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Research Article

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Synthesis and antioxidant activity of some albendazole derivatives

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ABSTRACT

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 antioxidant activity. Among the five derivatives which were synthesized, one product showed a significant antioxidant activity.

Keywords: Benzimidazole, Synthesis, Antioxidant activity.

INTRODUCTION

Benzimidazole is a heterocyclic compound consisting of benzene ring fused with imidazole ring. The chemistry and pharmacology of benzimidazoles have been of great interest to medicinal chemistry, because its derivatives possessed various biological activities [1]. Moreover benzimidazoles are important intermediates in organic reaction. The antioxidant activity of benzimidazoles has been reported [2].

Antioxidants are nutrients that help to protect cells from a normal but damaging physiological process known as "oxidative stress". Such nutrients are a part of the natural makeup of many types of food, particularly fruits and vegetables. They also have been added to some foods and are available in the form of dietary supplements [3]. There has been growing demand for antioxidants due to report their effective defensive role against oxygen free radical toxicity in our body system. It has been determined that active oxygen molecules such as superoxide, hydroxyl and peroxyl radicals play an important role in oxidative stress related to the pathogenesis of different diseases such as Alzheimer, Parkinson and cataracts, and DNA damage leads to carcinogenesis [4].

Nowadays antioxidants arouse researchers' interest in both medical plants and synthetic compounds [5-10]. In our previous research, we reported some novel benzimidazole derivatives substituted at position1. Antioxidant properties of these compounds were investigated by employing in vitro system interaction of 2,2-diphenyl-1-picrylhydrazyl (DPPH), and scavenging of superoxide radical.

EXPERIMENTAL SECTION

Synthesis (Fig.1)
Suspension of albendazole (ABZ) 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 dichloromethan - 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.

Free Radical Scavenging Activity

The free radical scavenging activity of the synthesized compounds were measured by 1,1-diphenyl-2-picryl-hydrazil (DPPH) [11-13].

Briefly, 0.1 mM solution of DPPH in methanol was prepared and 1 ml of this solution was added to 3 ml of synthesized compounds and was allowed to stand at room temperature for 30 min, and then absorbance was read at 517 nm against blank samples. Lower absorbance of the reaction mixture indicated higher free radical scavenging activity. The radical-scavenging activity (RSA) was calculated as a percentage of DPPH discoloration, using the equation: % RSA = [(ADPPH−APrd)/ ADPPH] × 100. Where ADPPH is the absorbance value of the DPPH blank sample, and APrd is the absorbance value of the test solution. APrd was evaluated as the difference between the absorbance value of the test solution and the absorbance value of its blank.

Statistical Analysis

The statistical analysis was performed by one-way ANOVA analysis of variance, results were considered to be statistically significant with a 95 % confidence level ($P<0.05$).

RESULTS AND DISCUSSION

The structures of synthesized derivatives **1-6** were confirmed by infra red IR and ^{1}H NMR:

- *Methyl (1-benzoyl-5-(propylthio)-1H-benzo[d]imidazol-2-yl) carbamate (**1**)*

IR (KBr) v 2959, 1751, 1642, 1441,1240, 1091 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 3,74 (s, 3H, -OC**H$_3$**) ; δ 7,09 (dd, J = 9 Hz,1H, H-5) ; δ 7,33 (d, J = 9 Hz, 1H, H-4) ; δ 7,39 (d, J = 2 Hz, 1H, H-7); δ 7,45 (t, 1H, H-4'); δ 7,57 (t, 1H, H-3'); δ 7,91 (d, J = 2 Hz, 1H, H-2'); δ 11,69 (s, 1H, -N**H**CO-). Melting point: 135°C.

- *Methyl (1-(4-fluorobenzoyl)-5-(propylthio)-1H-benzo[d]imidazol-2-yl) carbamate (**2**)*

IR (KBr) v 2957, 1751, 1605,1507, 1430, 1238, 1159 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 2,89 (t, 2H, CH$_3$-CH$_2$-C**H$_2$**-S) ; δ 3,83 (s, 3H, -OC**H$_3$**) ; δ 7,27 (dd, J = 9 Hz,1H, H-5) ; δ 7,42 (d, J = 9 Hz, 1H, H-3'); δ 7,50 (d, J = 9 Hz, 1H, H-4) ; δ 7,94 (d, J = 2 Hz, 1H, H-7); δ 8,16 (d, J = 2 Hz, 1H, H-2'); δ 11,64 (s, 1H, -N**H**CO-). Melting point: 130°C.

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

IR (KBr) v 2952, 1727, 1667, 1539,1347, 1268 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 2,82 (t, 2H, CH$_3$-CH$_2$-C**H$_2$**-S) ; δ 3,73 (s, 3H, -OC**H$_3$**) ; δ 7,09 (dd, J = 9 Hz,1H, H-5) ; δ 7,33 (d, J = 9 Hz, 1H, H-4) ; δ 7,39 (d, J = 2 Hz, 1H, H-7); δ 8,87 (d, J = 2 Hz, 1H, H-2'); δ 8,98 (t, 1H, H-4'); δ 11,64 (s, 1H, -N**H**CO-). Melting point: 150°C.

- *Methyl (1-(4-methoxybenzoyl)-5-(propylthio)-1H-benzo[d]imidazol-2-yl) carbamate (**4**)*

IR (KBr) v 2957, 1789, 1622, 1443,1268, 1095 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 3,74 (s, 3H, -OC**H$_3$**) ; δ 7,09 (dd, J = 9 Hz,1H, H-5) ; δ 7,33 (d, J = 9 Hz, 1H, H-4) ; δ 7,39 (d, J = 2 Hz, 1H, H-7); δ 7,85 (d, J = 9 Hz, 1H, H-2'); δ 8,03 (d, J = 9 Hz, 1H, H-3'); δ 11,64 (s, 1H, -N**H**CO-). Melting point: 162°C.

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

IR (KBr) v 2954, 1687, 1630, 1590, 1443, 1270, 1095 cm-1; 1H NMR (300 MHz, DMSO-d6) δ 0,92 (t, 3H, CH3-CH2-CH2-S) ; δ 1,52 (m, 2H, CH3-CH2-CH2-S) ; δ 2,82 (t, 2H, CH3-CH2-CH2-S) ; δ 3,73 (s, 3H, -OCH3) ; 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, -NHCO-). Melting point: 170°C.

The radical scavenging activities of the synthesized compounds were estimated by comparing the percentage inhibition of formation of DPPH radicals by the compounds and those of trolox (Fig.2). This figure shows that the DPPH scavenging activity in both compounds was concentration-dependent and the compound **1 (Prd1)** exhibited considerably higher ($P<0.05$) DPPH radical-scavenging activities than ABZ at all concentrations assayed.

However, compounds **2-5** showed no significant activity. In fact the presence of an electron attractor groups on the aromatic ring influence the global activity of the derivative.

Overall, the compound **1** was able to inhibit the formation of DPPH radicals with a percentage inhibition of 63.19 % at the highest concentration. At this concentration, the DPPH radical scavenging capacity of this compound was almost similar to the trolox. It can be noted that compound **1** show average inhibitory values that give an idea of the interesting antioxidant activity of such synthesized compound, it must be noted, however, that there are a number of mechanisms by which antioxidants may function. The cascade leading to oxidative damage is complex and only free radical scavenging activity has been explored. The mechanism of anti-oxidant action can include suppressing reactive oxygen species formation, either by inhibition of enzymes or by chelating trace elements involved in free-radical production, scavenging reactive species and up-regulating or protecting anti-oxidant defenses [14].

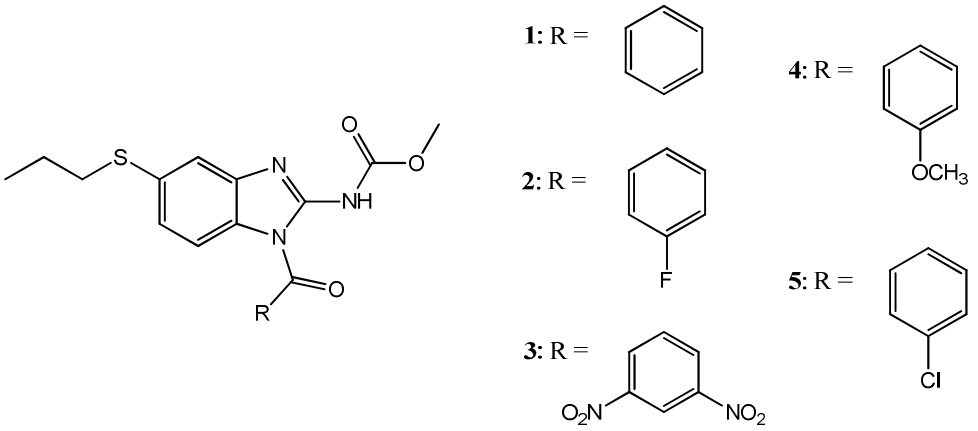

Figure 1: Scheme of the albendazole derivatives

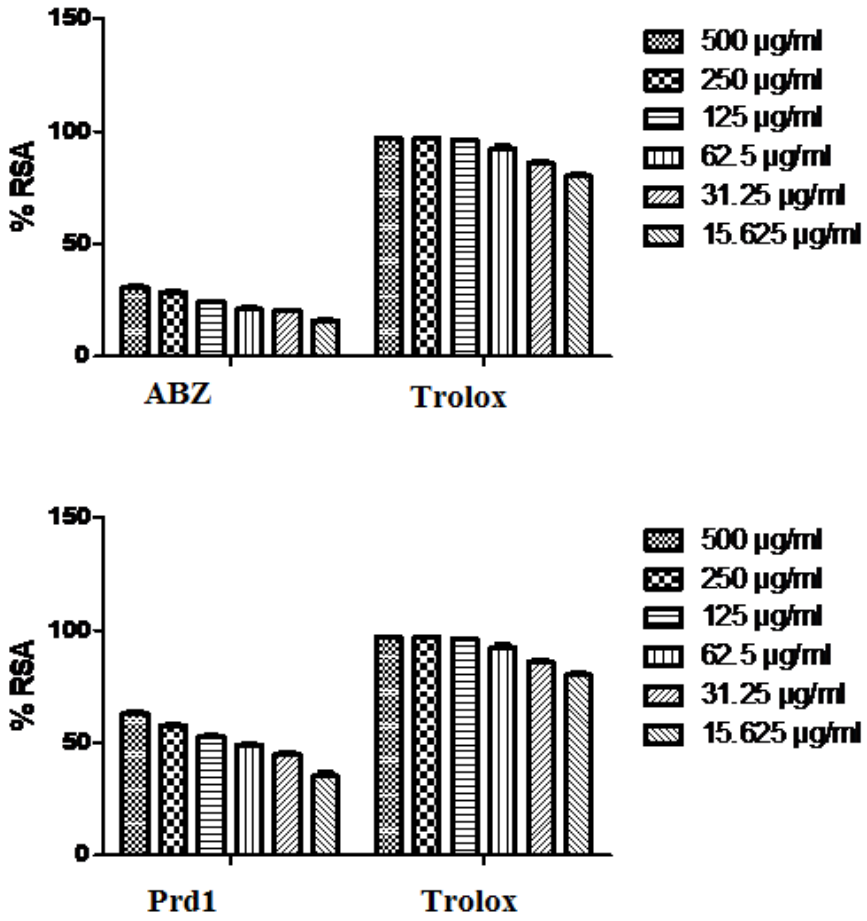

Figure 2: Free-radical scavenging activity of synthesized compounds measured using the DPPH assay (Prd1 and ABZ): Values are means ± SD of three determinations with respect to positive control (Trolox)

CONCLUSION

The new albendazole derivatives were synthesized. Then the compounds were screened for antioxidant activity. Among the derivatives which were synthesized, compound **1** showed a significant antioxidant activity.

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