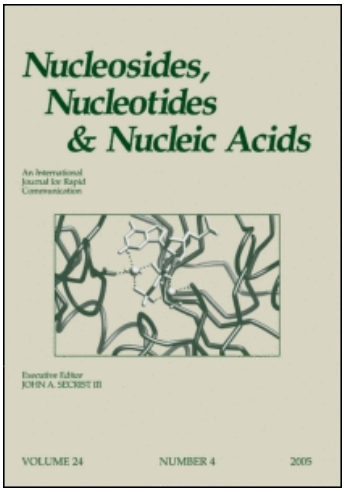

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Specific Recognition and Stabilization of an Abasic Site-Containing DNA Duplex by a Macrocyclic Bisacridine

M. P. Teulade-Fichou[a]; J. P. Vigneron[a]; J. M. Lehn[a]; N. Berthet[b]; J. Michon[b]; J. Garcia[b]; M. Jourdan[b]; J. Lhomme[b]
[a] Laboratoire de Chimie des Interactions Moléculaires, Paris, France [b] L. E. D. S. S., Chimie Bioorganique, Université Joseph Fourier, CNRS UMR, Grenoble, France

To cite this Article Teulade-Fichou, M. P. , Vigneron, J. P. , Lehn, J. M. , Berthet, N. , Michon, J. , Garcia, J. , Jourdan, M. and Lhomme, J.(1999) 'Specific Recognition and Stabilization of an Abasic Site-Containing DNA Duplex by a Macrocyclic Bisacridine', Nucleosides, Nucleotides and Nucleic Acids, 18: 6, 1351 — 1353
To link to this Article: DOI: 10.1080/07328319908044714
URL: http://dx.doi.org/10.1080/07328319908044714

NUCLEOSIDES & NUCLEOTIDES, 18(6&7), 1351–1353 (1999)

SPECIFIC RECOGNITION AND STABILIZATION OF AN ABASIC SITE-CONTAINING DNA DUPLEX BY A MACROCYCLIC BISACRIDINE

M.-P.Teulade-Fichou[a*], J.-P. Vigneron[a], J.-M. Lehn[a],
N. Berthet[b], J. Michon[b], J.Garcia[b], M. Jourdan[b], J. Lhomme[b]

a-Laboratoire de Chimie des Interactions Moléculaires, UPR 285, Collège de France, 11 place Marcelin Berthelot 75005 Paris, France.
b-L.E.D.S.S., Chimie Bioorganique, Université Joseph Fourier, CNRS UMR 5616, Grenoble, France.

ABSTRACT: A strong and specific stabilization of a DNA undecamer containing an analog of the abasic site has been induced by the macrocyclic Bisacridine **1**. ^{1}H NMR analysis and molecular modeling of the structure of the complex showed that the drug was specifically docked into the apurinic pocket.

The Bisacridine macrocycle **1**, that belongs to the cyclobisintercaland family compounds (CBIs), has been shown to associate strongly to nucleotides and oligonucleotides[1]. Furthermore, due to its particular geometrical features, *i.e.* a semi-closed conformation, the binding of **1** is selectively directed towards single stranded regions of nucleic acids that exhibit more accessible nucleic residues than double helical domains[2]. Based on these properties, the interaction of compound **1** with the undecamer duplex **TX** containing a stable analog of the abasic site has been investigated. The loss of a nucleobase is one of the most frequent lesions in DNA which is cytotoxic and mutagenic and the design of ligands able to recognize the abasic lesion is thus a fundamental and challenging problem[3-5].

Bisacridine **1** was shown to cleave a ^{32}P-labeled duplex oligonucleotide containing one abasic site. In order to study the mode of binding of **1**, we prepared duplex oligonucleotide **TX** that contains a stable analog **X** of the abasic site. Thermal denaturation experiments of

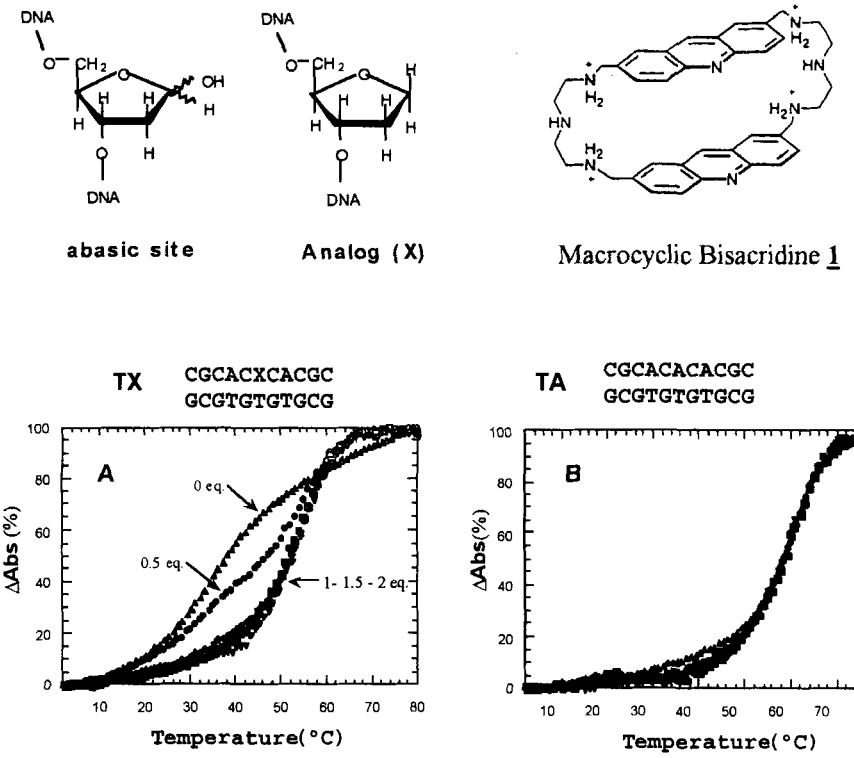

Figure 1: Melting temperature curves (A) of the undecamer **TX** (X= 3-hydroxy-2-(hydroxymethyl) tetrahydrofuran]and (B) of the regular analog **TA** in the presence of **1** (0-2eq). Phosphate Buffer 10mM, EDTA 1mM, NaCl 20mM, pH 7.0.

TX have been conducted in the presence of **1** (Fig 1A). Increasing amounts of the macrocycle induced a strong enhancement of the melting temperature of the duplex, the effect being maximal at a 1/1 molar ratio [**1**]/[**TX**] (ΔTm= + 13.8°C) (Fig 1A). By contrast, the macrocycle had no effect on melting of the fully paired duplex analog **TA** (Fig 1B).

EPR experiments involving displacement by Bisacridine **1** of an abasic site probe labeled by a nitroxide confirmed the specificity of the binding. Furthermore irradiation of a mixture of **TX** and of Bisacridine **1** induced specific cleavages in the vicinity of the abasic site on both strands of the duplex. These results, obtained by three different methods, unambiguously demonstrate that **1** binds specifically and cleaves AP site.

Study of the interaction between the drug and the undecamer **TX** by ^{1}H NMR spectroscopy and molecular modeling showed that the macrocycle was specifically inserted into the abasic pocket with one acridine unit replacing the missing base and the other one

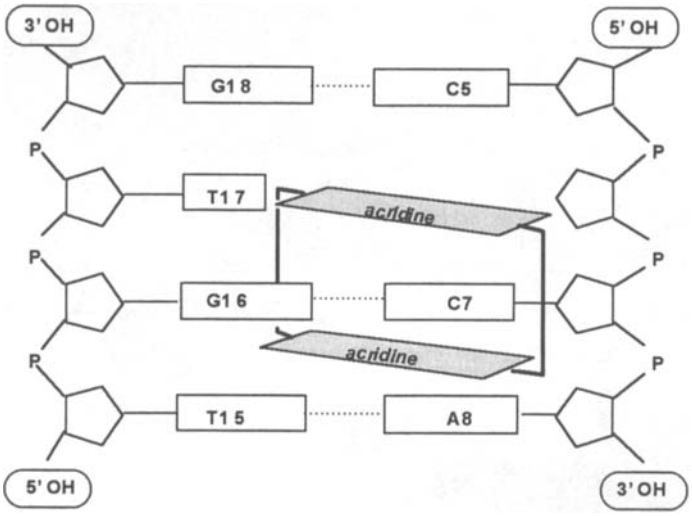

Figure 2 : Schematic representation of the interaction between duplex **TX** and compound **1**.

intercalated between the two adjacent base pairs ; the two linkers being positioned in each groove (Fig 2).

The potential of Bisacridine **1** and other CBI compounds to act as reagents for the stabilization of short-lived single stranded regions and for the detection of locally altered structures in DNA is currently under investigation.

REFERENCES

1- Teulade-Fichou, M.-P.;. Vigneron, J.-P.;. Lehn, J.-M. *J. Supramol. Chem.*, **1995**, 5, 139-147

2-Blacker, A.J.; Teulade-Fichou, M.-P.; Vigneron, J.-P.; Lehn, J.-M. *Bioorg. Med .Chem. Lett.* **1998**, 8, 601-606

3- Fkyerat, A.; Demeunynck, M.;. Constant, J.-F.; Michon, P.; Lhomme, J. *J. Amer Chem. Soc.*, **1993**, 115, 9952-9959 .

4- Berthet, N.; Constant, J.-F.; Demeunynck, M.; Michon, P.; Lhomme, J. *J. Med. Chem.*, **1997**, 40, 3346-3352.

5- Coppel, Y.; Berthet, N.; Coulombeau, C.; Coulombeau, Ce.; Garcia, J.; Lhomme, J. *Biochemistry*, **1997**, 36, 4817-4830.