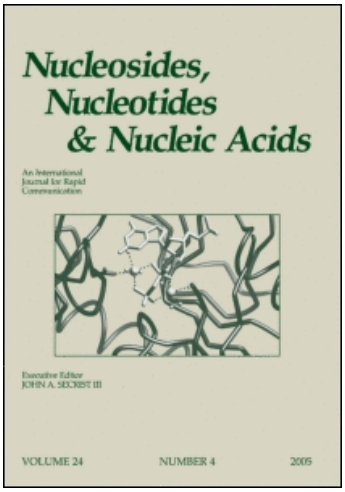

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Molecular Recognition of Quadruplex DNA by Quinacridine Derivatives

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ABSTRACT

The interaction of monomeric and dimeric quinacridines with quadruplex DNA has been investigated using a variety of biophysical methods. Both series of compounds were shown to exhibit a high affinity for the G4 conformation with two equivalent binding sites. As shown from the SPR and dialysis experiments the macrocyclic dimer appears more selective than its monomeric counterpart.

Key Words: Quadruplex DNA; Molecular recognition; Dibenzophenanthrolines.

During the past decade, quadruplex DNA structures have attracted attention since their formation at the end of chromosomes may inhibit telomerase, an enzyme which is essential for the unlimited replicative potential of tumour cells.

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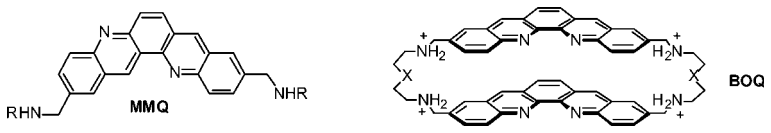
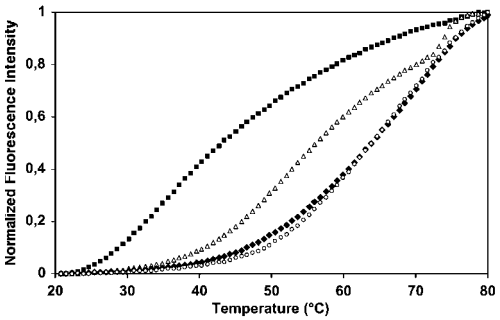


Molecular recognition of DNA quadruplexes by synthetic compounds is therefore a growing field of research which could lead to the development of new anti-cancer agents. We have synthesized monomeric quinacridine derivatives (**MMQ**) and macrocyclic dimers (**BOQ**) that are able to recognize four-stranded DNA with high affinities.

The interaction of quinacridines with DNA quadruplexes has been investigated using oligonucleotides, which mimic the human telomeric repeat sequence and form intramolecular quadruplexes. Fluorescence resonance energy transfer (FRET) Tm experiments with the doubly-labeled oligonucleotide F21T revealed a significant stabilization of the G4 conformation in the presence of **MMQ1 (**Fig. 1).[1] This effect is strongly increased with compounds substituted by amino-side chains bearing 4 or 6 positive charges (**MMQ3, MMQ10**, Fig. 1).[1,2] This recognition was associated with a potent anti-telomerase activity in vitro (IC_{50}values of 29-300 nM) and **MMQs** are thus considered lead compounds.

Biosensor-surface plasmon resonance (SPR) methods indicate also a high affinity of **BOQ1** for the quadruplex conformation ($K > 1\times10^7\,M^{-1}$) with two equivalent binding sites. Furthermore, competition dialysis experiments confirmed that the quadruplex binding specificity of **BOQ1** is higher than that of the monomeric series (Fig. 2).[3]

(A)



(B)

Compound	R	ΔTm (°C)
MMQ1	$(CH_2)_2CH_3$	+12.5
MMQ3	$(CH_2)_3\,N(CH_3)_2$	+19.7
MMQ10	$(CH_2)_3N(CH_3)(CH_2)_3NH_2$	+21

Figure 1. A) Melting curves of oligonucleotide F21T 5′-Fluo-$(GGGT_2A)_3G_3$-3′ Tamra measured by FRET. DNA alone, (close squares), +MMQ1 (open triangles) +MMQ3 (closed diamonds); +MMQ10 (open circles). [F21T] = 0.2 μM, [MMQ] = [1 μM]. B) Chemical structure and ΔTm values.

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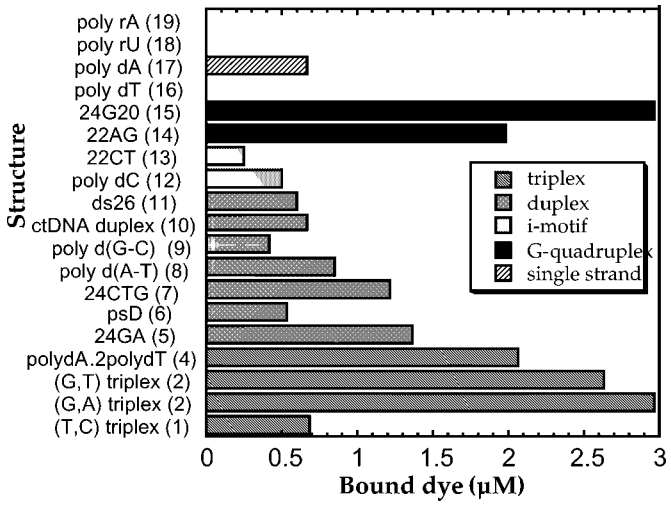

Figure 2. Competition dialysis experiments using $\mathbf{BOQ_1}$ (X = NH). The amount of drug bound to the various nucleic acid structures is shown as a bar graph. The free ligand concentration in the experiment was 1 μM, and the total concentration of each nucleic acid conformational form was 75 μM (expressed in nucleotides, base pairs, triplets or tetrads).

It is clear that both series of compounds represent an exciting new development opportunity for targeting DNA quadruplexes.

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