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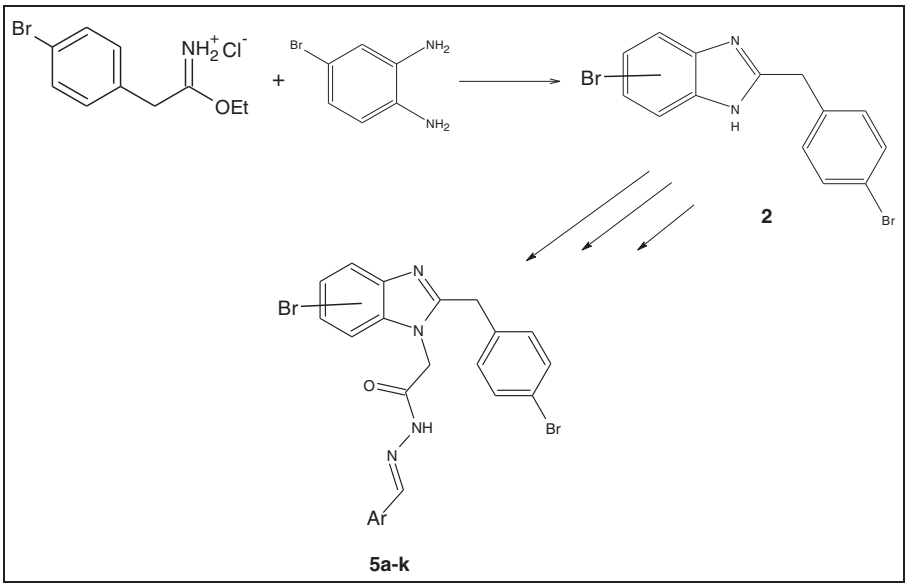

4-Bromo-*o*-phenylenediamine and ethylimido-*p*-bromophenylacetate, **1**, were subjected to microwave irradiation to synthesize benzimidazole derivative, compound **2**. Ester derivative, **3**, and hydrazide derivative, **4**, of compound **2** were also synthesized, respectively. Finally, compound **4** was treated with 11 different aromatic aldehydes to obtain benzimidazole derivatives containing imine function. All reactions were carried out with microwave irradiation and conventional heating, and results were compared. Some of the newly synthesized compounds showed moderate antimicrobial activity against some tested organisms.

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INTRODUCTION

Benzimidazole has become a privileged structure and an important pharmacophore in modern drug discovery [1–4]. Some benzimidazole derivatives with different biological activities, such as anticancer [5,6], antihelmintic [7,8], antimicrobial [9–11], antifungal [12], antihistaminic [13,14], and antitumor [15], have been revealed in literature. Also, some drugs containing benzimidazole skeleton (Fig. 1), such as thiabendazole, flubendazole (antihelmintic) [14], Imet 3393 (anticancer) [16], and Astemizole (antihistaminic) [16], are present for medicinal use (Fig. 1). Moreover, benzimidazole nucleolus is naturally found in the structure of vitamin B12 and shows similarities with adenine and guanine [17].

Because of these reasons, benzimidazole derivatives have been studied by numerous scientists, and so far some, methods have been developed to synthesize these compounds [18–20]. The most common method for this process is using an *o*-phenylenediamine derivative and a carboxylic acid or an aromatic aldehyde as intermediate [19,20]. Also, microwave technology has been used to synthesize benzimidazole derivatives, and important changes have been seen on yield and reaction time [3,9,21]. In this report, a new synthetic method is proposed for benzimidazole derivatives and benzimidazole containing imine function under microwave irradiation starting from new intermediates. The structure of new compounds was identified by IR, ^{1}H-NMR, ^{13}C-NMR, elemental analysis, and mass spectroscopic techniques.

RESULTS AND DISCUSSION

Chemistry. Firstly, compound **1**, ethylimido-*p*-bromophenylacetate hydrochloride, was prepared according to the Pinner method [22,23] (Scheme 1).

o-Phenylenediamine derivatives and aromatic aldehydes or carboxylacids are mostly used for preparation of

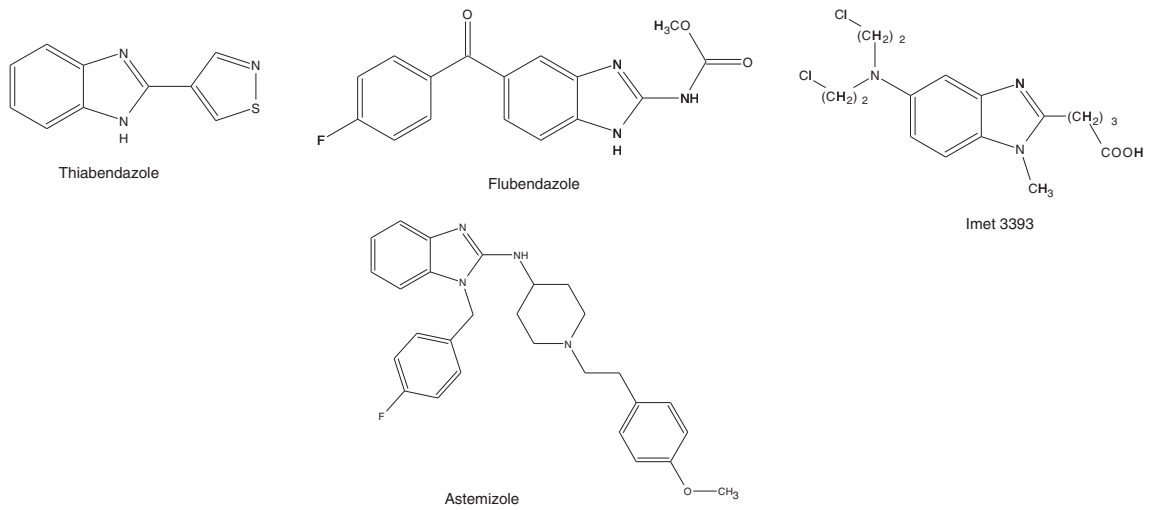


Figure 1. Some drugs containing benzimidazole skeleton.

benzimidazole compounds. For the synthesis of potential biological active benzimidazole compounds, secondly, a simple method was developed using *p*-bromo-*o*-phenylenediamine and ethylimido-*p*-bromophenylacetate, compound **1**, with microwave irradiation and classical method, and then compound **2**, 5(6)-bromo-2-(4-bromobenzyl)-1*H*-benzimidazol, was obtained. Compound **3** was prepared with treatment of compound **2** and ethyl bromoacetate in acetone. Then, compound **3** was reacted with hydrazine monohydrate in ethanol to synthesize compound **4**. Compound **4** was treated with 11 different aromatic aldehydes to obtain benzimidazoles containing imine function, compounds **5a–k** (Scheme 2).

Spectral analyses of newly synthesized compounds are suitable with the proposed structures (Fig. 2). IR spectra of each compound gave a C═N band at about 1620 cm^{-1} and C═O bands at about 1730, 1650, and 1690 cm^{-1} for compounds **3**, **4**, and **5a–k**, respectively. Compound **2** showed an NH signal at 3159, and no NH signal was seen for compound **3**. Also, new C═O and C-O band formations proved the alkylation reaction of compound **2**. Compound **4** had new C═O and NH and NH_2 bands at 1659 and 3298–3100 cm^{-1}. Compounds **5a–k** had no NH_2 band because of imine formation, and new C═O bands were between 1702 and 1677 cm^{-1}.

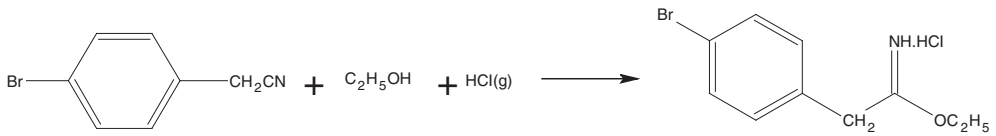
^{1}H-NMR spectra of each compound gave compatible signals with the structures. N-H, NH_2, and O-H signals were controlled by changing with D_2O addition to DMSO-d_6 solution of compounds. An N-H signal was shown at 12.51 ppm for compound **2** and 11.49–11.86 ppm for compounds **5a–k**. When ^{1}H-NMR spectra of compounds **3**, **4**, and **5a–k** were compared, it was seen that some of the protons of these compounds have two sets of signals at different ppm. This is because of the compounds, which have arylene-hydrazide structure, that exist as *E*/*Z* geometrical isomer from C═N double bond and *cis*/*trans* amide conformer at the CO-NH single bond. According to the literature [24–28], compounds that have C═N double bond prefers *E* geometrical isomer in DMSO-d_6, and *Z* isomers can be preferred in less polar solvents. N-CH_2 and N-H signals were observed in two sets of signals because of *cis*/*trans* conformer. The ratio in each case was calculated by using ^{1}H-NMR data. *E*/*Z* and *cis*/*trans* geometrical isomer of compounds **5a–k** (Scheme 3) and selected ^{1}H-NMR spectrum are given in and Fig. 3.

In addition, all compounds have suitable molecular ions according to the literature [29] that originated from ^{79}Br (50.7%) and ^{81}Br (49.3%).

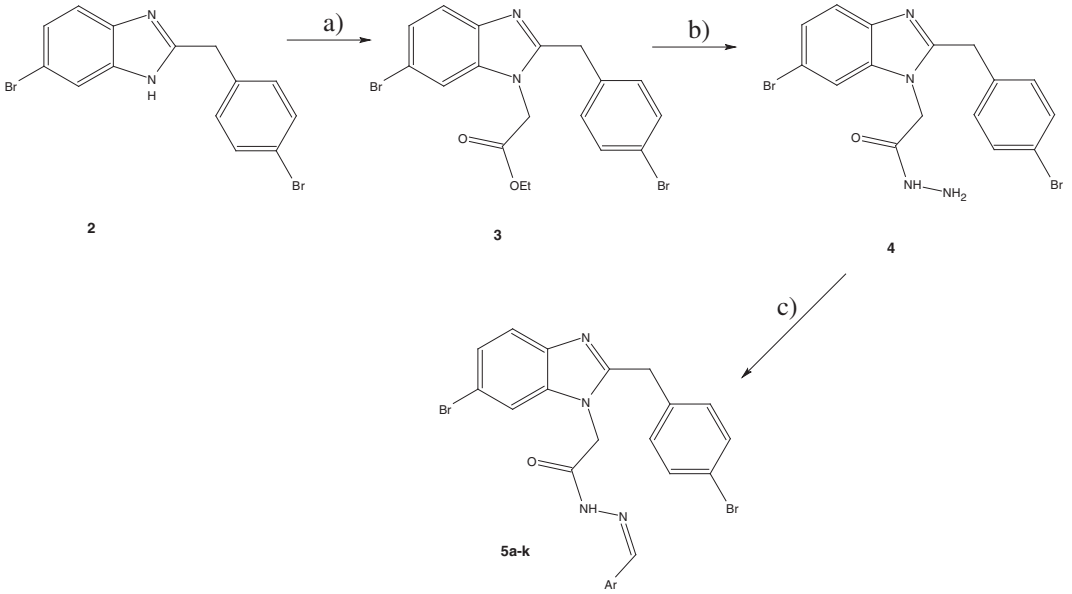
Antimicrobial activity. Compounds **2**, **3**, **4**, **5c**, **5e**, and **5h** showed antimicrobial activity against some tested organisms, and results are given in Table 2.

Conclusion. An efficient method for the synthesis of benzimidazole derivatives containing imine function using the microwave technology has been described. All reactions were carried out with conventional heating in order to compare. All compounds are new and identified by spectral data.

Scheme 1. Synthetic pathway for compound **1**.



Scheme 2. Conditions: a) $BrCH_2COOEt$, K_2CO_3, Acetone; b) $NH_2NH_2{\cdot}H_2O$, EtOH; c) AcOH, EtOH, aromatic aldehyde.



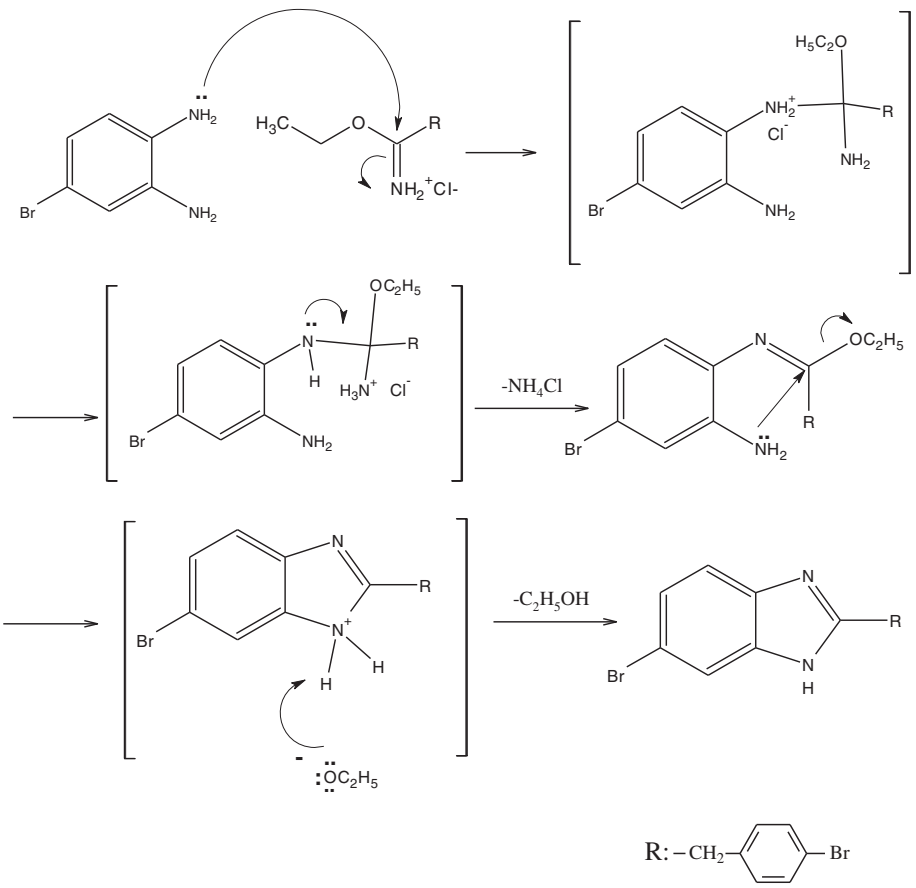
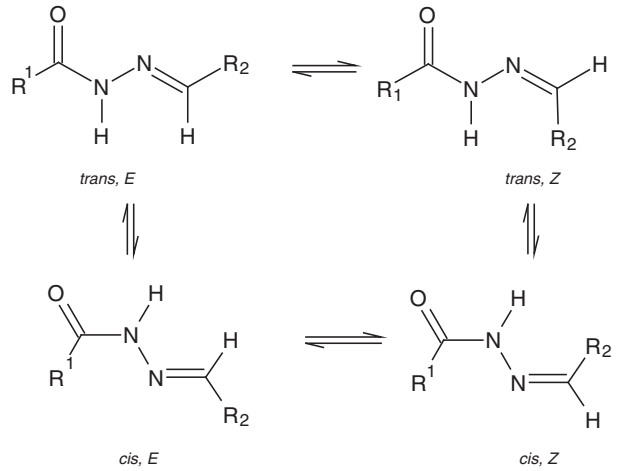


Figure 2. Proposed mechanism for synthesis of compound **2**.

Scheme 3. *E/Z* geometrical isomer and *cis*/*trans* amid conformer of compound **5a–k**.



EXPERIMENTAL

All the chemicals were supplied from Merck (Darmstadt, Germany), Aldrich, and Fluka (Buchs SG, Switzerland). Melting points were determined on capillary tubes on a Büchi oil heated melting point apparatus (Essen,Germany) and uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were performed on Varian-Mercury 200 and 400 MHz spectrophotometer (Varian, Darmstadt, Germany) in DMSO-d_6 using TMS as internal standard. The IR spectra were recorded on a Perkin-Elmer 100 FTIR spectrophotometer (California,USA) as KBr pellets. The elemental compositions were determined on a Carlo Erba 1106 CHN analyzer (Heraeus, Hanau, Germany); the experimental values were in agreement (±0.4%) with the calculated ones. Mass spectra were recorded on Thermo Scientific Quantum Access max LC/MS spectrophotometer (Thermo-scientific, Florida, USA). A monomode CEM Discover microwave (Linfort, Germany) was used to carry out microwave reactions in 30 mL microwave process vials with temperature control by infrared detection temperature sensor. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60F 2.54, 0.2 mm thickness).

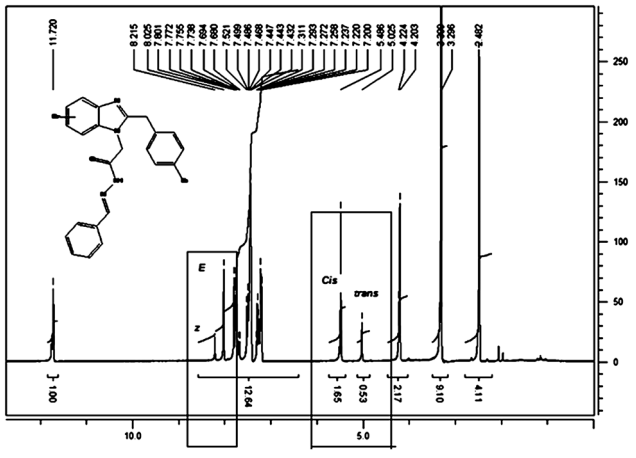


Figure 3. ^{1}H-NMR spectrum of compound **5a**.

Synthesis of 5(6)-bromo-2-(4-bromobenzyl)-1*H*-benzimidazole (2)

Conventional method. To a well stirred solution of 4-bromo-*o*-phenylenediamine (0.01 mol) in methanol (25 mL), compound **1** (0.012 mol) was added and stirred at room temperature overnight. After the reaction was completed (monitored by TLC, ethyl acetate : hexane 3:1), the product was precipitated by the addition of water, and it was filtrated, dried, and recrystallized by ethanol–water (1:1) or acetone–water (1:1).

Microwave method. 4-Bromo-*o*-phenylenediamine (0.01 mol) and compound **1** (0.012 mol) in methanol (10 mL) were taken in a closed vessel. Then, it was irritated in microwave at 60°C for 10 min (hold time) at 300 W maximum power. After the reaction was completed (monitored as stated above), the mixture was cooled to room temperature and taken in a beaker. The product was precipitated by the addition of water, and the purification methods mentioned above were applied.

Yield: 67 (for conventional method) and 78% (for microwave method); mp 176°C; IR (KBr): 1620 (C═N), 3057 (Ar-CH), 3159 (N-H) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 4.16 (2H, s, CH_2), 7.69–7.25 (7H, m, Ar-H), 12.51 (1H, br, N-H); ^{13}C-NMR (DMSO-d_6, 50 MHz): 34.83, 114.39, 120.38, 124.98, 131.78, 132.06, 132.28, 137.28, 155.22; MS: *m*/*z* 369/367/365 (M + H). *Anal*. Calcd for $C_{14}H_{10}Br_2N_2$: C, 45.94; H, 2.75; N, 7.65. Found: C, 45.97; H, 2.74; N, 7.66.

Synthesis of ethyl [5(6)-bromo-2-4(bromobenzyl)-1*H*-benzimidazole-1-yl]acetate (3)

Conventional method. To a solution of compound **2** (0.01 mol) in acetone (30 mL), dry K_2CO_3 (0.25 mol) was added and stirred for 20–25 min. Then, ethyl bromoacetate (0.012 mol) was added to a solution and stirred overnight. After the reaction was completed (monitored by TLC, ethyl acetate : hexane 3:1), the product was precipitated by the addition of water and was filtrated, dried, and recrystallized by ethanol to afford the desired product.

Microwave method. A solution of compound **2** (0.01 mol) in acetone (10 mL) was taken in a closed vessel, and dry K_2CO_3 (0.025 mol) was added. The mixture was irritated in microwave at 90°C for 5 min (hold time) with pressure control. Then, the mixture was cooled to room temperature, and ethyl bromoacetate (0.012 mol) was added. Again, it was irritated in microwave at 90°C for 10 min (hold time) at 300 W maximum power. After the reaction was completed (monitored as stated above), the mixture was cooled and taken in a beaker, and the product was precipitated by addition of water. The purification methods mentioned above were applied to yield the pure product.

Yield: 95 (for conventional method) and 98% (for microwave method); mp 194–195°C; IR (KBr): 1217 (C-O), 1609 (C═N), 1734 (C═O), 2979 (C-H) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 1.07 (3H, t, CH_3, J = 7.2), 3.97 (2H, q, OCH_2, J = 7.2), 4.22 (2H, s, CH_2), 5.19 (2H, s, N-CH_2), 7.79–7.19 (7H, m, Ar-H); ^{13}C-NMR (DMSO-d_6, 50 MHz): 15.60, 35.74, 47.12, 60.33, 112.78, 114.23, 120.43, 123.67, 130.89, 131.17, 134.12, 137.32, 145.90, 157.69, 170.45; MS: *m*/*z* 455/453/451 (M + H). *Anal*. Calcd for $C_{18}H_{16}Br_2N_2O_2$: C, 47.82; H, 3.57; N, 6.20. Found: C, 47.80; H, 3.55; N, 6.24.

Synthesis of 2-[5(6)-bromo-2(4-bromobenzyl)-1*H*-benzimidazol-1-yl]acetohydrazide (4)

Conventional method. To a solution of compound **3** (0.01 mol) in dry ethanol (25 mL), hydrazine monohydrate (0.025 mol) was added, and it was refluxed for 6 h (monitored by TLC, ethyl acetate : hexane 3:1). After cooling the mixture to room temperature, a white solid appeared. This crude

product was filtrated, dried, and recrystallized from ethanol to yield the pure product.

Microwave method. A solution of compound **3** (0.01 mol) in dry ethanol (10 mL) and hydrazine monohydrate (0.025 mol) were taken in a closed vessel. The mixture was irritated in microwave at 130°C for 10 min (hold time) at 300 W maximum power. After the reaction was completed (monitored as stated above), the mixture was cooled to room temperature and taken in a beaker, and the white solid appeared. This crude product was filtrated, and the purification methods mentioned above were applied.

Yield: 60 (for conventional method) and 80% (for microwave method); mp 249–251°C; IR (KBr): 1613 (C=N), 1659 (C=O), 3049 (Ar-CH), 3298 (NH, NH_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 4.21 (2H, s, CH_2), 4.36 (2H, s, NH_2), 4.82 (2H, s, N-CH_2), 7.72–7.23 (7H, m, Ar-H), 9.50 (1H, s, NH); ^{13}C-NMR (DMSO-d_6, 50 MHz): 32.12, 44.58, 111.88, 119.66, 123.65, 126.52, 128.63, 130.06, 135.07, 138.85, 141.53, 156.26, 165.36; MS: *m/z* 441/439/437 (M + H). *Anal*. Calcd for $C_{16}H_{14}Br_2N_4O$: C, 43.86; H, 3.22; N, 12.79. Found: C, 43.90; H, 3.20; N, 12.77.

General synthetic procedure for 2-[5(6)-bromo-2-(4-bromobenzyl)-1*H*-benzimidazol-1-yl]-*N′*-[phenylmethylene] acetohydrazide (5a–k)

Conventional method. To a solution of compound **4** (0.01 mol) in dry ethanol (20 mL) (containing 0.5 mL glacial acetic acid), corresponding aromatic aldehyde (0.01 mol) was added, and the mixture was refluxed for 4–6 h (monitored by TLC, ethyl acetate : hexane 3:1). After cooling the mixture to room temperature, a white solid appeared. This crude product was filtrated and washed with ethanol to obtain the desired product.

Microwave method. A solution of compound **4** (0.01 mol) in dry ethanol (10 mL) (containing 0.25 mL glacial acetic acid) and corresponding aromatic aldehyde (0.01 mol) were taken in a closed vessel. The mixture was irritated in microwave at 120–130°C for 5–10 min at 300 W maximum power. After the reaction was complete (monitored as stated above), the mixture was cooled to room temperature and taken in a beaker, and a white solid appeared. This crude product was filtrated, and the purification methods mentioned above were applied.

2-[5(6)-Bromo-2-(4-bromobenzyl)-1H-benzimidazol-1-yl]-N′-[phenylmethylene]acetohydrazide (5a). Yield: 61 (for conventional method) and 82% (for microwave method); mp 268–269°C; IR (KBr): 1620 (C=N), 3057 (Ar-CH), 3159 (N-H) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 4.20 (2H, s, CH_2), 5.02 and 5.49 (2H, s, N-CH_2, *trans* and *cis* amid conformer, *cis*/*trans* ratio 78/22), 7.20–7.80 (12H, m, Ar-H), 8.22 and 8.02 (1H, s, N=CH, *E*/*Z* geometrical isomer, *E*/*Z* ratio 70/30), 11.72 (1H, br, N-H); ^{13}C-NMR (DMSO-d_6, 100 MHz): 32.95, 45.21, 114.11, 114.98, 120.43, 120.84, 124.99, 127.86, 129.46, 130.72, 131.86, 134.70, 136.55, 138.15, 141.96, 144.80, 155.58, 168.56; MS: *m/z* 529/527/525 (M + H). *Anal*. Calcd for $C_{23}H_{18}Br_2N_4O$: C, 52.50; H, 3.45; N, 10.65. Found: C, 52.53; H, 3.47; N, 10.61 (Table 1).

2-[5(6)-Bromo-2-(4-bromobenzyl)-1H-benzimidazol-1-yl]-N′-[4-(methylphenyl)[methylene]acetohydrazide (5b). Yield: 54 (for conventional method) and 79% (for microwave method); mp 271–272°C; IR (KBr): 1610 (C=N), 1699 (C=O), 3021 (Ar-H), 3193 (N-H) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.34 (3H, s, CH_3), 4.20 (2H, s, CH_2), 5.02 and 5.48 (2H, s, N-CH_2, *trans* and *cis* amid conformer, *cis*/*trans* ratio 75/25), 7.18–7.82 (11H, m, Ar-H), 7.98 and 8.02 (1H, s, N=CH, *E*/*Z* geometrical isomer, *E*/*Z* ratio 73/27), 11.71 (1H, br, N-H); ^{13}C-NMR (DMSO-d_6, 50 MHz): 20.15, 35.95, 48.21, 112.10, 114.55, 118.31, 120.22, 124.07, 126.86, 129.16, 131.02, 133.56, 135.17, 138.54, 139.57, 141.11, 147.02, 154.94, 166.91; MS: *m/z* 543/541/539 (M + H). *Anal*. Calcd for $C_{24}H_{20}Br_2N_4O$: C, 53.36; H, 3.73; N, 10.37. Found: C, 53.33; H, 3.78; N, 10.34.

2-[5(6)-Bromo-2-(4-bromobenzyl)-1H-benzimidazol-1-yl]-N′-[4-(florophenyl)[methylene]acetohydrazide (5c). Yield: 64 (for conventional method) and 83% (for microwave method); mp 260–261°C; IR (KBr): 1614 (C=N), 1699 (C=O), 2945 (C-H), 3011 (Ar-H), 3188 (N-H) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 4.21 (2H, s, CH_2), 5.50 and 5.02 (2H, s, N-CH_2, *trans* and *cis* amid conformer, *cis*/*trans* ratio 75/25), 7.22-7.80 (11H, m, Ar-H), 8.02 and 8.21 (1H, s, N=CH, *E*/*Z* geometrical isomer, *E*/*Z* ratio 75/25), 11.83 (1H, br, N-H); ^{13}C-NMR (DMSO-d_6, 50 MHz): 36.70, 48.93, 110.18, 112.50, 116.99, 120.95, 122.97, 126.96, 129.49, 132.42, 133.94, 134.99, 136.98, 141.05, 143.72, 146.74, 157.29, 168.81; MS: *m/z* 547/545/543 (M + H). *Anal*. Calcd for $C_{23}H_{17}Br_2$ FN_4O: C, 50.76; H, 3.15; N, 10.30. Found: C, 50.72; H, 3.17; N, 10.32.

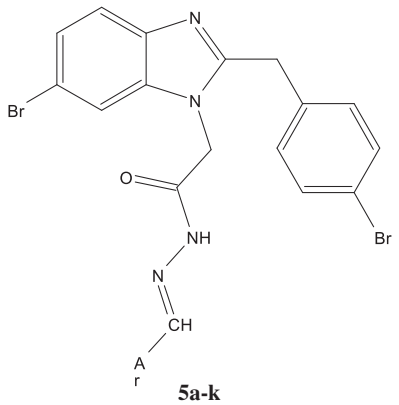
2-[5(6)-Bromo-2-(4-bromobenzyl)-1H-benzimidazol-1-yl]-N′-[4-(chlorophenyl)methylene]acetohydrazide (5d). Yield: 69 (for conventional method) and 80% (for microwave method); mp 255–256°C; IR (KBr): 1590 (C=N), 1699 (C=O), 2951 (C-H), 3091 (Ar-H), 3207 (N-H) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 4.21 (2H, s, CH_2), 5.52 and 5.03 (2H, s, N-CH_2, *trans* and *cis* amid conformer, *cis*/*trans* ratio 75/25), 7.19–7.82 (11H, m, Ar-H), 8.02 and 8.21 (1H, s, N=CH, *E*/*Z* geometrical isomer, *E*/*Z* ratio 70/30), 11.82 (1H, br, N-H); ^{13}C-NMR (DMSO-d_6, 100 MHz): 32.69, 45.01, 113.90, 114.78, 120.22, 120.62, 124.78, 129.34, 131.65, 131.73, 133.45, 134.96, 136.35, 137.92, 141.74, 143.24, 155.40 (2C), 168.46; MS: *m/z* 563/561/559 (M + H). *Anal*. Calcd for $C_{23}H_{17}Br_2$ ClN_4O: C, 49.27; H, 3.06; N, 9.99. Found: C, 49.23; H, 3.10; N, 9.97.

2-[5(6)-Bromo-2-(4-bromobenzyl)-1H-benzimidazol-1-yl]-N′-[(2,3-dihydroxyphenyl)methylene]acetohydrazide (5e). Yield: 54 (for conventional method) and 75% (for microwave method); mp 271–272°C; IR (KBr): 1275, 1282 (C-O), 1610 (C=N), 1697 (C=O), 2963 (C-H), 3043 (Ar-H), 3154 (N-H), 3420 (O-H) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 4.21 (2H, s, CH_2), 5.06 and 5.47 (2H, s, N-CH_2, *trans* and *cis* amid conformer, *cis*/*trans* ratio 75/25), 7.20–7.84 (10H, m, Ar-H), 8.23 and 8.33 (1H, s, N=CH, *E*/*Z* geometrical isomer, *E*/*Z* ratio 73/27), 9.20 (1H, s, OH), 9.65 (1H, s, OH), 11.70 (1H, br, N-H); ^{13}C-NMR (DMSO-d_6, 50 MHz): 33.94, 44.82, 113.17, 114.02, 116.96, 120.29, 120.91, 124.06, 124.97, 125.71, 131.61, 132.76, 136.15, 141.77, 145.92, 146.18, 147.07, 149.95, 157.41, 158.01, 168.90; MS: *m/z* 561/559/557 (M + H). *Anal*. Calcd for $C_{23}H_{18}Br_2N_4O_3$: C, 49.49; H, 3.25; N, 10.04. Found: C, 49.52; H, 3.26; N, 10.04.

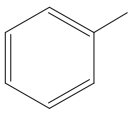
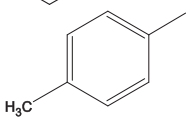
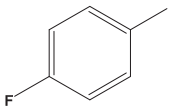
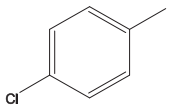
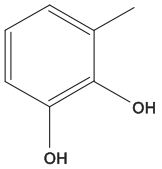
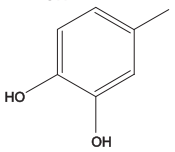
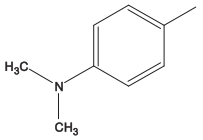
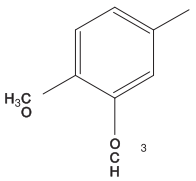
2-[5(6)-Bromo-2-(4-bromobenzyl)-1H-benzimidazol-1-yl]-N′-[(3, 4-dihydroxyphenyl)methylene]acetohydrazide (5f). Yield: 63 (for conventional method) and 80% (for microwave method); mp 289–290°C; IR (KBr): 1281 (C-O), 1621 (C=N), 1678 (C=O), 2932 (C-H), 3062 (Ar-H), 3164 (N-H), 3535 (O-H) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 4.19 (2H, s, CH_2), 5.00 and 5.47 (2H, s, N-CH_2, *trans* and *cis* amid conformer, *cis*/*trans* ratio 75/25), 6.46–7.85 (10H, m, Ar-H), 7.85 and 8.00 (1H, s, N=CH, *E*/*Z* geometrical isomer, *E*/*Z* ratio 71/29), 9.20 (1H, s, OH), 9.53 (1H, s, OH), 11.54 (1H, br, N-H); ^{13}C-NMR

Table 1

Reaction conditions of compound **5a–k**.

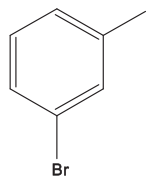
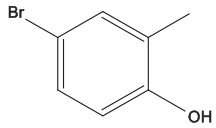
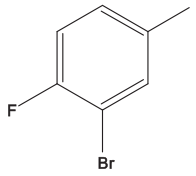


5a-k

		Thermal		Microwave irradiation		
Product	Ar	Time (h)	Yield (%)	Temperature (°C)	Time (min)	Yield (%)
5a		5	61	120	10	82
5b		5.5	54	125	8	79
5c		4.5	64	125	7	83
5d		4.5	69	130	5	80
5e		4	54	120	7	75
5f		4.5	63	120	8	80
5g		5.5	61	130	6	80
5h		6	53	130	8	78

(Continued)

Table 1
(*Continued*)

Product	Ar	Time (h)	Yield (%)	Temperature (°C)	Time (min)	Yield (%)
5i		6	65	130	9	78
5j		6	57	130	7	68
5k		5	62	125	10	73

(DMSO-d_6, 50 MHz): 31.92, 45.59, 111.79, 115.94, 121.29, 124.16, 125.97, 127.91, 130.69, 132.75, 139.92, 142.01, 143.93, 145.27, 148.36, 150.49, 154.41, 156.17, 167.83; MS: *m/z* 561/559/557 (M + H). *Anal*. Calcd for $C_{23}H_{18}Br_2N_4O_3$: C, 49.49; H, 3.25; N, 10.04. Found: C, 49.53; H, 3.27; N, 10.01.

2-[5(6)-Bromo-2-(4-bromobenzyl)-1H-benzimidazol-1-yl]-N′-{[4-(dimetilamino)phenyl]methylene}acetohydrazide (5g). Yield: 61 (for conventional method) and 80% (for microwave method); mp 289–290°C; IR (KBr): 1551, 1603 (C═N), 1677 (C═O), 2904 (C-H), 3052 (Ar-H), 3178 (N-H); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.97 (6H, s, 2×N-CH_3), 4.20 (2H, s, CH_2), 4.99 and 5.44 (2H, s, N-CH_2, *trans* and *cis* amid conformer, *cis*/*trans* ratio 75/25), 6.74–7.56 (11H, m, Ar-H), 8.44 and 8.51 (1H, s, N═CH, *E*/*Z* geometrical isomer, *E*/*Z* ratio 70/30), 11.89 (1H, br, N-H); ^{13}C-NMR (DMSO-d_6, 50 MHz): 34.70, 39.57, 49.23, 110.98, 111.59, 117.59, 121.45, 122.91, 125.96, 132.13, 133.54, 136.91, 141.92, 143.42, 146.75, 157.29 (2C), 168.11; MS: *m/z* 572/570/568 (M + H). *Anal*. Calcd for $C_{25}H_{23}Br_2N_5O$: C, 52.74; H, 4.07; N, 12.30. Found: C, 52.71; H, 4.09; N, 12.32.

2-[5(6)-Bromo-2-(4-bromobenzyl)-1H-benzimidazol-1-yl]-N′-[(3,4-dimethoxyphenyl)methylene]acetohydrazide (5h). Yield: 53 (for conventional method) and 78% (for microwave method); mp 285–286°C; IR (KBr): 1238, 1269 (C-O), 1576, 1601 (C═N), 1690 (C═O), 2991 (C-H), 3003 (Ar-H), 3203 (N-H) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.82 (6H, br, 2×OCH_3), 4.36 (2H, s, CH_2), 5.23 and 5.95 (2H, s, N-CH_2, *trans* and *cis* amid conformer, *cis*/*trans* ratio 75/25), 6.46–7.85 (10H, m, Ar-H), 7.90 and 8.10 (1H, s, N═CH, *E*/*Z* geometrical isomer, *E*/*Z* ratio 73/27), 9.20 (1H, s, OH), 9.53 (1H, s, OH), 11.54 (1H, br, N-H); ^{13}C-NMR (DMSO-d_6, 100 MHz): 29.23, 47.84, 55.94, 56.10, 112.02, 116.22, 117.27, 119.62, 121.49, 122.50, 126.99, 127.05, 130.08, 131.70, 131.94, 131.99, 133.40, 145.20, 145.37, 149.48, 151.30, 154.33, 166.02; MS: *m/z* 589/587/586 (M + H). *Anal*. Calcd for $C_{25}H_{22}Br_2N_4O_3$: C, 51.22; H, 3.78; N, 9.56. Found: C, 51.26; H, 3.81; N, 9.57.

2-[5(6)-Bromo-2-(4-bromobenzyl)-1H-benzimidazol-1-yl]-N′-[(3-bromophenyl)methylene]acetohydrazide (5i). Yield: 65 (for conventional method) and 78% (for microwave method); mp 264–265°C; IR (KBr): 1590, 1601 (C═N), 1702 (C═O), 2957 (C-H), 3015 (Ar-H), 3202 (N-H) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 4.22 (2H, s, CH_2), 5.05 and 5.55 (2H, s, N-CH_2, *trans* and *cis* amid conformer, *cis*/*trans* ratio 79/21), 7.21–8.01 (11H, m, Ar-H), 8.06 and 8.15 (1H, s, N═CH, *E*/*Z* geometrical isomer, *E*/*Z* ratio 79/21), 11.85 (1H, br, N-H); ^{13}C-NMR (DMSO-d_6, 50 MHz): 30.11, 48.81, 110.32, 111.14, 123.49, 124.19, 126.90, 127.15, 130.12, 132.91, 139.42, 142.90, 143.13, 149.27, 150.30, 150.71, 156.21, 156.74, 169.13; MS: *m/z* 603/605/607/609 (M + H). *Anal*. Calcd for $C_{23}H_{17}Br_3N_4O$: C, 45.65; H, 2.83; N, 9.26. Found: C, 45.62; H, 2.81; N, 9.29.

2-[5(6)-Bromo-2-(4-bromobenzyl)-1H-benzimidazol-1-yl]-N′-[(2-hydroxy-5-bromophenyl)methylene]acetohydrazide (5j). Yield: 57 (for conventional method) and 68% (for microwave method); mp 255–256; IR (KBr): 1275 (C-O), 1615 (C═N), 1695 (C═O), 2989 (C-H), 3031 (Ar-H), 3154 (N-H), 3480 (O-H) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 4.23 (2H, s, CH_2), 5.06 and 5.54 (2H, s, N-CH_2, *trans* and *cis* amid conformer, *cis*/*trans* ratio 69/31), 6.87–7.96 (10H, m, Ar-H), 8.28 and 8.33 (1H, s, N═CH, *E*/*Z* geometrical isomer, *E*/*Z* ratio 73/27), 10.44 (1H, s, OH), 11.78 (1H, br, N-H); ^{13}C-NMR (DMSO-d_6, 50 MHz): 35.12, 49.51, 109.12, 112.74, 125.94, 128.18, 129.90, 130.52, 131.19, 133.71, 137.69, 142.71, 145.86, 145.97, 150.13, 152.42, 157.01, 157.93, 170.11; MS *m/z* 620/622/624/626 (M + H). *Anal*. Calcd for $C_{23}H_{17}Br_3N_4O_2$: C, 44.48; H, 2.76; N, 9.02. Found: C, 44.46; H, 2.78; N, 9.05.

2-[5(6)-Bromo-2-(4-bromobenzyl)-1H-benzimidazol-1-yl]-N′-[(3-bromo-4-florophenyl)methylene]acetohydrazide (5k). Yield: 62 (for conventional method) and 73% (for microwave method); mp 235–236°C; IR (KBr): 1597, 1610 (C═N), 1792 (C═O), 2925 (C-H), 3062 (Ar-H), 3202 (N-H) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 4.20 (2H, s, CH_2), 5.05 and 5.53 (2H, s, N-CH_2, *trans* and *cis* amid conformer, *cis*/*trans* ratio 73/27), 7.20–7.81

Table 2

Antimicrobial activity of the compounds (μg/mL).

	Microorganisms and minimal inhibition concentration								
Comp. no.	Ec	Yp	Pa	Sa	Ef	Bc	Ms	Ca	Sc
2	—	—	—	31.3	31.3	31.3	31.3	62.5	31.3
3	—	—	—	—	—	—	125	500	250
4	—	—	—	—	—	—	250	500	250
5a	—	—	—	—	—	—	—	—	—
5b	—	—	—	—	—	—	—	—	—
5c	—	—	—	—	—	—	—	>500	500
5d	—	—	—	—	—	—	—	—	—
5e	—	—	—	250	500	250	—	—	—
5f	—	—	—	—	—	—	—	—	—
5g	—	—	—	—	—	—	—	—	—
5h	—	—	—	—	—	—	125	—	—
5i	—	—	—	—	—	—	—	—	—
5j	—	—	—	—	—	—	—	—	—
5k	—	—	—	—	—	—	—	—	—
Amp.	2	32	>128	2	2	<1			
Strep.							4		
Flu.								<8	<8

Ec, *E. coli* ATCC 25922; Yp, *Y. pseudotuberculosis* ATCC 911; Pa, *P. aeruginosa* ATCC 43288; Sa, *S. aureus* ATCC 25923; Ef, *E. faecalis* ATCC 29212; Bc, *B. cereus* 702 Roma; Ms, *M. smegmatis* ATCC607; Ca, *C. albicans* ATCC 60193; Sc, *S. cerevisiae* RSKK 251; Amp., ampicillin; Strep., Streptomycin; Flu., Fluconazole; —, no activity.

(10H, m, Ar-H), 8.00 and 8.20 (1H, s, N=CH, *E/Z* geometrical isomer, *E/Z* ratio 75/25), 11.86 (1H, br, N-H); ^{13}C-NMR (DMSO-d_6, 50 MHz): 32.73, 47.32, 111.13, 113.98, 126.44, 128.28, 129.41, 129.55, 129.78, 131.39, 132.39, 133.66, 139.10, 142.17, 147.45, 149.90, 151.03, 153.98, 157.01, 158.27, 168.14; MS: *m/z* 621/623/625/627 (M + H). *Anal*. Calcd for $C_{23}H_{16}Br_3FN_4O$: C, 44.33; H, 2.59; N, 8.99. Found: C, 44.29; H, 2.60; N, 9.03.

Antimicrobial activity assay. All test microorganisms were obtained from the Hifzissihha Institute of Refik Saydam (Ankara, Turkey) and were as follows: *Escherichia coli* ATCC35218, *Yersinia pseudotuberculosis* ATCC911, *Pseudomonas aeruginosa* ATCC43288, *Enterococcus faecalis* ATCC29212, *Staphylococcus aureus* ATCC25923, *Bacillus cereus* 709 Roma, *Mycobacterium smegmatis* ATCC607, *Candida albicans* ATCC60193, and *Saccharomyces cerevisiae* RSKK 251. All the newly synthesized compounds were weighed and dissolved in DMSO to prepare extract stock solution of 10,000 μg/mL.

The antimicrobial effects of the substances were tested quantitatively in respective broth media by using double microdilution, and the minimal inhibition concentration values (in μg/mL) were determined. The antibacterial and antifungal assays were performed in Mueller–Hinton broth (Difco, Detroit, MI) at pH 7.3 and buffered yeast nitrogen base (Difco, Detroit, MI) at pH 7.0, respectively. The microdilution test plates were incubated for 18–24 h at 35°C. Brain heart infusion broth (Difco, Detroit, MI) was used for *M. smegmatis* and incubated for 48–72 h at 35°C. The minimal inhibition concentration was defined as the lowest concentration that showed no growth. Ampicillin (10,000 μg/mL), streptomycin (10,000 μg/mL), and fluconazole (2000 μg/mL) were used as standard antibacterial and antifungal drugs, respectively. DMSO with dilution of 1:10 was used as solvent control [30,31]. The results are shown in Table 2.

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