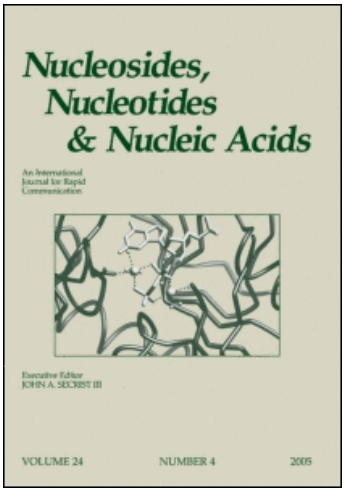

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Girault, I. , Ravanat, J. L. , Frier, C. , Fontecave, M. , Cadet, J. and Décout, J. L.(1999) '5-Deazaflavins: New Very Efficient DNA Photosensitisers, Synthesis of Oligonucleotide Conjugates', Nucleosides, Nucleotides and Nucleic Acids, 18: 6, 1345 — 1347
To link to this Article: DOI: 10.1080/07328319908044712
URL: http://dx.doi.org/10.1080/07328319908044712

NUCLEOSIDES & NUCLEOTIDES, 18(6&7), 1345–1347 (1999)

5-DEAZAFLAVINS: NEW VERY EFFICIENT DNA PHOTOSENSITISERS, SYNTHESIS OF OLIGONUCLEOTIDE CONJUGATES

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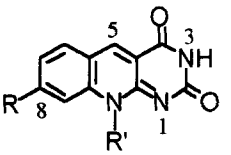
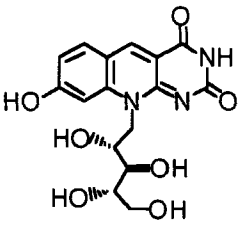
ABSTRACT: In order to study electron transfer processes through the DNA double helix, we have synthesised a series of 5-deazaflavin derivatives **1-4** and demonstrated their ability to induce very efficiently 2'-deoxyguanosine and DNA oxidations by electron transfer from guanine. 5-Deazaflavin-oligonucleotide adducts were also synthesised for the study of electron transfers through double or triple helix formed with their complementary sequence.

8-hydroxy-5-deazariboflavin **5** is a very interesting cofactor involved in the repair of DNA pyrimidine cyclobutane dimer lesions at the active site of the repair enzymes DNA photolyases.[1] After light excitation, energy is transferred from the 5-deazaflavin chromophore to the other reduced cofactor FAD in order to catalyse the redox repair reaction. On the other hand, 5-deazaflavin derivatives can be photoreduced very efficiently in the presence of EDTA as electron donor to lead to the deazaflavin radical which combines high reactivity with a very low redox potential. This radical was used *in vitro* as a reductor to photoreactivate flavoproteins and metalloenzymes.[2] In a program devoted to the study of electron transfer processes through the DNA double helix, we are investigating the DNA photosensitisation properties of flavins, deazaflavins and their oligonucleotide adducts.



1: R = H, R' = CH_3
2: R = H, R' = $(CH_2)_6OH$
3: R = OCH_3, R' = $(CH_2)_6OH$
4: R = OH, R' = $(CH_2)_6OH$



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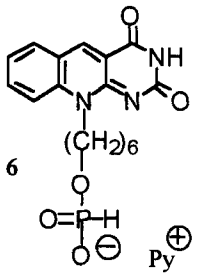

6

We have previously reported the synthesis of flavin-oligonucleotide adducts and evidenced their ability to induce, upon light exposure, the selective cleavage of a DNA complementary target at guanine sites.[3] We report here the DNA photosensitisation properties of 5-deazaflavin derivatives and the synthesis of deazaflavin-oligonucleotide adducts.

Different 5-deazaflavin derivatives **1-4** were synthesised from 6-chlorouracil and *N*-alkylanilines. Their ability to photoinduce 2'-deoxyguanosine and DNA oxidation was investigated. Preliminary results indicates that 5-deazaflavins are much more efficient than riboflavin to induce 2'-deoxyguanosine photooxidation. 2,2-Diamino-4-[2-deoxy-ß-D-*erythro*-pentofuranosyl)amino]-5-(*2H*)-oxazolone is the main product observed indicating that deazaflavins are mostly type I photosensitisers.[4] Formation of the two diastereoisomers of 4-hydroxy-8-oxo-4,8-dihydro-2'-deoxyguanosine[5] shows that the excited deazaflavins are also able to generate in a minor extent singlet oxygen through a type II mechanism.

In order to attach the 5-deazaflavin ring at the 5'-end of oligonucleotides, the H-phosphonate **6** was prepared in 83 % yield by reaction of compound **2** with phosphorous acid in the presence of 2,4,6-triisopropylbenzenesulfonyl chloride in pyridine. Compound **6** was coupled in the presence of adamantanecarboxylic acid chloride at the 5'-hydroxyl end of a protected $d(T)_{11}$ oligonucleotide attached to its solid-phase support of synthesis and obtained by the phosphoramidite method. After deprotection in the presence of sodium hydroxide, the deazaflavin-$d(T)_{11}$ adduct obtained in 75 % yield was purified by HPLC on reversed-phase and anion-exchange chromatography. It was characterised by absorption spectrophotometry (λ = 392 nm), ^1H and ^{31}P NMR spectrometry. In a similar way, a triple-helix forming 5-deazaflavin-oligonucleotide adduct complementary of the polypurine tract (PPT) of HIV 1, a 16 nucleotide polypurine sequence present in the *nef* and *pol* genes, was prepared.

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