Synthesis of aminoacyl thiazolidones as potential antitumour agents

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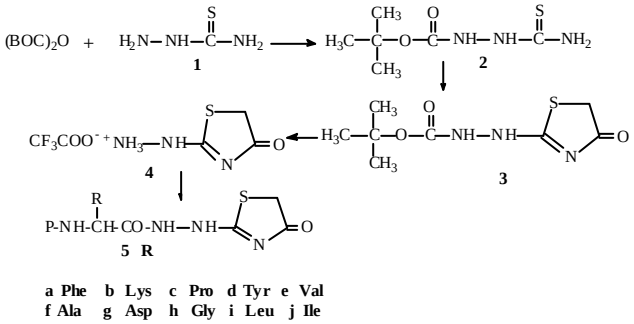
Introduction

Recently, antitumour drugs with reduced toxicity have been developed by linking them to small peptides or amino acids residues [1]. The roles of the conjugated peptide in these compounds serve as a substrate for designated enzymes that are produced and secreted preferentially by tumour tissue. These remarks indicate that it may be possible to develop highly selective chemotherapy strategies that are based on the selective expression of receptors in tumour vasculature.

The use of heterocycles as scaffolds to optimally place substituents in protease pockets is an important strategy for the search of protease inhibitors with improved pharmacokinetic properties. Heterocycles containing amino acids would facilitate incorporation of the scaffold while offering several possibilities of variation. Thiazole and thiazolidone scaffolds are interesting because they present several biological properties such as antimicrobial, anti-parasitic, anti-inflammatory, anticonvulsant, anticancer and antituberculosis activities, among others.

The above remarks lead us to investigate the synthesis of a new series of peptidyl compounds, containing a 4-thiazolidone heterocyclic and an amino acid moiety. Here we report the synthesis of these new series of compounds and their in vivo antitumour evaluation[2].



Results and Discussion

To obtain the newly compounds **5a-e**, a classical strategy of peptide synthesis was used that's included protection using $(BOC)_2O$, ciclisation with chloroacetic acid, unmasking (TFA/ CH_2Cl_2) and amino acid condensation using DCC and OH-Su to as carbonyl activating agents. A series of nine derivatives were obtained with a range of yield of 15-98%.

The antitumour activity of compounds **5a-e** and intermediate compound (**3**) was tested against murine sarcoma S-180 in six Swiss albino mice (25-28g) for each tested product. The pre-clinical trial began forty eight (48) hours after the implantation of the tumour and longed for eight (8) days of treatment, with the dose of 250mg/ kg/ day, using the intraperitoneal way. All products of the series **5a-e** and intermediate compound **3** were able to inhibit the growth of the tumour mass on the assays as showed in **table**.

Table. Antitumour activity results of 4-thiazolidone and peptidyl derivatives

Comp.	Dose (mg/kg/)	Tumour reduction (%)	Number of dead
3	250	73	3
5a	250	80	0
5b	250	71	0
5c	250	78	0
5d	250	62	0
5e	250	58	0

Between peptidyl compounds, phenyalanine (**5a**) and proline (**5c**) derivatives were the most active of them. It seems that a bulky side chain is important to obtain a better antitumour profile. According to the standard of National Cancer Institute a substance is considered active if it inhibits the tumour growth by 50%.

Conclusion

Thiazolidone-4 derivatives **5a-e** compounds presented excellent results against sarcoma S180 such as lower toxicity when compared with non-latentiated intermediate, **3** leading us to proceed with antitumour researching of these compounds, looking for these appreciative results.

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