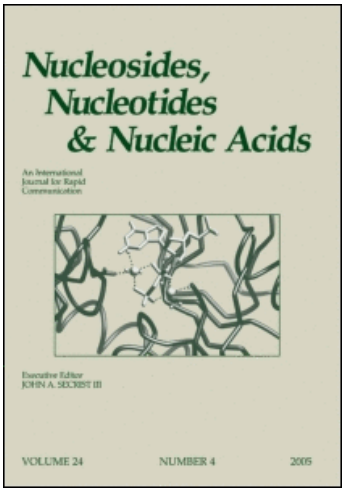

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

New Nucleobase Analogs for the Extension of the Triple Helix Recognition Code

David Lengeler[a]; Klaus Weisz[a]
[a] Institut für Organische Chemie, Freie Universität Berlin, Berlin

To cite this Article Lengeler, David and Weisz, Klaus(1999) 'New Nucleobase Analogs for the Extension of the Triple Helix Recognition Code', Nucleosides, Nucleotides and Nucleic Acids, 18: 6, 1657 — 1658
To link to this Article: DOI: 10.1080/07328319908044813
URL: http://dx.doi.org/10.1080/07328319908044813

NUCLEOSIDES & NUCLEOTIDES, 18(6&7), 1657–1658 (1999)

NEW NUCLEOBASE ANALOGS FOR THE EXTENSION OF THE TRIPLE HELIX RECOGNITION CODE

David Lengeler and Klaus Weisz*
Institut für Organische Chemie, Freie Universität Berlin, Takustr. 3, D-14195 Berlin

ABSTRACT: Molecular modeling was used to design novel nucleobases for the specific recognition of Watson-Crick base pairs within a triple helix. The synthesis for one of the nucleoside analogs is described in detail. Preliminary NMR measurements on the monomeric nucleobases in apolar solvents indicate preferred association modes and affinities towards a guanosine-cytidine Watson-Crick base pair.

Targeting double helical DNA with an oligonucleotide to form a triple helical structure offers an attractive approach to specifically modulate gene expression at the DNA level (antigene strategy). Unfortunately, with natural nucleobases the recognition is mostly limited to homopurine tracts of the double helix. Thus, novel base analogs are required to extend the recognition code to all four possible Watson-Crick base pairs, prerequisite for targeting any arbitrary sequence of genomic DNA.

In a first step we have performed semi-empirical calculations on several designed nucleobases which were expected to satisfy the various steric and electronic requirements for effective recognition of a CG base pair in a parallel triple helix motif. Interaction energies between the Watson-Crick base pair and the third base analog were determined in vacuo on the PM3 (tm) level. Due to their favorable energy of hydrogen bond formation, the three substituted 4-pyridinyl(2)-imidazoles **1**, **2** and **3** were selected as possible candidates in triple helix forming oligonucleotides.

The synthesis of the pyridinyl-imidazole ribosides is outlined in fig. 1. Starting with 2,6-dibromopyridine the heterocyle is lithiated with butyllithium and subsequently reacted with N,N-dimethylacetamide at –80 °C to give 2-acetyl-6-bromo-pyridine in an overall yield of 55 %. After bromination of the acetyl group by addition of Br_2 in glacial

acetic acid, ring closure to the substituted imidazole is achieved with formamide at 190°C within 3 hrs. Glycosylation of the heterocyclic base to give **1** was carried out under Vorbrüggen conditions. Substitution of the bromo substituent in **1** by standard methods should lead to nucleosides **2** and **3**.

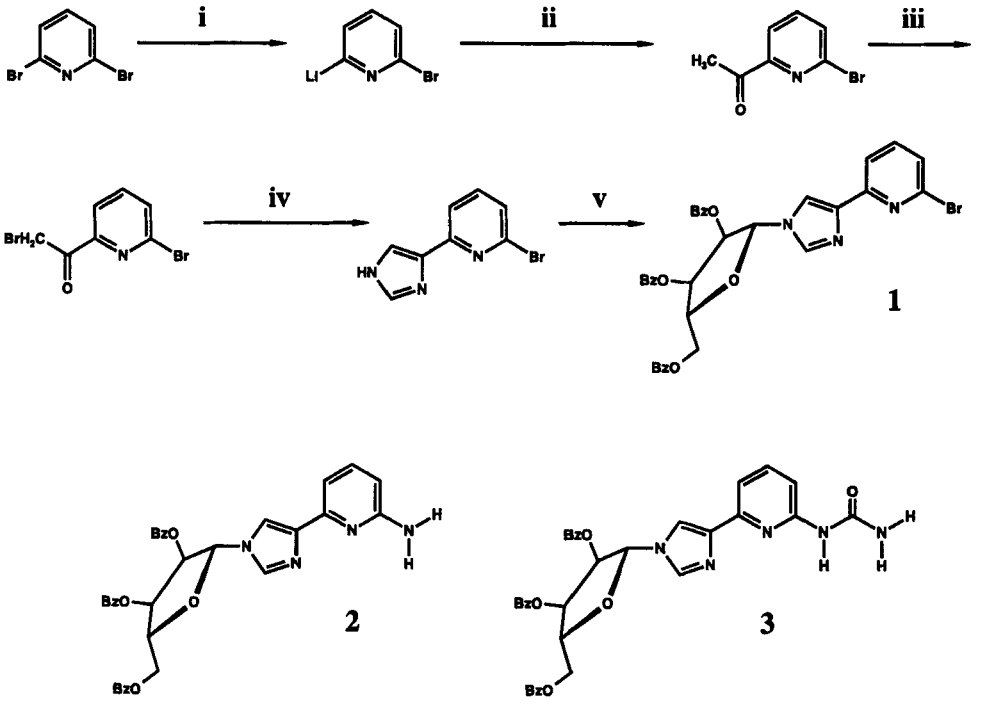

Fig. 1. i) nBuLi, -70 °C; ii) N,N-dimethylacetamide, -80 °C; iii) Br_2, HOAc, 34 %; iv) formamide, 190 °C, 3 hrs, 74 %; v) Vorbrüggen conditions, 37 %.

We have performed preliminary NMR experiments on suitably derivatized guanosine, cytidine and **1** in CD_2Cl_2 at ambient and low temperatures. In this apolar solvent equimolar amounts of cytidine and guanosine strongly associate to form stable Watson-Crick GC base pairs. Addition of **1** results in a downfield shift of the non-hydrogen bonded cytosine amino proton. At the same time the guanine imino proton remains unaffected indicating the formation of a hydrogen bond between **1** and the amino proton of an intact GC base pair. Further NMR experiments on different base analogs are expected to yield preferred association modes as well as affinities towards the canonical base pair on the monomeric level.