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

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

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N. Berthet<sup>b</sup>, J. Michon<sup>b</sup>, J. Garcia<sup>b</sup>, M. Jourdan<sup>b</sup>, J. Lhomme<sup>b</sup>

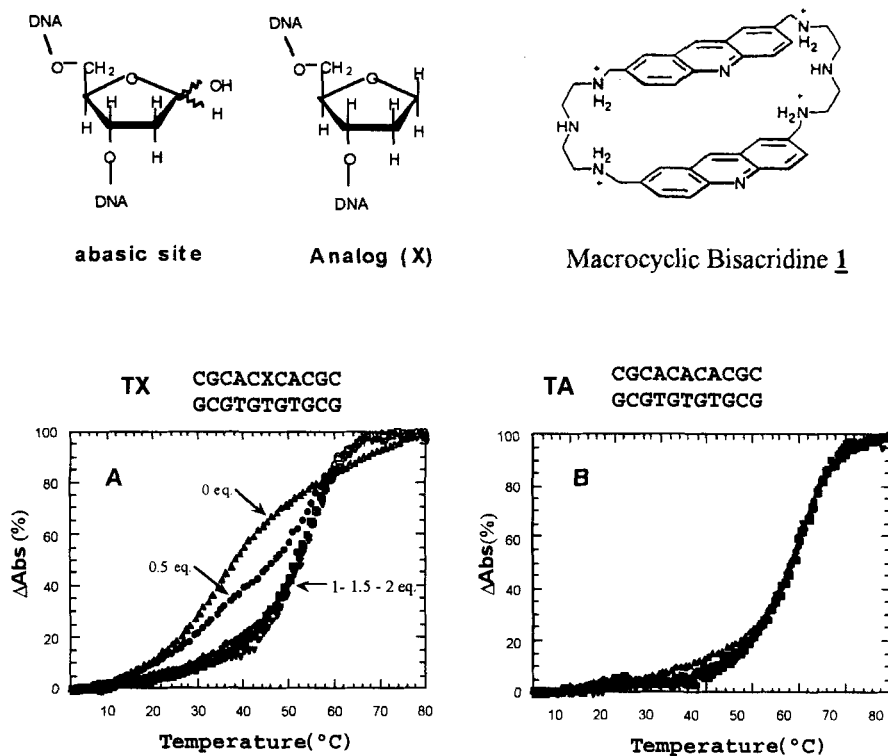
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**ABSTRACT:** A strong and specific stabilization of a DNA undecamer containing an analog of the abasic site has been induced by the macrocyclic Bisacridine **1**. <sup>1</sup>H NMR analysis and molecular modeling of the structure of the complex showed 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<sup>1</sup>. 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<sup>2</sup>. 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<sup>3-5</sup>.

Bisacridine **1** was shown to cleave a <sup>32</sup>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

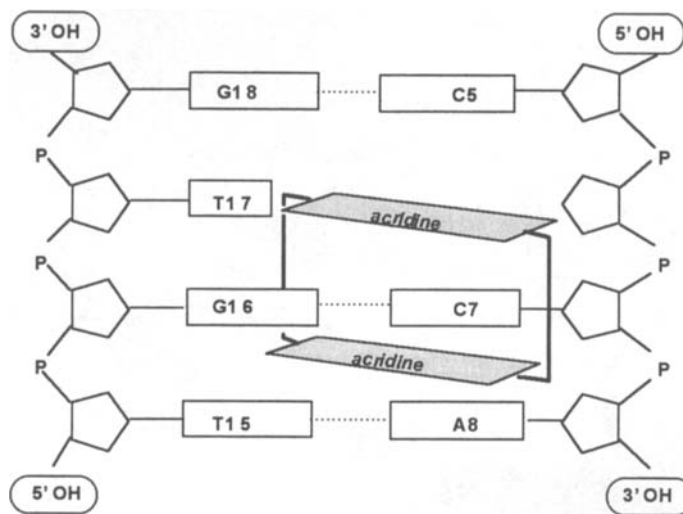


**Figure 1:** Melting temperature curves (A) of the undecamer **TX** (X= 3-hydroxy-2-(hydroxymethyl) tetrahydrofuran]and (B) of the regular analog **TA** in the presence of **1** (0-2eq). Phosphate Buffer 10mM, EDTA 1mM, NaCl 20mM, pH 7.0.

**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**] ( $\Delta T_m = +13.8^\circ\text{C}$ ) (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  $^1\text{H}$  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.

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