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Synthesis of dextran conjugates with cationic porphyrin telomerase inhibitors

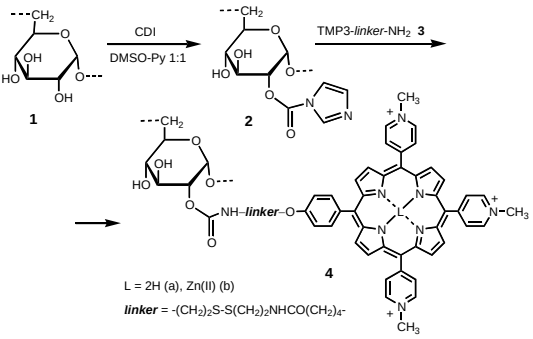
L.V. Dubey, V.V. Negrutska, I.Ya. Dubey

Institute of Molecular Biology and Genetics, Natl. Acad. of Sci. of Ukraine
150 Zabolotnogo str., Kyiv-03680, Ukraine
E-mail: dubey@imbg.org.ua

Telomerase is a promising target for anticancer drugs [1]. Cationic tetra(N-methylpyridinium)porphyrin TMPyP is known as active telomerase inhibitor with antitumor properties. Biocompatible polymers are considered efficient carriers for drug delivery to the tumors. We have prepared the conjugates of cationic porphyrin with dextran, a polysaccharide widely used in pharmaceutics as a polymer support.

Dextran **1** was activated with 1,1'-carbonyldiimidazole (CDI). Imidazolide **2** can react with aliphatic amines in slightly basic medium to form the carbamate bond. It is difficult to functionalize TMPyP, in contrast to its tricationic analog TMP3. We have found that TMP3 and its Zn(II) complex are as potent telomerase inhibitors as TMPyP standard (complete inhibition at 5-7 μM in TRAP assay in all cases). Both TMP3 and Zn-TMP3 demonstrate antiproliferative activity *in vitro* in tumor cell cultures (HeLa, MCF-7, LLC lines) with EC_{50} in the range 1-7 μM.

We have obtained the reagents **3a,b** with aminoalkyl linker containing the S-S-bond. They were used to attach TMP3 to the activated polymer. Conjugation was performed in carbonate buffer (50 mM, pH 7.5). The products were purified by gel filtration on Sephadex G-25. Porphyrin content in various samples of dextran-TMP3 conjugates **4a,b** was 20-40 μmol/g. TMP3 was linked to dextran reversibly via the biolabile disulfide bond that can be easily cleaved within the cell by reducing agents. Indeed, the overnight treatment of **4a** with dithiothreitol (0.2 M, pH 7.5) resulted in ca. 90% porphyrin cleavage from the support. So nanoconjugates **4** are expected to release the drug in tumor cells.



1. *Ruden M., Puri N.* Novel anticancer therapeutics targeting telomerase // Cancer Treat. Rev.-2013.-**39**.-P. 444-456.