Nanochemistry and biotechnology

Interaction of Pheophorbide-*a* and its derivatives with quadruplex DNA nanostructure

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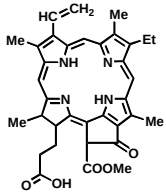
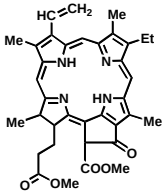
Guanine-rich sequences of telomeric DNA can fold into specific four-stranded assemblies called G-quadruplexes (G4). Stabilization of these structures by small molecules often results in the inhibition of telomerase, a tumor-associated enzyme responsible for telomere elongation, so quadruplex DNA is a promising targets for the development of novel anticancer drugs.

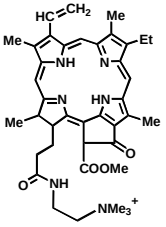
Some porphyrins are efficient G4 ligands with anticancer properties. We have recently found the derivatives of a natural porphyrin Pheophorbide-*a* (Pheo) to inhibit telomerase *in vitro* at low micromolar concentrations. In this work we have studied the interaction of Pheo, its methyl ester (Me-Pheo) and cationic derivative (Cat-Pheo) with nano-sized antiparallel G-quadruplex Tel22 formed by folding the telomeric oligonucleotide d[AGGG(TTAGGG)$_3$] in the presence of Na^+ cations.



Pheo



Me-Pheo



Cat-Pheo

The binding affinities were determined using a FID (Fluorescent Intercalator Displacement) assay based on the displacement of Thiazole Orange dye from its fluorescent complexes with DNA by tested ligands resulting in concentration-dependent fluorescence decrease. All compounds showed high affinity to G4-DNA with binding constants K_b in the range $(2.1–5.6)\times10^6$ M^{-1}. Complexes with duplex DNA were much less stable, and the most efficient telomerase inhibitor Cat-Pheo demonstrated the highest selectivity for quadruplex *vs*. duplex DNA (K_b ratio ~64).