Synthesis of Ligand-Directed Polyethyleneimine-Binding Antitumor Trifluorothymidine Prodrug Bearing the Fluorescent Label

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Trifluorothymidine is capable of influencing processes of the tumor growth. In addition to its properties as a chemotherapeutic and antiviral agent, trifluorothymidine is also a promising imaging agent due to the presence of the trifluoromethyl group as the label for 19F MRI. However, the use of trifluorothymidine as a drug is hampered by the rapid degradation and low-efficient uptake by target cells. One of the most interesting solutions to this problem is the use of diverse macromolecular drug delivery systems, and polyethyleneimine (PEI) is considered to be the most promising vehicle due to a large number of the amino groups, which provide the attachment of different residues. To enhance the release of the drug from the vehicle inside the cells, PEI was coupled with urocanic acid, which can provide the formation of an acid-labile P-N bond with trifluorothymidine 5’-monophosphate. Biotin as the reporter molecule and the urocanic acid residue were grafted onto 25 kDa polyethyleneimine by its treating with corresponding N-hydroxysuccinimide activated esters. To visualize the cellular uptake, the fluoresceine residue was introduced into the polymer by its treatment with fluorescein isothiocyanate. Phosphorylation of the modified polyethyleneimine conjugate with N,N’-dimethylaminopyridine derivative of trifluorothymidine 5’-monophosphate led to the desired composite, containing trifluorothymidine. The polymer conjugate was isolated from the low-molecular reactants by centrifugal filtration on a “Centricon” concentrator and characterized by the UV-vis, 1H, 19F, and 31P NMR methods. The amount of the imidazolyl groups and biotin and trifluorothymidine residues in the resultant polymer was evaluated by 1H NMR.

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