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Inhibition of UGT1A9 activity demonstrated for acridine antitumor agent C-1748 may implicate drug-drug interactions

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UDP-glucuronosyltransferases (UGTs) are phase II conjugating enzymes catalyzing glucuronidation reaction of many exogenous and endogenous substances. Glucuronides are more polar than the native compounds which facilitates their excretion. UGT isoenzymes are in the spotlight in respect to antitumor therapy as glucuronidation is the major route of elimination for many anticancer drugs. Moreover, some drug-drug interactions can be explained on the basis of UGTs inhibition. The objective of the present study was to explore the inhibitory effect of C-1748, an acridine antitumor agent, toward isoenzyme UGT1A9 in order to predict the potential for drug-drug interactions. C-1748 showed strong cytotoxic activity against colon cancer cells and high anti-tumor activity against prostate carcinoma xenografts which allowed its selection for preclinical studies. Previous results indicated that C-1748 undergoes glucuronidation with human liver and intestinal microsomes. Our studies showed that C-1748 is not a substrate for UGT1A9, however it exerted dose-dependent inhibition toward this isoenzyme. The glucuronidation reactions of standard substrate 7-hydroxy-4-(trifluoromethyl)coumarin were conducted in the absence or presence of C-1748 and monitored by HPLC/UV-Vis method. The concentration of 0.25 mM of C-1748 inhibited more than 70% activity of UGT1A9. The inhibition kinetic type was determined to be noncompetitive on the basis of Lineweaver-Burk and Dixon plots and the inhibition kinetic parameter (K_i) was calculated to be 0.17 mM. Taking together, the presented UGT1A9 significant inhibition indicates the high possibility for drug-drug interactions in combined therapies using C-1748 anticancer agent. Therefore, clinical monitoring should be applied when co-administrating C-1748 with drugs mainly undergoing UGT1A9-mediated metabolism.

Biography

Anna Mróz has studied Biotechnology from Gdańsk University of Technology (Poland) and received her Master's degree in the year 2013. She is now a PhD student at the Department of Pharmaceutical Technology and Biochemistry, Gdańsk University of Technology. Her scientific interests are related to the investigation of metabolism of new active compounds against cancer. She is a co-author of two papers in the field of UDP-glucuronosyltransferases-mediated metabolism.

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