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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, in vitro antifungal evaluation and docking studies of novel derivatives of imidazoles and benzimidazoles

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Abstract

A series of imidazole and benzimidazole derivatives was designed and prepared in good yields via convenient and efficient two steps synthetic route using readily available starting materials. The structures of the synthesized compounds and their intermediates were characterized by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy, and MS spectra. The in vitro antifungal activities of the targeted compounds were evaluated against *Candida Albicans, Cryptococcus neoformans, Aspergillus niger*, and *Microsporum gypseum*. The results showed that some of these azole-derivatives exhibited good to excellent antifungal activities against the used strains especially *C. neoformans* and *A. niger*. For example, compound **6b**, 1-[2-Phenyl-2-(3-phenyl-propoxy)-ethyl]-1H-imidazole, was quite effective on the *C. neoformans, A. niger*, and *M. gypseum* with MIC 1.95 μg mL^{-1}. The in silico molecular docking study was also done on the synthesized compounds and the results showed they have minimum binding energy and relatively good affinity toward cytochrome P450. According to the in vitro antifungal results and molecular docking studies, the compounds **6a–d** can be selected as lead compounds for further pharmaceutical investigations.

Keywords Imidazole · Benzimidazole · Epoxides · Synthesis · Molecular docking · Antifungal activity

Introduction

In the recent decades, the numbers of fungal infections have been increased markedly and present continuous problem to human health (Zhao et al. 2017). In connection with this, the threat for immunocompromised patients is more serious, and the reports show that the occurrence of fungal infection for patient with AIDS, patient undergoing anticancer chemotherapy, and organ transplant have increased since 1980 (Zhao et al. 2017; Ascioglu et al. 2002; Pfaller and Diekema 2007; Brown et al. 2012). Fungal infections are often caused by three major pathogens, which include *Candida Albicans*, *Cryptococcus neoformans*, and *Aspergillus niger*. On the basis of the structure, conventional antifungal agents can be divided into four categories including azoles (e.g. fluconazole, itraconazole, voriconazole), polyene (e.g. amphotericin B, nystatin), antimetabolites (e.g. S-fluorocytosine), and echinocandines (e.g. caspofungin) (Campoy and Adrio 2017).

Among antifungal agents, the azoles derivatives are the most widely used and studied in antifungal therapy (Sheehan et al. 1999). These agents reduce endogenous concentration of ergosterol by inhibiting the activity of fungal lanosterol 14-α-demethylase. The ergosterol is a sterol found in fungal cell and playing a vital role in the membranes maintenance (Revie et al. 2018). In spite of the broad list of antifungal agents, narrow antifungal range, drug resistance, and low bioavailability, makes treatment of fungal infection unsatisfactory. This condition have led to a continuing search for discovering and developing new fungicidal agents (Zirngibl 1998; Shukla et al. 2016) and stimulated medicinal chemists to synthesize new compounds having potent antifungal activity (Campoy and Adrio 2017; Shrestha et al. 2017; Zhao et al. 2018; Yusuf et al. 2017; Fang et al. 2017; Chandrika et al. 2018).

Considering the high demand for new compounds having antifungal activity (Khalafi-Nezhad et al. 2002, 2003; Khalafi-Nezhad and Mokhtari 2004; Karimiyan et al. 2015) and in continuation of research program in the field of biologically active heterocyclic compounds and antifungal agents (Özel Güven et al. 2007; Keller et al. 2015;

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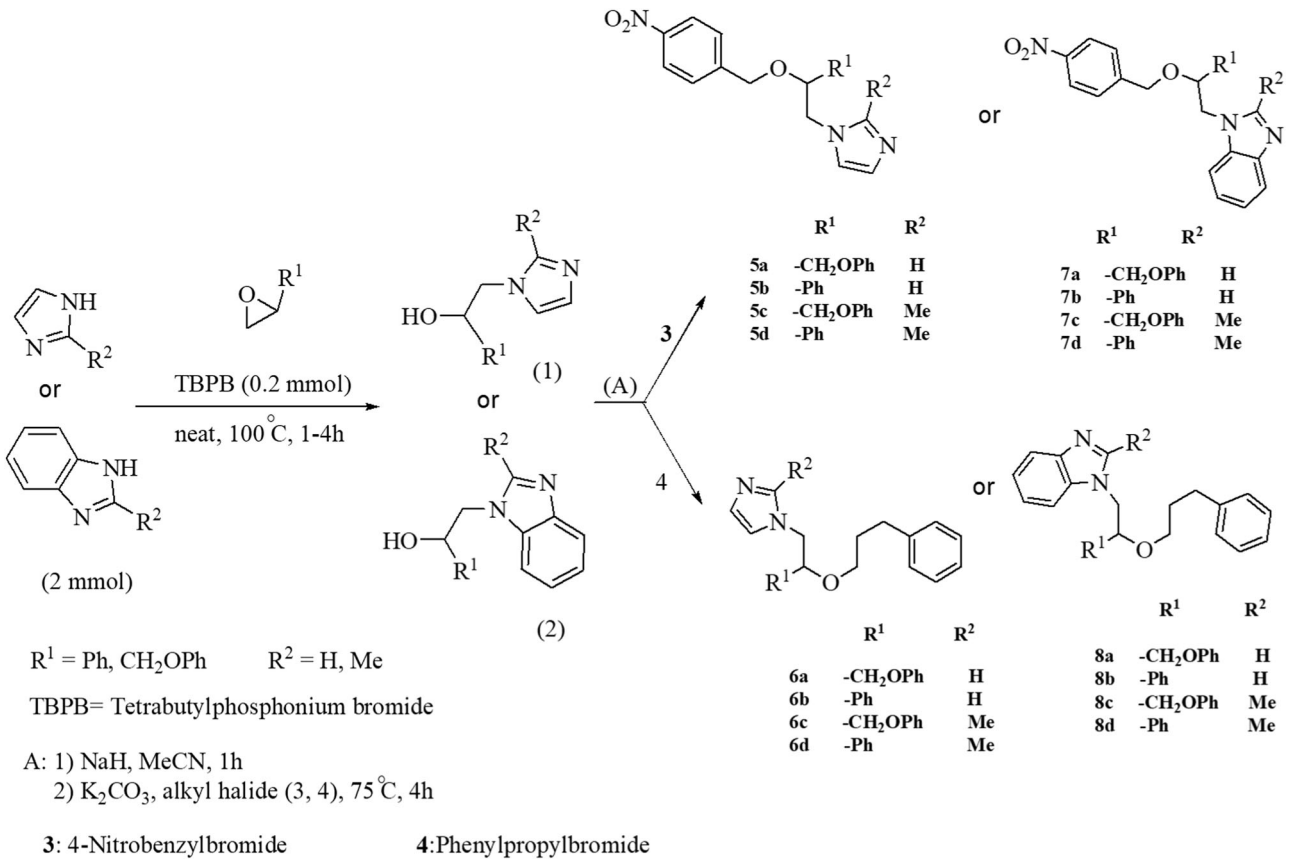


Scheme 1 Synthetic pathway of the targeted compounds

Chandrika et al. 2016). Herein, we report the synthesis, antifungal evaluation and molecular-docking studies (Meng et al. 2011) of a number of previously unreported imidazole and benzimidazole derivatives.

Material and methods

All the chemicals used in this study were purchased from Fluka, Merck, and Sigma-Aldrich and used without further purification. All solvents were freshly distilled prior to use. Chemical reactions were monitored by TLC (Merck, silica gel 60 F_{254}). Visualization was achieved by using one of the following methods: iodine stain (I_2 on silica gel) or UV light. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian 400 and 100 MHz spectrometer, respectively. Mass spectra were recorded using an Agilent 5975C VL MSD with triple-axis detector.

The chemical structures were drawn in MarvinSketch and the optimized 3D structure geometry and energy minimization and optimization obtained using Hyperchem 7.0. The energy-minimized compounds were read as input for *AutoDock Vina 4.2*. In order to carry out the docking molecular modeling, all the compounds were docked into the active site of 14a-demethylase which was obtained from Protein Data Bank (http://www.pdb.org/pdb/home/home.do).

Experimental

General procedure for preparation of the intermediate compounds (1 and 2)

The reaction was carried out by heating the mixture of azole (2.2 mmol), epoxide (2 mmol), and tetrabutylphosphonium bromide (TBPB) (0.2 mmol) for 1–4 h at 100 °C. After completion of the reaction (TLC monitoring), the reaction mixture was then allowed to cool, and washed with brine (3 × 15 mL). The organic layer was separated dried over anhydrous Na_2SO_4 and after evaporation of the solvent the pure (2-hydroxyalkyl)azoles was obtained by carrying out column chromatography using a solvent mixture of n-hexane and ethyl acetate (7/3) (Scheme 1).

General procedure for preparation of the compounds 5a–8d

To a solution of the pure (2-hydroxyalkyl)azoles (1 or 2) (1.5 mmol) in anhydrous acetonitrile (5 mL), sodium

hydride (1.5 mmol) was added and stirred at 82 °C. After 1 h, K_2CO_3 (1.5 mmol) is added and the reaction mixture was stirred for 30 min. Following that the corresponding alkyl halide (1.2 mmol) in anhydrous acetonitrile (5 mL) was added dropwise over a 30 min period and the reaction mixture was stirred for an additional 4 h. After completion of the reaction (TLC monitoring), the solvent was removed from vacuum and the highly pure products were obtained by preparative column chromatography.

1-[2-(4-Nitro-benzyloxy)-3-phenoxy-propyl]-1H-imidazole (5a) Yield: (65%), dense brown oil, IR (NaCl): υ_{max} = 3110, 2929, 1661, 1599, 1528, 1271, 1107 cm^{-1}. 1H-NMR (DMSO, d6, 400.20 MHz): δ = 8.21 (d, 2H, 3JHH = 8.1), 7.93 (d, 2H, 3JHH = 8.1), 7.42 (s, 1H, NH), 7.36–7.24 (m, 2H), 7.19–7.07 (m, 4H), 6.91 (s, 1H, =CHN), 4.98 (d, 1H, 2JHH = 11.2, Ar–CH_2–O), 4.85 (d, 1H, 2JHH = 11.2, Ar–CH_2–O), 4.51 (dd, 1H, 2JHH = 9.7 Hz, 3JHH = 5 Hz, CH_2–O), 4.46 (dd, 1H, 2JHH = 9.7 Hz, 3JHH = 5.6 Hz, CH_2–O), 4.35 (m, 1H, CH), 4.10 (dd, 1H, 2JHH = 14.4 Hz, 3JHH = 3.7 Hz, N-CH_2), 4.02 (dd, 1H, 2JHH = 14.4 Hz, 3JHH = 7.1 Hz, N-CH_2). 13C-NMR (DMSO, d6, 100.64 MHz): δ = 162.2 (C, Ar–O), 158.1 (C, Ar–NO_2), 146.8 (C, Ar), 136.7 (NCHN, Imidazole), 131.7 (CH, Ar), 130.1 (CH, Ar), 129.9 (CH, Ar), 129.1 (2 × CH, Ar), 125.9 (2 × CH, Ar), 122.2 (CH, Ar), 121.0 (CH, Ar), 115.7 (CH, Ar), 114.1 (CH, Ar), 72.5 (Ar–CH_2–O), 70.4 (CH_2–O), 62.8 (CH–O), 43.1 (N-CH_2). MS *m/z* calcd. for $C_{19}H_{19}N_3O_4$: 353.13: found 353.1 (M+).

1-[2-(4-Nitro-benzyloxy)-2-phenyl-ethyl]-1H-imidazole (5b) Yield: (68%), dense yellow oil, IR (NaCl): υ_{max} = 3117, 3046, 2925, 1674, 1599, 1492, 1271, 1107 cm^{-1}. 1H-NMR (DMSO, d6, 400.20 MHz): δ = 8.37 (d, 2H, 3JHH = 8.8 Hz), 8.27 (d, 2H, 3JHH = 8.8 Hz), 7.66–7.13 (m, 7H), 6.83 (s, 1H, =CHN), 4.62 (d, 1H, 2JHH = 11.4 Hz, Ar–CH_2–O), 4.57 (d, 1H, 2JHH = 11.5 Hz, Ar–CH_2–O), 4.27 (dd, 1H, 3JHH = 7.92 Hz, 3JHH = 3.85 Hz, CH–O), 4.14 (dd, 1H, 2JHH = 14 Hz, 3JHH = 3.84 Hz, N-CH_2), 4.03 (dd, 1H, 2JHH = 14 Hz, 3JHH = 7.92 Hz, N-CH_2). ^{13}C-NMR (DMSO, d6, 100.64 MHz): δ = 137.9 (C, Ar–NO_2), 135.8 (NCHN, Imidazole), 134.9 (C, Ar), 134.1 (C, Ar), 133.5 (CH, Ar), 133.3 (CH, Ar), 130.2 (CH, Ar), 129.4 (CH, Ar), 129.1 (2 × CH, Ar), 128.5 (2 × CH, Ar), 128.1 (CH, Ar), 126.9 (CH, Ar), 119.9 (CH, Ar), 76.2 (Ar–CH_2–O), 71.1 (CH–O), 51.3 (N-CH_2). MS *m/z* calcd. for $C_{18}N_{17}N_3O_3$: 323.1: found 323.1 (M+).

2-Methyl-1-[2-(4-nitro-benzyloxy)-3-phenoxy-propyl]-1H-imidazole (5c) Yield: (65%), dense brown oil, IR (NaCl): υ_{max} = 3110, 3082, 2932, 1679, 1599, 1528, 1496, 1271, 1107 cm^{-1}. 1H-NMR (DMSO, d6, 400.20 MHz): δ = 8.35 (d, 2H, 3JHH = 8.7), 8.14 (d, 2H, 3JHH = 8.7), 7.3 (t, 1H), 7.1 (s, 1H), 7.08–6.91 (m, 4H), 6.68 (s, 1H, =CHN), 4.45–4.35 (m, 2H, CH_2-O), 4.34 (dd, 1H, 2JHH = 11 Hz, 3JHH = 3.68 Hz, Ar–CH_2–O), 4.24 (dd, 1H, 2JHH = 11 Hz, 3JHH = 5.68 Hz, Ar–CH_2–O), 4.07–4.04 (m, 1H, CH), 3.94 (dd, 1H, 2JHH = 14 Hz, 3JHH = 3.56 Hz, N-CH_2), 3.85 (dd, 1H, 2JHH = 14 Hz, 3JHH = 7.62 Hz, N-CH_2), 2.31 (s, 3H, CH_3). 13C-NMR (DMSO, d6, 100.64 MHz): δ = 163.8 (C, Ar–O), 158.4 (C, Ar–NO_2), 150.8 (NCN, Imidazole), 134.8 (C, Ar), 131.2 (CH, Ar), 130.0 (CH, Ar), 130.0 (2 × CH, Ar), 129.9 (CH, Ar), 124.4 (2 × CH, Ar), 121.7 (CH, Ar), 120.7 (CH, Ar), 115.0 (CH, Ar), 114.9 (CH, Ar), 76.8 (Ar–CH_2–O), 72.8 (CH_2–O), 66.8 (CH–O), 45.6 (N-CH_2), 13.0 (CH_3). MS *m/z* calcd. for $C_{20}H_{21}N_3O_4$: 367.1: found 367.1 (M+).

2-Methyl-1-[2-(4-nitro-benzyloxy)-2-phenyl-ethyl]-1H-imidazole (5d) Yield: (77%), brown solid, m.p.: 61–63 °C, IR (KBr): υ_{max} = 3110, 3082, 2929, 2875, 1666, 1587, 1464, 1203, 1057 cm^{-1}. 1H-NMR (DMSO, d6, 400.20 MHz): δ = 8.21 (d, 2H, 3JHH = 8.2 Hz), 7.60 (d, 2H, 3JHH = 8.2 Hz), 7.49–7.30 (m, 5H), 7.12 (s,1H), 6.88 (s, 1H, =CHN), 4.79 (d, 1H, 2JHH = 11 Hz, (Ar–CH_2–O), 4.65 (d, 1H, 2JHH = 11 Hz, (Ar–CH_2–O), 4.87 (dd, 1H, 2JHH = 14.5 Hz, 3JHH = 2.8 Hz, N-CH_2), 4.55 (dd, 1H, 3JHH = 7.48 Hz, 3JHH = 2.8 Hz, CH–O), 4.34 (dd, 1H, 2JHH = 14.5 Hz, 3JHH = 7.48 Hz, N-CH_2), 2.45 (s, 3H, CH_3). 13C-NMR (DMSO, d6, 100.64 MHz): δ = 151.2 (NCN, Imidazole), 146.7 (C, Ar–NO_2), 133.5 (C, Ar), 133.1 (C, Ar), 132.4 (CH, Ar), 130.0 (CH, Ar), 129.2 (CH, Ar), 128.3 (CH, Ar), 127.9 (2 × CH, Ar), 127.4 (2 × CH, Ar), 123.7 (2 × CH, Ar), 120.8 (CH, Ar), 74.1 (Ar–CH_2–O), 68.4 (CH–O), 47.2 (N-CH_2), 14.95 (CH_3). MS *m/z* calcd. for $C_{19}H_{19}N_3O_3$: 337.3: found 337. 3(M+).

1-[3-Phenoxy-2-(3-phenyl-propoxy)-propyl]-1H-imidazole (6a) Yield: (76%), dense yellow oil, IR (NaCl): υ_{max} = 3117, 2939, 1674, 1599, 1499, 1246, 1106 cm^{-1}. 1H-NMR (DMSO, d6, 400.20 MHz): δ = 7.63 (s, 1H, NH), 7.33–7.11 (m, 8H), 6.98–6.94 (m, 3H), 6.91 (s, 1H, =CHN), 4.26 (dd, 1H, 2JHH = 11.7 Hz, 3JHH = 5.9 Hz, CH_2–O), 4.17 (dd, 1H, 2JHH = 14.2 Hz, 3JHH = 7 Hz, N-CH_2), 3.98 (dd, 1H, 2JHH = 14.2 Hz, 3JHH = 3.4 Hz, N-CH_2), 3.93–3.87 (m, 2H, CH_2–O, CH–O), 3.55 (m, 1H, CH_2–O), 3.35 (m, 1H, CH_2–O), 2.57 (m, 2H, CH_2), 1.71 (m, 2H, CH_2). ^{13}C-NMR (DMSO, d6, 100.64 MHz): δ = 161.4 (C, Ar–O), 158.7 (C, Ar), 142.1 (NCHN, Imidazole), 138.4 (CH, Ar), 130.0 (2 × CH, Ar), 128.8 (CH, Ar), 128.7 (CH, Ar), 128.6 (2 × CH, Ar), 126.2 (CH, Ar), 126.1 (CH, Ar), 121.3 (CH, Ar), 120.5 (CH, Ar), 114.9 (CH, Ar), 77.2 (CH_2–O), 69.1 (CH_2–O), 67.4 (CH–O), 47.6 (N-CH_2), 31.9 (ArCH_2), 31.6 (CH_2). MS *m/z* calcd. for $C_{21}H_{24}N_2O_2$: 336.1: found 336.1 (M+).

1-[2-Phenyl-2-(3-phenyl-propoxy)-ethyl]-1H-imidazole (6b) Yield: (78%), dense brown oil, IR (NaCl): υ_{max} = 3107, 2925, 1674, 1599, 1499, 1228, 1111 cm^{-1}. 1H-NMR (DMSO, d6, 400.20 MHz): δ = 7.56 (s, 1H, NH), 7.40–7.14 (m, 10H), 7.07 (s, 1H, =CHN), 6.87 (s, 1H, =CHN), 4.53 (dd, 1H, 3JHH = 8.1 Hz, 3JHH = 3.9 Hz, CHO), 4.22 (dd, 1H, 2JHH = 14.1 Hz, 3JHH = 3.9 Hz, N-CH_2), 4.14 (dd, 1H, 2JHH = 14.1 Hz, 3JHH = 8.1 Hz, N-CH_2), 3.26 (m, 1H, CH_2–O), 3.12 (m, 1H, CH_2–O), 2.02 (m, 2H, CH_2), 1.67 (m, 2H, CH_2). ^{13}C-NMR (DMSO, d6, 100.64 MHz): δ = 142.0 (NCHN, Imidazole), 139.6 (C, Ar), 138.2 (C, Ar), 128.9 (CH, Ar), 128.7 (2 × CH, Ar), 128.6 (CH, Ar), 128.4 (2 × CH, Ar), 128.3 (2 × CH, Ar), 127.1 (2 × CH, Ar), 126.1 (CH, Ar), 120.4 (CH, Ar), 81.0 (CH–O), 67.9 (CH_2–O), 52.4 (N-CH_2), 31.9 (CH_2), 31.4 (CH_2). MS *m/z* calcd. for $C_{20}H_{22}N_2O$: 306.1: found 306.1 (M+).

2-Methyl-1-[3-phenoxy-2-(3-phenyl-propoxy)-propyl]-1H-imidazole (6c) Yield: (80%), dense brown oil, IR (NaCl): υ_{max} = 3110, 2932, 1663, 1599, 1499, 1285, 1246 cm^{-1}. ^{1}H-NMR (DMSO, d6, 400.20 MHz): 7.33–7.01 (m, 8H), 6.98–6.94 (m, 3H), 6.74 (s, 1H, =CHN), 4.17 (dd, 1H, 2JHH = 10.26 Hz, 3JHH = 2.68 Hz, CH_2–O), 4.06 (dd, 2JHH = 10.26 Hz, 3JHH = 4.8 Hz, 1H, CH_2–O), 4.05 (dd, 1H, 2JHH = 14.6 Hz, 3JHH = 3.8 Hz, N-CH_2), 3.95 (dd, 1H, 2JHH = 14.6 Hz, 3JHH = 7.56 Hz, N-CH_2), 3.89–3.87 (m,1H, CH–O), 3.54 (m, 1H, CH_2–O), 3.30 (m, 1H, CH_2–O), 2.45 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 1.72 (m, 2H, CH_2). ^{13}C-NMR (DMSO, d6, 100.64 MHz): δ = 160.1 (C, Ar–O), 158.7 (NCN, Imidazole), 144.9 (C, Ar), 142.0 (CH, Ar), 130.0 (2 × CH, Ar), 128.7 (2 × CH, Ar), 128.6 (2 × CH, Ar), 126.7 (CH, Ar), 126.1 (CH, Ar), 121.3 (CH, Ar), 120.6 (CH, Ar), 114.9 (CH, Ar), 77.6 (CH_2–O), 69.3 (CH_2–O), 67.3 (CH–O), 47.0 (N-CH_2), 31.8 (CH_2), 31.6 (CH_2), 13.25 (CH_3). MS *m/z* calcd. for $C_{22}H_{26}N_2O_2$: 350.1: found 350.1 (M+).

2-Methyl-1-[2-phenyl-2-(3-phenyl-propoxy)-ethyl]-1H-imidazole (6d) Yield: (79%), dense orange oil, IR (NaCl): υ_{max} = 3114, 2932, 1656, 1531, 1499, 1278, 1107 cm^{-1}. 1H-NMR (DMSO, d6, 400.20 MHz): δ = 7.39–7.13 (m, 10H), 7.06 (s, 1H), 6.75 (s, 1H, =CHN), 4.55 (dd, 1H, 3JHH = 7.96 Hz, 3JHH = 4.24 Hz, CH–O), 4.10 (dd, 1H, 2JHH = 14.42 Hz, 3JHH = 8 Hz, N-CH_2), 3.88 (dd, 1H, 2JHH = 14.42 Hz, 3JHH = 4.24 Hz, N-CH_2), 3.26 (m, 1H, CH_2–O), 3.15 (m, 1H, CH_2–O), 2.24 (s, 3H, CH_3), 2.03 (m, 2H, CH_2), 1.89 (m, 2H, CH_2). 13C-NMR (DMSO, d6, 100.64 MHz): δ = 141.4 (NCN, Imidazole), 136.4 (C, Ar), 135.2 (C, Ar), 134.3 (CH, Ar), 133.8 (CH, Ar), 133.4 (CH, Ar), 131.2 (CH, Ar), 130.0 (CH, Ar), 129.7 (2 × CH, Ar), 128.7 (2 × CH, Ar), 128.5 (CH, Ar), 126.1 (CH, Ar), 119.9 (CH, Ar), 75.3 (CH_2–O), 69.3 (CH–O), 45.2 (N-CH_2), 32.1 (CH_2), 31.4 (CH_2), 13.06 (CH_3). MS *m/z* calcd. for $C_{21}H_{24}N_2O$: 320.1: found 320.1 (M+).

1-[2-(4-nitro-benzyloxy)-3-phenoxy-propyl]-1H-benzimidazole (7a) Yield: (66%), dense brown oil, IR (NaCl): υ_{max} = 3170, 2931, 1632, 1599, 1529, 1497, 1270, 1102 cm^{-1}. 1H-NMR (DMSO, d6, 400.20 MHz): δ = 8.49 (s, 1H, NH), 8.17 (d, 2H, 3JHH = 7.9 Hz), 8.10 (d, 1H), 7.82 (d, 2H, 3JHH = 7.9 Hz), 7.81–7.52 (m, 3H), 7.29–6.87 (m, 5H), 5.06 (d, 1H, 2JHH = 10.5 Hz, (Ar–CH_2–O), 4.89 (d, 1H, 2JHH = 10.5 Hz, Ar–CH_2–O), 4.78 (dd, 1H, 2JHH = 10 Hz, 3JHH = 3 Hz, CH_2–O), 4.66 (dd, 2JHH = 10 Hz, 3JHH = 5.1 Hz, 1H, CH_2–O), 4.32 (m. 1H, CH–O), 4.10 (dd, 1H, 2JHH = 13.5 Hz, 3JHH = 3.2 Hz, N-CH_2), 4.00 (dd, 1H, 2JHH = 13.5 Hz, 3JHH = 6.9 Hz, N-CH_2). ^{13}C-NMR (DMSO, d6, 100.64 MHz): δ = 162.2 (C, Ar–O), 154.3 (C, Ar–NO_2), 153.0 (C, Ar), 152.6 (C, Ar), 144.3 (NCHN, benzimidazole), 137.1 (C, Ar), 132.0 (CH, Ar), 131.5 (2 × CH, Ar), 128.4 (2 × CH, Ar), 125.6 (2 × CH, Ar), 121.8 (CH, Ar), 121.4 (CH, Ar), 121.1 (CH, Ar), 120.0 (CH, Ar), 113.1 (CH, Ar), 110.2 (CH, Ar), 78.2 (CH_2–O), 73.6 (CH_2–O), 64.8 (CH–O), 46.4 (N-CH_2). MS *m/z* calcd. for $C_{23}H_{21}N_3O_4$: 403.1: found 403.1 (M+).

1-[2-(4-nitro-benzyloxy)-2-phenyl-ethyl]-1H-benzimidazole (7b) Yield: (61%), dense yellow oil, IR (NaCl): υ_{max} = 2939, 1615, 1517, 1499, 1282, 1157 cm^{-1}. ^{1}H-NMR (DMSO, d6, 400.20 MHz): δ = 8.15 (s, 1H, NH), 8.11 (d, 2H, J = 8.0), 7.94 (d, 2H, J = 8.0), 7.74–7.69 (m, 4H), 7.67–7.42 (m, 5H), 4.87 (d, 1H, J = 11.1, CH_2–O), 4.76 (d, 1H, J = 11.3, CH_2–O), 4.58 (dd, 1H, 3JHH = 8.15 Hz, 3JHH = 3.81 Hz, CH–O), 4.27 (dd, 1H, 2JHH = 14.3 Hz, 3JHH = 3.81 Hz, N-CH_2), 4.21 (dd, 1H, 2JHH = 14.3 Hz, 3JHH = 8.15 Hz, N-CH_2). ^{13}C-NMR (DMSO, d6, 100.64 MHz): δ = 162.3 (C, Ar–O), 145.2 (C, Ar), 143.9 (NCHN, Benzimidazole), 138.5 (C, Ar), 135.4 (C, Ar), 130.9 (C, Ar), 130.0 (CH, Ar), 129.8 (CH, Ar), 128.8 (CH, Ar), 128.1 (2 × CH, Ar), 127.7 (CH, Ar), 126.9 (CH, Ar), 126.2 (2 × CH, Ar), 121.2 (CH, Ar), 120.7 (CH, Ar), 114.8 (CH, Ar), 110.3 (CH, Ar), 72.4 (CH_2–O), 66.9 (CH–O), 50.0 (N-CH_2). MS *m/z* calcd. for $C_{22}H_{19}N_3O_3$: 373.1: found 373.1 (M+).

2-Methyl-1-[2-(4-nitro-benzyloxy)-3-phenoxy-propyl]-1H-benzimidazole (7c) Yield: (68%), dense yellow oil, IR (NaCl): υ_{max} 3059, 2925, 1628, 1532, 1462, 1270, 1102 cm^{-1}. 1H-NMR (DMSO, d6, 400.20 MHz): δ = 8.29 (d, 2H, 3JHH = 8.8 Hz), 8.00 (d, 2H, 3JHH = 8.8 Hz), 7.6–7.3 (m, 4H), 7.1–6.9 (m, 5H), 4.75 (d, 1H, J = 10.5, Ar–CH_2–O), 4.72 (d, 1H, J = 10.5, Ar–CH_2–O), 4.28 (dd, 1H, 2JHH = 11 Hz, 3JHH = 3.1 Hz, CH_2–O), 4.21 (dd, 1H, 2JHH = 10.9 Hz, 3JHH = 5 Hz, CH_2–O), 4.01 (dd, 1H, 2JHH =

13.7 Hz, 3JHH = 6.8 Hz, N-CH_2), 4.21 (m, 1H, CH–O), 3.95 (dd, 1H, 2JHH = 13.7 Hz, 3JHH = 3 Hz, N-CH_2), 2.56 (s, 3H, CH_3). 13C-NMR (DMSO, d6, 100.64 MHz): δ = 163.8 (C, Ar–O), 158.5 (C, Ar–NO_2), 152.3 (C, Ar), 150.8 (NCN, Benzimidazole), 142.6 (C, Ar), 135.7 (C, Ar), 134.6 (CH, Ar), 131.1 (2 × CH, Ar), 130.1 (2 × CH, Ar), 124.2 (2 × CH, Ar), 122 (CH, Ar), 121.8 (CH, Ar), 121.7 (CH, Ar), 118.6 (CH, Ar), 115.2 (CH, Ar), 110.4 (CH, Ar), 74.7 (CH_2–O), 72.2 (CH_2–O), 66.9 (CH–O), 43.5 (N-CH_2), 13.9 (CH_3). MS *m/z* calcd. for $C_{24}H_{23}N_3O_4$: 417.1: found 417.1 (M+).

2-Methyl-1-[2-(4-nitro-benzyloxy)-2-phenyl-ethyl]-1H-benzimidazole (7d) Yield: (71%), dense orange oil, IR (NaCl): υ_{max} 3101, 2988, 1628, 1529, 1266, 1102 cm^{-1}. ^{1}H-NMR (DMSO, d6, 400.20 MHz): δ = 8.32 (d, 2H, *J* = 8.3), 8.14 (d, 2H, *J* = 8.3), 7.73–7.67 (m, 2H), 7.61–7.11 (m, 7H), 4.93 (d, 1H, J = 11.1, Ar–CH_2–O), 4.86 (d, 1H, *J* = 11.1, Ar–CH_2–O), 4.68 (dd, 1H, 3JHH = 8.12 Hz, 3JHH = 3.64 Hz, CH–O), 4.50 (dd, 1H, 2JHH = 14.56 Hz, 3JHH = 3.64 Hz, N-CH2), 4.41 (dd, 1H, 2JHH = 14.56 Hz, 3JHH = 8.12 Hz, N-CH_2), 2.37 (s, 3H, CH_3). ^{13}C NMR (DMSO, d6, 100.64 MHz): δ = 160.1 (C, Ar–NO_2), 142.8 (NCN, benzimidazole), 141.1 (C, Ar), 139.5 (C, Ar), 134.7 (C, Ar), 130.4 (C, Ar), 129.5 (CH, Ar), 129.3 (CH, Ar), 126.4 (2 × CH, Ar), 128.9 (CH, Ar), 128.1 (2 × CH, Ar), 127.8 (CH, Ar), 127.2 (CH, Ar), 122.7 (CH, Ar), 119.7 (CH, Ar), 115.9 (CH, Ar), 110.1 (CH, Ar), 71.2 (CH_2–O), 68.6 (CH–O), 47.8 (N-CH_2), 13.2. MS *m/z* calcd. for $C_{23}H_{21}N_3O_3$: 387.1: found: 387.1 (M+).

1-[3-phenoxy-2-(3-phenyl-propoxy)-propyl]-1H-benzimidazole (8a) Yield: (73%), dense yellow oil, IR (NaCl): υ_{max} = 3171, 2925, 1669, 1497, 1259, 1098 cm^{-1}. ^{1}H-NMR (DMSO, d6, 400.20 MHz): δ = 8.25 (s, 1H, NH), 7.66 (d, 2H), 7.59–7.47 (m, 4H), 7.27–7.17 (m, 8H), 4.46 (dd, 1H, 2JHH = 9.82 Hz, 3JHH = 4.2 Hz, CH_2–O), 4.41 (dd, 1H, 2JHH = 9.82 Hz, 3JHH = 5.1 Hz, CH_2–O), 4.23 (m, 1H, CH–O), 4.06 (dd, 1H, 2JHH = 14.61 Hz, 3JHH = 3.12 Hz, N-CH_2), 4.00 (dd, 1H, 2JHH = 14.61 Hz, 3JHH = 7.93 Hz, N-CH_2), 3.30 (m, 1H, CH_2–O), 3.09 (m, 1H, CH_2–O), 2.13 (m, 2H, CH_2), 1.25 (m, 2H, CH_2). 13C-NMR (DMSO, d6, 100.64 MHz): δ = 156.7 (C, Ar–O), 144.4 (NCHN, Benzimidazole), 143.9 (C, Ar), 141.4 (C, Ar), 134.2 (C, Ar), 130.5 (CH, Ar), 130.1 (CH, Ar), 128.8 (2 × CH, Ar), 128.6 (2 × CH, Ar), 126.4 (2 × CH, Ar), 123.2 (CH, Ar), 122.7 (CH, Ar), 121.8 (CH, Ar), 119.9 (CH, Ar), 115.4 (CH, Ar), 110.8 (CH, Ar), 74.1 (CH_2–O), 68.2 (CH_2–O), 67.8 (CH–O), 44.2 (N-CH_2), 32.6 (CH_2), 31.5 (CH_2). MS *m/z* calcd. for $C_{25}H_{26}N_2O_2$: 386.2: found 386.2 (M+).

1-[2-phenyl-2-(3-phenyl-propoxy)-ethyl]-1H-benzimidazole (8b) Yield: (78%), dense brown oil, IR (NaCl): υ_{max} = 3154, 2925, 1654, 1599, 1462, 1243, 1047 cm^{-1}. 1H-NMR (DMSO, d6, 400.20 MHz): δ = 8.27 (s, 1H, NH), 7.56–7.49 (m, 3H), 7.38–7.25 (m, 6H), 7.22–7.18 (m, 5H), 4.40 (dd, 1H, 3JHH = 8.2 Hz, 3JHH = 3.92 Hz, CH-O), 4.29 (dd, 1H, 2JHH = 14.2 Hz, 3JHH = 3.92 Hz, N-CH2), 4.23 (dd, 1H, 2JH = 14.2 Hz, 3JHH = 8.2 Hz, N-CH_2), 3.54 (m, 1H, CH_2–O), 3.25 (m, 1H, CH_2–O), 2.06 (m, 2H, CH_2), 1.68 (m, 2H, CH_2). ^{13}C-NMR (DMSO, d6, 100.64 MHz): δ = 155.9 (C, Ar), 144.6 (NCHN, Benzimidazole), 141.5 (C, Ar), 138.6 (C, Ar), 134.6 (C, Ar), 130.3 (2 × CH, Ar), 129.8 (CH, Ar), 129.2 (2 × CH, Ar), 128.7 (2 × CH, Ar), 127.8 (CH, Ar), 127.1 (CH, Ar), 125.5 (CH, Ar), 121.1 (CH, Ar), 120.7 (CH, Ar), 115.4 (CH, Ar), 110.8 (CH, Ar), 77.4 (CH_2-O), 65.6 (CH–O), 47.6 (N-CH_2), 31.5 (CH_2), 30.8 (CH_2). MS *m/z* calcd. for $C_{24}H_{24}N_2O$: 356.1: found 356.1 (M+).

2-Methyl-1-[3-phenoxy-2-(3-phenyl-propoxy)-propyl]-1H-benzimidazole (8c) Yield: (75%), dense orange oil, IR (NaCl): υ_{max} = 3066, 2929, 1640, 1599, 1497, 1247, 1125 cm^{-1}. 1H-NMR (DMSO, d6, 400.20 MHz): δ = 7.55–7.31 (m, 4H), 7.20–7.11 (m, 5H), 7.09–6.86 (m, 5H), 4.48 (dd, 1H, 2JHH = 10.34 Hz, 3JHH = 4.56 Hz, CH_2–O), 4.38 (dd, 1H, 2JHH = 10.34 Hz, 3JHH = 4.48 Hz, CH2-O), 4.16 (dd, 1H, 2JHH = 15.02 Hz, 3JHH = 3.76 Hz, N-CH2), 4.11 (dd, 1H, 2JHH = 15.02 Hz, 3JHH = 8.68 Hz, N-CH_2), 3.52 (m, 1H, CH–O), 3.96 (m, 1H, CH_2–O), 3.07 (m, 1H, CH_2–O), 2.60 (s, 3H, CH_3), 2.30 (m, 2H, CH_2), 1.54 (m, 2H). 13C-NMR (DMSO, d6, 100.64 MHz): δ = 158.7 (C, Ar–NO_2), 152.9 (C, Ar), 142.8 (NCN, Benzimidazole), 141.8 (C, Ar), 135.8 (C, Ar), 130.0 (2 × CH, Ar), 128.6 (2 × CH, Ar), 128.5 (2 × CH, Ar), 126.0 (2 × CH, Ar), 121.8 (CH, Ar), 121.6 (CH, Ar), 121.3 (CH, Ar), 118.6 (CH, Ar), 115.0 (CH, Ar), 110.4 (CH, Ar), 76.9 (CH_2–O), 69.2 (CH_2–O), 67.4 (CH–O), 45.3 (N-CH_2), 31.6 (CH_2), 31.5 (CH_2), 14.6 (CH_3). MS *m/z* calcd. for $C_{26}H_{28}N_2O_2$: 400.2: found 400.2 (M+).

2-Methyl-1-[2-phenyl-2-(3-phenyl-propoxy)-ethyl]-1H-benzimidazole (8d) Yield: (70%), dense yellow oil, IR (NaCl): υ_{max} 3093, 2933, 1525, 1454, 1106 cm^{-1}. 1H-NMR (DMSO, d6, 400.20 MHz): δ = 7.59–7.52 (m, 4H), 7.43–7.35 (m, 5H), 7.23–7.09 (m, 5H), 4.65 (dd, 1H, 3JHH = 8.65 Hz, 3JHH = 3.84 Hz, CH–O), 4.42 (dd, 1H, 2JHH = 14.98 Hz, 3JHH = 8.64 Hz, N-CH_2), 4.32 (dd, 1H, 2JHH = 14.98 Hz, 3JHH = 3.84 Hz, N-CH_2), 3.20 (m, 1H, CH_2–O), 2.95 (m, 1H, CH_2–O), 2.55 (s. 3H, CH_3), 2.32 (m, 2H, CH_2), 1.58 (m, 2H, CH_2). ^{13}C-NMR (DMSO, d6, 100.64 MHz): δ = 152.9 (C, Ar), 142.7 (NCN, Benzimidazole), 141.8 (C, Ar), 139.6 (C, Ar), 135.8 (C, Ar), 129.0 (CH, Ar), 128.69 (2 × CH, Ar), 128.66 (2 × CH, Ar), 128.5 (2 × CH, Ar), 127.2 (2 × CH, Ar), 126.0 (CH, Ar), 121.7 (CH, Ar), 121.5 (CH, Ar), 118.5 (CH, Ar), 110.8 (CH, Ar),

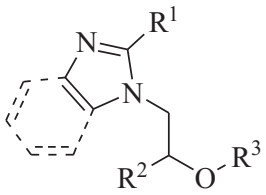


Fig. 1 The structural modifications on the azole core

80.2 (CH_2–O), 67.6 (CH–O), 49.9 (N-CH_2), 31.7 (CH_2), 31.4 (CH_2), 14.1 (CH_3). MS *m/z* calcd. for $C_{25}H_{26}N_2O$: 370.2: found 370.2 (M+).

Results and discussion

Chemistry

It is well-known that small changes in the chemical structure of the biologically active molecule are altering their biological and chemical properties. Thus, the aim of the this study is preparation of the novel imidazole and benzimidazole derivatives, which contain the (2-hydroxyalkyl) azoles core and evaluation of their antifungal activities. This structure was selected because of (Fig. 1) its similarity to the miconazole, which has good antifungal properties. Various groups attached to the (2-hydroxyalkyl)azoles play important roles in their antifungal activities by altering their physiochemical properties. For instance, changing the length of the alkyl chain could change the solubility, which alter bioavailability or various linkers that could affect the 3D structure and result in different hydrophobic interactions and hydrogen-bonding. Figure 1 summarizes the main structural modifications which are made in this study including changing the azole core and its substituent (R^1), etheric side chains (R^2 and R^3).

Based on these modifications, 16 imidazole and benzimidazole derivatives were designed (Fig. 2) and synthesized via the two-steps synthetic pathway (Scheme 1). In the first step, the (2-hydroxyalkyl) azoles 1 or 2 were synthesized via nucleophilic ring-opening reaction of commercially available epoxides with imidazoles and benzimidazoles in the presence of TBPB under solvent-free conditions. The reactions were performed at 100 °C and two products were obtained. The major products were (2-hydroxyalkyl)azole with a yield of 70–87%, which was isolated and purified by column chromatography. It should be noted that the presence of TBPB is essential for performing this reaction, and in the absence of it, the reaction took long time to occur and the yield was low.

In the second step, the (2-hydroxylalkyl)azoles 1 or 2 which were prepared and purified in the first step was alkylated by 4-nitro-benzyl bromide (3) and 3-phenylpropyl chloride (4). The reactions were done in the presence of sodium hydride (NaH) and produced the desired products (**5a**–**8d**) in refluxing anhydrous acetonitrile. The highly pure products were obtained by column chromatography with 61–80% yield. The structure of all the final products, as well as all of intermediates was confirmed by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy, and MS spectra.

Antifungal studies

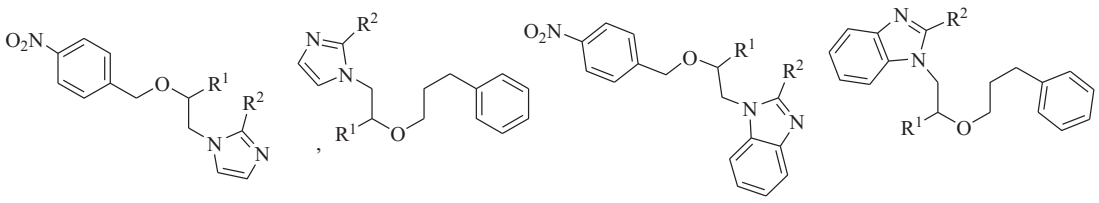
The antifungal activity of the target compounds was evaluated against four important fungal pathogens including *C. albicans, C. neoformans, A. niger*, and *Microsporum gypseum* (*M. gypseum*). The minimum inhibitory concentrations (MICs) and the minimum fungicidal concentrations (MFCs) of the target compound were determined using Broth micro-dilution methods in 96-well microtest plates according to the National Committee for Clinical Laboratory Standards (NCCLS) (Pfaller MA et al. 2002). Briefly, compounds were dissolved in DMSO and serially diluted in growth medium. The inoculum suspension was added to each well and incubated at 35 °C.

Table 1 presents the results for in vitro antifungal activity of the target compounds **5a**–**5d**, **6a**–**6d**, **7a**–**7d**, and **8a**–**8d**. As shown in Table 1 (entries 5–8), the antifungal screening showed that some of the target compounds showed good inhibition against several tested fungal strains. For instance, the MIC values of the compounds **6a**–**6d** were very low and we see moderate to excellent in vitro antifungal activity of these compounds against *C. neoformans*, *A. niger*, and *M. gypseum*.

In addition, the compound **6b** 1-[2-Phenyl-2-(3-phenyl-propoxy)-ethyl]-1H-imidazole (Table 1, entry 6, Fig. 3) showed the most antifungal activity compared to all other targeted compounds against *C. neoformans, A. niger*, and *M. gypseum*.

The compound **5b** also showed similar activity against *C. neoformans* and *A. niger* with MIC of 1.95 μg mL^{-1} concentrations. By the above observations and relationships between the structure of the target compounds and the detected antifungal activities, it could be deduced that in most cases the imidazole derivatives showed better fungistatic abilities than benzimidazole derivatives. It could also be deduced that methyl substituents on imidazole nuclei reduced antifungal activities (e.g. compare the MICs of **5a**–**5d** with those of **6a**–**6d**). In addition, the incorporation of phenylpropyl substituent exerted more important influence on antifungal activities than 4-nitro-benzyl substituent for imidazole series (Table 1, entries 1–8). It seems that in this series the suitable increase of carbon linker length was favorable to the fungicidal efficacies.

On the other hand, in the benzimidazoles derivatives, only the compound **7c** (Table 1, entry 11) showed middle



5 6 7 8

	R^1	R^2
5a	$-CH_2OPh$	H
5b	-Ph	H
5c	$-CH_2OPh$	Me
5d	-Ph	Me

	R^1	R^2
6a	$-CH_2OPh$	H
6b	-Ph	H
6c	$-CH_2OPh$	Me
6d	-Ph	Me

	R^1	R^2
7a	$-CH_2OPh$	H
7b	-Ph	H
7c	$-CH_2OPh$	Me
7d	-Ph	Me

	R^1	R^2
8a	$-CH_2OPh$	H
8b	-Ph	H
8c	$-CH_2OPh$	Me
8d	-Ph	Me

Fig. 2 The structure of the targeted compounds

Table 1 Antifungal in vitro activities of the target compounds (μg mL^{-1})

Entry	Compound	*C. neoformans*		*C. albicans*		*A. niger*		*M. gypseum*	
		MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
1	**5a**	62.5	62.5	125	125	62.5	>125	62.5	>125
2	**5b**	1.95	31.2	125	>125	1.95	>125	31.2	>125
3	**5c**	31.2	31.2	125	125	31.2	31.2	62.5	125
4	**5d**	31.2	62.5	125	125	7.81	>125	62.5	>125
5	**6a**	1.95	15.6	62.5	125	1.95	125	3.90	125
6	**6b**	1.95	15.6	15.6	15.6	1.95	15.6	1.95	15.6
7	**6c**	15.6	15.6	62.5	125	3.90	15.6	7.81	31.2
8	**6d**	15.6	15.6	62.5	62.5	3.90	>125	15.6	125
9	**7a**	31.2	>125	125	>125	31.2	>125	62.5	>125
10	**7b**	31.2	125	125	>125	62.5	>125	62.5	>125
11	**7c**	15.6	>125	31.2	>125	15.6	>125	31.2	>125
12	**7d**	31.2	31.2	62.5	>125	62.5	>125	62.5	>125
13	**8a**	31.2	125	62.5	>125	31.2	>125	62.5	>125
14	**8b**	62.5	31.2	62.5	>125	31.2	>125	125	>125
15	**8c**	31.2	31.2	62.5	>125	31.2	>125	62.5	>125
16	**8d**	31.2	31.2	62.5	>125	62.5	>125	62.5	>125
17	Fluconazole	15.6	31.2	1.95	7.81	15.6	31.2	15.6	31.2

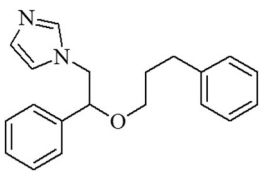


Fig. 3 The structure of the compound 6b

antifungal activity against *C. neoformans* and *A. niger* at MIC 15.6 μg mL^{-1} concentrations, and other derivatives showed poor antifungal activities with MICs between 31.2 and 125 μg mL^{-1} against all the tested strains (Table 1, entries 9, 10 and 12–16).

Based on these results, the compounds **5b** and **6a–6d** which have shown relatively good in vitro antifungal properties can be used as good candidates for in vivo assay and as lead compounds for further investigation

Molecular modeling

To further justify and better rationalize the observed in vitro antifungal activity; the synthesized molecules were docked into the active site of cytochrome P450 using *Autodock Vina 4.2* to determine the best in silico conformation.

Figure 4 shows that in the compound **6b** the imidazole ring is situated in a polar region, and is pointed towards the heme plane and a ring nitrogen atom coordinating the iron ion. In addition, the phenyl group of compound **6b** makes *Van der Waals* and hydrophobic interactions with Tyr 318, Phe 236, Val 510, and Leu 380. The phenylpropyl chain is located in a lipophilic part of active site constituted mainly

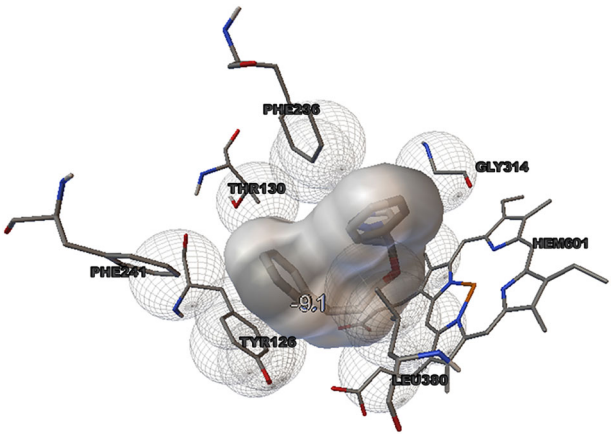


Fig. 4 Three-dimensional conformation of the compound **6b** docked in the active site of CYP51

Table 2 Binding energy and inhibition constant of the compounds (**3a–3d**), (**4a–4d**), (**5a–5d**), and (**6a–6d**)

Compounds	Energy (kJ mol^{-1})
5a	−9.2
5b	−9.4
5c	−9.4
5d	−9.8
6a	−8.7
6b	−9.1
6c	−9.4
6d	−9.2
7a	−10.3
7b	−10.8
7c	−9.3
7d	−9.1
8a	−9.5
8b	−10.4
8c	−9.1
8d	−9.2

by hydrophobic side chain Thr 130, Tyr 126, Phe 236, and Phe 241 (non-polar interactions).

Table 2 shows the binding energy of the 16 compounds. These results of the in silico studies revealed that all of the synthesized molecules showed relatively good binding energy toward the active site of CYP51 ranging from −8.7 to −10.8 kJ mol^{-1}.

Conclusion

In conclusion, we have successfully synthesized a series of novel imidazole and benzimidazole derivatives through a simple, and efficient synthetic route starting from commercially available epoxides and alkyl halides. The structures of all the synthesized compounds were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, and MS spectra, and their antifungal activities were evaluated against *C. albicans, C. neoformans, A. niger*, and *M. gypseum*. Most of the synthesized compounds were found to have in vitro antifungal activities in varying degrees from poor to excellent against all tested fungi. Among them, those that have imidazoles and phenylpropyl substituent showed very good to excellent antifungal activities. Hence, the present study strongly suggest that the target compounds **6a–6d** and **5b** which contain imidazole core, should be potential candidates for in vivo bioassay analysis and as lead compounds for the development of novel fungicides. The molecular docking study showed that the moderate to good affinity of all the new targeted compounds and the highly bioactive **6b**, 1-[2-Phenyl-2-(3-phenyl-propoxy)-ethyl]-1H-imidazole, could bind with the active sites of cytochrome P450 through the hydrogen bonding. Further investigation, including the in vivo evaluation and some effect of structure on antifungal activities, such as other azole rings, substituent on aromatic nuclei, and the length of the linker at aromatic group are now in progress in our group.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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