

ALBENDAZOLE AND ITS ANALOGUES

J. El harti *, M. Ansar, J. Taoufik.

Laboratory of Medicinal Chemistry, Faculty of Medicine and Pharmacy, BP 6203, Rabat Institute,
University Mohammed V Souissi, Rabat, Morocco.

* ja.elharti@um5s.net.ma

Abstract:

The efficacy of albendazole 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. Other authors have synthesized analogues of albendazole that have a better activity against some parasites namely; *Toxocara cani*, *Giardia lamblia*, *Entamoeba histolytica* and *Taenia crassiceps*.

Keywords: Albendazole, Prodrug, Anti-parasitic activity.

Introduction

The cystic echinococcosis or hydatidosis is a disease prevalent in the cattle country especially in the developing countries, where it constitutes a real public health problem. It can reach up to 5% of the population in highly endemic areas [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 intrapritoneal 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 [2-9].

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.

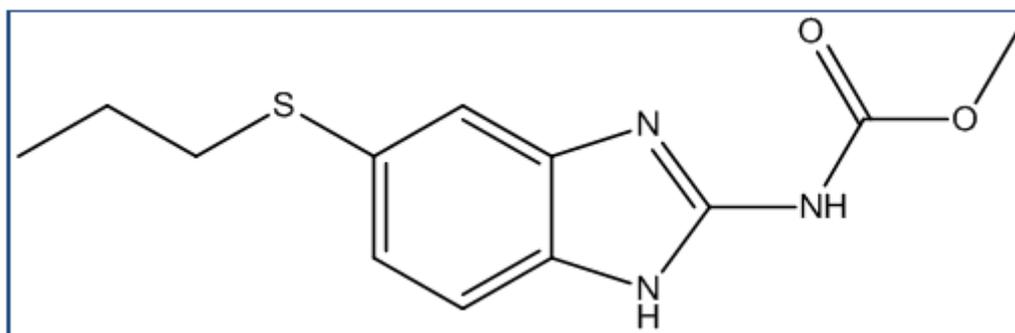


Fig. 1: Chemical structure of albendazole

Albendazole

Albendazole (ALB) is a typical, broad spectrum benzimidazole antiparasitic agent, first approved for human use in 1982. The recommended dosage schedule for echinococcosis is: 400 mg to 800mg for 28 days. Can repeat every 14 days for three cycles. ALB is relatively insoluble in water and most organic solvents, properties that influence its absorption and behaviour in the body. In the mouse and rat oral absorption of ALB is about 20-30% and in cattle it is about 50%, compared to about 1-5% in humans. As it undergoes very rapid first pass metabolism in all species, the unchanged drug has not been reliably detected in plasma. Plasma levels of the initial oxidised metabolites (the sulphoxide and sulphone) (Fig. 2) in all species are much higher than of the parent drug. The sulphoxide is generally considered to be the active metabolite responsible for the therapeutic activity of ALB [10-12].

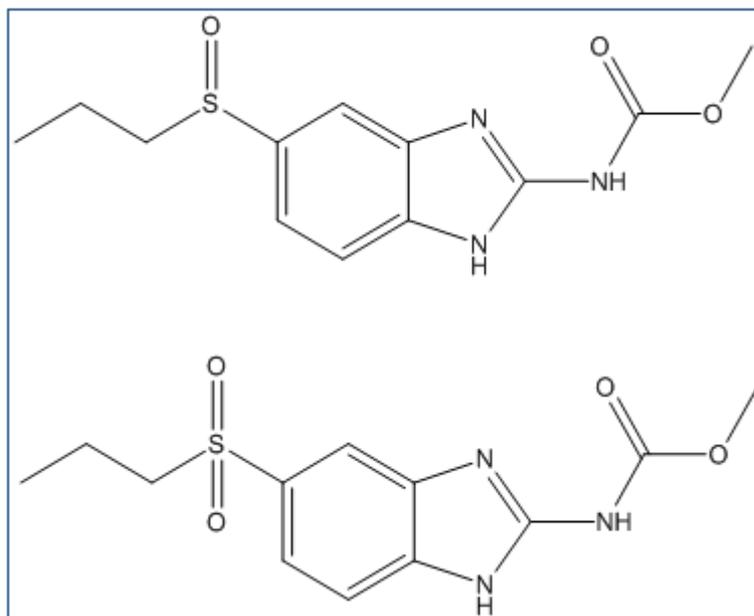


Fig. 2: Chemical structures of albendazole sulphoxide and albendazole sulphone

Albendazole prodrugs

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 [13], it is a reaction between albendazole and tert-butyloxycarbonyl (Boc). The ester produced is theoretically easily metabolizable (Fig.3).

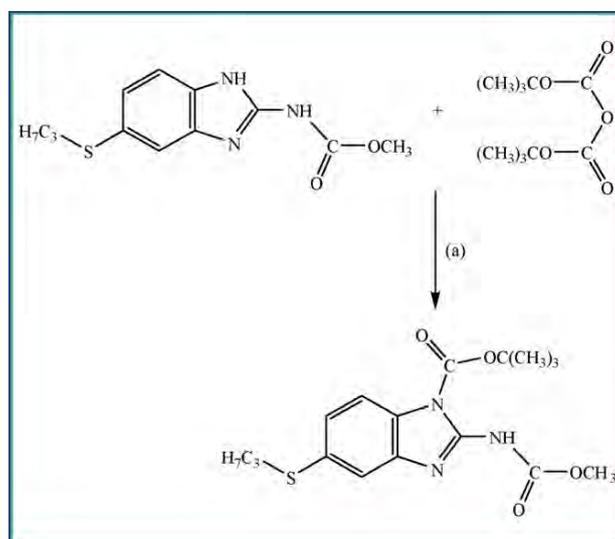


Fig.3: Ester carbamate of albendazole

Herna'ndez-Luis et al [14], 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 (Fig4).

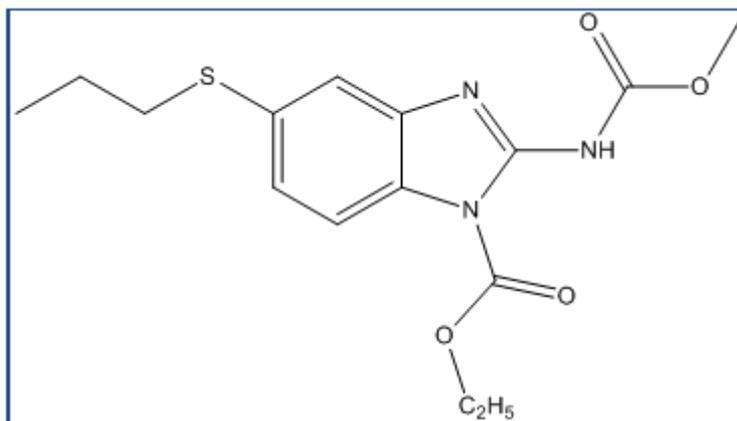


Fig. 4: Ester ethyl of albendazole

Márquez-Navarro et al [15], reported new prodrugs. The nitro group can facilitate hydrolysis of the prodrug by the mesomeric effect (Fig. 5).

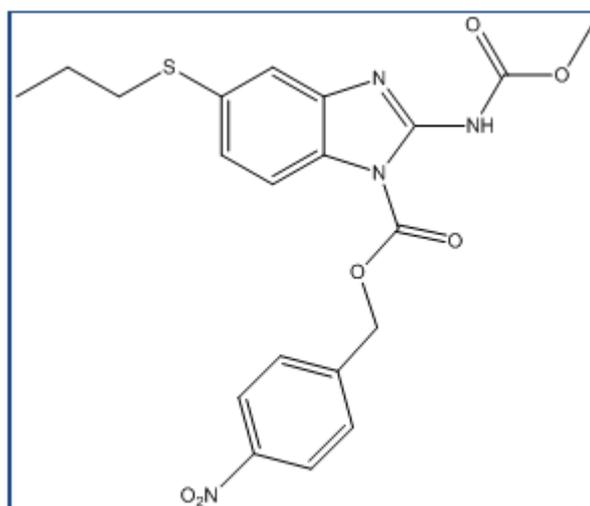


Fig. 5 : Ester nitro aromatic of albendazole

Two prodrugs of albendazole (N-methoxycarbonyl-N'-[2-nitro-4-propylthiophényl] thiourea and N-methoxycarbonyl-N'-[2-nitro-5-propylthiophényl] thiourea) have been described by Hernández-Luis et al [16]. The solutions that were proposed could not significantly improve the absorption of albendazole (Fig. 6).

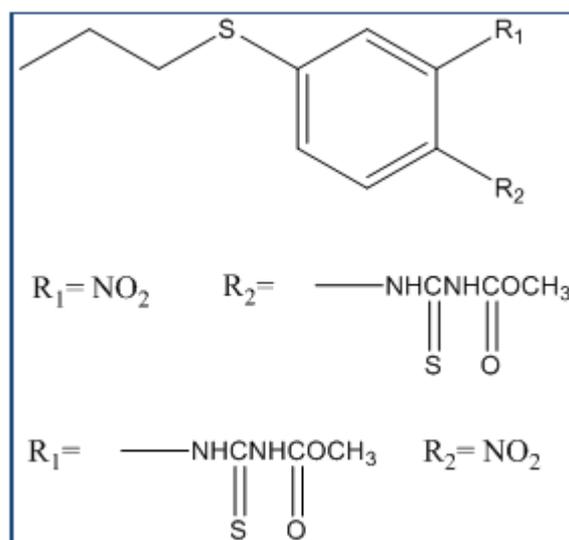


Fig. 6: Two auto generated prodrugs of albendazole after intestinal metabolisation

In this prodrug approach, El harti et al [17], have synthesized six N-acyl derivatives of albendazole and have tested their activity protoscolicide in vitro. The results showed the importance of the hydrogen number 1 for the activity anti scolex of *Echinococcus granulosus* (Fig.7).

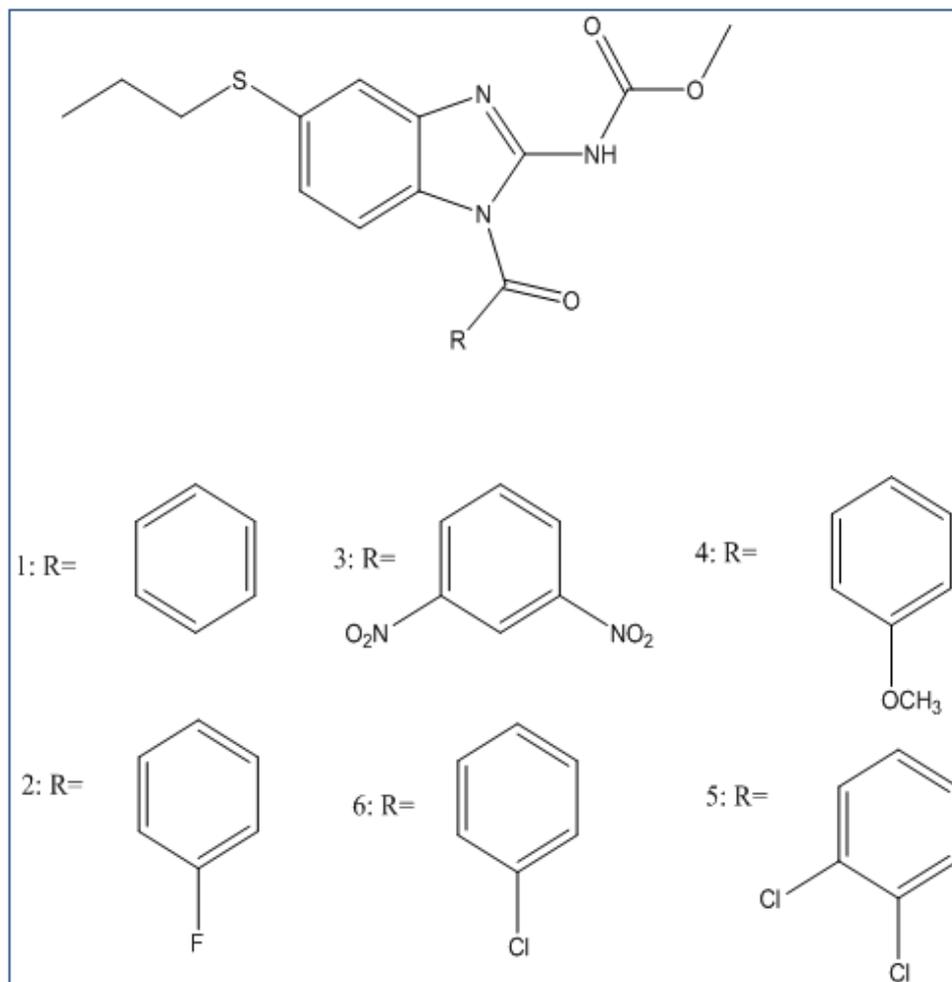


Fig.7: N-acyl derivatives of albendazole

Difficulty of synthesis of derivatives of albendazole is the production of two isomers which are difficult to separate. Most often the racemic mixture is used to perform biological tests.

Anthelmintic activity against *Toxocara canis*

Márquez-Navarro et al [15], reported a more active derivative than albendazole on the larvae of *Toxocara canis* at 0.18M (relative mobility 40% and 80%, respectively). This derivative can be considered as a prodrug of albendazole (Fig.8).

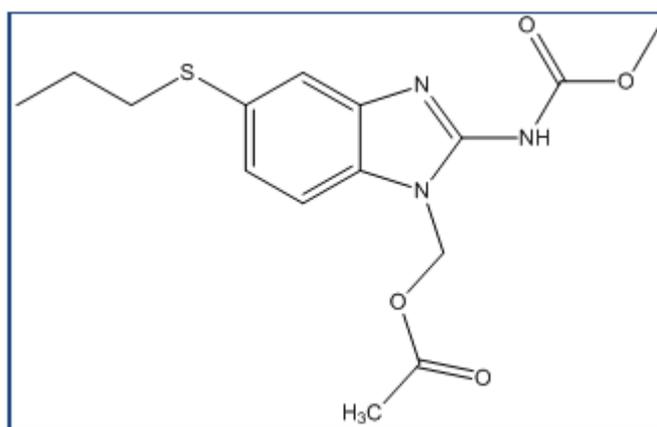


Fig.8: inverted ester derivative of albendazole

Activity against *Giardia lamblia*

Two compounds have been reported by-Navarrete Vazquez et al [18], these derivatives showed comparable activity to albendazole against *Giardia lamblia*. This study also showed that the hydrogen number 1 is not important for this activity (Fig.9).

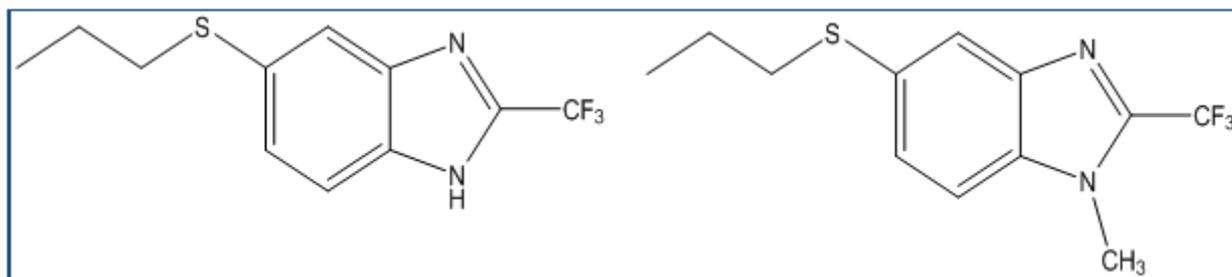


Fig.9: Trifluoro analogues of albendazole

Activity against *Entamoeba histolytica*

Several benzimidazole derivatives have been reported by Valdez et al [19], among them three direct analogues of albendazole. These analogues showed a more important activity than metronidazole and albendazole anti *Entamoeba histolytica* (Fig.10).

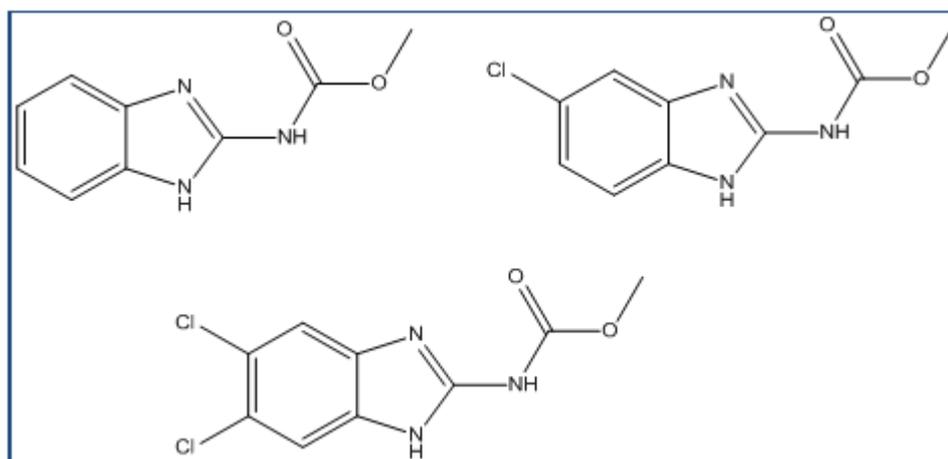


Fig.10: Chlorated analogues of albendazole

Activity against *Taenia crassiceps* cysts

A set of 13 benzimidazole derivatives were synthesized by Palomares-Alonso et al [20], and their in vitro activities were evaluated against *Taenia crassiceps* cysts, using albendazole sulfoxide as reference. Among the investigated compounds, two analogues showed good cysticidal activity (Fig.11).

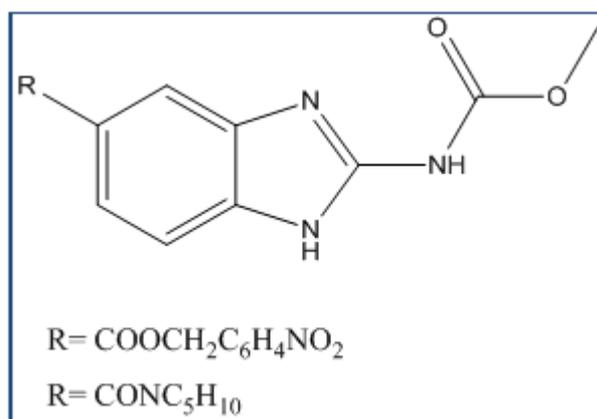


Fig.11: Analogues with activity against *Taenia crassiceps*

Conclusion

Albendazole analogues that have been reported in the literature are limited; the prodrugs described are not completely soluble in water. Search for new derivatives or analogues of albendazole remains a major area of research in the fight against parasitic diseases.

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