Synthesis and Antimicrobial Activity of Some Novel Furyl and Benzimidazole Substituted Benzyl Ethers

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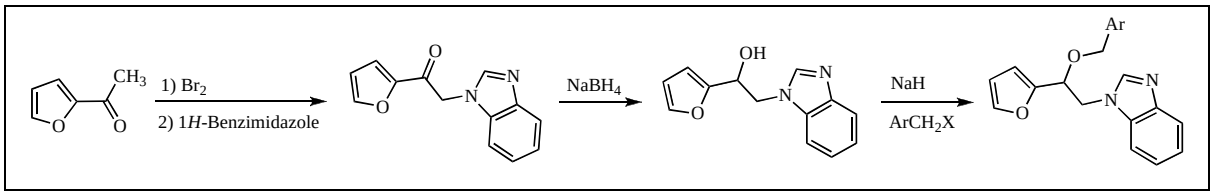

In this study, a series of novel furyl and benzimidazole substituted benzyl ethers were synthesized and evaluated for antibacterial and antifungal activities against *S. aureus,* Methicillin resistant *S. aureus* (MRSA), *E. coli, C. albicans* and *C. krusei*. Compound **6f** and **6h** exhibited the most potent anti-bacterial activity with lowest MIC values of 3.12 μg/mL against *S aureus and MRSA*, respectively.

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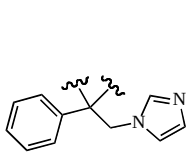
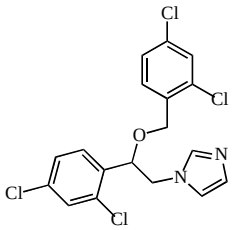
INTRODUCTION

The synthesis of a new class of antibacterial and antifungal agents against especially Gram-positive drug resistant bacteria and some fungi are urgently 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 (Formula I) which is thought to be largely responsible for imparting of antifungal activity, such as clotrimazole, miconazole (Formula II), 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] and furan [1], respectively. On the other hand, recently highly potent antifungal [4] and antibacterial [5] activities of the benzimidazoles have been reported in our previous studies. These encouraging results prompted us to replace phenyl and imidazole ring of the miconazole type structure to furan and benzimidazole, respectively, with the aim of finding new



I

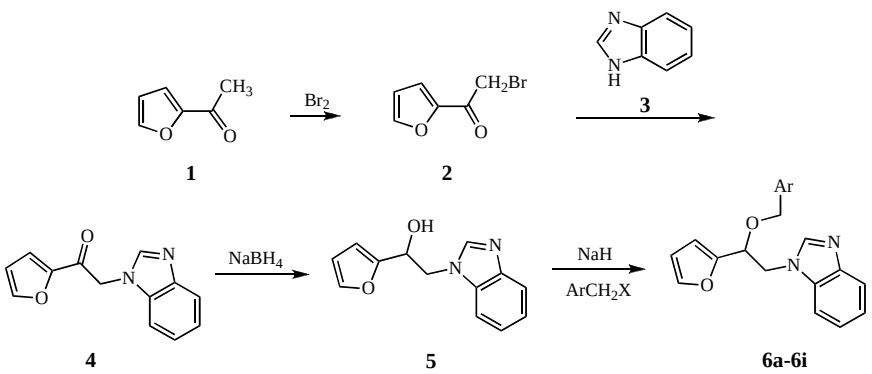


II

agents with higher antifungal and/or antibacterial activity.

Chemistry. The synthetic pathways for preparation of the targeted compounds listed in Table 1 is shown in Scheme I. 1-Furan-2-yl-ethanone **1** was brominated with bromine in dioxane-ether mixture to obtain 2-bromo-1-furan-2-yl-ethanone **2**. Dehydrohalogenation between **2** and 1*H*-benzimidazole **3** led to 2-(1*H*-benzimidazol-1-yl)-1-(furan-2-yl)ethanone **4**. Reduction of **4** with $NaBH_4$ gave 2-(1*H*-benzimidazol-1-yl)-1-(furan-2-yl)ethanol **5**. Targeted compounds **6a – 6i** were obtained by the etherification of **5** with the appropriately substituted

Scheme I



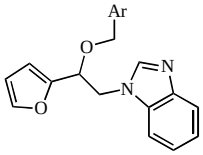
benzyl halides in the presence of sodium hydride. In the ^{1}H NMR spectrum of ketone **4**, CH_2 protons appeared as a singlet at δ 5.43. In the spectrum of alcohol **5**, the methine proton (C*H*-CH_2) occurred as a doublet of doublets at δ 5.06 (J=7.8 and 3.8 Hz) due to the adjacent diastereotopic methylene group, and the diastereotopic methylene group adjacent to the benzimidazole nitrogen was observed as a doublet of doublets at δ 4.40 (J=14.5, 7.8 Hz), δ 4.50 (J=14.5, 3.8 Hz). In the spectrum of compound **6a**, which was typical of the benzyl ethers **6a–6i**, the methine proton (C*H*-CH_2) occurred as a doublet of doublets at δ 4.58 (J=7.6 and 4.8 Hz) due to the adjacent diastereotopic methylene group, the protons of the methylene ether group appeared as a pair of coupled doublets at δ 4.14 and 4.42 (J=11.6 Hz), while the diastereotopic methylene group adjacent to the benzimidazole nitrogen was observed as a doublet of doublets at δ 4.38 (J=14.4, 4.4 Hz) and 4.48 (J=14.4, 7.6 Hz).

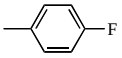
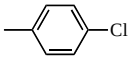
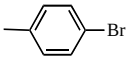
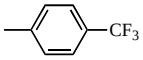
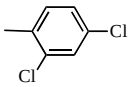
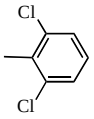
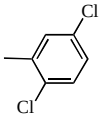
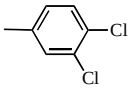
RESULTS AND DISCUSSION

All described benzyl ethers **6a – 6i** were tested *in vitro* for antibacterial activity against Gram-positive *Staphylococcus aureus*, Methicillin-resistant *Staphylococcus aureus* (MRSA), Gram-negative *Escherichia coli* bacteria, and for anti-fungal activity against *Candida albicans* and *Candida krusei* by the diffusion method [4,5]. The compounds giving a good growth inhibition zone in this method were further tested

Table 1

Formulas and *in vitro* antibacterial activities as MIC (μg/mL) for **6a - 6i**



No	Ar	*S. aureus* ATCC25923	*MRSA* ATCC43300	*C. albicans* ATCC10231	*C. krusei* ATCC6258	*E. coli* ATCC25922
6a		12.5	25	25	50	NT
6b		12.5	25	50	50	NT
6c		12.5	25	25	50	>50
6d		6.25	12.5	25	50	>50
6e		12.5	12.5	50	25	NT
6f		3.12	12.5	12.5	25	50
6g		NT	NT	NT	NT	NT
6h		6.25	3.12	50	25	NT
6i		6.25	6.25	50	50	NT
Ampicillin		0.78	25	-	-	>50
Fluconazole		-	-	1.56	25	-
Miconazole				0.19	0.78	
Ciprofloxacin						0.39

* NT : Not tested. since no clear visible inhibition zone at the disc diffusion method

by the macro-broth dilution assay [6] to determine their MIC values, which are listed in Table 1. 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 was not taken for the initial solution because of the high DMSO concentration (12.5 %). According to the obtained results, unexpectedly, the antifungal activity has been found less than the antibacterial activity of the synthesized compounds **6a – 6i** . Surprisingly, some of the compounds exhibited better activity against gram-positive bacteria *S. aureus* and *MRSA*. It appears that halogenated benzyl substitution enhance the antibacterial activities against *S. aureus* and *MRSA*. This finding was also put forward by other researchers [7]. The best results were obtained with compounds **6f**, **6i**, and **6h**, which have two chlorine atoms at different positions of the phenyl ring. Interestingly, while the same substitutions are on the C-2,6 position, **6g** has no activity. This means that the position of halogen substitutions should be effective to modulate the activity. None of the compounds were active against *E. Coli*.

CONCLUSION

We have discovered that introduction of the benzimidazole and furan moities to the miconazole type structure, allowed us to obtain the desired good profile of Gram-positive antibacterial activity against *S. aureus* and *MRSA*. *In vivo* and cytotoxicity studies of the best active compounds **6f** and **6h**, are necessary to fully evaluate the potential of these compounds.

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). Mass spectra were taken on a Waters ZQ micromass LC-MS spectrometer (Waters Corporation, Milford, MA, USA) by using ESI (+) method. Elemental analysis were performed on LECO 932 CHNS (Leco-932, St. Joseph, MI, USA) instrument and were within ± 0.4 % of the theoretical values.

2-(1*H*-Benzimidazol-1-yl)-1-(furan-2-yl)ethanone (4). Under an argon atmosphere, bromine (38 mmole) was added dropwise over 30 minutes period to an ice-cold solution of (**1**) (30 mmol) in 18 mL of dioxane-ether (1:2). The reaction mixture was warmed to ambient temperature and stirred for 12 hours, then quenched with 20 mL of saturated aqueous ammonium chloride. The organic layer was separated and extracted with ether and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the product (**2**) was obtained by column chromatography using hexane-ethyl acetate. Then, it was dissolved in 12 mL of dioxane-ether (4:1). This solution was added over 60 minutes to an ice-cold solution of (**3**) (138 mmole) in 15 mL of methanol under argon atmosphere. The reaction mixture was warmed to ambient temperature and stirred for an additional 18 hours, then diluted with 20 mL of water and extracted with chloroform. Organic extract was dried (sodium sulfate), concentrated under reduced pressure and residue was separated by column chromatography (silica gel/chloroform-methanol). The ketone was obtained as yellowish solid and recrystallized from ethyl acetate-hexane, 3.45 g (51 %), mp 152-156 °C; IR: CO 1673 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 5.43 (s, 2H), 6.64 (dd, 1H, J= 3.6, 1.6 Hz), 7.25-7.35 (m, 4H), 7.70 (d, 1H, J= 1.6 Hz), 7.81 (m, 1H), 7.98 (s, 1H); ^{13}C NMR (deuteriochloroform): δ 50.4, 109.8, 113.5, 119.0, 120.7, 122.9, 123.8, 134.5, 143.5, 144.0, 147.7, 151.2, 181.1. ESI (+) m/e 227 (M+1, 100). *Anal*. Calcd. for $C_{13}H_{10}N_2O_2$ **.** 0.25HOH: C, 67.67; H, 4.58; N, 12.14. Found: C, 67.42; H, 4.26; N, 12.16.

2-(1*H*-Benzimidazol-1-yl)-1-(furan-2-yl) ethanol (5). A solution of $NaBH_4$ (6.36 mmole) in 13.5 mL ethanol was added dropwise to an ice-cold solution of ketone (**4**) (6.36 mmole) in 26 mL of ethanol. After all the solution was added, the reaction mixture was warmed to ambient temperature and stirred for an additional 90 minutes. The solution was diluted with ether and brine, and then extracted with ether. Organic extract was dried (sodium sulfate) and solvent was removed under reduced pressure. The alcohol (**5**) was obtained as solid 1 g (69 %), mp 134-136 °C; ^{1}H NMR (deuteriochloroform): δ 4.25 (br s, 1H), 4.37 (dd, 1H, J= 14.5, 7.8 Hz), 4.47 (dd, 1H, J= 14.5, 3.8 Hz), 5.06 (dd, 1H, J= 7.8, 3.8 Hz), 6.22-6.31 (m, 2H), 7.04-7.42 (m, 5H), 7.73 (s, 1H). ^{13}C NMR (deuteriochloroform): δ 50.3, 66.4, 107.7, 110.2, 110.8, 119.0, 123.4, 123.9, 133.3, 140.3, 142.6, 143.3, 153.5. ESI (+) m/e 229 (M+1, 100). *Anal*. Calcd. for $C_{13}H_{12}N_2O_2$ **.** 0.3HOH: C, 66.83; H, 5.43; N, 11.98. Found: C, 66.89; H, 5.29; N, 11.92.

General procedure for the preparation of benzyl ethers 6a - 6i. To a solution of alcohol **5** (0.530 mmole) in 1.2 mL DMF was added NaH (0.663 mmole) in small fractions. The appropriate benzyl halide (0.530 mmole) in 0.6 mL of DMF was then added dropwise. The mixture was stirred at room temperature for 2 hours and the excess of 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 (sodium sulfate) and then evaporated to dryness. The crude residue was purified by chromatography on a silica-gel column using chloroform-methanol to obtain the title compounds.

1-(2-(Benzyloxy)-2-(furan-2-yl)ethyl)-1*H*-benzimidazole (6a). Yield 40 %, oily; ^{1}H NMR (deuteriochloroform): δ 4.14 (d, 1H, J= 11.6 Hz), 4.38 (dd, 1H, J= 14.4, 4.4 Hz), 4.42 (d, 1H, J= 11.6 Hz), 4.48 (dd, 1H, J= 14.4, 7.6 Hz), 4.58 (dd, 1H, J= 7.6, 4.8 Hz), 6.22 (d, 1H, J= 3.2 Hz), 6.27-6.30 (m, 1H), 6.90-6.94 (m, 2H), 7.07-7.12 (m, 3H), 7.14-7.22 (m, 3H), 7.39 (m, 1H), 7.72 (m, 1H), 7.84 (s, 1H). ^{13}C NMR (deuteriochloroform): δ 48.5, 71.1, 72.2, 109.8, 110.1, 110.8, 120.3, 122.5, 123.3, 128.0, 128.1, 128.6, 133.9, 137.1, 143.1, 143.5, 144.0, 150.7. ESI (+) m/e 319 (M+1, 100). *Anal*. Calcd. for $C_{20}H_{18}N_2O_2$ **.** HOH: C, 71.41; H, 5.99; N, 8.32. Found: C, 71.55; H, 5.68; N, 8.18.

1-(2-(4-Fluorobenzyloxy)-2-(furan-2-yl)ethyl)-1*H*-benzimidazole (6b). Yield 26 %, oily; ^{1}H NMR (deuteriochloroform): δ 4.11 (d, 1H, J= 11.6 Hz), 4.38 (d, 1H, J= 11.6 Hz), 4.43 (dd, 1H, J= 14.2, 4.2 Hz), 4.53 (dd, 1H, J= 14.4, 8.4 Hz), 4.60 (dd, 1H, J= 8.4, 4.0 Hz), 6.26 (d, 1H, J= 3.2 Hz), 6.30-6.33 (m, 1H), 6.77 (t, 2H, J= 8.6 Hz), 6.83-6.89 (m, 2H), 7.19-7.24 (m, 3H), 7.41 (s,

1H), 7.77 (d, 1H, J= 6.8 Hz), 8.03 (s, 1H). ^{13}C NMR (deuteriochloroform): δ 47.5, 69.2, 70.8, 108.7, 108.8, 109.5, 114.1, 114.3, 118.7, 121.8, 122.4, 128.5, 128.6, 131.5, 132.4, 140.8, 142.3, 142.4, 149.3, 160.1, 162.6. ESI (+) m/e 337 (M+1, 100). *Anal.* Calcd. for $C_{20}H_{17}FN_2O_2$. 0.3HOH: C, 70.28; H, 5.19; N, 8.19. Found: C, 70.13; H, 4.59; N, 8.13.

1-(2-(4-Chlorobenzyloxy)-2-(furan-2-yl)ethyl)-1*H*-benzimidazole (6c). Yield 36 %, oily; ^{1}H NMR (deuteriochloroform): δ 4.29 (d, 1H, J= 12.8 Hz), 4.40 (d, 1H, J= 12.8 Hz), 4.43 (dd, 1H, J= 14.4, 4.4 Hz), 4.55 (dd, 1H, J= 14.4, 8.4 Hz), 4.64 (dd, 1H, J= 8.4, 4.4 Hz), 6.29 (d, 1H, J= 3.2 Hz), 6.30-6.33 (m, 1H), 6.86 (d, 1H, J= 8.0 Hz), 6.93 (dd, 1H, J= 8.2, 1.8 Hz), 7.17-7.26 (m, 5H), 7.42 (s, 1H), 7.74 (dd, 1H, J= 6.2, 1.4 Hz), 7.85 (s, 1H). ^{13}C NMR (deuteriochloroform): δ 48.5, 70.3, 72.2, 109.6, 110.1, 110.8, 120.6, 122.4, 123.2, 128.7, 129.2, 133.8, 133.9, 135.6, 143.6, 143.7, 144.1, 150.6. ESI (+) m/e 353 (M+1, 100), 355 (M+2+1, 33). *Anal.* Calcd. for $C_{20}H_{17}ClN_2O_2$. 0.25HOH: C, 67.23; H, 4.94; N, 7.83. Found: C, 67.13; H, 5.38; N, 7.61.

1-(2-(4-Bromobenzyloxy)-2-(furan-2-yl)ethyl)-1*H*-benzimidazole (6d). Yield 34 %, oily; ^{1}H NMR (deuteriochloroform): δ 4.09 (d, 1H, J= 12 Hz), 4.35 (d, 1H, J= 12 Hz), 4.39 (dd, 1H, J= 14.8, 4.0 Hz), 4.51 (dd, 1H, J= 14.8, 8.4 Hz), 4.57 (dd, 1H, J= 8.4, 3.6 Hz), 6.24 (d, 1H, J= 3.6 Hz), 6.32 (dd, 1H, J= 3.4, 1.8 Hz), 6.76 (d, 2H, J= 8.8 Hz), 7.17-7.25 (m, 5H), 7.41-7.43 (m, 1H), 7.75 (d, 1H, J= 7.6 Hz), 7.84 (s, 1H). ^{13}C NMR (deuteriochloroform): δ 48.5, 70.3, 72.2, 109.7, 110.1, 110.8, 120.5, 122.0, 122.6, 123.3, 129.6, 131.7, 133.9, 136.1, 143.5, 143.6, 144.1, 150.6. ESI (+) m/e 397 (M+1, 100), 399 (M+2+1, 100). *Anal.* Calcd. for $C_{20}H_{17}BrN_2O_2$. 0.25HOH: C, 59.78; H, 4.39; N, 6.97. Found: C, 59.52; H, 4.18; N, 6.77.

1-(2-(4-(Trifluoromethyl)benzyloxy)-2-(furan-2-yl)ethyl)-1*H*-benzimidazole (6e). Yield 42 %, oily; ^{1}H NMR (deuteriochloroform): δ 4.22 (d, 1H, J= 12.4 Hz), 4.40-4.46 (m, 2H), 4.50-4.60 (m, 2H), 6.27 (d, 1H, J= 2.8 Hz), 6.32-6.33 (m, 1H), 7.04 (d, 2H, J= 8.0 Hz), 7.16-7.28 (m, 3H), 7.32 (d, 2H, J= 8.4 Hz), 7.42 (m, 1H), 7.75 (d, 1H, J= 8.0 Hz), 7.86 (s, 1H). ^{13}C NMR (deuteriochloroform): δ 48.5, 70.3, 72.5, 109.6, 110.2, 110.8, 120.5, 122.6, 123.3, 125.4, 125.5, 127.8, [129.7, 130.0, 130.3, 130.6], 133.9, 141.1, 143.5, 143.7, 144.1, 150.4. ESI (+) m/e 387 (M+1, 100). *Anal.* Calcd. for $C_{21}H_{17}F_3N_2O_2$. 0.5HOH: C, 63.79; H, 4.58; N, 7.09. Found: C, 63.63; H, 4.33; N, 7.10.

1-(2-(2,4-Dichlorobenzyloxy)-2-(furan-2-yl)ethyl)-1*H*-benzimidazole (6f). Yield 45 %, oily; ^{1}H NMR (deuteriochloroform): δ 4.1 (d, 1H, J= 11.6 Hz), 4.36 (d, 1H, J= 11.6 Hz), 4.38 (dd, 1H, J= 14.0, 4.0 Hz), 4.5 (dd, 1H, J= 14.0, 8.4 Hz), 4.56 (dd, 1H, J= 8.4, 4.0 Hz), 6.24 (d, 1H, J= 2.8 Hz), 6.30-6.32 (m, 1H), 6.81 (d, 2H, J= 8.0 Hz), 7.03 (d, 2H, J= 8.0 Hz), 7.17-7.21 (m, 2H), 7.41 (s, 1H), 7.74 (d, 1H, J= 7.6 Hz), 7.82 (s, 1H). ^{13}C NMR (deuteriochloroform): δ 48.5, 70.3, 72.3, 109.7, 110.1, 110.8, 120.5, 122.5, 123.3, 128.7, 129.3, 133.9, 134.0, 135.6, 143.6, 144.1, 150.7. ESI (+) m/e 387 (M+1, 100), 389 (M+2+1, 59), 391 (M+4+1, 9.5). *Anal.* Calcd. for $C_{20}H_{16}Cl_2N_2O_2$. 0.75HOH: C, 59.94; H, 4.40; N, 6.99. Found: C, 59.93; H, 4.12; N, 6.93.

1-(2-(2,6-Dichlorobenzyloxy)-2-(furan-2-yl)ethyl)-1*H*-benzimidazole (6g). Yield 49 %, mp 79-80 °C; ^{1}H NMR (deuteriochloroform): δ 4.40-4.54 (m, 2H), 4.52 (d, 1H, J= 10.8 Hz), 4.70 (d, 1H, J= 10.8 Hz), 4.74-4.78 (m, 1H), 6.32 (dd, 1H, J= 2.8, 2.0 Hz), 6.37 (d, 1H, J= 2.8 Hz), 7.01 (dd, 1H, J= 9.0, 7.0 Hz), 7.10 (d, 2H, J= 8.4 Hz), 7.19-7.27 (m, 3H), 7.42 (s, 1H), 7.73 (d, 1H, J= 6.4 Hz), 8.05 (s, 1H). ^{13}C NMR (deuteriochloroform): δ 47.7, 64.8, 72.1, 108.7, 108.8, 109.6, 118.3, 122.1, 122.6, 127.3, 129.2, 131.3, 132.0, 135.5, 139.5, 141.9, 142.4, 149.2. ESI (+) m/e 387 (M+1, 100), 389 (M+2+1, 65), 391 (M+4+1, 11). *Anal.* Calcd. for $C_{20}H_{16}Cl_2N_2O_2$: C, 62.03; H, 4.16; N, 7.23. Found: C, 61.8; H, 4.13; N, 7.22.

1-(2-(2,5-Dichlorobenzyloxy)-2-(furan-2-yl)ethyl)-1*H*-benzimidazole (6h). Yield 48 %, mp 89-92 °C; ^{1}H NMR (deuteriochloroform): δ 4.38 (d, 1H, J= 12.8 Hz), 4.45 (d, 1H, J= 13.2 Hz), 4.68 (dd, 1H, J= 14.4, 4.0 Hz), 4.76 (dd, 1H, J= 14.4, 7.6 Hz), 4.88 (dd, 1H, J= 7.6, 4.4 Hz), 6.37-6.43 (m, 2H), 7.10-7.2 (m, 3H), 7.35-7.39 (m, 2H), 7.44-7.51 (m, 2H), 7.85-7.91 (m, 1H), 8.49 (s, 1H). ^{13}C NMR (deuteriochloroform): δ 48.3, 67.9, 73.8, 109.6, 110.4, 110.8, 120.7, 122.4, 123.2, 128.9, 129.0, 130.4, 130.9, 133.0, 134.0, 136.9, 143.7, 143.9, 150.2. ESI (+) m/e 387 (M+1, 100), 389 (M+2+1, 66), 391 (M+4+1, 12). *Anal.* Calcd. for $C_{20}H_{16}Cl_2N_2O_2$. 0.5HOH: C, 60.61; H, 4.32; N, 7.10. Found: C, 60.86; H, 4.10; N, 7.15 .

1-(2-(3,4-Dichlorobenzyloxy)-2-(furan-2-yl)ethyl)-1*H*-benzimidazole (6i). Yield 40 %, oily; ^{1}H NMR (deuteriochloroform): δ 4.17 (d, 1H, J= 12.4 Hz), 4.39 (d, 1H, J= 12.8 Hz), 4.48 (dd, 1H, J= 14.0, 4.4 Hz), 4.59 (dd, 1H, J= 14.0, 8.4 Hz), 4.65 (dd, 1H, J= 8.4, 4.4 Hz), 6.32 (d, 1H, J= 3.6 Hz), 6.38-6.46 (m, 1H), 6.74 (dd, 1H, J= 8.0, 1.6 Hz), 7.11 (d, 1H, J = 1.6), 7.18 (d, 1H, J= 8.0 Hz), 7.26-7.31 (m, 3H), 7.49 (s, 1H), 7.82 (d, 1H, J= 8.0 Hz), 7.88 (s, 1H). ^{13}C NMR (deuteriochloroform): δ 48.4, 69.7, 72.7, 109.7, 110.2, 110.8, 120.6, 122.5, 123.3, 126.9, 129.6, 130.6, 131.9, 132.6, 133.9, 137.4, 143.5, 143.6, 143.9, 150.4. ESI (+) m/e 387 (M+1, 100), 389 (M+2+1, 61), 391 (M+4+1, 10). *Anal.* Calcd. for $C_{20}H_{16}Cl_2N_2O_2$: C, 60.61; H, 4.32; N, 7.07. Found: C, 60.28; H, 4.35; N, 7.01.

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