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Synthesis and Biological Activities of Some Benzimidazoles Derivatives

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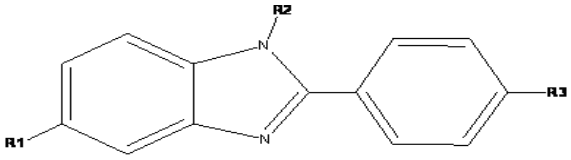
ABSTRACT: A set of six novel benzimidazoles compounds were prepared, this includes 5-Nitro-2-phenyl -1-ethylbenzimidazol (**5**),2-(p-Bromophenyl)-5-nitro-1-ethylbenzimidazol (**6**), 2- (p-Bromophenyl- 5-nitro-1–cyclopentylbenzimidazol(**7**),2-(p-Bromophenyl)-5-nitro-1-cyclopentylbenzimidazol (**8**),5-Amino-2-(p-Bromophenyl)-1-ethylbenzimidazol (**9**), and 5-Amino-(2- (p- Bromophenyl)- 1- cyclopentylbenzimidazol (**10**). The chemical structures of these compounds were elucidated using NMR and elemental analysis. The biological activity of these compounds as fungicides was tested against three commercially known fungicides (C. albicans, patient isolate C. glabrata and C. krusei).The biological activity of two compounds was found to be comparable to that of the commercially available fungicides (**6** and **9**). @JASEM

Key words: Benzimidazole; Antifungal Agent; Fungicides; Aldehyde; Derivative; Chemical Synthesis.

Benzimidazole derivatives are known to have microbial activities (Khainar,1981; Kruse *et al.*,1989; Islam *et al.*,1991; Habernickel,1992; Fukuda *et al.*,1985; Nakano *et al.*,1999), especially antifungal activity(Can-Eke *et al.*,1998; Ku *et al.*,2004; Ayhan-Kilcigil *et al.*, 2004). Anti-inflammatory. (Göker et al.,1999) ,and antioxidant (Abdel-Rahman *et al.*,1983; Soliman *et al.*,1984; Coburn *et al.*,1987; Habib *et al.*,1989; Göker *et al.*,2002). In this context, it has been found that benzimidazole derivatives to retard especial type of fungus that attack certain class of patients such as cancer chemotherapy and HIV patients. In particular, candidacies is the fungal infection most that is frequently associated with HIV-positive patients (Ozden *et al.*, 2004; Ozden *et al.*,2005). Benzimidazole derivatives were found to retard Cryptococcosis growth, which is the main cause of morbidity in AIDS patients.

Benzimidazole fungicides are systemic pesticides widely used in agriculture for pre- and post-harvest treatment for control of a wide range of fungi (Küçflkgflzel *et al.*, 2001; El-Gaby *et al*.,2002; Ku *et al*.,1996).This excessive use of pesticides (Fungicides in general represents approximately 20 to 25 percent of total usage pesticides) in different applications results in emerging environmental problems, this contaminates plant, and thus, affects animal, and human health.

The limited number of available antifungal compounds urges to synthesize new compounds with a potential use as fungicides, in particular, those attack people with suppressed immune system e. g. candidacies is the fungus infection that is most frequently associated with HIV-positive patients. In this paper, I report the preparation of a series of six benzimidazoles compounds (Figure 1). The biological activity of these compounds as fungicides is investigated. Two of the six investigated compounds showed antifungal activity.



5	R1 = NO_2	R2 = C_2H_5	R3 = H
6	R1 = NO_2	R2 = C_2H_5	R3 = Br
7	R1 = NO_2	R2 = 	R3 = Br
8	R1 = NH_2	R2 = C_2H_5	R3 = H
9	R1 = NH_2	R2 = C_2H_5	R3 = Br
10	R1 = NH_2	R2 = 	R3 = Br

Fig 1: Chemical structures of chemical compound prepared in this study

MATERIALS AND METHODS

General Method: Melting points were determined with an Electro thermal (Electro thermal Eng. Ltd, Essex, UK) melting point apparatus and are uncorrected. 1H NMR spectra were measured with a Varian Mercury 400,400MHz instrument (California, USA) using TMS internal standard and DMSO-d. all Chemical shifts were reported as δ (ppm) values. ESMS were obtained with a Waters ZQ Micro mass LC-MS spectrometer (Milford, MA, USA) with positive electro spray ionization. Elemental analyses (C, H, N,S) were determined on aleco CHNS 932 instrument (St. Joseph, MI, USA), and were within ± 0.4% of the theoretical values. All instrumental

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analyses were performed at Bin Hayyan Laboratory, (Aqaba special economic zone).

Materials: The chemical reagents used in the synthesis were purchased from E. Merck (Darmstadt, Germany) and Aldrich (Milwaukee, MI, USA). Compound **8** was used as a crude product for further reaction.

General Procedure for the Preparation of the Compounds (5-7): The appropriate aldehyde derivative (1.5 mmol) was dissolved in 5 ml of Ethanol. Then, 0.01 mole of $Na_2S_2O_5$ in 5 ml of water was added in portions to the cooled ethanol solution. The precipitate formed was filtered off and dried. A total of 1.2 mmol of this precipitate and 1.2 mmol of compound 3 or 4 in 5 ml of DMF were heated at 100 °C for 8 h. At the end of this period the reaction mixture was cooled, and poured into water. The precipitate was collected and re-crystallized from ethanol-water mixture.

General Procedure for the Preparation of the Compounds (8-10): 5-Nitrobenzimidazole derivatives **5 -7** (1 mmol) in 10 ml of hot ethanol and 10 ml of 6 N of HC1 were refluxed and $SnCl_2$.2H20 was added in portions until the starting material was completely exhausted. The ethanol was decanted, the residue was made alkaline with KOH, then, extracted with ethanol acetate, and washed with water. The ethanol acetate was evaporated slowly and the residue crystallized from ethanol.

Elemental Analysis and NMR Data: 5-Nitro-2-phenyl -1-ethyl benzimidazol (5) : Analytical Calculated for $C_{16}H_{15}N_3O_2$: C, 66.19; H, 5.55; N, 14.47. Found: C, 65.97; H, 5.18; N, 14.49; Yield 65%, M.p. 156-158 °C; ES (+) 282 (M+H); '1HNMR (DMSO-d6) 6 0.73 (t, 3H, CH_3), 1.66-1.71 (m, 2H, CH_2), 4.37 (t, 2H, CH_2), 7.62-7.65 (m, 3H, H-3 ',4',5'), 7.81-7.98 (m, 2H, H-2 ',6'), 7.96 (d,1H, Jo 8.8 Hz, H-7), 8.24 (d,1H, Jo 8.8 Hz, Jm 2 Hz, H-6), 8.59 (d, 1H, Jm 2 Hz, H-4).

2- (p-Bromophenyl)- 5-nitro- 1-ethyl benzimidazol (6) : Analytical Calculated for $C_{16}H_{14}BrN_3O_2$: C, 64.20; H, 4.71; N, 14.03. Found: C, 63.93; H, 4.38; N, 14.25; Yield (58)%, M.p. 178-180 ° C; ES (+) 300 (M+H); '1HNMR (DMSO-d6) 6 0.73 (t, 3H, CH_3), 1.65-1.71 (m, 2H, CH_2), 4.35 (t, 2H, CH_2), 7.45-7.49 (m, 2H, H-3 ',5'), 7.88-7.91 (m, 2H, H-2',6'), 7.96 (d, 1H, Jo 8.8 Hz, H-7), 8.22 (d, 1H, Jo 8.8 Hz, H-6), 8.58 (s, 1H, H-4).

2- (p-Bromophenyl- 5-nitro-1 –cyclopentyl benzimidazol (7) : Analytical Calculated for $C_{18}H_{16}BrN_3O_2$: C, 66.45; H, 4.95; N, 12.91. Found: C, 66.86; H, 5.24; N, 12.57; Yield (85)%, M.p. 148-150 °C; ES (+) 326 (M+H); '1HNMR (DMSO-d6) δ 1.682.16 (m, 8H, CH_2), 4.85-4.89 (m, 1H, CH), 7.45-7.49 (m, 2H, H-3',5'), 7.78-.7.82 (m, 2H, H-2',6'), 7.89 (d, 1H, Jo 9.2 Hz, H-7), 8.17 (d, 1H, Jo 9.2 Hz, Jm 2 Hz, H-6), 8.58 (d, 1H, Jm 1.6 Hz, H-4).

2- (p-Bromophenyl)- 5-nitro- 1-cyclopentyl benzimidazol (8) **:** Analytical Calculated for $C_{18}H_{16}BrN_3O_2$: C, 55.75; H,4.18; N, 10.88; O,8.28 Found: C, 56.06; H, 4.0; N, 10.76;O,9.1Yield (71)%, M.p. 199-201 °C; ES (+) 296 (M+H); '1HNMR (DMSO-d6) δ 1.63-2.15 (m, 8H, CH_2), 4.68-4.77 (m, 1H, CH), 4.83 (s, 2H, NH_2), 6.61 (d, 1H, Jo 8.8 Hz, H-6), 6.81 (s, 1H, H-4), 7.28 (d, 1H, Jo 8.8 Hz, H-7), 7.36-7.40 (m, 2H, H-3',5'), 7.65-7.69 (m, 2H, H-2',6').

5-Amino-2- (p-Bromophenyl) -1- ethyl benzimidazol (9) **:** Analytical Calculated for $C_{16}H_{16}BrN_3$: C, 71.35; H, 5.98; N, 15.60. Found: C, 70.95; H, 5.73; N, 15.36; Yield (75)%, M.p. 130-132 °C; ES (+) 270 (M+H); '1HNMR (DMSO-d6) 0.7 (t, 3H, CH_3), 1.62-1.68 (m, 2H, CH_2), 4.12 (t, 2H, CH_2), 4.8 (s, 2H, NH_2), 6.63 (d, 1H, Jo 8.4 Hz, H-6), 6.79 (s, 1H, H-4), 7.29 (d, 1H, Jo 8.4 Hz, H-7), 7.36-7.40 (m, 2H, H-2' ,6'), 7.74-7.78 (m, 2H, H-3',5').

5-Amino- (2- (p- Bromophenyl)- 1- cyclopentyl benzimidazol (10) : Analytical Calculated for $C_{18}H_{18}BrN_30$: C, 72.75; H, 6.77; N, 14.13. Found: C, 73.06; H, 6.42; N, 13.76; Yield (82)%, M.p. 193-195 °C; ES (+) 296 (M+H); '1HNMR (DMSO-d6) δ 1.63-2.15 (m, 8H, CH_2), 4.68-4.77 (m, 1H, CH), 4.83 (s, 2H, NH_2), 6.61 (d, 1H, Jo 8.8 Hz, H-6), 6.81 (s, 1H, H-4), 7.28 (d, 1H, Jo 8.8 Hz, H-7), 7.36-7.40 (m, 2H, H-3 ',5'), 7.65-7.69 (m, 2H, H-2',6'). 'C^{13} NMR (DMSO-d6)δ 25.19, 30.45, 57.74, 103.39, 112.74, 116.22, 116.43, 125.99, 128.31, 132.16, 132.25, 144.83, 145.37, 152.46, 162.06, 164.52.

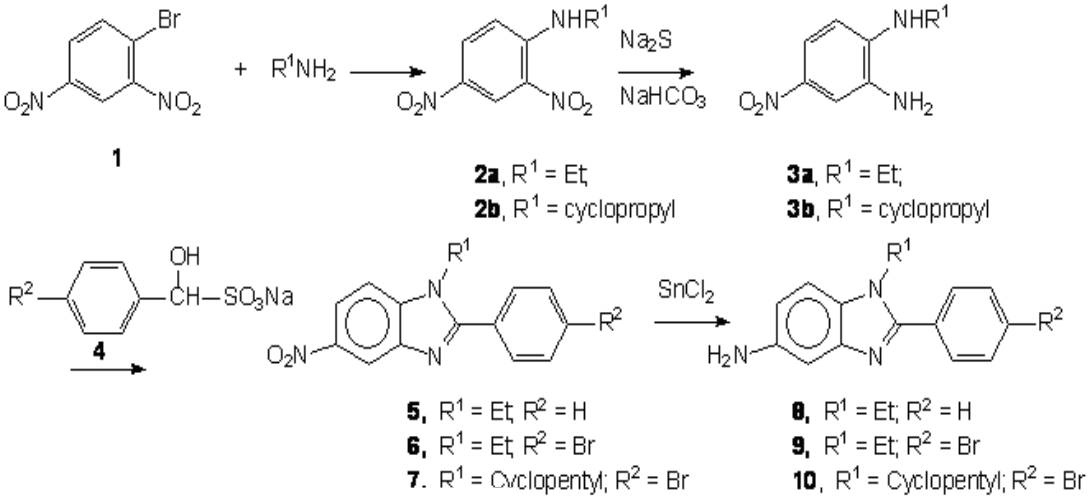
*Antifungal Activity Assay***:** The yeasts are grown on Sabouraud Dextrose Broth (Difco) media; the yeasts were incubated for 72 h at 20-25°C. The antifungal activity tests were carried out at pH 7.2 in Sabouraud Dextrose Broth and the 2-fold dilution was applied. A set of tubes containing only inoculated broth were kept as controls. After incubation for 72 h at 20-25°C, the last tube with no yeast growth was recorded to represent minimum inhibitory concentration (MIC), expressed in µg/ml.

RESULTS AND DISCUSSION

Compounds (**1**) and (**2**) were prepared from1-Bromo-2,4-dinitrobenzene by reaction with (ethyl amine;cyclopentylamine) in DMF according to the literature (Wurlitzer *et al.*,1978) The 2-nitro group of compounds (**1**)and (**2**) was reduced to 2-amino (**3** and **4**) by using $Na_2S/NaHCO_3$ in methanol(Wurlitzer *et al.*,1988). Condensation of o-phenylenediamines (**3** and **4**) with the $Na_2S_20_5$ adduct of appropriate benzaldehydes in DMF (Ridley *et al.*, 1985). gave (**5-7**).Reduction of compounds(**5-7**) with $SnCl_2.2H_2O$ produced (**8-10**).

The *in vitro* antifungal activity of the compounds was tested by the tube dilution technique (Hausler *et al.*,1991). Each of the test compounds and standards miconazole and fluconazole were dissolved in 10% DMSO, at concentrations of 100 µg/ml. Further dilutions of the compounds and standards in the test medium were performed at the required quantities of 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 µg/ml concentrations. The final concentration was 10^5 CFU/ml. The MICs were defined as the lowest concentration of the compounds that prevented visible growth of the fungus. It was determined that the solvent had no antifungal activity against any of the test microorganisms.

All the compounds were tested for their *in vitro* growth inhibitory activity against C. albicans, patient isolate C. glabrata and C. krusei (Table1). Compounds **6, 7, 8** and **9** possessed comparable activity to fluconazole against C. albicans with a MIC of 12.5 µg/ml. None of the compounds was superior to the standards used against any fungus.



Scheme 1. Preparation rout of the compounds

Table 1. The *in vitro* antifungal activity of the prepared compounds (MIC, µg/ml)

Compound	C. albicans	C. glabrata	C.krusei
5	25	25	12.5
6	12.5	6.25	6.25
7	25	25	12.5
8	25	25	12.5
9	12.5	12.5	6.25
10	25	25	12.5
Fluconazole	12.5	3.125	3.125
Miconazole	6.25	3.125	1.56

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