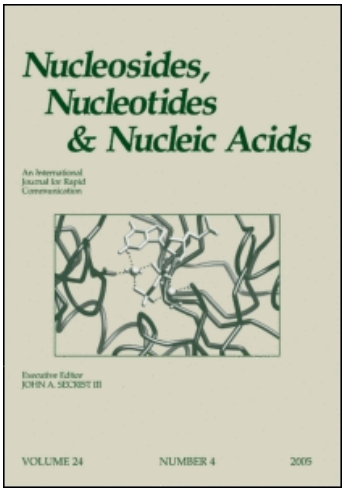

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Diamino-Antraquinone: A New Intercalating Agent. Synthesis and Linking to Oligodeoxynucleotide

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To cite this Article Puskás, Lászió , Czombos, József and Bottka, Sándor(1995) 'Diamino-Antraquinone: A New Intercalating Agent. Synthesis and Linking to Oligodeoxynucleotide', Nucleosides, Nucleotides and Nucleic Acids, 14: 3, 967 — 968
To link to this Article: DOI: 10.1080/15257779508012512
URL: http://dx.doi.org/10.1080/15257779508012512

NUCLEOSIDES & NUCLEOTIDES, 14(3-5), 967-968 (1995)

DIAMINO-ANTRAQUINONE: A NEW INTERCALATING AGENT. SYNTHESIS AND LINKING TO OLIGODEOXYNUCLEOTIDE

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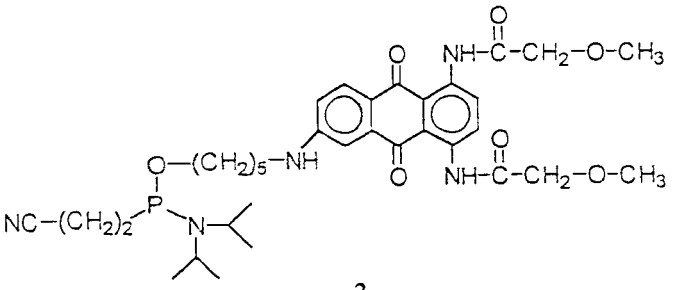
ABSTRACT: Phosphoramidite derivative of 1,4-diamino antraquinone was synthesized, characterized, and incorporated into oligonucleotides. Intercalative interaction between the dye and the nucleic acid was confirmed by CD spectroscopy.

Conjugates of nonnucleosidic nature can modify the existing features of the oligonucleotides favourably. Intercalating agents tethered to oligomers increase the stability of duplex formation.[1,2] We report here the synthesis of a new intercalating dye, which can be coupled to synthethic oligonucleotides. This molecule was designed by PM3 semiempiric computer calculation method. On the basis of the computer model, enhanced binding was anticipated between the dye and the DNA, because the amino groups of the antraquinone formed new hydrogen bonds with the nucleic acid bases.



3

1,4-dihydroxy-6-chloro-antraquinone was synthesized starting from 4-chloro-phtalic anhydride and hydroquinone and then converted to the 1,4-diamino derivative (1) according to described procedure.[3] In order to attach a linker arm to the dye, chlorine atom at the position 6 was substituted by 5-hydroxy-pentylamine.

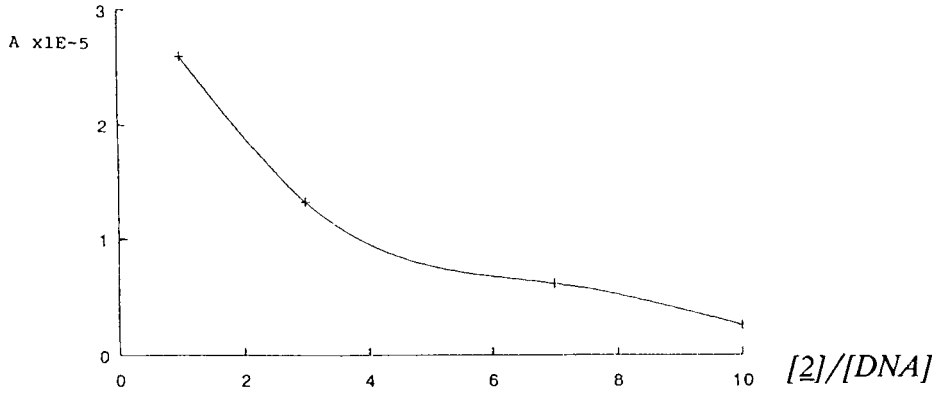


FIG. 1 CD-band intensities at 550 nm vs. 1,4-di-(methoxyacetamino)-6-(5-hydroxy-pentylamino)-antraquinone (2) concentration (related to human DNA concentration).

Subsequent acylation of the 1,4-diamino groups with methoxyacetic anhydride led to the protected derivative (2). The identity of this compound was confirmed by ^{1}H- and ^{13}C-NMR spectroscopy. Phosphitylation with bis-(N,N-diisopropylamino)-2-cyanoethoxy phosphine gave the requested phosphoramidite 3. (^{31}P-NMR δ = +147.76; +147.85ppm)

The capability of intercalation was proved by CD spectroscopy. Purified human DNA solution in water was mixed with growing concentrations of 2. CD band intensity at 550 nm showed a significant decrease. This decrease exhibited a characteristic concentration dependence (FIG. 1).

The phosphoramidite synthon (3) could be coupled to the 5' position of oligodeoxynucleotides by the standard solid support procedure. Coupling time was not optimized; with 2 min reaction time >95% yield was achieved. The purification of the oligonucleotide conjugate was performed by reverse phase HPLC following ammonia deprotection. Studies on thermodynamics of duplex binding are in progress.

Acknowledgement. This work was supported by the Hungarian Science Fund (OTKA T5277).

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