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Synthesis and antimicrobial activity of novel 2-[4-(1*H*-benzimidazol-1-yl)phenyl]-1*H*-benzimidazoles

Mehmet ALP[1,*], **Ali Hakan GÖKER**[1], **Nurten ALTANLAR**[2]
[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ankara University, Tandoğan, Ankara, Turkey
[2]Department of Microbiology, Faculty of Pharmacy, Ankara University, Tandoğan, Ankara, Turkey

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Abstract: A new class of 2-[4-(1*H*-benzimidazol-1-yl)phenyl]-1*H*-benzimidazoles (**13**–**22**) were synthesized via cyclocondensation reaction of the substituted 1,2-phenylenediamines (**1, 4**–**12**) and 1-(4-formylpheny)-1*H*-benzimidazole (**3**). The synthesized compounds were evaluated for antibacterial and antifungal activities against *S. aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Candida albicans* by the tube dilution method. Compounds **13**, **15**, **18**, **20**, and **21** have moderate antifungal activity against *C. albicans.*

Key words: 1*H*-Benzimidazole, antimicrobial activities, methicillin resistant *Staphylococcus aureus*, *Candida albicans*

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections were first detected in hospitals (healthcare-acquired/associated (HA) MRSA). However, in recent years infections have emerged in the community (community-acquired/associated (CA) MRSA) and also from livestock (livestock-associated (LA) MRSA). Consequently, MRSA can no longer be considered an exclusive healthcare-associated problem and it cannot be fought by hospital infection prevention and control measures alone.[1]

Most of the antibiotics currently in use can be classified as follows: β-lactam and glycopeptide antibiotics targeting cell wall biosynthesis; aminoglycoside, tetracycline, and macrolide antibiotics targeting protein synthesis; and fluoroquinolones targeting DNA gyrase and topoisomerase. To tackle the problem of drug resistance, one can focus on these proven targets and develop new drugs to overcome drug-induced resistance caused by mutations of the targets or modifications of the antibiotics.[2]

In our previous papers, we have reported the synthesis of some 2-phenyl-1*H*-benzimidazole derivatives (**I**, **II**, **III**, Figure) and their promising antimicrobial activities.[3–6] These results prompted us to investigate a series of new 2-[4-(1*H*-benzimidazol-1-yl)phenyl]-1*H*-benzimidazoles to evaluate their antistaphylococcal and antifungal activities.

2. Results and discussion

All the benzimidazole compounds prepared herein were screened for their potential in vitro antibacterial activities against *S. aureus*, MRSA, and antifungal activities against *Candida albicans.* The in vitro minimal inhibitory concentrations (MIC_{100}) of the compounds were determined using the microbroth dilution method

*Correspondence: malp@pharmacy.ankara.edu.tr

reported by the National Committee for Clinical Laboratory Standards.[7,8] Sultamicillin and fluconazole were used as references. The MIC_{100} results for the test compounds are shown in the Table. The synthesized compounds and reference drugs were dissolved in DMSO-H_2O (50%), at a concentration of 200 μg/mL. The concentration was adjusted to 50 μg/mL by 4-fold dilution with media culture and bacteria solution (DMSO concentration was 12.5% in the first tube). Bacterial and fungal tubes were incubated at 36 °C for 18 h and 48 h, respectively. All compounds showed poor antibacterial activities against *S. aureus* and MRSA. Compounds **13**, **15**, **18**, **20**, and **21** had moderate antifungal activity against *C. albicans* with 6.25 μg/mL MIC_{100} value.

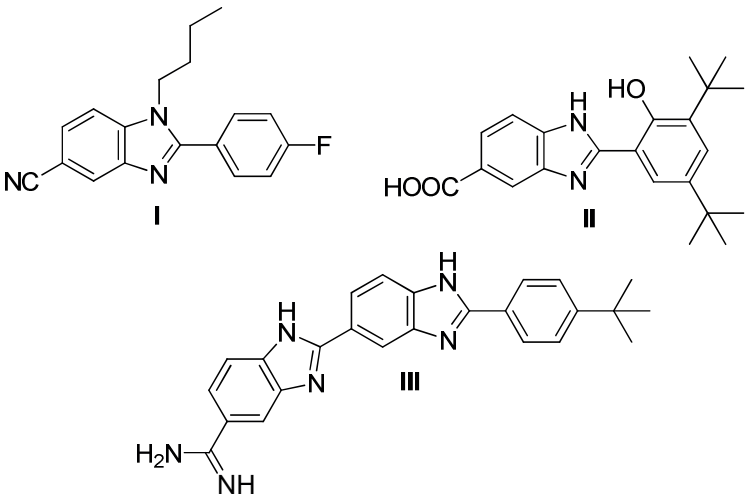
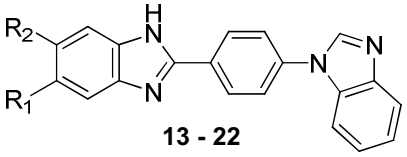


Figure. Structures of previously reported benzimidazoles possessing antibacterial activities.

Table. Formula and in vitro antimicrobial activities for **13**–**22**.



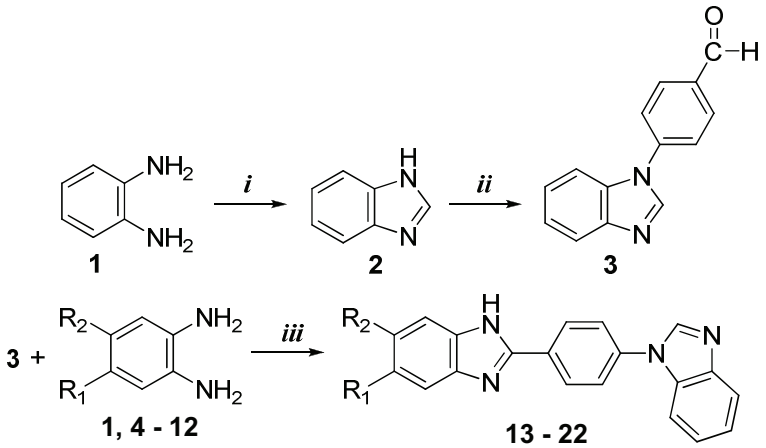
No.	R_1	R_2	Antimicrobial activities (MIC, μg/mL)		
			S. aureus ATCC25923	MRSA ATCC43300	C. albicans ATCC10231
13	H	H	50	25	6.25
14	CH_3	H	50	25	12.5
15	CN	H	50	50	6.25
16	COOH	H	50	50	12.5
17	NO_2	H	50	25	12.5
18	Cl	H	50	25	6.25
19	F	H	50	25	12.5
20	CH_3	CH_3	25	25	6.25
21	Cl	CH_3	50	50	6.25
22	Cl	Cl	50	25	12.5
Sultamicillin			0.78	25	-
Fluconazole			-	-	1.56

3. Experimental

Uncorrected melting points were measured on a Büchi B-540 capillary melting point apparatus. ^{1}H (400 MHz) NMR spectra were recorded employing a Varian Mercury 400 MHz FT spectrometer; chemical shifts (δ) are in ppm relative to TMS and coupling constants (J) are reported in hertz. Mass spectra were obtained on a Waters Micromass ZQ connected with a Waters Alliance HPLC, using the ESI(+) method, with a C-18 column. Elemental analyses were performed using a Leco CHNS-932. Water and/or chloroform solvation of the final compounds was compatible with elemental analysis results and proton NMR confirmed the presence of chloroform. All the reagents and solvents were purchased from Sigma-Aldrich Chemical Co. or Fischer Scientific. Compounds **2**[9] and **3**[10] were synthesized as described in the literature.

3.1. Chemistry

The synthetic pathway for the preparation of the targeted benzimidazoles **13**–**22** is shown in the Scheme. The 1*H*-benzimidazole (**2**) was built by cyclization of *o*-phenylenediamine (**1**) and formic acid. The reaction of **2** with 4-fluorobenzaldehyde in DMF in the presence of anhydrous K_2CO_3 gave 1-(4-formylpheny)-1*H*-benzimidazole (**3**). Condensation of commercial *o*-phenylenediamines (**1**, **4**–**12**) with **3** in DMF afforded the corresponding benzimidazoles, **13**–**22**. Benzimidazoles can display annular 1,3-tautomerism in imidazole moiety.[6,11–13] Therefore, the names of the compounds are given as included tautomerism.



Scheme. Synthesis of 2-[4-(1*H*-benzimidazol-1-yl) phenyl]-1*H*-benzimidazole derivatives. Reagents and conditions: (i) Formic acid; (ii) 4-Fluorobenzaldehyde, anhydr. K_2CO_3, DMF; (iii) $Na_2S_2O_5$, DMF.

3.2. General synthesis of 13–22

A mixture of commercial o-phenylendiamines **1, 4**–**12** (1 mmol), 1-(4-formylpheny)-1H-benzimidazole (**3**) (1 mmol), and $Na_2S_2O_5$ (1 mmol) in DMF (3 mL) was heated at 110–120 °C for 3 h.[14] The reaction mixture was cooled, poured into H_2O, and the solid was filtered. The residue was purified by column chromatography using chloroform/methanol (100:10) as eluant.

2-[4-(1*H*-Benzimidazol-1-yl)phenyl]-1*H*-benzimidazole 13

Yield 48%, mp 199–200 °C, ^{1}H NMR (DMSO-d_6) δ: 7.24 (m, 2H), 7.37 (m, 2H), 7.57 (d, 1H, J = 7.2), 7.71 (d, 1H, J = 7.6), 7.76 (dd, 1H, J = 7.2, J = 1.2), 7.81 (dd, 1H, J = 6.8), 7.91 (d, 2H, J = 8.4), 8.42 (d, 2H,

J = 8.8), 8.68 (s, 1H), MS (ESI+) m/z (rel intensity): 311 (M+H, 100), Anal. for $C_{20}H_{14}N_4 \cdot 0.75\ H_2O \cdot 0.25\ CHCl_3$, Calc. C, 68.76, H, 4.48, N, 15.83, Found C, 68.43, H, 4.22, N, 15.47.

2-[4-(1*H*-Benzimidazol-1-yl) phenyl]-5(6)-methyl-1*H*-benzimidazole 14

Yield 30%, mp 104 °C (bubb.) 245 °C (dec.), ^{1}H NMR (DMSO-d_6 + NaH + one drop D_2O) δ: 2.39 (s, 3H), 6.81 (d, 1H, J = 8), 7.31–7.41 (m, 4H), 7.70–7.81 (m, 4H), 8.44 (d, 2H, J = 8.4), 8.62 (s, 1H), MS (ESI+) m/z (rel intensity): 325 (M+H, 67), 204 (100), Anal. for $C_{21}H_{16}N_4 \cdot H_2O \cdot 0.25\ CHCl_3$, Calc. C, 68.56, H, 4.94, N, 15.05, Found C, 68.31, H, 4.72, N, 14.88.

2-[4-(1*H*-Benzimidazol-1-yl)phenyl]-1*H*-benzimidazole-5(6)-carbonitrile 15

Yield 35%, mp 333–335 °C, ^{1}H NMR (DMSO-d_6) δ: 7.30–7.38 (m, 2H), 7.60 (dd, 1H, J = 8.4, J = 1.2), 7.73–7.80 (m, 3H), 7.92 (d, 2H, J = 8.8), 8.16 (s, 1H), 8.42 (d, 2H, J = 8.8), 8.66 (s, 1H), MS (ESI+) m/z (rel intensity): 336 (M+H, 100), Anal. for $C_{21}H_{13}N_5 \cdot 1.66 \cdot H_2O$, Calc. C, 69.05, H, 4.50, N, 19.17, Found C, 69.26, H, 4.21, N, 18.79.

2-[4-(1*H*-Benzimidazol-1-yl)phenyl]-1*H*-benzimidazole-5(6)-carboxylic acid 16

Yield 56%, mp 344–346 °C, ^{1}H NMR (DMSO-d_6 + NaH + one drop D_2O) δ: 7.28 (d, 1H, J = 8.4), 7.35–7.40 (m, 2H), 7.52 (dd, 1H, J = 8, J = 1.6), 7.63 (d, 2H, J = 8.4), 7.71 (d, 1H, J = 7.2), 7.80 (d, 1H, J = 7.2), 8.06 (d, 1H, J = 1.2), 8.50 (d, 2H, J = 8.4), 8.60 (s, 1H), MS (ESI+) m/z (rel intensity): 355 (M+H, 100), Anal. for $C_{21}H_{14}N_4O_2 \cdot 2.2 \cdot H_2O$, Calc. C, 64.01, H, 4.70, N, 14.22, Found C, 63.83, H, 4.93, N, 14.03.

2-[4-(1*H*-Benzimidazol-1-yl)phenyl]-5(6)-nitro-1*H*-benzimidazole 17

Yield 36%, mp 313–315 °C, ^{1}H NMR (DMSO-d_6) δ: 7.30–7.39 (m, 2H), 7.74–7.80 (m, 3H), 7.95 (d, 2H, J = 8.8), 8.14 (dd, 1H, J = 8.8, J = 2.4), 8.43 (d, 2H, J= 8.4), 8.49 (s, 1H), 8.68 (s, 1H), MS (ESI+) m/z (rel intensity): 356 (M+H, 100), Anal. for $C_{20}H_{13}N_5O_2 \cdot 2H_2O$, Calc. C, 61.37, H, 4.37, N, 17.89, Found C, 61.20, H, 4.32, N, 17.70.

2-[4-(1*H*-Benzimidazol-1-yl)phenyl]-5(6)-chloro-1*H*-benzimidazole 18

Yield 25%, mp 88 °C (bubb.) 268 °C (dec.), ^{1}H NMR (DMSO-d_6 + NaH + one drop D_2O) δ: 7.06 (dd, 1H, J = 8.8, J = 2), 7.32 (m, 2H), 7.52 (d, 1H, J = 8.8), 7.55 (d, 1H, J = 2), 7.67 (d, 1H, J = 7.2), 7.75 (3H), 8.36 (s, 2H, J = 8.8), 8.59 (s, 1H), MS (ESI+) m/z (rel intensity): 345 (M+H, 45), 347 (M+H+2, 14), 214 (100), Anal. for $C_{20}H_{13}ClN_4 \cdot H_2O \cdot 0.3\ CHCl_3$, Calc. C, 61.16, H, 3.87, N, 14.05, Found C, 60.86, H, 3.66, N, 13.77.

2-[4-(1*H*-Benzimidazol-1-yl)phenyl]-5(6)-fluoro-1*H*-benzimidazole 19

Yield 30%, mp 267–268 °C, ^{1}H NMR (DMSO-d_6 + NaH + one drop D_2O) δ: 6.88 (m, 1H), 7.29 (dd, 1H, J = 10, J = 2), 7.33–7.41 (m, 2H), 7.51 (m, 1H), 7.72–7.82 (m, 4H), 8.43 (d, 2H, J = 8.8), 8.63 (s, 1H), MS (ESI+) m/z (rel intensity): 329 (M+H, 54), 206 (100), Anal. for $C_{20}H_{13}FN_4 \cdot 0.5\ H_2O \cdot 0.75\ CHCl_3$, Calc. C, 58.38, H, 3.48, N, 13.12, Found C, 58.54, H, 3.45, N, 12.91.

2-[4-(1*H*-Benzimidazol-1-yl)phenyl]-5,6-dimethyl-1*H*-benzimidazole 20

Yield 20%, mp 286–288 °C, ^{1}H NMR (DMSO-d_6) δ: 2.34 (s, 6H), 7.32–7.40 (m, 4H), 7.74 (d, 1H, J = 8), 7.81 (d, 1H, J = 7.2), 7.88 (d, 2H, J = 8.8), 8.37 (d, 2H, J = 8.8), 8.67 (s, 1H), MS (ESI+) m/z (rel intensity): 339

(M+H, 62), 211 (100), Anal. for $C_{22}H_{18}N_4 0.5\ H_2O \cdot 0.75\ CHCl_3$, Calc. C, 62.53, H, 4.56, N, 12.82, Found C, 62.52, H, 4.34, N, 12.70.

2-[4-(1*H*-Benzimidazol-1-yl)phenyl]-5-chloro-6-methyl-1*H*-benzimidazole 21

Yield 45%, mp 332–333 °C, ^{1}H NMR (DMSO-d_6 + NaH + one drop D_2O) δ: 2.38 (s, 3H), 7.33–7.41 (m, 3H), 7.45 (s, 1H), 7.65 (d, 2H, J = 8.4), 7.70 (d, 1H, J = 7.6), 7.80 (d, 1H, J = 8), 8.46 (d, 2H, J = 8.4), 8.59 (s,1H), MS (ESI+) m/z (rel intensity): 359 (M+H, 53), 361 (18), 221 (100) Anal. for $C_{21}H_{15}ClN_4 1.2\ H_2O$, Calc. C, 66.29, H, 4.60, N, 14.72, Found C, 66.23, H, 4.21, N, 14.47.

2-[4-(1*H*-Benzimidazol-1-yl) phenyl]-5,6-dichloro-1*H*-benzimidazole 22

Yield 21%, mp 364–366 °C, ^{1}H NMR (DMSO-d_6) δ: 7.30–7.38 (m, 2H), 7.73 (dd, 1H, J = 7.6, J = 1.6), 7.77–7.80 (m, 2H), 7.91 (d, 2H, J = 8.4), 7.96 (s, 1H), 8.38 (d, 2H, J= 8.4), 8.66 (s, 1H), MS (ESI+) m/z (rel intensity): 379 (M+H, 80), 381 (M+H+2, 49), 252 (100), Anal. for $C_{20}H_{12}Cl_2N_4 0.75\ H_2O$, Calc. C, 61.16, H, 3.46, N, 14.26, Found C, 61.08, H, 3.56, N, 14.17.

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