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Full Length Original Research Paper

Spectrochemical study of a new albendazole derivative

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Abstract: The hydatidosis is a cosmopolitan parasitic disease that stays a real public health problem in the countries of strong endemic. The treatment essentially calls on the surgery that includes morbidity and mortality significant, from where the interest to develop the medical treatment whose main representative is the albendazole. The efficiency of this molecule is proven but limited by its bad biodisponibility due to its weak absorption by the organism.
In order to improve the biodisponibility of this molecule we synthesized an ester prodrug of albendazole to solubility completely modified in relation to the princeps. This synthesis has been achieved with an output of 75%. The structure of the synthesis product has been verified and established by spectrometry of infrared molecular absorption, and by spectrometry of nuclear magnetic resonance of the proton.

Keywords: Albendazole, Synthesis, Prodrug, Spectroscopy.

Introduction

Hydatidosis or cystic echinococcosis is an anthropozoonose common to man and herbivorous mammals. This parasitic disease is due to the presence and development in the body of the larval form of *Echinococcus granulosus*, the adult form is hosted by carnivores, mostly dogs [1]. Hydatid disease is a public health problem in endemic areas represented by all the countries of sheep farming especially the countries of the Mediterranean [2].

There are currently three options for treating hydatid disease: chemotherapy, puncture-aspiration method in addition to surgery known as standard treatment for this disease. Completely curative surgery with total pericystectomy is not always feasible and the risk of recurrence ranging from 2 to 15% [3].

Under ideal conditions, the mortality rate ranges from 0.9 to 3.6% during the first intervention, with significant morbidity, the risk increases with the number of interventions, 6% in the second and 20% in the third intervention [4].

Surgery presents indications against temporary and absolute, related to the condition of patients, refusal of surgery and inaccessibility to hospitals, especially in countries with high endemicity, where hydatidosis represents a major public health problem.

The development of medical treatment is important because chemotherapy can be used in patients of all ages and it is less constrained by the condition of patients than surgery [3]. To find effective chemotherapy that can improve the care of patients with this infection, several drugs have been tried, even those who had limited effect and it is only with the benzimidazole carbamates that the practice of chemotherapy was possible.

Several molecules of this family have been tried in the medical treatment of hydatid cyst. Mebendazole and flubendazole were less effective in the treatment of hydatid disease. Poor

absorption of these two molecules is probably responsible for the low efficiency. Albendazole is more interesting currently; it is reserved for the treatment of hydatidosis complicated and recurrent inoperable.

To improve the bioavailability of albendazole, some authors have synthesized derivatives esters or amides as prodrugs of this compound [5-8]. In this prodrug approach, we have synthesized a *N*-alkoxy derivative of albendazole and we proposed its spectrochemical study.

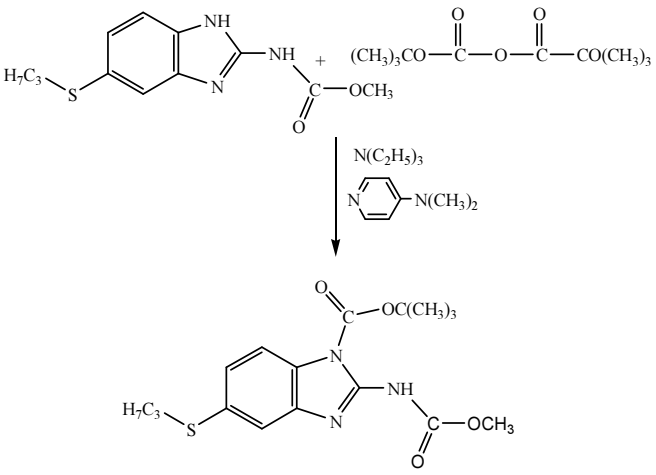
Material and Methods

The new ester (1-tert-butyloxycarbonyl-5-propylthio-1-H-benzimidazol-2-ylcarbamate (ABZ-Boc) was synthesized from of albendazole (ABZ) and tert-butyloxycarbonyl under an atmosphere of nitrogen in the presence of triethylamine and 4-dimethylaminopyridine [9,10].

The experimental yield is expressed as a percentage of isolated pure products. The compound was identified and characterized by infrared spectrometry (IR) spectroscopy of proton nuclear magnetic resonance (1 H NMR) and UV-visible spectrometry.

Synthesis of ABZ-Boc (scheme 1)

Under nitrogen at room temperature, maintain the magnetic stirring solution of albendazole in dichloromethane. Add successively triethylamine, tert-butyloxycarbonyl anhydride and 4-dimethylaminopyridine. After 7 hours of contact, evaporated to dryness under reduced pressure. Dissolve the residue in a minimum of water, acidify with dilute acetic acid at 10%. Extracted with chloroform, the organic phase washed with water, dried over calcium chloride. Filtered and evaporated to dryness. 75% yield.



Scheme 1: Synthesis of carbamate of albendazole

Spectrochemical study

FTIR spectroscopy

The IR spectrum of pure ABZ-Boc derivative was measured, using an FTIR spectrophotometer (Jasco FT/IR-460 plus) using KBr pelleting. The scans were executed from 4000 cm^{-1} to 500 cm^{-1}.

^{1}H NMR spectroscopy

The ^{1}H NMR spectrum of ABZ-Boc was recorded at 25° using the NMR spectrometer (AVANCE 300 Bruker) employing DMSO-d_6 as a solvent. The H^1 NMR chemical shifts ($\Delta\delta$) are expressed in ppm relative to tetramethylsilane (TMS) used as reference (TMS δ = 0). Coupling constants J are expressed in Hz.

UV spectroscopy

The absorbance measurements were performed on a UV spectrophotometer (Perkin) using a quartz cell of 1 cm. The concentration used was 10µg/ml.

Results and Discussion

UV spectrum

The UV spectrum of the ABZ shows two wavelength at the absorption maximum, the first λ max is 294 nm corresponding to a molar extinction

coefficient at the absorption maximum ε-max = 10610 l.cm^{-1}.mole and the second λ max is at 214 nm corresponding to ε-max = 53050 l.cm^{-1}.mole.

The spectrum of Boc-ABZ is similar to that of ABZ, but with a hypsochromic effect at the first absorption peak.

Infrared spectrum (IR)

IR spectra of ABZ and ABZ-Boc have a similar look with any differences some time. Thus the spectrum of the ABZ present, an absorption peak of stretching vibration, characteristic of the NH bond as a band of medium intensity at 3323 cm^{-1} and a bending vibration at 1525 cm^{-1}, stretching bands and deformation characteristics of aliphatic carbons respectively 2958 cm^{-1} and 1450 cm^{-1}, a stretching band of the double bonds of the aromatic ring at 1590 cm^{-1} and a strong peak of stretching vibration corresponding to the group carbonyl C = O at 1634 cm^{-1}.

In the spectrum of ABZ-Boc was a decrease in the intensity of NH stretching vibration (3323 cm^{-1}) and as it is an ester, the main difference is the appearance of a stretching vibration characteristic of the > N-C = O intensive at 1750 cm^{-1}.

^{1}H NMR spectrum

To confirm the structure of the new ester synthesized, spectral study of the proton nuclear magnetic resonance was performed.

The 1H NMR spectrum of ABZ, taken in chloroform and in a magnetic field of 300 MHz this:

- At 0.92 ppm a triplet corresponding to the three protons C**H**$_3$-CH$_2$-CH$_2$-S-,
- At 1.53 ppm a multiplet corresponding to two protons of CH$_3$-C**H**$_2$-CH$_2$-S-,
- At 2.83 ppm a triplet corresponding to two protons of CH$_3$-CH$_2$-C**H**$_2$-S-,
- At 3.74 ppm a singulet corresponding to three protons of-O-C**H**$_3$,
- At 7.35 ppm a doublet corresponding to one aromatic proton **H$_6$**,
- At 7.72 ppm a doublet corresponding to one aromatic proton **H$_4$**,
- At 7.99 ppm a doublet corresponding to one aromatic proton **H$_7$**,
- At 11.63 ppm a singulet corresponding to one proton of the -N**H**-CO-.

The spectrum of ABZ-Boc is mainly characterized by the appearance of the characteristic peak of the tert-butyl group (O-C (CH$_3$)$_3$) at 1.37 ppm as singulet corresponding to 9 protons.

Conclusion

The spectral studies carried out confirmed the structure of the new derivative of albendazole. Prospects of our work will be the determination of chronic toxicity on rats for a period of three months and a pharmacokinetic study in animals to ensure that it behaves as a prodrug, which will improve intestinal absorption of albendazole.

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