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Pharmacological Evaluation of *N*-(6-allyl-1,3-benzodioxol-5-yl)-N-(*tert*-butoxycarbonyl) valynamide related as antitumour agent

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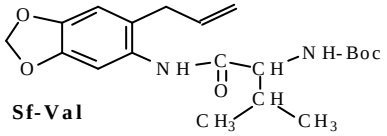
Introduction

The methylenedioxy unit, present in Safrole *synthon*, can be identified in the clinical antitumour agents, as etoposide and teniposide. Safrole is metabolically activated to electrophilic intermediates that bind to cellular DNA[1]. The DNA-binding properties from safrole, can be explored in drug design for obtain bioactive compounds. In view to obtain more selective and less toxic drugs, research is often directed to exploit latentiation of bioactive compounds, as approaches using small peptides or amino acids residues[2]. As part of a research program aiming synthesis and pharmacological evaluation of novel possible antitumour prototype compounds, we describe here the preliminary pharmacological evaluation of *N*-(6-allyl-1,3-benzodioxol-5-yl)-N-(*tert*-butoxycarbonyl) valyn- amide (**Sf-Val**, figure), previously related as potent antitumour agent (with inhibition of 83% at 35mg/kg against sarcoma 180)[3]. We also investigated the capacity of Sf-Val stimulates Interferon(IFN)-γ (immunological mediator of the anti-tumour protection) and Nitric Oxide (NO) (indicator of macrophages activation)[4] by murine spleen cells[5].



Sf-Val

Results and Discussion

In an initial approach to exploit this compound, we decided verify the citotoxicity against growth of tumour cell lines, using the MTT assay. As shown in **table I**, **SF-Val** exhibited a non-citotoxicity in tumour cells line assay. The *in vivo* and *in vitro* results can suggest that **SF-Val** needs undergo metabolization or spontaneous chemical breakdown after administration to liberate the cytotoxic (anti-proliferative) specie. These results stimulate us to investigate the toxic profile of this drug, using assay against *Artemia salina L.* and *in vivo* acute toxicity, using intraperitoneal way in males *suiss* adult mice. In general, the compound showed a non-toxicity profile against *Artemia salina L.*, with CL_{50} equal 571µg/mL, a value beyond range of cytotoxic (anti-proliferative) anticancer drugs. The *in vivo* acute toxicity reveal that in doses of 250mg and 500mg/kg, this compound was not toxic, without deaths or behavioral effects during the assay. These results indicate that this compound presents apparent index of therapeutic safety. Spleen cells cultured with Sf-Val (25µg/mL by 72 hs) produced IFN-γ [2,3ng/mL-Standard Curve(SC) 0,3 to 5 ng/mL] and NO (8,6µM/mL-SC 3,1 to 50µM/mL), suggesting an activation of immune system by this compound.

Table I: IC_{50}* (against tumour cells growth) and CL_{50}* (against *Artemia salina* L.) values for Safrole and Sf-Val

Comp.	IC_{50} (µg/mL)				CL_{50} (µg/mL)
	HL-60	HCT-8	MDA-435	SF-295	
Safrole	16,9	5,85	16,97	5,26	<10
Sf-Val	>25	>25	>25	>25	571

*IC_{50} and CL_{50} values were calculated from five concentrations, obtained from at least three independent experiments.

Conclusions

Preliminary pharmacological and immunological evaluation of Sf-Val showed a low toxicity, a range of significant in vivo antitumor activity and inactivity in vitro assays, what could indicate a action as prodrug in tumour tissue, while Sf-Val was able active cells of immune system eliciting the production of immunoregulators molecules.

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