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Research Article

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Synthesis of a combined prodrug of albendazole and metronidazole

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ABSTRACT

The treatment of hydatidosis is primarily surgical but can cause morbidity or mortality, hence the interest in many cases of medical treatment whose main representative is albendazole. The efficacy of this compound against Echinococcus granulosus cysts is proved, but limited by its poor bioavailability. Some prodrugs of albendazole have been described but no bioavailability study has shown their interest to present. The new a combined prodrug of albendazole and metronidazole was synthesized. The compound thus prepared was characterized by this physical (TLC) and spectral data (ESI-MS).

Keywords: Albendazole, Synthesis, Prodrug.

INTRODUCTION

It is known that benzimidazole derivatives include heterocyclic compounds that have received the most attention because of their applications in areas as diverse [1].

Currently the basic approaches for treatment of hydatid disease are surgery and chemotherapy. However, operative leakage may lead to dissemination of viable protoscolices to adjacent tissues and thus to intraperitoneal hydatid disease, hence the interest in many cases of medical treatment whose main representative is albendazole (Fig. 1). The efficacy of this compound is proved, but limited by its poor bioavailability. Such a disadvantage requires long duration cures which can cause side effects, including liver [2-4].

Albendazole (Fig. 1) is practically insoluble in water and insoluble in most organic solvents, this has a direct impact on its poor bioavailability [5,6]. In order to improve the solubility of albendazole some solutions have been reported, first via complex formation and development of new dosage forms [7-9], second by prodrug approach, indeed two prodrugs of albendazole (N-methoxycarbonyl-N'-[2-nitro-4-propylthio phényl] thiourea and N-methoxycarbonyl-N'-[2-nitro-5-propylthiophényl] thiourea) have been described [10]. The solutions that were proposed could not significantly improve the absorption of albendazole.

The search for new analogues of albendazole is interesting for several reasons: limited therapeutic arsenal, the problem of bioavailability and the emergence of resistance.

Some authors have synthesized derivatives esters or amides as prodrugs of this compound. Other research has focused on derivatives of albendazole in order to increase its effectiveness.

In this paper the new promised prodrug was designed by combining albendazole and metronidazole.

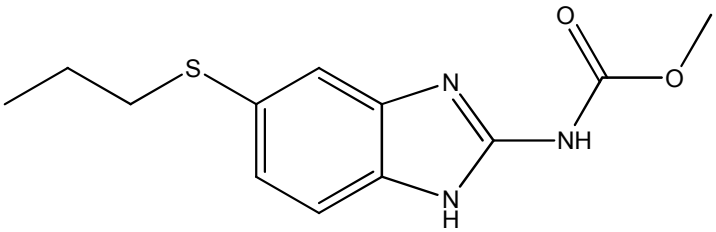

Figure 1: Chemical structure of albendazole

EXPERIMENTAL SECTION

Into an ice-cooled solution of metronidazol and triethylamine in dichloromethane was added chloroacetyl chloride dropwise under stirring. The reaction mixture was further stirred at 5°C for 45 min. Dichloromethane was distilled off and the residue was taken in chloroform. The chloroform layer was washed with water and dried over sodium sulfate. The filtrate was concentrated to give a brown semisolid (product **1**).

The mixture of albendazole (ABZ) and sodium hydride in Tetrahydrofuran (THF) was stirred for 3 hours. The product **1** was added and stirred for 24 hours. The THF is removed under vaccuo, the residu is washed, extracted with dichloromethan and recrystallised from dichloromethan - petroleum ether (product **2**) (Fig. 2).

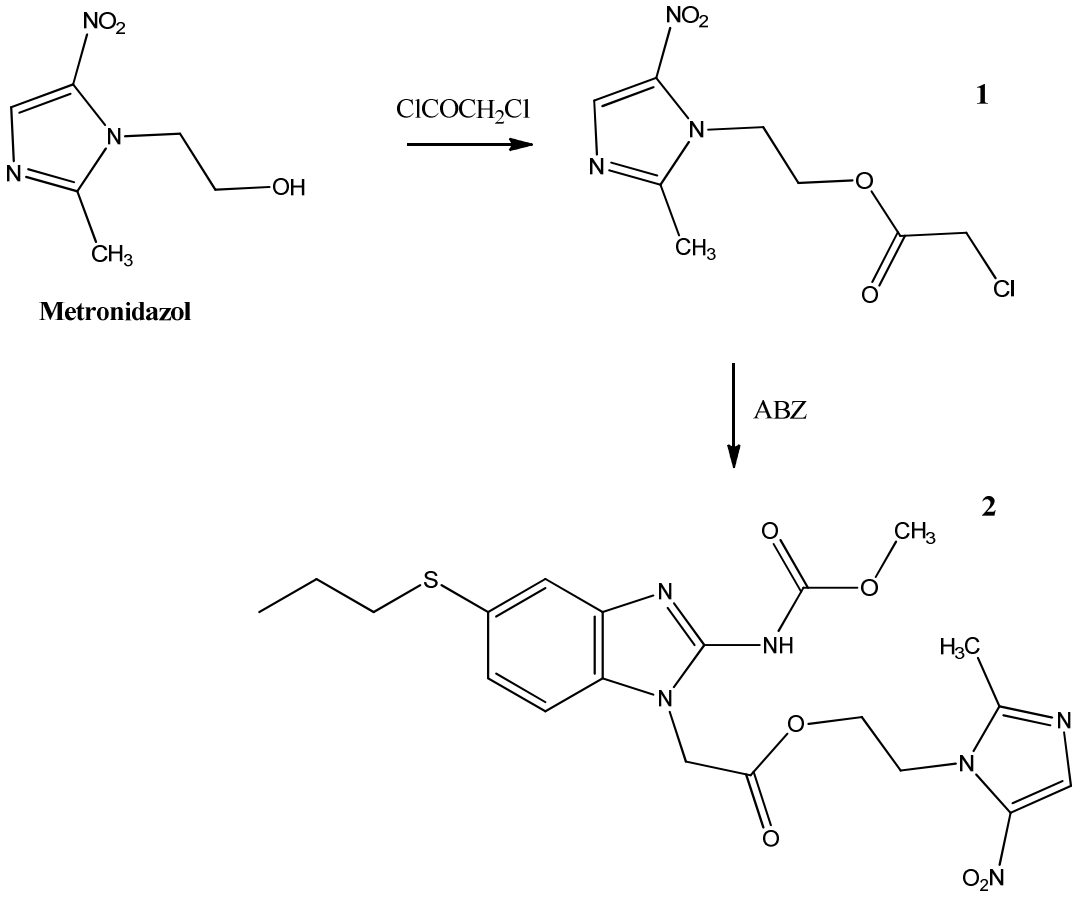

Figure 2: Scheme of the synthesis of a combined prodrug

RESULTS AND DISCUSSION

All reactions were followed by TLC 0.25 mm silica gel plates (Ethyl acetate / Hexane: 7/3). The structure of synthesized derivative **2** was confirmed by Electronspray Ionisation Mass spectra (ESI-MS) data (Fig. 3).

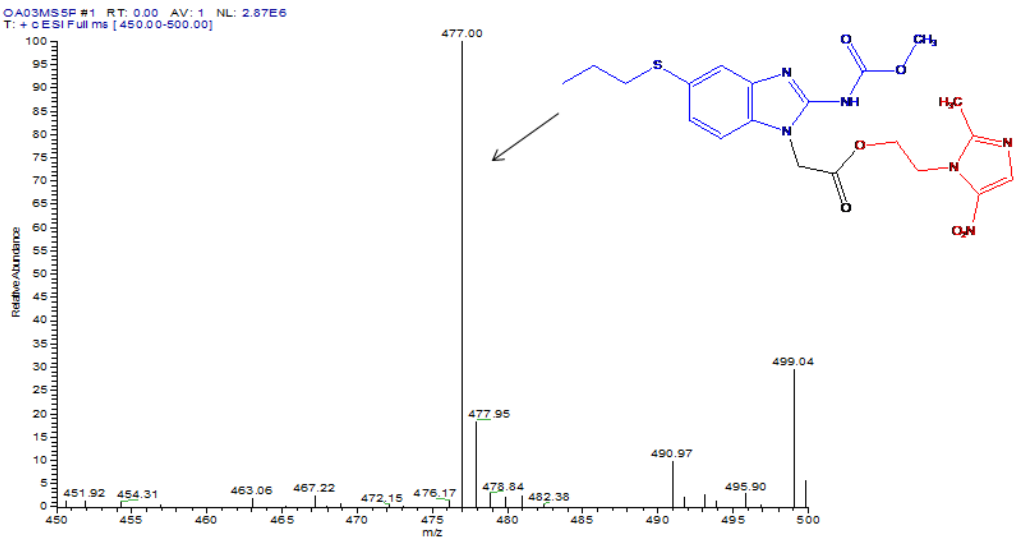

Figure 3: Electronspray Ionisation Mass spectra (ESI-MS) of a combined prodrug

The poor bioavailability of albendazole is due to its lipophilicity, in fact it is practically insoluble in water and insoluble in most organic solvents. Thus it has been classified according to the Biopharmaceutics Classification System (BCS) in class IV (poorly soluble, poorly permeable) where the interest of the research of novels prodrugs.

Prodrug was reported by Ansar et al [11], it is a reaction between albendazole and tert-butyloxycarbonyl (Boc). The ester produced is theoretically easily metabolizable (Fig.4a).

Herna'ndez-Luis et al [12], have synthesized several prodrugs of albendazole. These prodrugs have been tested on hydrolysis by esterases and by pH. The results showed that the ethyl is the most promising prodrug (Fig. 4b).

Márquez-Navarro et al [13], reported new prodrugs. The nitro group can facilitate hydrolysis of the prodrug by the mesomeric effect (Fig. 4c).

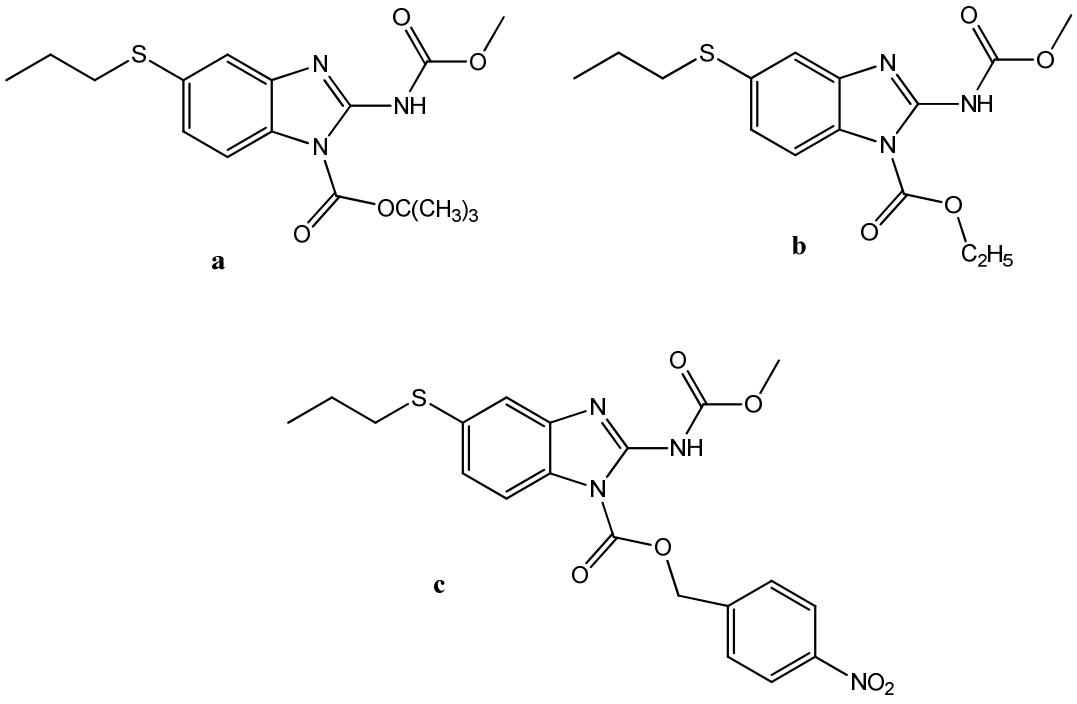

Figure 4 : Chemical structures of some albendazole prodrugs

Albendazole is a well known broad spectrum anthelmintic. An *in-vitro* study reported albendazole to be a more effective antigiardial agent as compared to metronidazole [14].

The proposed prodrug may associate the potential of the two molecules. Metronidazole has good bioavailability and can theoretically be used as a vehicle for driving albendazole. The prodrug is its interest in the treatment of giardiasis and hydatid disease. A bioavailability study will be performed to assess the behavior of this new prodrug.

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