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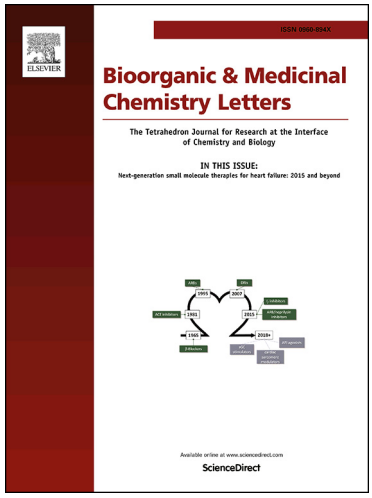

Design, synthesis and antineoplastic activity of novel hybrids of podophyllotoxin and indirubin against human leukaemia cancer cells as multifunctional anti-MDR agents

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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

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ABSTRACT

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 resistent K562/VCR cells with an IC_{50} value of 0.076 ± 0.008 μM. 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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