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Conjugation of Sinapic Acid Analogues with 5-Fluorouracil: Synthesis, Preliminary Cytotoxicity, and Release Study

ABSTRACT

Tripartite prodrug approach is a promising strategy to improve the therapeutic efficacy of orally administrated drugs having a low bioavailability. 5-Fluorouracil is a primary chemotherapeutic agent used in the treatment of many solid tumors. The oral use of 5-fluorouracil suffers from many challenges, which are principally contributed to the erratic activity of dihydropyrimidine dehydrogenase in the GIT. In this work, five integrates were prepared as tripartite mutual prodrugs by connecting sinapic acid and four of its analogues to 5-fluorouracil through amenable ester bond. Chemical structures of the prepared integrates were defined by studying their FTIR, ^1H -NMR, and ^{13}C -NMR spectra. Initiatory cytotoxicity study was verified for these integrates via MTT test versus four cancer cell lines including HeLa, MCF-7, AMN3, and SKG. The in vitro study of releasing the active drug from the synthesized integrates was followed spectrometrically using a human serum. The results of the cytotoxicity study after 24 hr of treatment revealed that the synthesized integrates by themselves have a non-toxic activity toward the test cell lines. In contrast, the results of the same study but after 72 hr of treatment indicated the potential antitumor activity of the tested prodrugs which indicates the effective release of the active components from these prodrugs. Also, the data gathered from the release study utilizing a human serum indicated that these integrates can release the active agents pursued pseudo first order kinetics. It is concluded that the synthesized integrates could be considered as mutual prodrugs and that may be improved the clinical applications of 5-Fluorouracil.