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Synthesis and evaluation of cembranoid type diterpene derivatives as potential antitumor agents

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Statement of the Problem: Croton laevigatus Vahl. (Euphorbiaceae) is an arbor that is found mainly in Yunnan, Guangdong, and Hainan Provinces of China. Its roots and leaves have been commonly used as a folk medicine in the Dai nationality of China for the treatment of injury from fall and fracture, malaria and stomachache. In our previous work, we have reported the studies on the chemical composition of the leaves of C. laevigatus Vahl. and seven cembranoids were isolated. The antitumor activity of these compounds were evaluated against HeLa cells and neocrotocembraneic acid showed modest cytotoxic activity. Moreover, this natural product has a high content in C. laevigatus Vahl. (0.7% of the plant's dry weight) which laid the material foundation for the structural modification. However, there was no study on the structural modification and structure–activity relationship (SAR) of neocrotocembraneic acid related to the antitumor purpose. This stimulated us with great interest to focus on structural modification of neocrotocembraneic acid in order to obtain the initial structure-activity relationship and find novel derivatives with potential antitumor activity. Methodology & Theoretical Orientation: Taking neocrotocembraneic acid as the starting material, the target compounds were synthesized by condensation reaction and click reaction. Their antitumor activities in vitro were evaluated for HeLa, K562 and K562A/02 by MTT. Findings: Eleven novel derivatives were synthesized and the structures were characterized by ^{1}H-NMR, ^{13}C-NMR and ESI-MS. MTT assay showed that some cembrane derivatives exhibited antitumor activities. In particular, compounds 2f showed good antitumor activity against HeLa and compounds 2e showed promising antitumor activity against K562 and K562A/02. Conclusion & Significance: Some derivatives have demonstrated promising antitumor activities against K562/A02 cell lines which were worth further studying.

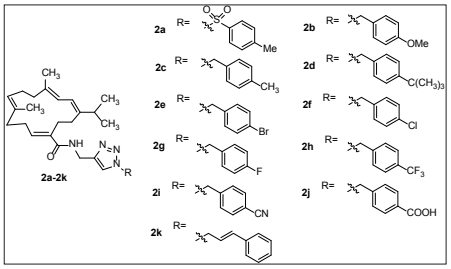

Figure 1. The amide derivatives of neocrotocembraneic acid

IC50 (μmol/L) RF				
Compound	**HeLa**	**K562**	**K562/A02**	**RF**
2e	**30.5**	**18.0**	**20.3**	**1.13**
2f	**11.4**	**22.7**	**35.1**	**1.55**
VP-16	**21.1**	**8.2**	**35.1**	**4.3**

Table 1. In vitro antitumor activities of compound 2e and 2f

Biography

Hai Shang's research interest focuses on structure modification, activity evaluation and mechanism of action of natural products. He carried out studies on structural optimization of natural pruducts, such as podophyllotoxin, neocrotocembraneic acid and matrine, and found that some derivatives have moderate to good antitumor activity. In addition, a few derivatives of podophyllotoxin and neocrotocembraneic acid exhibited the potential of anti-multidrug resistance by inhibiting the efflux function of P-gp. His research will contribute to the development of novel anticancer drugs with multidrug-resistance modulating potential.

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