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Synthesis And Scolicidal Activity Of Some Benzimidazoles Derivatives

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Abstract: The basic approaches for treatment of hydatid disease are surgery and chemotherapy. The Albendazole is the drug of reference in the medical treatment of hydatidosis, but its efficacy is limited by its poor bioavailability. The new benzimidazole derivatives were synthesized from the albendazole. The compounds thus prepared were characterized by their physical (TLC, M.P) and spectral data (IR and NMR). Then the compounds were screened for anti-parasitic activity against protoscolices of *Echinococcus granulosus.*
Keywords: Benzimidazole, Synthesis, Anti-parasitic activity.

Introduction

Hydatidosis, cosmopolitan zoonosis is a problem of public health in endemic areas represented by all countries of sheep farming especially in the Mediterranean countries.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[1].

The administration of albendazole is done through oral and leads to albendazole sulfoxide as active metabolite. The use of albendazole for prolonged periods may induce hepatic toxicity. The efficacy of this compound against *Echinococcus granulosus* cysts is proved, but limited by its poor bioavailability[2-4].

Several studies have aimed to increase the absorption of albendazole to obtain optimal serum concentrations of albendazole sulfoxide, as active metabolite, by galenic devices (emulsion or liposome), or by taking this molecule during a meal rich in lipids[5].

Two prodrugs of albendazole (N-methoxy carbonyl-N-[2-nitro-4-propylthiophényl] thiourea and N-methoxycarbonyl-N-[2-nitro-5-propylthi ophényl] thiourea) have been described. However the biotransformation study in rats showed that the concentration of albendazole after oral administration of these prodrugs is less than that obtained after administration of albendazole itself [6].

In this paper the compounds **1-7** were designed as albendazole prodrugs. Then these derivatives have been the subject of a study of the antiparasitic activity against protoscolices of *Echinococcus granulosus.*

Materials and methods

Synthesis (Scheme 1)

Suspension of albendazole in tetahydrofuran (THF) was mixed with an equivalent of sodium hydride and stirred for 3 hours. The aromatic acyl chloride was added and stirred for 24 hours. The THF is removed under vaccuo, the residue is washed, extracted with dichloromethan and recrystallised from dichlorométhan - hexane.

All reactions were followed by TLC 0.25 mm silica gel plates (Ethyl acetate / Hexane: 7/3). IR spectra of the compounds were recorded on Perkin-Elmer FT-IR Spectrophotometer by using KBr discs, ^{1}H NMR spectra were recorded on Bruker 300 MHz. The Melting Points of the synthesized products were taken by an ordinary banc koffler apparatus.

Protoscolices viability assay

The protoscolices were taken from hydatid cysts of the human liver infested after surgery. Protoscolices were maintained in a physiological salin, and their viability was determined prior to the experiments under the microscope.

The synthesized derivatives **1-7** were solubilized in DMSO and the resulting solutions are diluted subsequently to obtain the same concentration of 10 mM.

A fraction of each test product (200µl) is brought into contact with the same volume of the suspension of protoscolices for 15 minutes in water bath at 37 °C. In parallel, a control test was conducted to assess the impact of DMSO on the protoscolices.

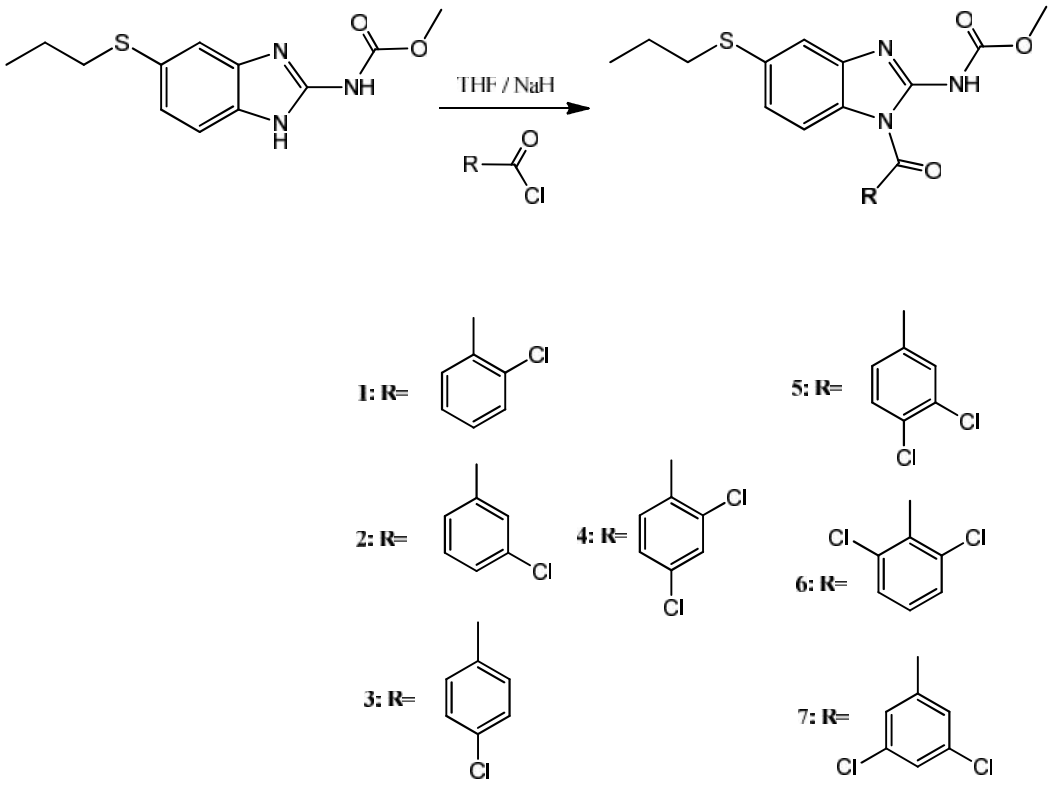
The viability of protoscolices was determined by vital staining with neutral red (10µl, 1%) and staining postvitale using methylene blue (10µl, 1%). The percentage of inhibition of protoscolices was determined by counting number of dead protoscolices to total protoscolices, each test was performed 3 times[7-9].

Results and discussion

The structures of synthesized derivatives **1-7** were confirmed by infra red IR and ^{1}H NMR data:

- Methyl (1-(2-chlorobenzoyl)-5-(propylthio)-1H-benzimidazol-2-yl) carbamate (1)

IR (KBr) ν 2956, 1692, 1620, 1586, 1443, 1267, 1094 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6) δ 0,92 (t, 3H, C**H$_3$**-CH$_2$-CH$_2$-S) ; δ 1,52 (m, 2H, CH$_3$-C**H$_2$**-CH$_2$-S) ; δ 2,83 (t, 2H, CH$_3$-CH$_2$-C**H$_2$**-S) ; δ 3,73 (s, 3H, -OC**H$_3$**) ; δ 7,09 (dd, J = 6 Hz,1H, H-5) ; δ 7,33 (d, J = 9 Hz, 1H, H-4) ; δ 7,41 (d, J = 2 Hz, 1H, H-7); δ 7,51 (dd, J = 3 Hz, 1H, H-3'); δ 7,74 (d, J = 2 Hz, 1H, H-4'); δ 7,77 (d, J = 2 Hz, 1H, H-2'); δ 11,69 (s, 1H, -N**H**CO-). Melting point: 190°C.



Scheme 1: Synthesis of the benzimidazole derivatives 1-7

- Methyl (1-(3-chlorobenzoyl)-5-(propylthio)-1H-benzimidazol-2-yl) carbamate (2)

IR (KBr) v 2957, 1696, 1621, 1586, 1443, 1268, 1095 cm^{-1}; ^1H NMR (300 MHz, DMSO-d6) δ 0,92 (t, 3H, C**H₃**-CH_2-CH_2-S) ; δ 1,52 (m, 2H, CH_3-C**H₂**-CH_2-S) ; δ 2,82 (t, 2H, CH_3-CH_2-C**H₂**-S) ; δ 3,74 (s, 3H, -OC**H₃**) ; δ 7,07 (dd, J = 6 Hz,1H, H-5) ; δ 7,34 (d, J = 9 Hz, 1H, H-4) ; δ 7,41 (d, J = 2 Hz, 1H, H-7); δ 7,54 (d, J = 9 Hz, 1H, H-3'); δ 7,64 (d, , J = 3 Hz 1H, H-4'); δ 7,68 (d, , J = 3 Hz 1H, H-2'); δ 7,88 (dd, J = 3 Hz, 1H, H-6'); δ 11,69 (s, 1H, -N**H**CO-). Melting point: 200°C.

- Methyl (1-(4-chlorobenzoyl)-5-(propylthio)-1H-benzimidazol-2-yl) carbamate (3)

IR (KBr) v 2954, 1687, 1630, 1590, 1443, 1270, 1095 cm^{-1}; ^1H NMR (300 MHz, DMSO-d6) δ 0,92 (t, 3H, C**H₃**-CH_2-CH_2-S) ; δ 1,52 (m, 2H, CH_3-C**H₂**-CH_2-S) ; δ 2,82 (t, 2H, CH_3-CH_2-C**H₂**-S) ; δ 3,73 (s, 3H, -OC**H₃**) ; δ 7,09 (dd, J = 6 Hz,1H, H-5) ; δ 7,31 (d, J = 9 Hz, 1H, H-4) ; δ 7,41 (d, J = 2 Hz, 1H, H-7); δ 7,54 (t, 1H, H-5'); δ 7,46 (d, J = 3 Hz 1H, H-3'); δ 7,89 (d, J = 9 Hz 1H, H-2'); δ 11,69 (s, 1H, -N**H**CO-). Melting point: 170°C.

- Methyl (1-(2,4-dichlorobenzoyl)-5-(propylthio) -1H-benzimidazol-2-yl) carbamate (4)

IR (KBr) v 2955, 1698, 1620, 1581, 1412, 1308, 1265, 1109 cm^{-1}; ^1H NMR (300 MHz, DMSO-d6) δ 0,92 (t, 3H, C**H₃**-CH_2-CH_2-S) ; δ 1,52 (m, 2H, CH_3-C**H₂**-CH_2-S) ; δ 2,82 (t, 2H, CH_3-CH_2-C**H₂**-S) ; δ 3,73 (s, 3H, -OC**H₃**) ; δ 7,09 (dd, J = 6 Hz,1H, H-5) ; δ 7,30 (d, J = 9 Hz, 1H, H-4) ; δ 7,41 (d, J = 2 Hz, 1H, H-7); δ 7,48 (d, J = 6 Hz 1H, H-3'); δ 7,69 (s, 1H, H-5'); δ 7,81 (d, J = 9 Hz 1H, H-2'); δ 11,69 (s, 1H, -N**H**CO-). Melting point: 132°C.

- Methyl (1-(3,4-dichlorobenzoyl)-5-(propylthio) -1H-benzo[d]imidazol-2-yl) carbamate (5)

IR (KBr) v 2956, 1789, 1685, 1604,1513, 1427, 1263 cm^{-1}; ^1H NMR (300 MHz, DMSO-d6) δ 0,92 (t, 3H, C**H₃**-CH_2-CH_2-S) ; δ 1,52 (m, 2H, CH_3-C**H₂**-CH_2-S) ; δ 2,82 (t, 2H, CH_3-CH_2-C**H₂**-S) ; δ 3,73 (s, 3H, -OC**H₃**) ; δ 7,09 (dd, J = 9 Hz,1H, H-5) ; δ 7,33 (d, J = 9 Hz, 1H, H-4) ; δ 7,40 (d, J = 2 Hz, 1H, H-7); δ 7,74 (d, J = 9 Hz, 1H, H-5'); δ 7,84 (dd, J = 9 Hz, 1H, H-6'); δ 8,04 (d, J = 2 Hz, 1H, H-2'); δ 11,64 (s, 1H, -N**H**CO-). Melting point: 186°C.

- Methyl (1-(2,6-dichlorobenzoyl)-5-(propylthio) -1H-benzimidazol-2-yl) carbamate (6)

IR (KBr) v 2955, 1711, 1621, 1587, 1442, 1268, 1094 cm^{-1}; ^1H NMR (300 MHz, DMSO-d6) δ 0,92 (t, 3H, C**H₃**-CH_2-CH_2-S) ; δ 1,55 (m, 2H, CH_3-C**H₂**-CH_2-S) ; δ 2,90 (t, 2H, CH_3-CH_2-C**H₂**-S) ; δ 3,32 (s, 3H, -OC**H₃**) ; δ 7,09 (dd, J = 6 Hz,1H, H-5) ; δ 7,30 (d, J = 9 Hz, 1H, H-4) ; δ 7,41 (d, J = 2 Hz, 1H, H-7); δ 7,55 (d, J = 6 Hz 1H, H-3'); δ 7,62 (m, 1H, H-4'); δ 12,38 (s, 1H, -N**H**CO-). Melting point: 115°C.

- Methyl (1-(3,5-dichlorobenzoyl)-5-(propylthio) -1H-benzimidazol-2-yl) carbamate (7)

IR (KBr) v 2955, 1711, 1624, 1587, 1442, 1269, 1095 cm^{-1}; ^1H NMR (300 MHz, DMSO-d6) δ 0,92 (t, 3H, C**H₃**-CH_2-CH_2-S) ; δ 1,52 (m, 2H, CH_3-C**H₂**-CH_2-S) ; δ 2,83 (t, 2H, CH_3-CH_2-C**H₂**-S) ; δ 3,73 (s, 3H, -OC**H₃**) ; δ 7,09 (dd, J = 6 Hz,1H, H-5) ; δ 7,30 (d, J = 9 Hz, 1H, H-4) ; δ 7,41 (d, J = 2 Hz, 1H, H-7); δ 7,76 (d, J = 2 Hz 1H, H-2'); δ 8,07 (d, J = 2 Hz 1H, H-4'); δ 11,66 (s, 1H, -N**H**CO-). Melting point: 192°C.

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 anti-hydatid cysts. The synthesized derivatives have different physicochemical properties from that of albendazole with substantially lower melting points (MP of albendazole = 210 ° C).

The study of the activity scolicide showed that the introduction of an aromatic ring at the nitrogen N1 preserves the activity. The presence of an electron attractor groups on the aromatic ring as chloro group influence the global activity of the derivative. Thus derivatives **4** and **5** showed good activity by 66% and 64% respectively, while the other derivatives showed a decrease in activity this is probably due to the position of the chloro group which is not favorable to good interaction with the active site (tubilin). The control experiments showed that DMSO did not affect the viability of the protoscolices and its use is justified by the fact that albendazole is insoluble in water and most organic solvents.

The design of prodrugs by chemical approach is usually done by the synthesis of derivatives easily metabolizable as esters or amides[10]. The main interest is to modify the physicochemical properties of the molecule being studied to increase its bioavailability. Derivatives **1-7** also contain an amide bond metabolizable what makes these compounds promising prodrugs of albendazole. In addition, despite their structural modifications, these derivatives have kept good activity scolicides.

In conclusion, among the derivatives synthesized the product **4** and **5** showed good activity and constitute promising prodrugs of albendazole. Perspective in these products will be a study of the bioavailability.

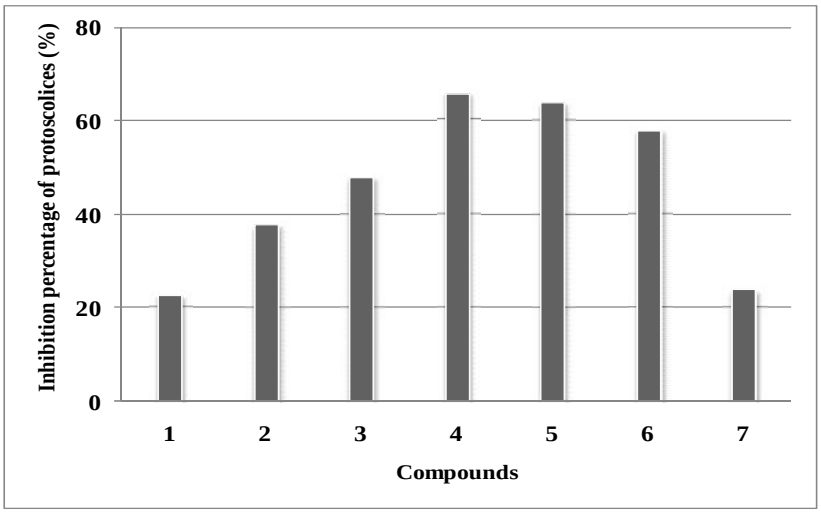


Fig. 1 Test results of *in vitro* viability of protoscolices.

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