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Short communication

# Synthesis and antimicrobial activities of some new benzimidazole derivatives

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**Abstract**

Some benzimidazolylbenzamides were synthesized and their antimicrobial activities against *Staphylococcus aureus*, *Streptococcus faecalis*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans* evaluated. It was shown that the compound **14** exhibited the best activity against *B. subtilis*, *P. aeruginosa* and *C. albicans*.


*Keywords:* Benzimidazoles; Benzamides; Antimicrobial activity

## 1. Introduction

In some previous papers [1–4], we reported the synthesis and antimicrobial activity of some benzimidazole-5(6)-carboxamido and 4-(1*H*-benzimidazol-2-yl)benzamide derivatives. Among them, compounds **I**, **II**, **III** and **IV** exhibited good antimicrobial activity. In this investigation, as a continuation on the synthesis of antimicrobial benzimidazoles, it was planned to modify the amide group to the anilide on the 2-phenyl benzimidazole moiety.

## 2. Chemistry

For the synthesis of the target compounds the reaction sequences outlined in the Scheme 1 are followed. 2-(4-Aminophenyl)-1*H*-benzimidazol (**1**) was prepared by heating of *o*-phenylenediamine with *p*-aminobenzoic acid in polyphosphoric acid (PPA). Arylcarboxylic acids were converted into acyl chlorides with $SOCl_2$ and their reaction with 2-(4-aminophenyl)-1*H*-benzimidazol (**1**) in $NaHCO_3$/ether/$H_2O$ gave the compounds **2**–**11**. 2-(3-Nitrophenyl)-1*H*-benzimidazole (**12**) was prepared via oxidative condensation of *o*-phenylenediamine, 3-nitrobenzaldehyde and sodium metabisulfite [5]. Treatment of 2-(3-nitrophenyl)-1*H*-benzimidazole with iodomethane in $K_2CO_3$/dry acetone gave the *N*-methylated product, 2-(3-nitrophenyl)-1-methyl-1*H*-benzimidazole (**13**). The reduction of **13** with $H_2$, Pd/C produced **14**. Acylation of **14** with chloroacetylchloride in dry acetone afforded 2-chloro-*N*-[3-(1-methyl-1*H*-benzimidazol-2-yl)-phenyl]-acetamide (**15**) [6]. Compound **15** was reacted with thiophenol and few drops of piperidine in dry benzene to give *N*-[3-(1-methyl-1*H*-benzimidazol-2-yl)-phenyl]-2-phenylthio-acetamide (**16**) [7]. Some physico-chemical properties and spectral findings are given in Table 1.

## 3. Experimental

Melting points were determined with a Büchi SMP-20 and Electrothermal melting point apparatus and are uncorrected. $^1$H NMR spectra were measured with a Bruker GmbH DPX-400, 400 MHz instrument using TMS internal standard and DMSO-$d_6$. All chemical shifts were reported as $\delta$ (ppm) values. EI MS were obtained with a VG Platform II, Micromass spectrometer with ionization energy maintained at 70 eV. Elemental analyses (C, H, and N) were determined on

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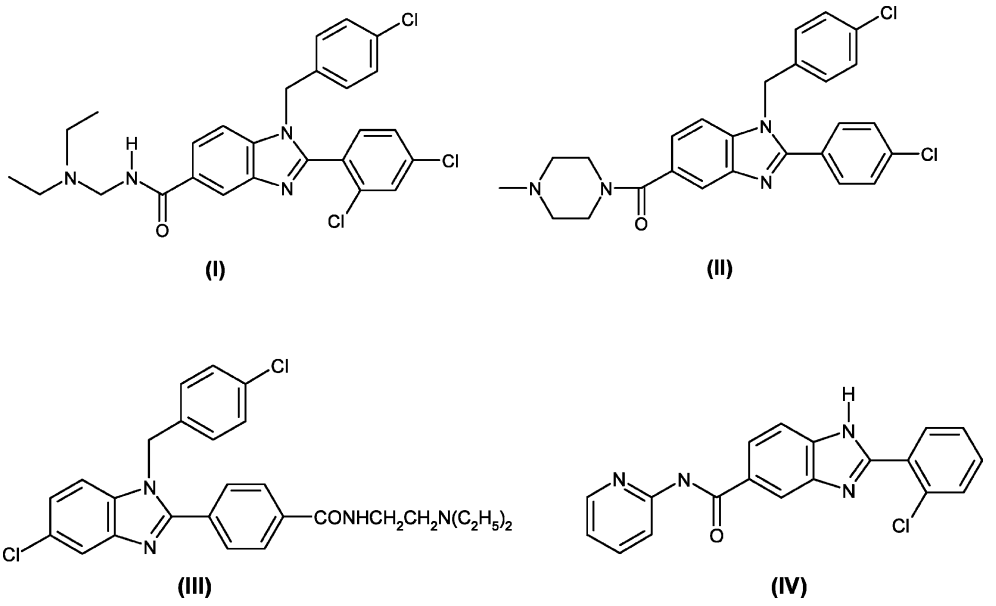
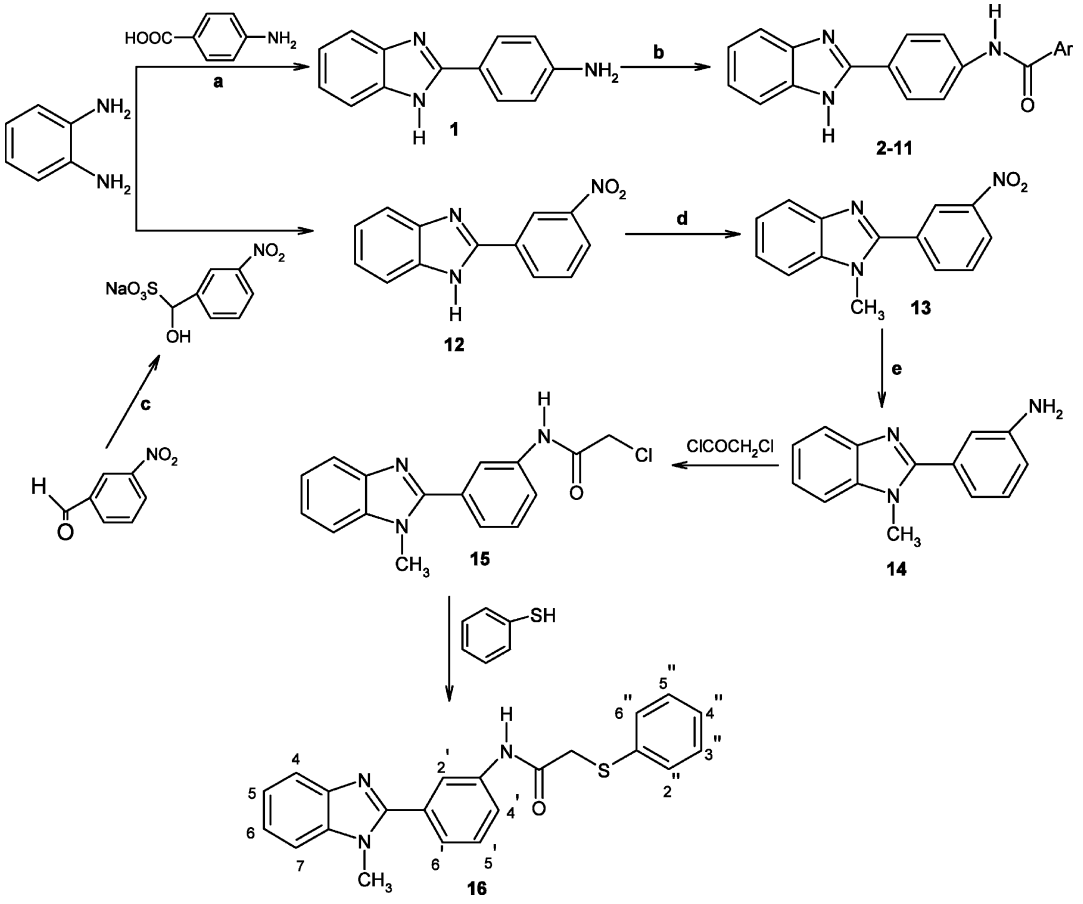
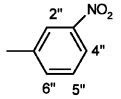
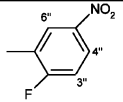
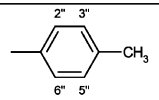
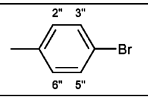
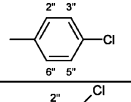
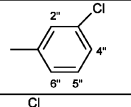
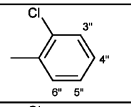
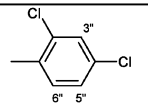
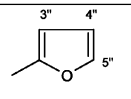



a Leco CHNS 932 instrument (St. Joseph, USA), and were within ±0.4% of the theoretical values. All instrumental analysis were performed at Scientific and Technical Research Council of Turkey. The chemical reagents used in synthesis were purchased from E. Merck (Darmstadt, FRG) and Aldrich (Milwaukee, USA). Column chromatography was accomplished on silica gel 60 (230–400 mesh ASTM). 2-(4-aminophe-




Scheme 1. Synthesis of the compounds **1**–**16**. Reagents: (a) PPA (b) corresponding acylchlorides (c) $NaHSO_3$ (d) $CH_3I$–$K_2CO_3$ (e) $H_2$, Pd/C.

Table 1
Some physico-chemical properties and spectral findings of compounds **3**–**11**

| No | Ar | Formula | Yield | M.p (°C) | $^1$H NMR (δ ppm) | Mass m/z (%) |
|---|---|---|---|---|---|---|
| **3** |  | $C_{20}H_{14}N_4O_3$ | 28 | 268-270 | 7.19-7.21 (m, 2H, H-5,6), 7.47 (d, 1H, $J_o$= 7.02 Hz, H-4), 7.59 (d, 1H, $J_o$= 7.17 Hz, H-7), 7.87 (td, 1H, $J_{o,o'}$= 7.99 Hz, H5"), 7.98 (d, 2H, $J_o$=8.75 Hz, H-3',5'), 8.19 (d, 2H, $J_o$= 8.73 Hz, H-2',6'), 8.43-8.48 (m, 2H, H-4",6"), 8.83 (td, 1H, $J_{m,m'}$=1.87, 1.88 Hz, H-2"), 10.82 (s, 1H, -NH), 12.89 (s, 1H, -NHCO-) | 317 (3.56), 209 (1.59), 167 (10.10), 149 (32.16), 119 (3.43), 103 (37.25),92 (2.30), 41 (100) |
| **4** |  | $C_{20}H_{13}FN_4O_3$ | 11 | 293 | 7.19-7.22 (m, 2H, H-5,6), 7.52 (d, 1H, $J_o$=6.93 Hz, H-4), 7.60 (d, 1H, $J_o$=7.15 Hz, H-7), 7.62-7.77 (m, 1H, H-3"), 7.89 (d, 2H, $J_o$= 8.66 Hz, H-3',5'), 8.18 (d, 2H, $J_o$= 8.67 Hz, H-2',6'), 8.42-8.53 (m, 1H, H-5"), 8.60 (dd, 1H, $J_{4",F}$=5.77 Hz, $J_o$=8.69 Hz, H-4"), 10.86 (s, 1H, -NH), 12.87 (s, 1H, -NHCO-) | 376 ( $M^{+\cdot}$) (0.06), 217 (1.21), 149 (3.21), 103 (18.73), 91 (2.45), 76 (10.59), 43 (100) |
| **5** |  | $C_{21}H_{17}N_3O$ | 5 | 320 | 2.2 (s, 3H, $CH_3$), 7.10-7.21 (m, 2H, H-5,6), 7.36 (d, 2H, $J_o$=8.12 Hz, H-3",5"), 7.5 (dd, 1H, $J_o$=6.80 Hz, $J_m$=1.54 Hz, H-4), 7.63 (d, 1H, $J_o$=7.0 Hz, H-7), 7.9 (d, 2H, $J_o$= 8.13 Hz, H-2", 6"), 7.96 (d, 2H, $J_o$= 8.73 Hz, H-3',5'), 8.14 (d, 2H, $J_o$= 8.69 Hz, H-2',6'), 10.38 (s, 1H, -NH), 12.78 (s, 1H, -NHCO-) | 327 ($M^{+\cdot}$) (0.25), 145 (12.45), 91 (1.04), 58 (15.00), 41 (100) |
| **6** |  | $C_{20}H_{14}BrN_3O$ | 16 | 335 | 7.18-7.22 (m, 2H, H-5,6), 7.58-7.62 (m, 2H, H-4,7), 7.78 (d, 2H, $j_o$=8.49 Hz, H-3",5"), 7.93-7.97 (m, 4H, H-3',5',2",6"), 8.16 (d, 2H, $J_o$=8.69 Hz, H-2',6'), 10.56 (s, 1H, -NH), 12.96 (br.s, 1H, -NHCO-) | 391 ($M^{+\cdot}$) (1.27), 393 ($M+2^{+\cdot}$) (1.35), 184 (20.50), 182 (24.50), 155 (31.50), (153 (43.33), 103 (64.00), 91 (10.63), 49 (76.67), 41 (100) |
| **7** |  | $C_{20}H_{14}ClN_3O$ | 19 | 323 | 7.17-7.24 (m, 2H, H-5,6), 7.51-7.53 (m, 2H, H-4,7), 7.64 (d, 2H, $J_o$= 8.50 Hz, H-3",5"), 7.96 (d, 2H, $J_o$=8.72 Hz, H-3',5'), 8.02 (d, 2H, $J_o$=8.55 Hz, H-2",6"), 8.16 (d, 2H, $J_o$=8.71 Hz, H-2',6'), 10.54 (s, 1H, -NH), 12.84 (s, 1H, -NHCO-) | 347 ($M^{+\cdot}$) (22.35), 349 ($M+2^{+\cdot}$) (11.62), 139 (100), 113 (6.47), 111 (20.00), 76 (5.29), 43 (24.12), 41 (14.70) |
| **8** |  | $C_{20}H_{14}ClN_3O$ | 43 | 312 | 7.12-7.20 (m,2H, H-5,6), 7.52-7.71 (m, 4H, H-4,7,4",5"), 7.94-8.04 (m, 4H, H-3',5',2",6"), 8.12 (d, 2H, $J_o$=8.71 Hz, H-2',6'),10.58 (s, 1H, -NH), 12.84 (s, 1H, -NHCO-) | 347 ($M^{+\cdot}$) (94.16), 349 ($M+2^{+\cdot}$) (11.04), 310 (1.92), 181 (6.21), 179 (19.81), 139 (100), 113 (11.36), 111 (42.21), 43 (50.00) |
| **9** |  | $C_{20}H_{14}ClN_3O$ | 16 | 311 | 7.19-7.71 (m, 8H, H-4,5,6,7,3",4",5",6"), 7.89 (d, 2H, $J_o$=8.51 Hz, H-3',5'), 8.16 (d, 2H, $J_o$=8.49 Hz, H-2',6'), 10.76 (s, 1H, -NH), 12.76 (s, 1H, -NHCO-) | 347 ($M^{+\cdot}$) (5.33), 349 ($M+2^{+\cdot}$) (1.12), 149 (17.83), 139 (9.87), 111 (11.31), 73 (12.42), 56 (75.80), 43 (100) |
| **10** |  | $C_{20}H_{13}Cl_2N_3O$ | 69 | 242 | 7.19-7.21 (m, 2H, H-5,6), 7.53-7.64 (m, 3H, H-4,7,5"), 7.68 (d, 1H, $J_o$= 8.20 Hz, H-6"), 7.81 (d, 1H, $J_m$=1.88 Hz, H-3"), 7.87 (d, 2H, $J_o$=8.69 Hz, H-3',5'), 8.16 (d, 2H, $j_o$=8.67 Hz, H-2',6'), 10.79 (s, 1H, -NH), 12.60 (s, 1H, -NHCO-) | 381 ($M^{+\cdot}$) (71.76), 383 ($M+2^{+\cdot}$) (17.45), 385 ($M+4^{+\cdot}$) (27.45), 175 (43.14), 173 (100), 147 (10.39), 145 (37.25), 109 (18.53), 63 (28.24), 43 (11.86) |
| **11** |  | $C_{19}H_{15}N_3O_2$ | 5 | 301 | 6.73 (dd, 1H, $J_{4",3"}$=3.4 Hz, $J_{4",5"}$=1.72 Hz, H-4"), 7.17-7.21 (m, 2H, H-5,6), 7.39 (d, 1H, $J_{3",4"}$= 3.49 Hz, H-3"), 7.51 (d, 1H, $J_o$= 6.79 Hz, H-4), 7.64 (d, 1H, $J_o$= 7.07 Hz, H-7), 7.94 (d, 1H, $J_o$= 8.72 Hz, H-3',5'), 7.98 (dd, 1H, $J_{5",4"}$= 1.53 Hz, $J_{5",3"}$= 0.85 Hz, H-5"), 8.14 (d, 2H, $J_o$= 8.70 Hz, H-2',6'), 10.40 (s, 1H, -NH), 12.82 (s, 1H, -NHCO-) | 317 ($M^{+\cdot}$) (0.74), 109 (2.54), 91 (1.79), 76 (4.82), 63 (1.13), 57 (6.40), 43 (100), 41 (77.11) |

nyl)benzimidazole (**1**) (m.p.: 237 °C (Lit. [8] m.p.: 240 °C), *N*-[4-(1*H*-benzimidazol-2-yl)-phenyl]-benzamide (**2**) (m.p.: 335 °C (Lit. [8] m.p.: 333 °C), 2-(3-nitrophenyl)benzimidazole (**12**) (m.p.: 209 °C (Lit. [9] m.p.: 207–208 °C) and 2-(3-nitrophenyl)-1-methylbenzimidazole (**13**) (m.p.: 154 °C (Lit. [10] m.p.: 151–154 °C) were prepared in our laboratory. ATCC strains of the microorganism used in this study were obtained from the culture collection of Refik Saydam Health Institution of Health Ministry, Ankara, Turkey.

### 3.1. General procedure for the preparation of the N-[4-(1H-benzimidazol-2-yl)-phenyl]-benzamides (2–10)

Appropriate arylcarboxylic acids(1.5 mmol) were refluxed in benzene (5 ml) with $SOCl_2$ (5 ml) for 2 h at 80 °C. Then solvent and excess of $SOCl_2$ were evaporated completely and the residue was dissolved in ether (10 ml). This mixture was added to an ice-cold mixture of 2-(4-aminophenyl)benzimidazole (1.5 mmol), $NaHCO_3$ (3 mmol), ether (10 ml) and water (10 ml) during 1 h period. The mixture was stirred overnight at room temperature. The resultant precipitate was filtered, washed with 1 N HCl and then water, and purified by column chromatography using chloroform (25):isopropanol (1) as eluent.

### 3.2. Synthesis of the furan-2-carboxylic acid [4-(1H-benzimidazol-2-yl)-phenyl]-amide (11)

Preparation was same as for **2**–**10**, using furan-2-carboxylic acid as starting carboxylic acid.

### 3.3. Synthesis of the 3-(1-methyl-1H-benzimidazol-2-yl)-phenylamine (14)

To the 2-(3-nitrophenyl)-1-methylbenzimidazole dissolved in EtOH (10 ml) was added 10% Pd/C (10 mg) and the solution was hydrogenated at room temperature at 40 psi. The reaction was stopped after cessation of $H_2$ uptake. The catalyst was filtered through a bed of Celite, washed with EtOH and concentrated. The residue was purified by column chromatography using hexane (1):EtOAc (1) as eluent. M.p.: 153 °C, yield 79%.

$^1$H NMR ($\delta$ ppm): 3.85 (s, 3H, N–$CH_3$); 5.36 (br s, 2H, $NH_2$); 6.73 (d, 1H, $J_o = 7.96$ Hz, H-4′); 6.92 (d, 1H, $J_o = 7.53$ Hz, H-6′); 7.03 (s, 1H, H-2′); 7.18–7.30 (m, 3H, H-5,6,5′); 7.59 (d, 1H, $J_o = 7.74$ Hz, H-4); 7.64 (d, 1H, $J_o = 7.78$ Hz, H-7).

Mass (70 eV) *m*/*z* (%): 223 ($M^+$) (61.21), 222 (100), 208 (1.24), 207 (2.02), 195 (2.86), 192 (1.29), 179 (1.31), 119 (8.76), 117 (33.18), 91 (23.13), 77 (59.35), 63 (40.65), 43 (29.91), 41 (31.78).

### 3.4. Synthesis of the 2-chloro-N-[3-(1-methyl-1H-benzimidazol-2-yl)-phenyl]-acetamide (15)

0.673 mmol 3-(1-methyl-1*H*-benzimidazol-2-yl)-phenylamine was dissolved in 2 ml of dry acetone and treated drop by drop, with stirring, 0.026 ml chloroacetylchloride. 0.24 ml 2 N NaOH was then added and the mixture treated further with 0.026 ml chloroacetylchloride. The mixture was stirred for 1 h period at room temperature, made acidic with 1 N HCl, then extracted with EtOAc. The extract was washed with water, dried over $Na_2SO_4$ and evaporated. Residue was recrystallized from EtOH. M.p.: 339 °C, yield 52%.

$^1$H NMR ($\delta$ ppm): 4.01 (s, 3H, –$NCH_3$); 4.37 (s, 2H, –$CH_2$–); 7.59–8.00 (m, 7H, Ar–H); 8.29 (s, 1H, H-2′).

### 3.5. Synthesis of the N-[3-(1-methyl-1H-benzimidazol-2-yl)-phenyl]-2-phenylthio-acetamide (16)

2-Chloro-*N*-[3-(1-methyl-1*H*-benzimidazol-2-yl)-phenyl]-acetamide (0.33 mmol) was dissolved in dry benzene (1 ml), and thiophenol (0.055 g, 0.50 mmol) and few drops of piperidine were added. The reaction mixture was refluxed for 6 h on a water bath, precipitate was filtered off, washed with water, purified by column chromatography using chloroform (4):isopropanol (1) as eluent. M.p.: 158 °C, yield 10%.

$^1$H NMR ($\delta$ ppm): 3.89 (s, 3H, N–$CH_3$); 3.91 (s, 2H, $COCH_2$); 7.21–7.71 (m, 12H, Ar–H); 8.11 (d, 1H, $J_m = 1.62$ Hz, H-2′); 10.29 (s, 1H, NHCO).

Mass (70 eV) *m*/*z* (%): 373 ($M^+$) (57.60), 375 ($M^+2^+$) (2.97), 296(4.16), 264 (7.13), 250 (13.06), 222 (29.69), 207 (7.35), 123 (60.57), 108 (37.37), 77 (100), 63 (43.56), 43 (29.12), 41 (23.20).

## 4. Antimicrobial activity

The in vitro antimicrobial activity of the compounds was tested by the tube dilution technique [11]. Each of the test compounds and standards ampicillin trihydrate, miconazole and fluconazole was dissolved in 12.5% DMSO, at concentrations of 200 μg/ml, further dilutions of the compounds and standards in the test medium were prepared at the required quantities of 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 μg/ml concentrations. The final inoculum's size was $10^5$ CFU/ml. The minimum inhibitory concentrations (MIC) were defined as the lowest concentrations of the compounds that prevented visible growth. It was determined that the solvent had no antimicrobial activity against any of the test microorganism.

All the compounds were tested for their in vitro growth inhibitory activity against *Staphylococcus aureus* ATCC 25923, *Streptococcus faecalis* ATCC 19433 and *Bacillus subtilis* ATCC 6633 as Gram positive, *Escher-*

Table 2
The in vitro antifungal activity of the compounds **2**–**11**, **14**, **16**

| Comp. No | *S. aureus* | *S. faecalis* | *B. subtilis* | *E. coli* | *P. aeruginosa* | *C. albicans* |
|---|---|---|---|---|---|---|
| **2** | 100 | 100 | 50 | 50 | 25 | 25 |
| **3** | 50 | 50 | 25 | 50 | 25 | 12.5 |
| **4** | 50 | 50 | 50 | 50 | 50 | 25 |
| **5** | 100 | 100 | 50 | 50 | 25 | 25 |
| **6** | 50 | 50 | 50 | 50 | 50 | 50 |
| **7** | 25 | 50 | 50 | 50 | 50 | 25 |
| **8** | 100 | 100 | 50 | 100 | 50 | 25 |
| **9** | 50 | 50 | 25 | 25 | 25 | 25 |
| **10** | 50 | 50 | 25 | 50 | 50 | 25 |
| **11** | 50 | 50 | 50 | 50 | 50 | 25 |
| **14** | 50 | 50 | 12.5 | 25 | 25 | 6.25 |
| **16** | 50 | 50 | 25 | 50 | 25 | 25 |
| Ampicillin | 3.125 | 6.25 | 6.25 | 3.125 | 25 | |
| Fluconazole | – | – | – | – | – | 6.25 |
| Miconazole | – | – | – | – | – | 3.125 |

MIC, μg/ml.

*ichia coli* ATCC 23556 and *Pseudomonas aeruginosa* ATCC 10145 as Gram negative bacteria and *Candida albicans* ATCC 10231 as fungus. MIC values of the compounds and the standards are presented in Table 2.

### 4.1. Antibacterial activity assay

The cultures were obtained in Mueller-Hinton Broth (Difco) for all the bacteria after 18–24 h of incubation at 37±1 °C. Testing was carried out in Mueller-Hinton Broth at pH 7.4 and twofold dilution technique was applied. A set of tubes containing only inoculated broth was kept as controls. After incubation for 18–24 h at 37±1 °C, the last tube with no growth of microorganism was recorded to represent MIC expressed in μg/ml.

### 4.2. Antifungal activity assay

The yeasts were maintained in Sabouraud Dextrose Broth (Difco) after incubation for 48 h at 25±1 °C. Testing was performed in Sabouraud Dextrose Broth at pH 7.4 and the twofold dilution technique was applied. A set of tubes containing only inoculated broth was kept as controls. After incubation for 48 h at 25±1 °C, the last tube with no growth of yeast was recorded to represent MIC expressed in μg/ml.

## 5. Results and discussion

The antibacterial activity of all of the compounds against *S. aureus* and *S. faecalis* as Gram (+) and *E. coli* as a Gram (−) bacteria showed lower potencies than the control drug ampicillin. Some of the compounds (**2**, **3**, **5**, **9**, **14** and **16**) showed good activity with a MIC value of 25 μg/ml against *P. aeruginosa*, which was comparable to ampicillin. Compound **14** exhibited significant activity against *B. subtilis* with a 12.5 μg/ml. Among the tested compounds, **14** and **3** showed good antifungal activity against *C. albicans* with 6.25 and 12.5 μg/ml, respectively, which was comparable with fluconazole (6.25 μg/ml) and close to miconazole (3.125 μg/ml). As a result of antimicrobial activity, substitution of amine function to anilide at the 2-phenyl moiety of benzimidazole ring decreases the activity against *B. subtilis* and *C. albicans*. It was also observed that sulfur bearing compound (**16**) was found to be moderately active against the tested microorganism.

In conclusion, the similar antimicrobial activity results for compounds **2**–**11** with the previously reported 5 or 4′ amides of benzimidazole (**I**, **II**, **III** and **IV**) show that there is no important difference between the position of amide and the transformation of amide to anilide (**2**–**11**).

## Acknowledgements

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