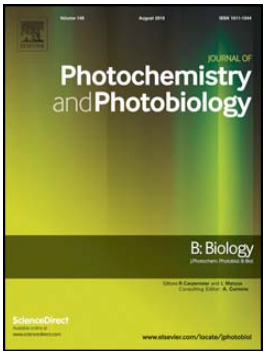

A 4:1 stoichiometric binding and stabilization of mitoxantrone-parallel stranded G-quadruplex complex established by spectroscopy techniques

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A 4:1 stoichiometric binding and stabilization of mitoxantrone-parallel stranded G-quadruplex complex established by spectroscopy techniques

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Highlights

- Absorbance of mitoxantrone shows hypo- and hyper-chromism with 15 nm red shift on binding.
- Fluorescence of mitoxantrone decreases and then increases with 8 nm red shift.
- Binding induces positive CD band at 645 nm and two exciton bands at 619 and 664 nm.
- Fluorescence lifetimes, 0.17 ns (91%) and 0.44 ns (9%), indicate dual binding mode.
- G-quadruplex Melting saturates on 4 mole equivalent addition of mitoxantrone by 25 ºC.

Abstract

Small molecule ligands which specifically bind and stabilize G-quadruplex structures in telomeric ends inhibit the activity of telomerase enzyme, an important marker for cancer. Understanding of the binding mode of ligand-G quadruplex complex is important for evaluating relative efficacy of anti-tumor drugs. The present study is focused on interaction of anti-tumor drug mitoxantrone (MTX) with tetra-molecular parallel stranded G-quadruplex sequence d-TTGGGGT using absorbance, fluorescence and circular dichroism spectroscopy techniques. Absorbance of mitoxantrone shows hypochromism up to MTX (D)/DNA quadruplex (N) ratio ~5, followed by hyperchromism up to D/N=0.21 accompanied by a red shift of 15 nm. The fluorescence emission of MTX shows decrease up to D/N ~5 and then increases with red shift of 8 nm. The two observed fluorescent lifetimes, 0.17 ns (91%) and 0.44 ns (9%), indicate dual binding mode. Absence of isobestic and isoemissive point indicates presence of multiple complexes. Circular Dichroism spectra showing positive induced band at 645 nm and two exciton bands centered at 619 and 664 nm suggest binding of mitoxantrone as a dimer. Proton NMR studies show intermolecular MTX-MTX short contacts confirming existence of stacked dimer of MTX. Thermal melting transitions of DNA saturate at D/N=4 with ΔT_m=25 ºC. The