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## 1-Methoxy-Canthin-6-One and Related $\beta$ -Carbolines: From Natural Compound to Synthesis and Biological Activities (Abstract)

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## Abstract

*Ailanthus altissima* Swingle (Simaroubaceae) is a medicinal plant used in traditional medicine as an antiviral and an antitumoral drug. Its roots have been successively extracted, at room temperature, with solvents of increasing polarity. The extracts were tested for their antiproliferative activity on HeLa (human cervical carcinoma cell line), at a dose of 10  $\mu\text{g}/\text{mL}$ . The chloroform extract, the most active in biological assays, was fractionated on a silica-gel column: the fractions obtained were assayed on the proliferation of the same cellular line, at a dose of 10  $\text{mg}/\text{mL}$ . The most active fraction (100% of cytotoxic activity) demonstrated to contain a single substance. The identification of this active substance, recognized as 1-methoxy-canthin-6-one, was performed by NMR methods. This indole alkaloid has shown antiproliferative and proapoptotic effects on several tumoral cell lines. In particular, it provoked mitochondrial membrane depolarization, mitochondrial release of cytochrome *c* and Smac/DIABLO, and caspase 3 activation on Jurkat cells (human leukemia cell line). The compound was active also on other tumor cell lines, HuH7 (hepatocellular carcinoma), NPA (human papillary carcinoma), and ARO (anaplastic thyroid cell line): the apoptosis-inducing activity was evident at a concentration of  $< 10 \mu\text{mol}/\text{L}$  until half maximal at about  $40 \mu\text{mol}/\text{L}$ . Peripheral blood mononuclear cells (PBMC) from healthy subjects have been used as control; in these cells, the alkaloid showed no proapoptotic activity. The effects of 1-methoxy-canthin-6-one, in combination with TRAIL (human recombinant tumor necrosis factor-related apoptosis-inducing ligand), has also been investigated on Jurkat cells using suboptimal concentrations of both agents, showing 45% apoptosis. Also, the TMRE (tetramethylrhodamine ethyl ester) bioassay resulted in a definite mitochondrial membrane depolarization, when alkaloid and TRAIL are used together, always using their suboptimal concentrations. The study of the possible synergism has shown that the alkaloid increases TRAIL R1 receptors, inducing JNK activation and c-Jun phosphorylation. JNK inhibition reduces only partly the synergism between alkaloid and TRAIL; therefore, other factors take part in TRAIL-induced apoptosis, besides TRAIL R1 upregulation. In order to obtain more information about biological properties of 1-methoxy-canthin-6-one and to investigate on chemical requirements responsible for its biological activity, a series of novel 1,4-disubstituted and 1,4,9-trisubstituted  $\beta$ -carbolines and tetracyclic derivatives were designed and synthesized. *In vitro* cytotoxic activities of these compounds were studied in a human tumor cell line panel. Almost all compounds demonstrated antiproliferative effects, in particular against prostate cancer cells PC-3, with an  $\text{IC}_{50}$  values ranging between 60 and 8  $\mu\text{M}$ . The most active derivatives were tested to evaluate the possible interaction with DNA and inhibition of topoisomerase I. None of these compounds were observed to stabilize the DNA-Topo I complex, thereby poisoning the reaction. In particular, 3-benzyl-1-methoxy-canthin-6-onium bromide exhibited strong inhibition of Topo I, with  $\text{IC}_{50}$  of 17.77  $\mu\text{M}$ .