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Full Length Research Paper

Synthesis and antimicrobial activity evaluation of some benzimidazole and indole derivatives

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In this study, 16 benzimidazole and indole derivatives were synthesized and tested for *in vitro* antimicrobial activity by tube dilution and disc diffusion susceptibility test methods. The *in vitro* antimicrobial activity of the compounds was carried out by determining minimum inhibitory concentration value against various Gram-positive, Gram-negative bacteria and *Candida* species fungi. The most active compound was 4-(5-methyl-3-phenyl-1*H*-indole) phenol (Compound 15) as shown by most inhibitory effect on *Candida albicans*, *Candida glabrata*, *Staphylococcus aureus* and *Bacillus subtilis*. Compound 15 showed better activity against yeast and Gram-positive bacteria than Gram-negative bacteria.

Key words: Benzimidazole, indole, minimum inhibitory concentration, antimicrobial activity.

INTRODUCTION

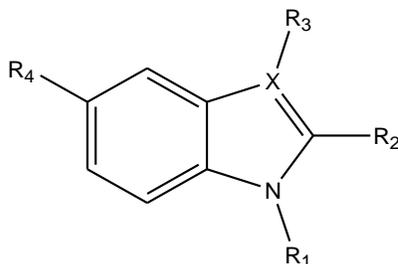
The incidence of morbidity and mortality by bacterial and fungal infections has increased globally mostly in developing countries due to the growing of antibacterial and antifungal drug resistance. It comprises serious problems such as increased resistance of microorganisms to a number of antimicrobial agents such as β -lactam antibiotics, macrolides, quinolones and vancomycin (Ozkay et al., 2010). *Candida* species and *Staphylococcus aureus* are the most known multi-drug resistant microbial pathogens. *Candida* species are the fourth leading cause of health care-associated bloodstream infections and are associated with significant morbidity and mortality (Rentz et al., 1998). *Candida albicans* and *Candida glabrata* can cause serious mucosal or systemic infection (Wingard, 1995). *C. albicans* is the most common cause of candidaemia. *C. glabrata* also causes approximately 5 to 15% of non-*albicans* *Candida* infections (Fidel, et al., 1999).

The emergence of fluconazole-resistant *C. glabrata* bloodstream infections has had important implications because therapy requires higher doses of fluconazole or the use of other antifungal agents such as echinocandins or polyenes (Pappas et al., 2004).

S. aureus is currently the most common cause of various infections such as nosocomial infections. Currently, the most important problem is methicillin-resistant *Staphylococcus aureus* (MRSA). Since MRSA strains are resistant to all β -lactam antibiotics, the therapeutic options are limited significantly.

Successful treatment of infectious diseases requires the availability of more effective new antimicrobial compounds. As pathogens mutate, continued success in treating infectious diseases requires a steady stream of new antimicrobial agents to which existing bacteria and fungi have not developed resistance.

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Compound	X	R ₁	R ₂	R ₃	R ₄	Synthesis method	Ref.
1	N	H	<i>p</i> -CH ₃ C ₆ H ₄	-	H	A	Al-Awadi et al. 2005 and Kabeer et al., 2012
2	N	H	<i>p</i> -CH ₃ OC ₆ H ₄	-	H	A	Algul et al., 2008
3	N	H	<i>p</i> -CH ₃ CH ₂ OC ₆ H ₄	-	H	A	Navarrete-Vazquez et al. 2006
4	N	H	<i>p</i> -NO ₂ C ₆ H ₄	-	H	A	Al-Awadi et al. 2005
5	N	H	<i>p</i> -ClC ₆ H ₄	-	H	A	Al-Awadi et al. 2005
6	N	H	<i>p</i> -ClC ₆ H ₄	-	OCH ₃	B	commercially available
7	N	H	3,5-diClC ₆ H ₃	-	H	B	Lee et al., 2007
8	N	C ₆ H ₅	<i>p</i> -CH ₃ C ₆ H ₄	-	H	C	Iyengar et al. 1997
9	N	C ₆ H ₅	<i>p</i> -ClC ₆ H ₄	-	H	C	Kassim et al., 2012
10	N	C ₆ H ₅	2,6-diCl C ₆ H ₃	-	H	C	-
11	N	<i>p</i> -ClC ₆ H ₄	<i>p</i> -OCH ₃ C ₆ H ₄	-	H	C	Iyengar et al. 1997
12	N	<i>p</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	-	H	C	Iyengar et al. 1997
13	N	<i>p</i> -ClC ₆ H ₄	<i>p</i> -N(CH ₃) ₂ C ₆ H ₄	-	H	C	-
14	N	<i>p</i> -ClC ₆ H ₄	2,6-diCl C ₆ H ₃	-	H	C	-
15	C	H	<i>p</i> -OHC ₆ H ₄	C ₆ H ₅	CH ₃	D	-
16	C	H	<i>p</i> -BrC ₆ H ₄	C ₆ H ₅	CH ₃	D	-

- The newly synthesized molecules.

Figure 1. Chemical structures of the synthesized compounds.

Extensive biochemical and pharmacological studies of benzimidazole and indole derivatives have confirmed their highly effectiveness against various strains of microorganisms (Sharma et al., 2009; Al-Qawasmeh et al., 2010; Göker et al., 2002; Ayhan-Kılıçgil and Altanlar, 2003; Pawar et al., 2004; Mahboobi et al., 2008; Ansari and Lal, 2009; Ryu et al., 2009), as well as have various therapeutic effects. Benzimidazole and indole cores were recognized by organism, because they are placed in the natural structure of Vitamin B₁₂ (Cyanocobalamine), tryptophane and serotonin (O'Neil et al., 2001; Fernandes et al., 2004). Although vitamin B₁₂ is capable of inducing the growth of bacteria, some of the benzimidazole derivatives such as Astemizol, Mebendazole, Enviroxim, Carbendazim and Benomyl repress the bacterial growth and have been used in clinics widely (The Merck Index, 1996). On the other hand, compounds which have indole moiety also act as anti-inflammatory drug, such as indometazin, etodolac and acemetacin.

Prompted by these observations, in the present study, some substituted benzimidazoles and indoles were synthesized as the lead compounds in order to examine their *in vitro* antimicrobial activities against different Gram-positive, Gram-negative bacteria and fungi in comparison

with control drugs.

In the present work, some 2-mono or 1,2-/2,5-disubstituted benzimidazoles (Compound 1-14) and 1,2 and 5-trisubstituted indoles (Compound 15 and 16) were synthesized (Figure 1) as the lead compounds in order to examine their *in vitro* antimicrobial activities against different Gram-positive, Gram-negative bacteria and the yeasts *Candida* species in comparison with two control drugs.

MATERIALS AND METHODS

In this study, we established two assays for testing and identifying new antimicrobial agents from a series of benzimidazole and indole derivatives. Some of the compounds have been synthesized before either by our group or by other scientist (Al-Awadi et al., 2005, Kabeer et al., 2012; Algul et al., 2008; Navarrete-Vazquez et al., 2006; Lee et al., 2007; Iyengar et al., 1997; Kassim et al., 2012).

Chemistry

The structures of the synthesized compounds (Figure 1) were characterized by FT-IR and ¹H-NMR, as well as MS spectra. FT-IR spectra were recorded on Varian FTS 1000 spectrophotometer and

$^1\text{H-NMR}$ spectra on a Varian Mercury 400 MHz FT-NMR spectrometer using tetramethylsilane (TMS) as an internal reference (chemical shift in δ ppm). Mass spectra were taken on a Agilent 6460 Triple Quadropol LC-MS instrument.

Synthetic methods

General method for the synthesis of 2-(*p*-substitutedphenyl)-1*H*-benzimidazoles derivatives

Method A: The 4-substituted benzoic acid (1.5 mmol), 1,2-phenylenediamine (1.0 mmol) and PPA (5 mL) were placed in a round bottomed flask. The mixture was heated and stirred at 180–200°C for 3–7 h. After the reaction was complete, the mixture was allowed to cool to room temperature and poured into cold water (50 mL). The mixture was neutralized with NaHCO_3 . The resulting precipitate was filtered off, washed several times with water and purified by recrystallization.

2-(*p*-Methylphenyl)-1*H*-benzimidazole (1)

Reagents: 1,2-phenylenediamine (0.108 g), 4-methylbenzoic acid (0.204 g), Yield: 84%; mp. 225°C (223–224°C, Al-Awadi et al., 2005).

2-(*p*-Methoxyphenyl)-1*H*-benzimidazole (2)

Reagents: 1,2-phenylenediamine (0.108 g), 4-methoxybenzoic acid (0.228 g); Yield: 74%; mp. 226°C (225°C) (Algul et al., 2008).

2-(*p*-Ethoxyphenyl)-1*H*-benzimidazole (3)

Reagents: 1,2-phenylenediamine (0.108 g), 4-ethoxy benzoic acid (0.249 g). Yield: 81%; mp. 148°C (149.4–150.3°C, Navarrete-Vazquez et al. 2006).

2-(*p*-Nitrophenyl)-1*H*-benzimidazole (4)

Reagents: 1,2-phenylenediamine (0.108 g), 4-nitrobenzoic acid (0.250 g). Yield: 65%; mp. 300°C (297–298°C) (Al-Awadi et al., 2005).

2-(*p*-Chlorophenyl)-1*H*-benzimidazole (5)

Reagents: 1,2-phenylenediamine (0.108 g), 4-chlorobenzoic acid (0.234 g). Yield: 80%; mp. 290°C (289–290°C) (Al-Awadi et al. 2005).

General method for synthesis of 5-non-methoxy-2-(*p*-chlorophenyl or 3,5-dichlorophenyl)-1*H*-benzimidazole derivatives

Method B. A solution of 4-methoxy-1,2-phenylenediamine or 1,2-phenylenediamine (1.0 mmol) and *p*-chlorobenzaldehyde or 3,5-dichlorobenzaldehyde (1.0 mmol) in ethanol (20 mL) was prepared. Aq 30% H_2O_2 (7.0 mmol) and aq 37% HCl (3.5 mmol) were added and the mixture was stirred at room temperature for 2–4 h. The mixture was quenched by adding H_2O (10 mL), extracted with EtOAc (3 × 10 mL) and the combined extracts were dried over MgSO_4 . The filtrate was evaporated and the solid obtained was

filtered, dried and crystallized from adequate solvent to obtain the corresponding benzimidazole.

2-(4-chlorophenyl)-5-methoxy-1*H*-benzimidazole (6) (commercially available)

Reagents: 4-methoxy-1,2-phenylenediamine (0.211 g), *p*-chlorobenzaldehyde (0.140 g), aq 30% H_2O_2 (0.7 mL) and aq 37% HCl (0.29 mL). Yield: 51.7%, mp. 229°C.

2-(3,5-Dichlorophenyl)-1*H*-benzimidazole (7)

Reagents: 1,2-phenylenediamine (0.108 g), 3,5-dichlorobenzaldehyde (0.175 g), aq 30% H_2O_2 (0.7 mL) and aq 37% HCl (0.29 mL). Yield: 60 %, mp. 249–251°C, (250 °C) (Lee et al., 2007).

General method for synthesis of 2-(*p*-substitutedphenyl or 2,6-dichlorophenyl)-1-phenyl-*p*-chlorophenyl-1*H*-benzimidazole derivatives:

Method C. A mixture of *N*-substituted-1,2-phenylenediamine (1.0 mmol), the corresponding benzaldehyde (1.1 mmol) and $\text{Na}_2\text{S}_2\text{O}_5$ (1.1 mmol) in DMF (10 mL) was heated to reflux for 4–7 h. After cooling, water (20 mL) was added and the mixture was extracted with AcOEt (3 × 15 mL). The organic layer was dried over magnesium sulfate and removed under vacuum. Purification was done by chromatography on silica gel eluting with chloroform and recrystallization from adequate solvent.

1-phenyl-2-(4-tolyl)-1*H*-benzimidazole (8)

Reagents: *N*-phenyl-1,2-phenylenediamine (0.184 g), *p*-toluenealdehyde (0.13 mL) and $\text{Na}_2\text{S}_2\text{O}_5$ (0.209 g). Yield 63%. mp. 142–144°C (143–145°C) (Iyengar et al. 1997).

2-(4-chlorophenyl)-1-phenyl-1*H*-benzimidazole (9)

Reagents: *N*-phenyl-1,2-phenylenediamine (0.184 g), *p*-chlorobenzaldehyde (0.154 g) and $\text{Na}_2\text{S}_2\text{O}_5$ (0.209 g). Yield 75%, mp 153–154°C (150.0–150.5°C) (Kassim et al., 2012).

2-(2,6-dichlorophenyl)-1-phenyl-1*H*-benzimidazole (10)

Reagents: *N*-phenyl-1,2-phenylenediamine (0.184 g), 2,6-dichlorobenzaldehyde (0.192 g) and $\text{Na}_2\text{S}_2\text{O}_5$ (0.209 g). Yield 16.4%. mp. 95–97°C, IR (cm^{-1}): 1595 ($-\text{C}=\text{N}$) cm^{-1} ; ^1H NMR (CDCl_3) δ ppm: 7,29–7,46 (m, 11H, Ar-H), 8,00–8,02 (d, 1H, $J=7,6$ Hz, Ar-H); MW: 339,22; EI-MS: 339,37 (M^+).

1-(4-chlorophenyl)-2-(4-methoxyphenyl)-1*H*-benzimidazole (11)

Reagents: *N*-(4-chlorophenyl)-1,2-phenylenediamine (2.19 g), 4-methoxybenzaldehyde (1.34 mL) and sodium metabisulfide (0.209 g). Yield 52.3%, mp 176–178°C, (183–185°C) (Iyengar et al., 1997).

1,2-bis(4-chlorophenyl)-1*H*-benzimidazole (12)

Reagents: *N*-(4-chlorophenyl)-1,2-phenylenediamine (0.219 g), 4-chlorobenzaldehyde (0.154 g) and $\text{Na}_2\text{S}_2\text{O}_5$ (0.209 g). Yield 41.3%, mp. 160–162°C (162–164°C) (Iyengar et al. 1997).

1-(4-chlorophenyl)-2-(4-dimethylaminophenyl)-1H-benzimidazole (13)

Reagents: N-(4-chlorophenyl)-1,2-phenylenediamine (0.218 g), 4-(dimethylamino)benzaldehyde (0.164 g) and $\text{Na}_2\text{S}_2\text{O}_5$ (0.209 g). Yield 64.3%. mp. 185-187°C. IR (cm^{-1}): 1600 ($-\text{C}=\text{N}$); ^1H NMR (CDCl_3) δ ppm: 2.98 (s, 6H, $-\text{CH}_3$), 6.59-6.62 (dd, 2H, $J=8.8$ Hz, Ar-H), 7.14-7.32 (m, 5H, Ar-H), 7.42-7.50 (dd, dd, 4H, $J=8.4$ and 8.8 Hz, Ar-H), 7.82-7.84 (d, 1H, $J=8$ Hz, Ar-H); MW: 347,84; EI-MS: 348,12 (M^++1).

1-(4-Chlorophenyl)-2-(2,6-dichlorophenyl)-1H-benzimidazole (14)

Reagents: N-(4-chlorophenyl)-1,2-phenylenediamine (0.209 g), 2,6-dichlorobenzaldehyde (0.192 g) and $\text{Na}_2\text{S}_2\text{O}_5$ (0.209 g). Yield 32.7%. mp. 84-86°C. IR (cm^{-1}): 1608 ($-\text{C}=\text{N}$); ^1H NMR (CDCl_3) δ ppm: 7.30-7.41 (m, 10H, Ar-H), 7.92-7.95 (d, 1H, $J=6.4$ Hz, Ar-H); MW: 373,66; EI-MS: 374,12 (M^++1).

General method for the synthesis of 2,3,5-trisubstituted indole derivatives:

Method D. A mixture of phenylhydrazine hydrochloride (2 mmol), ketones (2 mmol), ethanol (30 mL), and HCl (1 mL) was heated at 100°C for 24-48 h. The mixture was quenched by adding H_2O (10 mL), extracted with dichloromethane (3×10 mL) and the combined extracts were dried (MgSO_4). The filtrate was evaporated and crystallized from ethanol and finally dried in vacuum to give corresponding analytically pure indoles.

4-(5-Methyl-3-phenyl-1H-indole-2-yl)phenol (15)

Reagents: p-Tolylhydrazine HCl (316 mg), benzyl-4-bromophenyl ketone (424 mg). Yield: 71%, mp. 139-141°C, IR (cm^{-1}): 3327 ($-\text{NH}$), 1619 ($-\text{C}=\text{N}$); ^1H NMR ($\text{DMSO}-d_6$) δ ppm: 2,43 (s, 3H, $-\text{CH}_3$), 7,06-7,32 (m, 6H), 7,39-7,40 (m, 6H), and 8,09 (1H, s, $-\text{NH}$); MW: 299,37 EI-MS: 300,20 (M^++1).

2-(4-Bromophenyl)-5-Methyl-3-phenyl-1H-indole (16)

Reagents: p-Tolylhydrazine HCl (316 mg), benzyl-4-hydroxyphenyl ketone (424 mg). Yield 61%, mp. 148-150°C, IR (cm^{-1}): 3320 ($-\text{NH}$), 1614 ($-\text{C}=\text{N}$); ^1H NMR (D_2O) δ ppm: 2,43 (s, 3H, $-\text{CH}_3$), 4,90 (brs, 1H), 6,75-6,77 (d, 2H), 7,03-7,06 (dd, 1H), 7,25-7,44 (m, 8H) and 8,06 (1H, s, $-\text{NH}$); MW: 362,26 EI-MS: 363,32 (M^++1).

Microbiology

Antimicrobial susceptibility testing was performed by modification of the following literature methods (National Committee for Clinical Laboratory Standards, 2002; Alexopoulos and Mims, 1979; Ghannoum and Rice, 1999). We used microbial strains such as *S. aureus* ATCC 25925, *B. subtilis* ATCC 6633, *E. coli* ATCC 25923, *Aeromonas hydrophila* ATCC 95080 *Acinetobacter baumannii* ATCC 02026, *C. albicans* (clinical isolate strain), *Candida glabrata* ATCC 4322, *Candida parapsilosis* ATCC 22019 and *Candida glabrata* (clinical isolate strains). The yeast and bacterial cell inoculum were prepared from the stock culture grown in Tryptic Soy Broth (TSB) at 28°C for 24 h and Mueller-Hinton Broth (MHB) 37°C for 24 h, respectively. The microorganisms concentrations were adjusted according to McFarland 0.5 turbidity tubes ($\sim 10^5$ cells per mL) using sterilized TSB and MHB. Stock solutions of chemical derivatives

were prepared in DMSO at 1000 $\mu\text{g}/\text{mL}$. A modified macrodilution test was applied for antimicrobial activity and the experiments were run in duplicates independently.

For antifungal activity testing, 1 mL TSB was added to each of 10 sterilized test tubes. 1 mL of chemical derivative solution was added to the first tube and 2-fold dilutions of stock solution were of the yeast cell (McFarland 0.5) was prepared. Then, 10 μL of this stock solution was added to each tube except the last one which acted as control tube.

For antibacterial activity testing, 1 mL MHB was added to each of ten sterilized tubes. 1 mL of chemical derivative solution was added to the first tube and 2-fold dilutions of stock solution were prepared and the bacterial cell (McFarland 0.5) was prepared. Then, 10 μL of this stock solution was added to each tube except the last control tube. Only 2 ml of yeast and bacterial cell were added in to control tube without chemical and used as control for growing. All tubes were incubated at 28°C (for fungi) and at 37°C (for bacteria) for 24 h. After the incubation, the minimal inhibitory concentrations (MIC) (Tables 1 and 2) were noted by controlling the growth inhibition for each chemical compound. Fluconazole and Ampicillin were used as reference drug. The results of modified macrodilution test, some chemical compounds were determined active for *C. glabrata* ATCC 4322. Only active compounds were selected and tested for *C. glabrata*, by "Disc diffusion method". Dimethyl sulfoxide was used as the solvent to prepare desired solution (1 mg/mL) of the selected compounds initially. Different dilutions of isolated compound that is 31.25, 62.5, 125, 250 and 500 $\mu\text{g}/\text{mL}$ for each, were employed. Fluconazole was used as reference antifungal drug and DMSO was also tested for a possible antifungal activity. In this method, the filter paper discs (6 mm in diameter) were individually absorbed with 30 μL each of all concentrations (31.25, 62.5, 125, 250 and 500 $\mu\text{g}/\text{mL}$) and placed on Potato Dextrose Agar (PDA) plates, which had been previously inoculated with the tested microorganism, and was adjusted according to McFarland 0.5 using sterilized TSB. The Petri-plates were incubated at $28 \pm 1^\circ\text{C}$ for 24 h. The diameters of the inhibition zone were measured in mm.

RESULTS AND DISCUSSION

Chemical assays

The procedures for synthesis used in this study are illustrated in Figures 2 to 5. All benzimidazole derivatives were prepared according to a modified one-step reaction sequence in analogy to a method described (Bahrami et al., 2007; Navarrete-Vazquez et al., 2006).

We also determined the antimicrobial activity of some indole derivatives as shown in Figure 5. The compounds were synthesized according to modified indole synthesized method from p-tolylhydrazine HCl and the corresponding benzyl phenyl ketone in ethanol (Robinson, 1963).

Antimicrobial assay

We observed that substitution at the second position of the benzimidazole and indole rings played an important role on antimicrobial activity. These compounds also showed potent antimicrobial activity; however they have not been introduced into the pharmaceutical market yet.

In recent years, antimicrobial compounds, which target

Table 1. MIC values ($\mu\text{g}/\text{mL}^{-1}$) for microorganisms of the tested compounds (Bacterial).

Compound	<i>S. aureus</i>	<i>B. subtilis</i>	<i>A. hydrophila</i>	<i>A. baumannii</i>	<i>E. coli</i>
1	250	250	250	62.5	250
2	-	250	250	500	500
3	500	500	500	500	500
4	500	-	-	500	-
5	500	125	125	125	250
6	500	125	31.25	500	500
7	250	-	-	-	-
8	-	-	-	-	-
9	250	250	125	250	250
10	250	250	250	250	125
11	500	500	500	500	500
12	-	-	-	250	250
13	-	250	250	125	125
14	125	125	62.5	62.5	125
15	1.95	1.95	62.5	125	250
16	250	125	-	-	-
Ampicillin	*	*	31.25	15.62	31.25

- non-effective *effective in all concentrations used.

Table 2. MIC values ($\mu\text{g}/\text{mL}^{-1}$) for microorganisms of the tested compounds (Fungal).

Compound	<i>C. albicans</i>	<i>C. glabrata</i>	<i>C. parapsilosis</i>
1	125	*	125
2	62.5	*	250
3	31.25	*	1.95
4	250	-	-
5	62.5	*	125
6	250	*	250
7	250	-	-
8	125	-	-
9	125	*	62.5
10	500	-	-
11	125	-	-
12	250	-	-
13	62.5	250	500
14	125	*	7.81
15	3.90	*	7.81
16	125	*	-
Fluconazole	*	*	*

-, non-effective; *effective in all concentrations used.

directly bacterial DNA and therefore exhibit more selective effect, are beginning to investigate. Benzimidazole and indole rings are isosteres of basic structures of DNA bases (purine and pyrimidine moieties), which raises the possibility that these compounds could be antimetabolites of purine. Therefore, we also focused on investigation of antimicrobial activities of some new benzimidazole and indole derivatives.

The most active compound was 4-(5-methyl-3-phenyl-1H-indole) phenol (Compound 15) as shown by the most inhibitory effect on *C. albicans*, *C. glabrata*, *S. aureus* and *B. subtilis*. Additionally, we found that Compound 3 to *Candida parapsilosis*, Compound 6 to *Aeromonas hydrophila* and Compounds 1 and 14 to *Acinetobacter baumannii* were more effective than other compounds tested.

First, antibacterial and antifungal activities of all

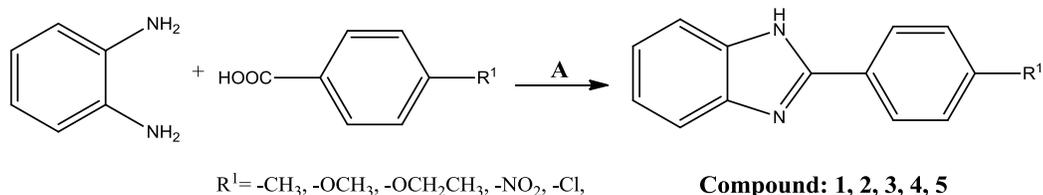


Figure 2. Synthesis of 2-(*p*-substitutedphenyl) benzimidazole compounds. A, Reagents and conditions: PPA

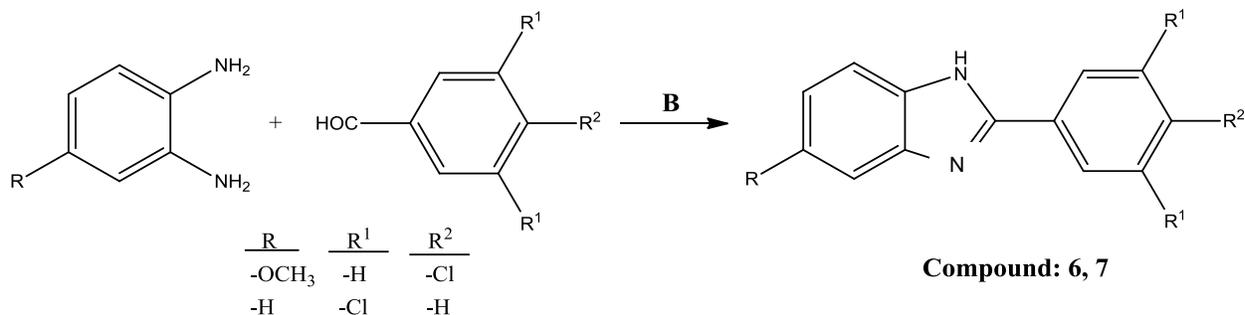


Figure 3. Synthesis of 5-non/methoxy-2-(*p*-chlorophenyl or 3,5-dichlorophenyl)-1*H*-benzimidazole derivatives. Reagents and conditions(B): 30% H₂O₂, 37% HCl.

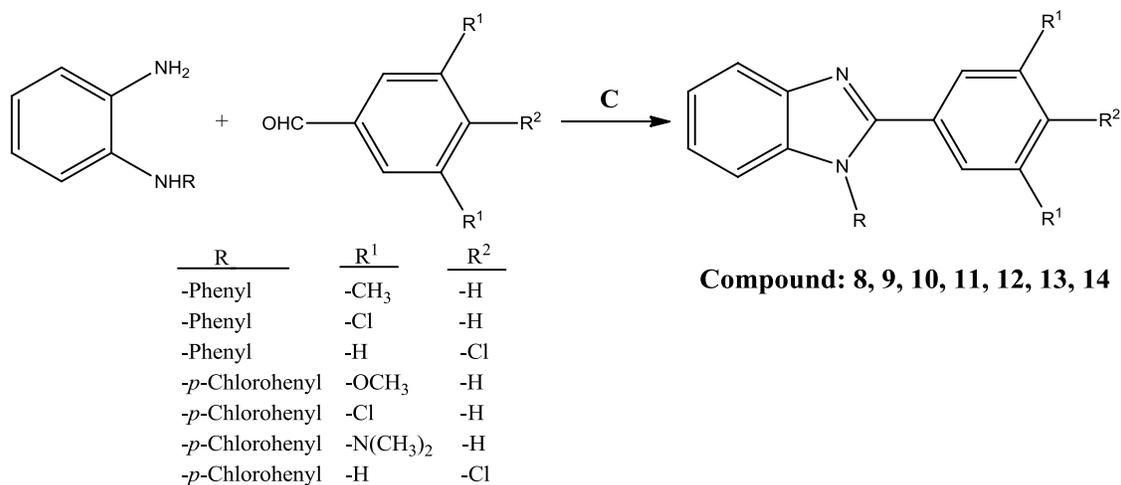


Figure 4. Synthesis of 2-(*p*-substitutedphenyl or 2,6-dichlorophenyl)-1-phenyl/*p*-chlorophenyl-1*H*-benzimidazole compound. Reagents and conditions : (C) Na₂S₂O₅, DMF/ reflux.

compounds were determined by tube dilution method; Ampicillin and Fluconazole were used as standard drugs, respectively. Results were also confirmed with the disc diffusion method.

All compounds showed low activity against *S. aureus* and *B. subtilis*, except Compound 15, which had considerable activity against these microorganisms. Different activity profiles of Compound 15 and 16 show that activity

is not just determined by main structure.

All compounds were also examined for antifungal activity. It was found that Compounds 1-3, 5, 6, 9, and 14-16 were fully susceptible to *C. glabrata* and Compound 3 and 14 had a significant activity against *C. albicans* and *C. parapsilosis*, respectively. Compounds 1-3, 5, 6, 9, and 14-16 showed activity against *C. glabrata* in all tested dilutions and these results were also confirmed

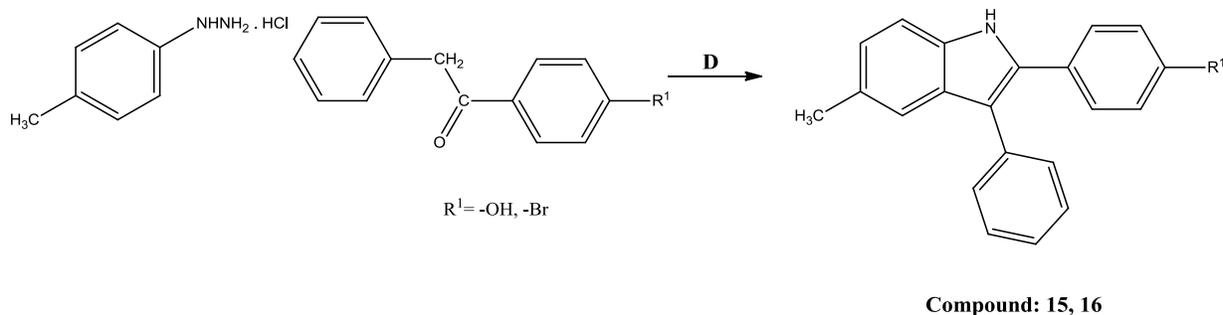


Figure 5. Synthesis of indole compounds. Reagents and conditions (**D**): HCl / EtOH.

with disc diffusion method. Generally, the compounds were active against *C. glabrata*.

As a result of this study, Compound 15 is a promising compound which is active in both methods, the other compound 3 showed promising activities in the medium level. Also, Compound 15 showed considerable activity against 10 different clinical strain of *C. Glabrata* in disc diffusion method with inhibition zone (18 mm) compared with Fluconazole inhibition zone (15 mm).

Conclusion

Nowadays, growing resistance of pathogens against anti-bacterial compounds used is a common and important problem, which shows clearly that research on new compounds against these pathogens is needed. We synthesized 16 novel substituted benzimidazole and indole derivatives and screened their antimicrobial activities. In future studies, novel derivatives of Compound 15 should be designed to reveal a new antifungal compound group. Among the investigated compounds, indole derivatives showed better antibacterial activity than benzimidazole derivatives. It was observed that substitution at the second position of the benzimidazole and indole rings played an important role on antimicrobial activity and increased activity when 4-OH substituted phenyl at the second position of the indole. Additionally, aromatic ring substitution at first position of benzimidazole ring decreased antimicrobial activity.

We need to study the *in vivo* and mode of action of these compounds to determine the potential of their anti-bacterial and antifungal activities.

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