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Enhancing the Yield of 10-Hydroxycamptothecin Glucuronide Prodrug.

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For chemotherapy, many chemotherapy target rapidly proliferating cells, these therapies might act at cell cycle. So the drug has not tumor specificity, it will cause severe side effects. In order to increase the tumor targeting, we accord to the strategy of prodrug. We design and synthesize glucuronide prodrug of 10-hydroxycamptothecin. Make the anti-tumor drug, 10-hydroxycamptothecin, conjugate with β-D-glucuronic acid to improve drug's tumor specific and water solubility. Then, 10-hydroxycamptothecin connect conjugate with β-D-glucuronic acid via a self-immolative 3-methylpiperazine benzyl ether linker. The linker improve the prodrug affinity for β-glucuronidase. However, the benzyl ether linkage is nonpolar groups, which reduce water solubility, then will increase cytotoxity to normal cell. In order to improve solubility of prodrug. We created the 3-methylpiperazine group on benzyl ether, it is tertiary amine which will improve water solubility and reduce the prodrug impermeability to normal cell. When the spacer including the 3-methylpiperazine group on benzyl ether, it is more bulk group than benzyl ether, this benzyl group conduction with the 10-hydorxycamptothecin have poor yield. For solving this problem, the spacer conjugate the 2-amino-5-hydroxybenzaldehyde first, then conduction with tricyclic ketone to form 10-hydorxycamptothecin.