SYNTHESIS OF NEW PEPTIDYL DERIVATIVES FROM 4-THIAZOLIDONE

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Abstract: In this work we report the synthesis of new heterocyclic compounds presenting a 4-thiazolidone nucleus and a peptidyl moiety. The synthesis has been achieved employing a strategy of peptide synthesis. Compounds **6a-e** were obtained in good overall yields and have been characterised by IR and the ^{1}H-NMR spectroscopy.

Introduction

The presence of the thiazole ring in compounds with a wide range of biological activities has contributed over the years to enlarge the interest for the closely related thiazolidones. Thiazole and thiazolidone nucleus are interesting because they present several biological properties like antimicrobial[1,2], anti-parasitic[3,4], antiinflammatory[5], anticonvulsant[6], cardiotonic[7] and analgesic and antitermic[8] activities, among others.

In addition to these findings it was found in Nature a group of cyclic peptides containing thiazolic heterocyclic rings, that are linked to amino acids blocks. Some of these cyclepeptides demonstrated antitumor and antimicrobial activities[9-12].

For some time, the interest for the design of prodrug containing an amino acid moiety or a peptidyl residue has increased. In fact, several research groups have been used amino acids looking for biologic active and low toxic molecules. As a matter of fact, the literature tells us that bioactive compounds have their activity improved when linked to amino acids[13-19]. These modifications have been based on the process of prodrug design as a way of molecular modification.

These facts concerned us to the synthesis of a new series of peptidyl compounds, embracing a 4-thiazolidone heterocyclic and a amino acid moiety. This paper reports the strategy of synthesising compounds **6a-e** applying the coupling reagents used in the peptide synthesis and the verification of their structures through spectroscopic means[20].

Results and discussion

In our strategy, we idealised initially to realise a protection of the amino group of thiosemicarbazide which is important to minimise the nucleophylic effect of primary amine of thiossemicarbazide that can difficult the ring formation. After that, a cyclisation reaction is easily realised in mild conditions. After removal of the protection group of heterocyclic ring, a condensation reaction with the several amino acids is proceed (Scheme I).

In order to protect the amine function of thiosemicarbazide we used the Boc (t-butoxycarbonyl) group, using the symmetrical anhydride $(Boc)_2O$ (di-tert-butoxycarbonyl) [21-22]. The reaction passes on basic mean (NaOH), using dioxane as solvent. The intermediary compound **3** was obtained with 55% yield. On the second step, the cyclisation is realised through the reaction of the Boc-thiosemicarbazide and monochloroacetic acid in the presence of sodium acetate, utilising ethanol as solvent under reflux to obtain **4** with 78% yield. For the remotion of the Boc group of 4-

thiazolidone, a classical cleavage conditions using TFA/ CH_2Cl_2 (1:1) [21-22] gives the deprotected 4-thiazolidone **5** (98% yield).

The last stage involves the condensation of the α-amino acids to the amine moiety of the 4-thiazolidone using DCC (dicyclohexilcarbodiimide) and N-hidroxisuccinimide to as a carbonyl activating agents [21-2]. We had chosen using Boc (t-butoxycarbonyl) for N-terminal protecting group for this series.

Following this strategy initially five new molecules, compounds **6a-e** were obtained. This method gave incomes in the average of 15% to 98% for all the amino acids used.

The structures of **6a-e** were confirmed by spectral (IR and ^{1}H-NMR) data. IR spectra

The IR spectra were obtained on FTIR spectrophotometer Brukker, model IFS66 using KBr pellets. Peptidyl derivatives exhibited NH and C=O bands in the 3329-3323 and 1745-1627 cm^{-1} regions attributed to common CONH-N. The characteristic common to lactams C=O stretchings were observed in the 1730-1710 cm^{-1} region.

^{1}H-NMR spectra were measured with a Varian UNITY plus 300 MHz spectrophotometer using $DMSO_{d6}$ as solvent and tetramethylsilane as an internal standard. Compounds **6a-e** displayed a single NH resonance (δ 7.9-8.0ppm), and the diagnostic S-CH_2 (δ3.48-3.27ppm). Concerning amino acid moiety, all compounds presented characteristic signals for NH and the proton linked to the chiral carbon. For the NH function, a characteristic doublet due to coupling with proton of chiral carbon (J=7.0 Hz) appeared δ 6.71-7.5ppm. Different chemical shifts for the groups next to the chiral center are observed, principally when bulky substituents are presented. Compound **6e** (a phenylalanine derivative) showed a multiplet (δ7.26-7.44ppm) indicating a typical aromatic hydrogen pattern. Some analytical data are shown in Table I

Scheme I

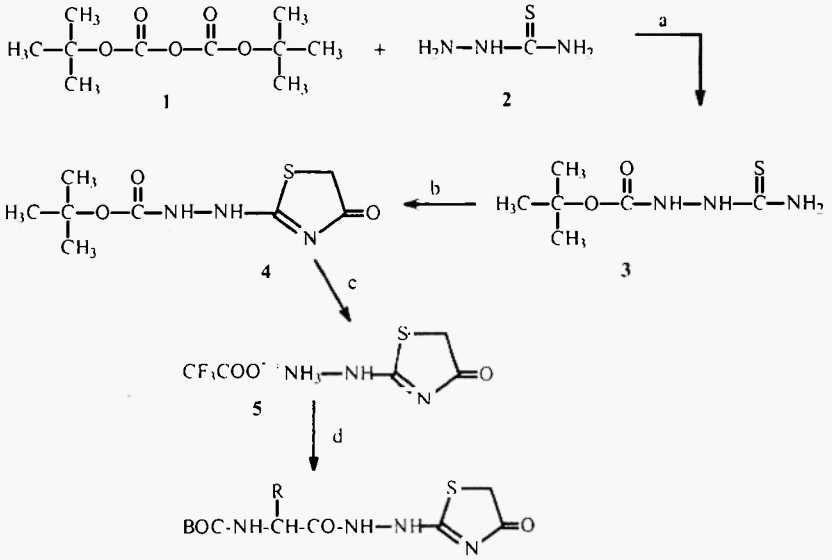

Table I- ***Analytical data 4-Thiazolidone derivatives***

Compound	M. p. [°C][a]	$[\alpha]_D^{20c}$	R_f[b]	Molecular Formula	Yield (%)
6a	113-5	+19.8	0,74	$C_{11}H_{18}N_4O_4$	96.7
6b	167-9	+15.4	0.78	$C_{13}H_{22}N_4O_4$	96.5
6c	93-5	+14.0	0.81	$C_{14}H_{23}N_4O_4$	15.0
6d	158-160	+19.8	0.80	$C_{14}H_{24}N_4O_4$	95.2
6e	160-2	+16.5	0.76	$C_{17}H_{22}N_4O_4$	98.10

[a] Column chromatography solvent: Ethyl acetate/hexane (5/5); [b] Solvent system: Ethyl acetate/hexane (7:3); [c] Solvent DMSO, 4mg/mL.

Conclusion

Finally, the peptidyl derivatives from 4-thiazolidones were synthetised. The strategy using Boc-protection of thiossemicarbazide are promising and can be using for the synthesis of others series of thiazolidones derivatives. The biologic activity of these compounds is being determined. Some compounds are being submitted to antimicrobial tests, against microorganisms like gram positive and negative, alcohol acid resistant bacteria (Ziche-Nielsen), as well as filamentous fungi and leaven. In order to evaluate the anti-tumour activity, are being realised essays against sarcoma 180. These results will be reported in up coming.

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