Fabrication of guaiazulene derivatives nano-prodrugs and their structure-activity evaluation

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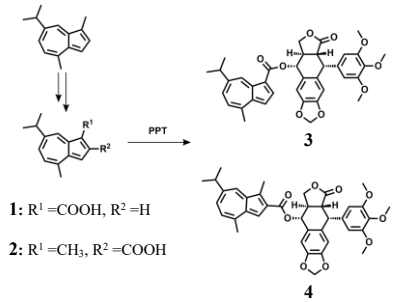
Combination chemotherapy and nanoparticle drug delivery have shown promising results in the treatment of cancer.[1)] The combination therapy offers modulation of different pathways in cancer, maximizing therapeutic efficacy and overcoming resistance mechanisms such as inflammation. On the other hand, nanoparticle regulate the side effects of drug by selectively delivery drug to the target area without harming healthy tissues.[2)] Herein, we reported the fabrication of nano-prodrugs composed of the conjugated guaiazulene anti-inflammatory agents and podophyllotoxin (PPT) anticancer drug for the delivery of combination chemotherapy by nanoparticle. The effect of prodrug molecular design on nano-prodrugs fabrication, release of therapeutic agents via hydrolysis, and anticancer efficacy will be investigated.

We first synthesized guaiazulene derivatives **1** and **2** having carboxyl group, and then leaded to guaiazulene-modified PPT prodrugs **3** and **4** (**Scheme 1**). Prodrug NPs of as-synthesized derivatives **3** and **4** were successfully fabricated by reprecipitation method,[3)] which had average sizes around 50 nm with high dispersion stability. The obtained prodrug NPs were then incubated with KPL-4 cell line and CHO-K1 cell line for 48 h. As a result, both of derivatives **3** and **4** showed appropriate drug efficacy with different drug release behaviors, which could be affected by bonding positions of guaiazulene (**Fig. 1**). We will also report the hydrolysis behavior of obtained nanoparticles with *in vitro* experiments.



Scheme 1 Synthetic procedure of guaiazulene-modified PPT prodrug

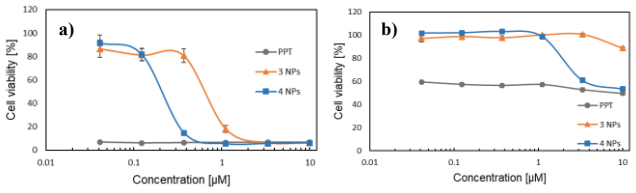


Figure 1 *in vitro* pharmacological activity of guaiazulene-conjugated PPT. a) KPL-4 cell, b) CHO-K1 cell
All results are indicated as mean ± standard deviation (n = 3)

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