Evaluation of the antitumour activity of peptidyl-like derivatives containing the 1,3-benzodioxole system

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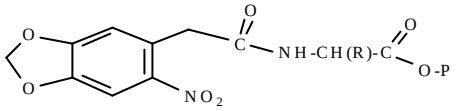
Introduction

The methylenedioxy unit, present in Safrole *synthon*, can be identified in the clinical antitumour agents, as etoposide and teniposide[1]. Safrole is metabolically activated to electrophilic intermediates that bind to cellular DNA[2]. The DNA-binding properties from safrole, can be explored in drug design for obtain bioactive compounds, as antitumour[3] and antiinflammatory[4] agents. 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[1]. As part of a research program aiming synthesis and pharmacological evaluation of novel possible antitumour prototype compounds, we describe here the *in vitro* antitumour activity of peptidyl-like derivatives containing the 1,3-benzodioxole system. The nitro group in six position of 1,3-benzodioxole system, was added in this series. We suppose that these group could act to form reactive oxygen species (citotoxic to tumour cell) and as internal cathalizator, to chemical breakdown of the peptidyl-residues, activating the latent form these compounds.

Results and discussion

The peptidyl-like derivatives were prepared as described in reference 3. and citotoxicity were evaluated against 4 tumor cell lines: MDA-MB 435 (human breast), HCT-8 (human colon carcinoma), HL-60 (human leukaemia) and SF-295 (human glyoblastoma), using the MTT assay[5]. Table **I** summarizes the IC_{50}(nM) dates for antitumour activity. The results indicated that compounds **04f** (tyrosine) and **04g** (lysine) have comparable and significant activities and are the most potent proliferation inhibitors in this series, with IC_{50} of 8,54 (HCT-8) and 5,4nM (HL-60), respectively. The growth of cancer cell lines was also inhibited by Safrole, but less potently (IC_{50} values of 32-100nM). The antimitotic activity was performed on the embryonic development of fertilized sea urchin eggs[6]. Safrole did not show any selectivity in this latter assay, which indicates safrole is acting as a *cell cycle-nonspecific* inhibitor agent. However, compound **04f** presented a fair antimitotic effect, mainly on 3rd cleavage and blastulae stages (62% and 99% of inhibition, at 10µg/mL, respectively), suggesting a time-dependent activity and a cell cycle-specific agent' action.

Table I: IC_{50} values [a] (nM) against tumour cells growth for



P = Protected group
R = side chain of Aminocids

peptidyl-like derivatives and Safrole.

Comp.	Entry[b]	HL-60	HCT-8	MDA- 435	SF-295
04a	Gly	41,2	29,6	56,7	46,4
04f	Tyr	>150	8,54	9,8	>150
04g	Lys	5,4	>150	9,1	31,6
Safrole		104	36	104	32

[a]IC_{50} values were calculated from five concentrations (0,1-150nM), obtained from at least three independent experiments. [b] Entry represent the aminoacid residue of the compounds.

Conclusions

In summary, the *in vitro* evaluation of antitumour activity for peptidyl-like derivatives containing the 1,3-benzodioxole system exhibited a range of significant activities, showing therapeutic potential as lead compounds and antitumour agents. In view obtain more information about the pro-drug property of **4f** and **4g** the *in vivo* studies are going.

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