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A PROMISING ORAL 5-FLUOROURACIL PRODRUG FOR LUNG TUMOR : SYNTHESIS, CHARACTERIZATION AND RELEASE

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ABSTRACT : The significance of 5-fluorouracil as an oral cytotoxic drug has been wondered in the last three decades because of its wavering plasma level. This obstacle can be related to the variable activity of the enzyme named dihydropyrimidine dehydrogenase that localizes on the intestinal mucosa. In this study, a prodrug consists of three active components, including 5,7-dimethoxy-4-phenylcoumarin, 5-fluorouracil and welcovorin was designed to afford the mutual release of these components utilizing a lactonization-promoted release framework. The target prodrug was synthesized through several linear schematic steps starting from a coumarin-derived compound. The spectroscopic data gathered from various spectroscopic instruments were established the chemical backbones of the target prodrug and its synthetic intermediates. The capacity of the prodrug to act as an orally derived agent was tested by investigating two issues. The first is the chemical stability of the prodrug in the HCl- (pH 1.2) and phosphate- (pH 6.8) buffered solutions. While, the second issue is the enzymatic hydrolysis of the prodrug in human serum to release the active components. The results obtained from the first issue revealed that the prodrug has intrinsic stability in the HCl- and phosphate-buffered solutions with $t_{1/2}$ scores of 36.44 and 20.85 hrs, respectively. Besides, the outcomes indicated the capacity of the prodrug to free its three active components in human serum with $t_{1/2}$ of 8.02 hrs, adjusting the pseudo-first-ordered kinetics. Accordingly, the authors concluded that the prodrug can act as a potent oral candidate for improving the therapeutic efficacy of 5-fluorouracil.

Key words : 5,7-dimethoxy-4-phenylcoumarin, 5-fluorouracil, welcovorin, prodrug, lung tumor.

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INTRODUCTION

Non-Small Cell Lung Tumor (N-SCLT) is an obstinate phenotype of tumor that is unvoiced progressed, hardly treated and increasingly developed the resistance versus many cytotoxic agents (Shi *et al*, 2020). Despite the recent encouragement in the fields of radiotherapy, surgery, and targeted chemotherapy, the survival period for the patients in the late stage of N-SCLT is very limited (Mustafa and Abdulaziz *et al*, 2021).

5-Fluorouracil (FU), a synthetic fluoropyrimidine, posses a wide-ranged activity spectrum versus different tumor phenotypes such as lung, prostate, pancreatic, gastric, breast, colorectal, and bladder cancers (Moath Kahtan Bashir *et al*, 2020; Mustafa *et al*, 2020). Besides its serious side effects and low affinity to tumorous cells, the administration of FU as an oral cytotoxic agent suffers from several obstacles, including the short plasma $t_{1/2}$, atypical intestinal absorption, and irregular plasma level (Zhu *et al*, 2019).

FU, as a pyrimidine analog, is metabolized inside the cell into many active metabolites involving 5-FdUMP (5-fluoro deoxyuridine monophosphate). These active metabolites disrupt the synthesis of RNA and the activity of an enzyme named thymidylate synthase (TS) (Ota *et al*, 2019). From a host of the biochemical modulators investigated to enhance the therapeutic efficacy of FU (Moath Khtan Bashir, Mustafa and Oglah, 2020; Mustafa and Abdulaziz, 2020, 2021), the agent known as welcovorin (WV, folinic acid, N5-Formyltetrahydrofolic acid) was the best (Mustafa *et al*, 2021).

WV can enhance the antineoplastic effect of 5-FdUMP on TS and consequently the therapeutic potency of FU (Pasban *et al*, 2019). TS is the target of the FU and represents the cornerstone enzyme in the *de novo* synthesis of thymidines, as shown in Fig. 1 (Aldewachi *et al*, 2020; Nejres *et al*, 2020; Nejres *et al*, 2020). WV is channelized across the cell membrane via a reduced-folate carrier and transformed into a metabolite named