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Synthesis and antimicrobial activity of some novel phenyl and benzimidazole substituted benzyl ethers

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Abstract—In this study, a series of novel phenyl- and benzimidazole-substituted benzyl ethers were synthesized and evaluated for antibacterial and antifungal activities against *Staphylococcus aureus*, Methicillin-resistant *S. aureus* (MRSA), *Escherichia coli*, *Candida albicans*, and *Candida krusei*. Compound **6g** exhibited the most potent antibacterial activity with lowest MIC values of 3.12 and 6.25 μg/mL against *S. aureus* and MRSA, respectively.

The synthesis of a new class of antibacterial and antifungal agents against especially Gram-positive drug-resistant bacteria and some fungi is urgent need nowadays, since these types of microorganisms are responsible for some infections in the acute and long-term care units in hospitals. Well-known azole derivatives, having a *gem*-phenyl-(1*H*-imidazol-1-ylmethyl) moiety (Fig. 1) which is thought to be largely responsible for imparting, antifungal activity, such as clotrimazole, miconazole (Fig. 2), econazole, and ketoconazole, have been developed for clinical uses.[1] SAR studies revealed that imidazole and phenyl rings which are also pharmacophoric portion of all these molecules can be replaced by the triazole.[2,3] In the literature, antibacterial activity of the azole class of compounds has been reported.[4] Recently highly potent antifungal[5] and antibacterial[6] activities of the benzimidazoles have been reported in our previous studies. These encouraging results prompted us to replace imidazole ring of the miconazole-type

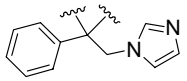

Figure 1. Structure of *gem*-phenyl-(1*H*-imidazol-1-ylmethyl) moiety.

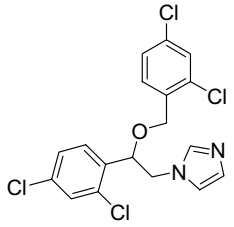

Figure 2. Structure of miconazole.

structure to benzimidazole with the aim of finding new agents with higher antifungal and/or antibacterial activity.

The synthetic pathways for preparation[7] of the targeted compounds listed in Table 1 are shown in Scheme 1. 1-Phenylethanone **1** was brominated with bromine in the presence of aluminum chloride in anhydrous ether to obtain 2-bromo-1-phenylethanone **2**. Dehydrohalogenation between **2** and 1*H*-benzimidazole **3** led to 2-(1*H*-benzimidazol-1-yl)-1-phenylethanone **4**. Reduction of **4** with $NaBH_4$ gave 2-(1*H*-benzimidazol-1-yl)-1-phenylethanol **5**. Targeted compounds **6a**–**i** were obtained by the etherification of **5** with the appropriately substituted benzyl halides in the presence of sodium hydride.

All described benzyl ethers **6a**–**i** were tested in vitro for antibacterial and antifungal activity.[8] According to the

Keywords: Phenyl; 1*H*-benzimidazole; Benzyl ether; Antibacterial; Antifungal.
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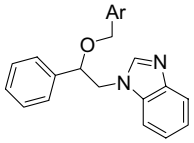
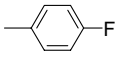
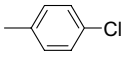
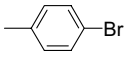
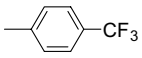
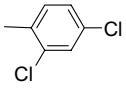
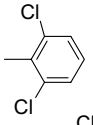
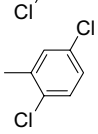
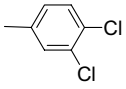
Table 1. Formulas and in vitro antibacterial activities as MIC (μg/mL) for **6a–i**

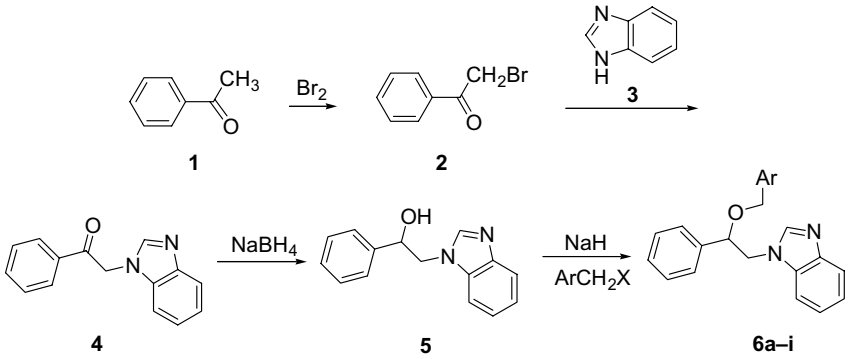


Compound	Ar	*S. aureus ATCC25923*	MRSA *ATCC43300*	*C. albicans ATCC10231*	*C. krusei ATCC6258*	*E. coli ATCC25922*
6a		25	25	25	25	NT
6b		12.5	25	25	25	NT
6c		3.12	12.5	25	25	NT
6d		3.12	12.5	25	25	NT
6e		6.25	12.5	25	12.5	NT
6f		3.12	12.5	25	25	NT
6g		3.12	6.25	12.5	12.5	NT
6h		NT	NT	NT	NT	NT
6i		3.12	25	12.5	25	NT
Ampicillin		0.78	25	—	—	—
Fluconazole		—	—	0.78	25	—
Miconazole		—	—	0.19	0.78	—
Ciprofloxacin		—	—	—	—	0.39

NT, not tested, since no clear visible inhibition zone at the disc diffusion method.

obtained results, unexpectedly, the antifungal activity has been found less than the antibacterial activity of the synthesized compound **6a–i**. Surprisingly, all of the synthesized compounds **6a–i** exhibited good to moderate activity against Gram-positive bacteria. The best activities were obtained with the compound **6g** which is having two chlorine atoms at the ortho positions of the phenyl ring. Compound **6a** without halogen substitution showed the least activity. Compound **6h** was not tested because of its oily structure. It appears that halogenated benzyl-substitution enhances the activity and also the position of halogen substitutions should be effective to modulate the activity. None of the compounds were active against *Escherichia coli*.

Imidazole-substituted benzyl ether derivatives which have similar structures to those of reported above have antimycotic as well as antibacterial activity were reported in the literature.[4] We have discovered that introduction of the benzimidazole moiety instead of imidazole moiety to the miconazole-type structure allowed us to obtain the desired good profile of Gram-positive antibacterial



Scheme 1. Synthetic pathway of the targeted compounds **6a**–**i**.

activity against *Staphylococcus aureus* and *MRSA*. In vivo and cytotoxicity studies of the best active compound **6g**, are necessary to fully evaluate the potential of this compound.

Acknowledgments

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7. *Experimental*. Melting points were recorded on Stuart Scientific SMP 1 instrument. IR spectra were recorded on Jasco FT-IR spectrometer, NMR spectra were recorded on Varian Mercury 400 MHz FT-NMR spectrometer (Varian Inc., Palo Alto, CA, USA). The mass spectra were taken on a Waters ZQ micromass LC-MS spectrometer (Waters Corporation, Milford, MA, USA) by using ESI (+) method. Elemental analysis was performed on LECO 932 CHNS (Leco-932, St. Joseph, MI, USA) instrument and was within ± 0.4% of the theoretical values.
*2-Bromo-1-phenylethanone (**2**) was prepared according to the literature*.[9]
*2-(1H-Benzimidazol-1-yl)-1-phenylethanone (**4**)*. 2-Bromo-1-phenylethanone (**2**) (4 g, 20.10 mmol) was dissolved in 8 mL of dioxane–ether (4:1). This solution was added to an ice-cold solution of (**3**) (11.87 g, 100.5 mmol) in 20 mL of methanol over 60 min under argon atmosphere. The reaction mixture was warmed to ambient temperature and stirred for an additional 18 h then diluted with 20 mL of water and extracted with chloroform. Organic extract was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and chromatographed on neutral silica gel using (200:1) chloroform–methanol as the eluent. The ketone (**4**) (2.85 g) was obtained as yellowish solid and recrystallized from ethyl acetate–hexane; yield: 60%, mp 154–156 °C, lit.[10] mp 151 °C. IR (KBr): 1673 cm^{-1} (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.54 (2H, s), 7.18–7.32 (3H, m), 7.50–7.58 (2H, t, J = 7.6 Hz), 7.64 (1H, t, J = 7.6 Hz), 7.84 (1H, d, J = 7.2 Hz), 7.91 (1H, s), 8.05 (2H, d, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.59, 109.49, 120.77, 122.57, 123.50, 128.28, 129.40, 134.45, 134.70, 143.78, 144.00, 191.49. ESI (+) *m/e* 237 (M+1, 100). Anal. found: C, 75.74; H, 5.08; N, 11.78. Calcd for $C_{15}H_{12}N_2O\cdot$ 0.1HOH: C, 75.68; H, 5.17; N, 11.77.
*2-(1H-Benzimidazol-1-yl)-1-phenylethanol (**5**) was prepared according to the literature*.[11] Yield: 88%, mp 104–106 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.22 (1H, dd, J = 14.4, 8.4 Hz), 4.29 (1H, dd, J = 14.0, 3.6 Hz), 5.07 (1H, dd, J = 8.0, 3.6 Hz), 6.16 (1H, s), 7.10 (1H, t, J = 8.0 Hz), 7.2 (1H, t, J = 7.6 Hz), 7.29–7.43 (7H, m), 7.69 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.25, 72.11, 110.00, 119.60, 122.60, 123.29, 126.15, 128.40, 128.97, 133.68, 141.47, 142.30, 143.72. ESI (+) *m/e* 239 (M+1, 100). Anal. found: C, 74.57; H, 5.71; N, 11.66. Calcd for $C_{15}H_{14}N_2O\cdot$0.15-HOH: C, 74.76; H, 5.98; N, 11.62.
*General procedure for the preparation of benzyl ethers (**6a**–**i**)*. To a solution of alcohol (**5**) (0.530 mmol) in 1.2 mL DMF was added NaH (0.663 mmol) in small fractions. The appropriate benzyl halide (0.530 mmol) in 0.6 mL DMF was then added dropwise. The mixture was stirred at room temperature for 2 h and the excess hydride was decomposed with a small amount of methyl alcohol. After evaporation to dryness under reduced pressure, the crude residue was suspended with water and extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and then evaporated to dryness. The crude residue was purified by chromatography on a silica-gel column using (50:1) chloroform–methanol as the eluent to obtain benzyl ethers (**6a**–**i**).
*1-(2-(Benzyloxy)-2-phenylethyl)-1H-benzimidazole (**6a**)*. Yield: 69%, mp 60–64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.17 (1H, d, J = 11.6 Hz), 4.48 (1 H, d, J = 11.6 Hz), 4.35 (1H, dd, J = 14.4, 4.0 Hz), 4.43 (1H, dd, J = 14.4, 8.0 Hz), 4.68 (1H, dd, J = 8.0, 4.0 Hz), 6.95–7.05 (2H, m), 7.17–7.22 (2H, m), 7.24–7.42 (9H, m), 7.82–7.86 (1H, m), 8.06 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.73, 71.05, 79.41, 110.00, 120.27, 122.52, 123.25, 126.94, 127.87, 127.99, 128.61, 129.04, 129.26, 134.03, 137.48, 138.41,

143.00, 143.98. ESI (+) *m/e* 329 (M+1, 100). Anal. found: C, 79.51; H, 6.16; N, 8.53. Calcd for $C_{22}H_{20}N_2O{\cdot}0.2HOH$: C, 79.58; H, 6.19; N, 8.43.

*1-(2-(4-Fluorobenzyloxy)-2-phenylethyl)-1H-benzimidazole (**6b**)*. Yield: 83%, mp 92–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12 (1H, d, J = 11.6 Hz), 4.42 (1H, d, J = 11.6 Hz), 4.36 (1H, dd, J = 14.4, 4.0 Hz), 4.42 (1H, dd, J = 14.4, 8.0 Hz), 4.67 (1H, dd, J = 8.0, 4.0 Hz), 6.82–6.88 (2H, m), 6.91–6.97 (2H, m), 7.25–7.44 (8H, m), 7.83–7.88 (1H, m), 8.15 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.60, 70.10, 78.97, 109.96, 115.11, 115.32, 119.71, 122.75, 123.36, 126.69, 128.92, 129.09, 129.38, 129.46, 132.92, 133.52, 137.89, 141.69, 143.42, 161.09, 163.54. ESI (+) *m/e* 347 (M+1, 100). Anal. found: C, 76.26; H, 5.45; N, 8.25. Calcd for $C_{22}H_{19}FN_2O$: C, 76.28; H, 5.53; N, 8.09.

*1-(2-(4-Chlorobenzyloxy)-2-phenylethyl)-1H-benzimidazole (**6c**)*. Yield: 73%, mp 114–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11 (1H, d, J = 11.6 Hz), 4.41 (1H, d, J = 11.6 Hz), 4.31 (1H, dd, J = 14.8, 4.0 Hz), 4.39 (1H, dd, J = 14.8, 8.4 Hz), 4.63 (1H, dd, J = 8.4,4.0 Hz), 6.88 (1H, d, J = 8.4 Hz), 7.13 (1H, d, J = 8.4 Hz), 7.24–7.34 (5H, m), 7.36–7.42 (3H, m), 7.81–7.85 (1H, m), 7.95 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.64, 70.21, 79.40, 109.93, 120.39, 122.53, 123.24, 126.90, 128.71, 129.13, 129.32, 133.73, 133.98, 135.92, 138.16, 143.23, 144.01. ESI (+) *m/e* 363 (M+1, 100), 365 (M+2+1, 33). Anal. found: C, 73.26; H, 5.21; N, 7.84. Calcd for $C_{22}H_{19}ClN_2O$: C, 72.82; H, 5.28; N, 7.72.

*1-(2-(4-Bromobenzyloxy)-2-phenylethyl)-1H-benzimidazole (**6d**)*. Yield: 64%, mp 112–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.09 (1H, d, J = 11.6 Hz), 4.39 (1H, d, J = 11.6 Hz), 4.34 (1H, dd, J = 14.8, 4.0 Hz), 4.41 (1H, dd, J = 14.8, 8.4 Hz), 4.64 (1H, dd, J = 8.4, 4.0 Hz), 6.83 (2H, d, J = 8.8 Hz), 7.22–7.43 (10H, m), 7.84 (1H, d, J = 8.4 Hz), 8.05 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.71, 70.25, 79.38, 110.05, 120.20, 121.90, 122.76, 123.41, 126.89, 129.16, 129.32, 129.45, 131.66, 133.88, 136.40, 138.07, 142.67, 143.83. ESI (+) m/e 408 (M+1, 100), 410 (M+2+1, 100). Anal. found: C, 64.86; H, 4.63; N, 7.06. Calcd for $C_{22}H_{19}BrN_2O$: C, 64.87; H, 4.70; N, 6.88.

*1-(2-(4-(Trifluoromethyl)benzyloxy)-2-phenylethyl)-1H-benzimidazole (**6e**)*. Yield: 59%, mp 74–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21 (1H, d, J = 12.4 Hz), 4.50 (1H, d, J = 12.4 Hz), 4.36 (1H, dd, J = 14.6, 4.0 Hz), 4.44 (1H, dd, J = 14.8, 8.4 Hz), 4.66 (1H, dd, J = 8.4, 4.0 Hz), 7.07 (2H, d, J = 8.0 Hz), 7.24–7.45 (10H, m), 7.83–7.87 (1H, m), 8.05 (1H, d, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.68, 70.18, 79.67, 109.99, 120.26, 120.31, 122.71, 122.76, 123.37, 123.41, 125.45, 125.49, 126.89, 127.75, 129.26, 129.38, 133.89, 137.93, 141.49, 142.94, 143.95. ESI (+) *m/e* 397 (M+1, 100). Anal. found: C, 69.59; H, 4.98; N, 7.09. Calcd for $C_{23}H_{19}F_3N_2O$: C, 69.69; H, 4.83; N, 7.07.

*1-(2-(2,4-Dichlorobenzyloxy)-2-phenylethyl)-1H-benzimidazole (**6f**)*. Yield: 54%, mp 84–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (1H, d, J = 12.8 Hz), 4.37 (1H, d, J = 12.8 Hz), 4.28 (1H, dd, J = 14.8, 4.0 Hz), 4.35 (1H, dd, J = 14.8, 8.0 Hz), 4.65 (1H, dd, J = 8.0, 4.0 Hz), 6.92 (1H, d, J = 8.4 Hz), 6.96 (1H, d, J = 8.8, 2.0 Hz), 7.15–7.36 (9H, m), 7.73–7.77 (1H, m), 7.9 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.67, 67.69, 80.21, 109.93, 120.34, 122.63, 123.33, 126.85, 127.31, 129.23, 129.33, 130.08, 133.74, 133.90, 134.19, 137.95, 142.99, 143.90. ESI (+) *m/e* 398 (M+1, 100), 399 (M+2+1, 77), 401 (M+4+1, 12). Anal. found: C, 66.17; H, 4.63; N, 7.18. Calcd for $C_{22}H_{18}Cl_2N_2O$: C, 66.51; H, 4.57; N, 7.05.

*1-(2-(2,6-Dichlorobenzyloxy)-2-phenylethyl)-1H-benzimidazole (**6g**)*. Yield: 76%, mp 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27 (1H, dd, J = 14.4, 4.0 Hz), 4.35 (1H, dd, J = 14.8, 8.0 Hz), 4.45 (1H, d, J = 10.8 Hz), 4.72 (1H, d, J = 10.8 Hz), 4.78 (1H, dd, J = 8.0, 4.0 Hz), 7.04–7.10 (1H, m), 7.15–7.29 (5H, m), 7.33–7.42 (5H, m), 7.75–7.79 (1H, m), 7.90 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.80, 66.14, 80.54, 109.79, 120.17, 122.36, 123.08, 126.88, 128.49, 129.01, 129.09, 130.23, 132.97, 133.84, 136.87, 138.39, 142.93, 143.89. ESI (+) m/e 398 (M+1, 100), 399 (M+2+1, 68), 401 (M+4+1, 13). Anal. found: C, 66.63; H, 4.46; N, 7.35. Calcd for $C_{22}H_{18}Cl_2N_2O$: C, 66.51; H, 4.57; N, 7.05.

*1-(2-(2,5-Dichlorobenzyloxy)-2-phenylethyl)-1H-benzimidazole (**6h**)*. Yield: 64%, oily. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 (1H, d, J = 12.8 Hz), 4.44 (1H, d, J = 12.8 Hz), 4.37–4.52 (2H, m), 4.78 (1 H, dd, J = 8.0, 4.4 Hz), 7.09–7.23 (3H, m), 7.25–7.44 (8H, m), 7.78–7.85 (1H, m), 8.02 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.64, 67.93, 80.85, 110.02, 120.24, 122.77, 123.51, 126.80, 128.85, 128.93, 129.26, 129.34, 130.47, 130.94, 133.01, 133.94, 137.14, 137.78, 142.54, 143.64. ESI (+) *m/e* 397 (M+1, 100), 399 (M+2+1, 68), 401 (M+4+1, 13). Anal. found: C, 64.85; H, 4.62; N, 6.72. Calcd for $C_{22}H_{18}Cl_2N_2O{\cdot}0.55HOH$: C, 64.89; H, 4.72; N, 6.87.

*1-(2-(3,4-Dichlorobenzyloxy)-2-phenylethyl)-1H-benzimidazole (**6i**)*. Yield: 46%, mp 82–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10 (1H, d, J = 12.4 Hz), 4.38 (1H, d, J = 12.8 Hz), 4.34 (1H, dd, J = 14.8, 3.6 Hz), 4.42 (1H, dd, J = 14.8, 8.0 Hz), 4.65 (1H, dd, J = 8.0, 4.0 Hz), 6.75 (1H, dd, J = 8.4, 1.6 Hz), 7.11 (1H, d, J = 2.0 Hz), 7.19 (1H, d, J = 8.4 Hz), 7.24–7.35 (5H, m), 7.37–7.44 (3H, m), 7.81–7.85 (1H, m), 7.96 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.58, 69.60, 79.87, 109.93, 120.43, 122.60, 123.33, 126.86, 129.25, 129.37, 129.51, 130.57, 131.86, 132.57, 133.95, 137.75, 137.87, 143.17, 143.90. ESI (+)*m/e* 397 (M+1, 100), 399 (M+2+1, 71), 401 (M+4+1, 12). Anal. found: C, 66.18; H, 4.48; N, 7.24. Calcd for $C_{22}H_{18}Cl_2N_2O$: C, 66.51; H, 4.57; N, 7.05.

8. *Antimicrobial assay*. All described benzyl ethers **6a**–**i** were tested in vitro for antibacterial activity against Gram-positive *Staphylococcus aureus*, Methicillin-resistant *S. aureus* (MRSA), Gram-negative *Escherichia coli* bacteria, and for anti-fungal activity against *Candida albicans* and *Candida krusei* by the diffusion method.[5,6] The compounds giving some growth inhibition zone in this method were further tested by the macro-broth dilution assay[12] to determine their MIC values, which are listed in Table 1. Since none of the compounds gave any inhibition zone against the *E. coli* by the diffusion method, their MIC values were not determined. The synthesized compounds and reference drugs were dissolved in DMSO–H_2O (50%), at a concentration of 400 μg/mL. The concentration was adjusted to 100 μg/mL by fourfold dilution with culture medium and bacterial solution at the first tube. Data were not taken for the initial solution because of the high DMSO concentration (12.5%).

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