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## Design, synthesis and antineoplastic activity of novel hybrids of podophyllotoxin and indirubin against human leukaemia cancer cells as multifunctional anti-MDR agents

Jing Wang\*, Li Long, Yongzheng Chen, Yingshu Xu and Lei Zhang\*

*School of Pharmacy, Zunyi Medical University, 6 West Xuefu Road, Zunyi 563003, PR China*

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## ABSTRACT

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To overcome cancer drug resistance, in present study, a series of podophyllotoxin-indirubin hybrids were designed, synthesized, and evaluated for anticancer efficacy against two human chronic myeloid leukemia cell cultures. Among them, compound **Da-1** was the most potent in resistant K562/VCR cells with an  $IC_{50}$  value of  $0.076 \pm 0.008 \mu\text{M}$ . Preliminary mechanism studies showed that **Da-1** significantly induced apoptosis and cell cycle arrest at the G2 phase. Decrease in mitochondrial membrane potential, accompanied by activated PARP cleavage, was observed in K562/VCR cells after incubation with **Da-1**. Meanwhile, **Da-1** caused the accumulation of intracellular ROS, regulated JNK and AKT signaling, and down-regulated the expression levels of P-gp and MRP1 proteins. Importantly, Western blotting revealed that **Da-1** could induce K562/VCR cells autophagy, by increasing the levels of Beclin1 and LC3-II. Finally, **Da-1** could disrupt microtubule organization, and binding mode to tubulin was investigated by using molecular modeling. Together, **Da-1** was a novel hybrid with potent antiproliferative activity and might be a promising agent for the treatment of drug-resistant leukemia cancer.

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\* Corresponding authors. Tel/Fax: +86-0851-28609627 (L. Zhang) ; +86-0851-28609627 (J. Wang)

E-mail addresses: [wangjing@zmc.edu.cn](mailto:wangjing@zmc.edu.cn) (J. Wang); [lzhang@zmc.edu.cn](mailto:lzhang@zmc.edu.cn) (L. Zhang)

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