PLANNING, SYNTHESIS AND CHARACTERIZATION OF *N*-(2,4-DINITROPHENYL)HISTIDINETHIOSEMICARBAZIDES AS POTENTIAL ANTITUMOUR AGENTS

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Introduction

Amino acids constitute the building blocks of proteins, hormones, and toxins, aside from being the formation units of neurotransmitters and nucleic bases, *e.g.,* adenine and guanine. Despite their great importance, the main core of the essential α-amino acids includes only 20 structurally simple molecules. These remarkable substances are easily recognised, absorbed and metabolised by the living beings, which base their complexity upon them. Even structurally modified amino acids play an important role in the metabolic pathways, once their main core remains recognisable to the biomolecules ruling the cells. Therefore, it is not surprising to suppose that the modifications at the amino acid structure aiming to incorporate recognised bioactive features can lead to new drugs.

In 1990, Varga *et al.* [1] studied the derivative 2,4-dinitrophenylglycine (2,4-DNP-Gly) as a ligand of the monoclonal antibody IgE, reporting a high level of affinity. Theoretical studies on the activity of a series of 2,4-DNP amino acids disclosed their antigen activity on the monoclonal antibody IgE [2]. Despite these results, the research involving 2,4-DNF modified amino acids has not been exploited appropriately in Medicinal Chemistry. In order to develop new antitumour compounds based on the amino acid framework, a series of N^{α}-(2,4-dinitrophenyl)-histidinethiosemicarbazides was planned, synthesised and characterised, starting from the L-histidine in four synthetic steps.

Methodology

All intermediates and target molecules were characterised by infrared spectroscopy (IV), using a Tensor27 spectroscope from Bruker. Hydrogen magnetic resonance (^{1}H NMR) analyses were performed at 300 and 400 MHz. Melting points (m. p.) were measured using a

digital melting point apparatus and are uncorrected. The planned N^{α}-(2,4-dinitrophenyl)-histidinethiosemicarbazide derivatives were obtained in four synthetic steps previously developed at the Laboratory of Design and Synthesis Applied to Medicinal Chemistry-***SintMed***® [3]. The starting material of this work was L-histidine, which undergoes an S_NAr with 1-chloro-2,4-dinitrobenzene, leading to the 2,4-DNP-histidine **1**. This is smoothly converted to the corresponding 2,4-DNP-histidine ethyl ester **2**, the precursor of the 2,4-DNP-histidine hydrazide **3** by reacting with hydrazine hydrate under reflux. Compound **3** is the key intermediate to access the N^{α}-(2,4-dinitrophenyl)-histidinethiosemicarbazides **4-10**. A solution of **3** and the appropriate aryl isothiocyanates in THF was refluxed for two hours until thin layer chromatography has indicated the reaction's completion. After isolation, all compounds were fully characterised, confirming their structures.

Results and discussion

The preparation of 2,4-DNP amino acid has occurred with total conversion of both reactants, however, the crystallisation process is difficult, giving the product in low yield. Fortunately, the ensuing steps have worked with good to excellent yields, in agreement with outcomes for similar reactions previously studied at ***SintMed***®. The general data for the intermediates and title compounds are described below.

Compound 1: yield 43%, m. p. 265.4-266.6 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3332 (NH), 3400-2900 (OH), 3100, 3081 (Ar CH), 1617 (C=O), 1580 (C=C);

Compound 2: yield 76%, m. p. 184.8-187.1 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3324 (NH), 3151, 3107 (ArC–H), 1744 (C=O), 1621 (C=C);

Compound 3: yield 77%, m. p. 169.7-172.3 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3367, 3312, 32030 (NH), 3104 (ArC–H), 1688 (C=O), 1616 (C=C);

Compound 4 (phenyl): yield 81%, m. p. 222.3-224.7 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3320 (NH), 3106 (Ar CH), 1697 (C=O);

Compound 5 (4-chlorophenyl): yield 89%, m. p. 212.7-214.7 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3357 (NH), 3153 (Ar CH), 1695 (C=O);

Compound 6 (4-cyanophenyl): yield 89%, m. p. 221.1-223.4 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3310 (NH), 3265 (Ar CH), 2233 (C≡N), 1698 (C=O);

Compound 7 (4-methylphenyl): yield 89%, m. p. 214.5-216.5 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3308 (NH), 3170 (Ar CH), 1697 (C=O);

Compound 8 (4-nitrophenyl): yield 90%, m. p. 219.7-220.9 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3349 (NH), 3094 (Ar CH), 1698 (C=O);

Compound 9 (3-chlorophenyl): yield 91%, m. p. 227.3-229.8 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3318 (NH), 1618 (C=O);

Compound 10 (4-methoxyphenyl): yield 56%, m. p. 141.8-143.8 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3329 (NH), 1618 (C=O).

These disclosed compounds are now under investigation for their antitumour profile, in order to establish the first structure activity relationship (SAR) pattern for the series, so that further analogues can be designed.

Conclusions

The synthesis of intermediates **1-3** and targeting compounds **3-10** is successfully carried out, leading to novel N^{α}-(2,4-dinitrophenyl)-histidinethiosemicarbazides with potential antitumour activity. All compounds are characterised, so that the further synthesis of other analogues can be easily achieved. The incorporation of the L-histidine framework in a series of thiosemicarcarbazides represents an outstanding strategy for the search of new bioactive compounds, opening the possibility of discovering of new lead molecules with innovative structural features.

Key words: 2,4-DNP amino acids; Thiosemicarbazides; Antitumoral activity.

References

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