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Preparation, characterization and in vitro evaluation of a new nucleotide analogue prodrug cyclodextrin inclusion complexes.

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Abstract

Bis(tbutyl-S-acyl-2-thioethyl)-cytidine monophosphate is a new cytotoxic mononucleotide prodrug which have been developed to reverse the cellular resistance to nucleoside analogues. Unfortunately, its in vivo utilisation was hampered by its poor water solubility, raising the need of a molecular vector capable to mask its physicochemical characteristics although without affecting its cytotoxic activity. Hydroxypropyl-beta-cyclodextrin was used to prepare the prodrug inclusion complexes, allowing it to be solubilized in water and hence to be used for in vitro and in vivo experiments. A molar ratio of the cyclodextrin: prodrug of 3 was sufficient to obtain complete solubilization of the prodrug. The inclusion complex was characterized by differential scanning calorimetry, which revealed the disappearance of the melting peak of the prodrug suggesting the formation of inclusion complex. Proton Nuclear Magnetic Resonance spectroscopy provided a definitive proof of the inclusion complex formation, which was evidenced by the large chemical shift displacements observed for protons located in the interior of the hydrophobic cyclodextrin cavity. The complex retained its cytotoxic activity as shown by in vitro cell survival assays on murine leukemia cells. These results provided a basis for potential therapeutic applications of co-formulation of this new nucleotide analogue with hydroxypropyl-beta-CD in cancer therapy.