Full Paper

Design, Synthesis and Antifungal Activity of Some New Imidazole and Triazole Derivatives

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Triazole and imidazole are incorporated into the structures of many antifungal compounds. In this study a novel series of 1,2,4-triazole, imidazole, benzoimidazole, and benzotriazole derivatives was designed as inhibitors of cytochrome P450 14α-demethylase (14DM). These structures were docked into the active site of MT-CYP51, using Autodock program. Sixteen compounds with the best binding energy were synthesized. The chemical structures of the new compounds were confirmed by elemental and spectral (^{1}H-NMR and Mass) analyses. All compounds were investigated for antifungal activity against *Candida albicans*, *Candida tropicalis*, *Candida glabrata*, *Candida parapeilosis*, *Candida kruzei*, *Candida dubliniensis*, *Aspergillus fomigatus*, *Aspergillus flavus*, *Microsporum canis*, *Microsporum gypseum*, *Trichophyton mentagrophyte*, *Epidermophyton floccosum*. Some compounds showed excellent in-vitro antifungal activity against most of the tested fungi. Compounds **2**, **9**, and **10** had antifungal activity against several resistant fungi against fluconazole and itraconazole.

Keywords: Antifungal activity / Docking / Imidazole / Triazole

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Introduction

In recent years, systemic fungal infections have become increasingly common, especially in the immunocompromised hosts with cancer or AIDS and in organ transplant cases [1, 2]. Among the antifungal agents, azoles were used widely in treatment of fungal infections. Recent epidemiological trends have confirmed the increasing importance of the infections caused by resistant fungal species to azoles [3]. Azole antifungals act by inhibiting lanosterol cytochrom P450 14-α-demethylase (CYP51) [4]. CYP51 is an essential enzyme in the sterol biosynthetic pathway in eukaryotes, where inhibition by azole drugs in fungi leads to a depletion of ergosterol [5].

The imidazoles are one of the two major classes of antifungal azole derivatives. Many of these drugs are limited in their clinical use by their spectrum of activity, potency, solubility, or side effects, but the imidazole group has contributed significantly to the therapy of both superficial and systemic mycotic infections. Newer antifungal imidazole derivatives are being developed and this chemical group is well represented with numerous clinically useful drugs [6].

Antifungal triazole derivatives presently under development represent a much needed advance in the field of antifungal chemotherapy. They are the second major chemical group of antifungal azole derivatives. In general, the triazole group appears to have a broader spectrum of antifungal activity and reduced toxicity when compared with the imidazole antifungal drugs [6]. There are many reports on the structure activity relationships of imidazole and triazole derivatives that show not only azole rings but also other moieties in the structure and streoisomerism of the molecule are effective on antifungal activity [7–9].

In this line, we have recently reported synthesis and also antifungal activity of several imidazole and triazole derivatives [10–12]. Here a series of azole compounds were designed by a generating virtual library of compounds. We investigated the active site of the MT-CYP51 (PDB code, 1E9X) using

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Autodock program and the structures were docked into the active site of this enzyme. In addition, we synthesized, and investigated antifungal activity of some new 1,2,4-triazole, benzotriazole, imidazole and benzimidazole analogues.

Chemistry

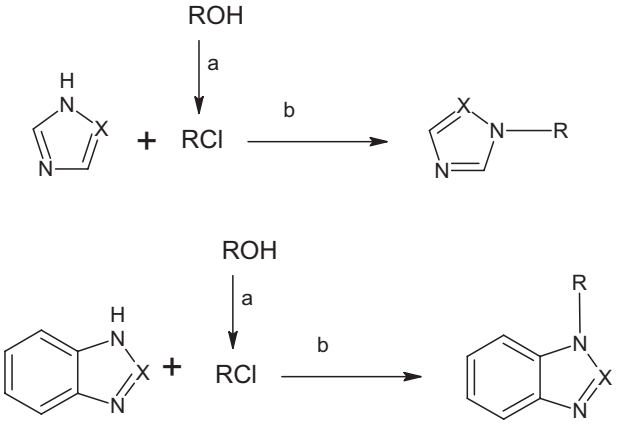
All compounds were prepared according to the method previously described with minor modification [10]. Imidazole or triazole, alkyl halide, potassium bicarbonate, tetraethylammonium iodide (TEAI) and NaOH in acetonitrile (30–40 mL) were refluxed for 24–48 h. Then, the reaction mixture was filtered and the solid was washed with acetonitrile. The solvent was evaporated *in vacuo* and the residue was washed with water and dichloromethane. The organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography using chloroform/ethanol for triazole and imidazole derivatives and dichloromethane/ethyl acetate for benzotriazole and benzimidazole derivatives to get the final compounds. The yield of reactions was 30–66.6% (Table 1). The synthetic route to these compounds is shown in Scheme 1.

As all alkyl halide used for these reactions were not commercially available, some of them were prepared from appropriate alcohols using $SOCl_2$ (Scheme 1).

Results and discussion

Modeling

All the compounds as well as fluconazole were docked into the active site of 14a-demethylase, which was obtained from Protein Data Bank (1E9X) using Autodock 3.0.5. All new azole compounds were characterized by a docking mode in the active site of the cytochrome P450 14-α-sterol demethylase. According to the data of FDEs, compound **11** had the maximum negative FDE and compound **13** had the lowest negative FDE (Table 2). Although most of compounds had FDE more than fluconazole, compounds **1**, **2**, **6**, **7** showed antifungal activities more than fluconazole. Therefore, there is no correlation between antifungal activity and FDE.



Scheme 1. X=N or C, (a) $SOCl_2$, pyridine, (b) NaOH, K_2CO_3, TEAI, acetonitrile.

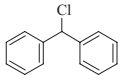
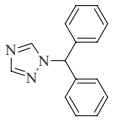
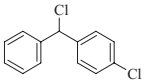
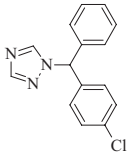
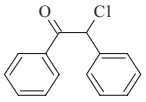
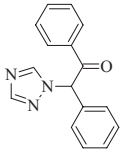
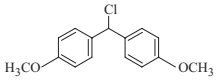
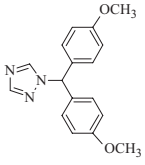
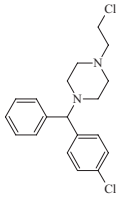
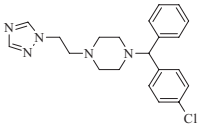
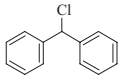
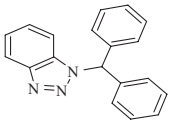
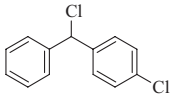
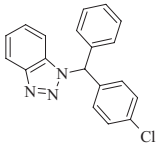
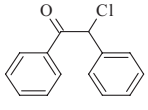
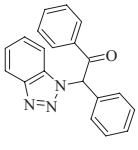
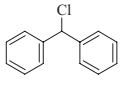
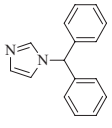
Antifungal Assay

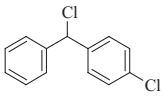
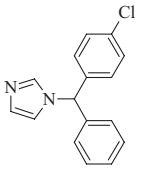
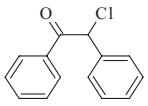
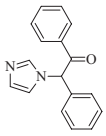
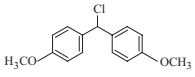
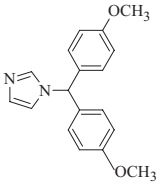
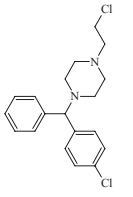
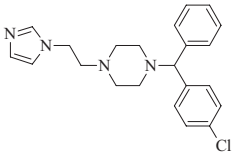
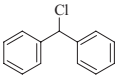
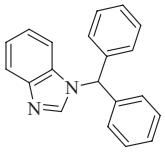
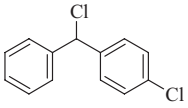
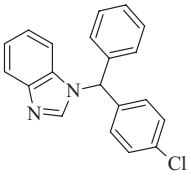
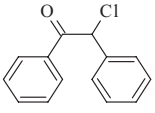
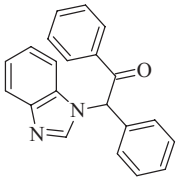
The stock solution of compounds was prepared in DMSO at a concentration of 200 mg/mL. Agar dilution assay and microdilution method were used to establish the minimum inhibitory concentration (MIC) as well as minimum fungicidal concentration (MFC) of synthetic derivatives [13, 14]. The compounds were diluted in solid and broth media to obtain final concentration from 0.0312 to 256 μg/mL, using PDA and RPMI 1640 media. The inocula of the molds and yeasts were prepared from 2-7 days mature colonies grown. Fluconazole and itraconazole or griseofulvin, depending on the kind of fungus was used as positive and the solvents of the compounds as negative blanks. The results are presented in Tables 3, 4, and 5. As shown in Table 4, compounds **1**, **2**, **3**, **9**, **10**, and **16** had good antifungal effects against tested clinical species of Candida. Some compounds like compounds **9** and **10** showed the most antifungal activity against *Candida tropicalis* and *Candida albicans*, which were resistant to fluconazole as well as itraconazole. Compounds **3**, **5**, **9**, **10**, and **16** had the most antifungal activity against standard species of *Candida* (Table 3). The result of antifungal assay against *Aspergillus* species showed that compounds **1**, **2**, **3**, **9**, and **10** had good activities (Table 5). All of the compounds also were tested against several *Dermatophytes* such as *Trichophyton mentagrophyte*, *Epidermophyton floccosum* and the compounds **1**, **2**, **3**, **5**, **8**, **9**, **10**, **11**, **15**, **16** had the most antifungal activities (Table 5). As shown in Tables 3, 4, and 5, compounds **3**, **9**, and **10** had antifungal activity against all the tested fungi and compounds **12**, **13**, and **14** did not show any antifungal effect against investigated fungi in range 0.0312 to 256 μg/mL.

SAR

The structural activity study shows that antifungal activity is dependent on the heterocyclic moiety as well as on the nature of the substituents. The best MFC was 0.5 μg/mL that was observed for compounds **9** against clinical *Candida albicans* and **10** against standard *Candida albicans* and *Candida kruzei*. Compounds **9** and **10** were also effective against all the tested fungi; these compounds have imidazole ring and smaller size than the other compounds. Also, these compounds are very close to clotrimazole and may be attributed to the better penetration into fungi cell. In series benzimidazoles, compound **14** did not have any antifungal activity but compounds **15** and **16** showed moderate to low antifungal activities. The benzotriazoles derivatives also showed very low antifungal effect against investigated fungi exception

Table 1. Synthesis of compounds **1**–**16**.

Entry	Azole ring	Alkyl or aryl halide	Product	Time [h]	Yield [%]
1				24	55
2				24	36
3				24	40
4		 (**4a**)		24	30
5		 (**5b**)		24	30
6				48	49
7				48	48
8				48	49
9				24	66.6

10				24	50
11				30	46.6
12		 (**4a**)		24	40
13		 (**5b**)		38	40
14				36	53
15				36	56.6
16				36	66.6

(4a) and **(5b)** were prepared from appropriate alcohols using $SOCl_2$ (Scheme 1).

Microsporum canis. Although it has been reported that a series of 2-(4-methoxy-phenyl)-1,2,4-triazole [15] and some methoxyquinoline triazole derivatives [16] showed good antifungal activity, here the activity decreased by introduction of methoxy group on triazoles as well as imidazole derivatives. Furthermore, the compounds with two methoxy groups in imidazole series like compound **12** did not show any antifungal activity. We have previously reported that the antifungal activity was decreased by the presence of methoxy group on benzotriazoles derivatives, too [10]. Introducing of ethyl piperazine moiety in compound **13** resulted in reduced antifungal activity, compared to compound **10**. However, there is no correlation between FDE and antifungal activity for all cases, and compounds with low antifungal effect like compound **12** and **13** have the lowest negative FDE value (Table 2).

Table 2. Docking results of synthesized compounds into the active site of MT-CytP51 (1E9X).

Entry	log*p*	Final docking energy
1	1.9	−10.53
2	1.67	−11.02
3	2.25	−11.07
4	−0.09	−9.28
5	1.45	−9.04
6	2.34	−11.42
7	2.11	−12.47
8	2.69	−9.68
9	1.37	−10.51
10	1.15	−10.65
11	1.72	−13.84
12	−0.61	−8.42
13	0.93	−8.32
14	1.63	−8.88
15	1.41	−11.39
16	1.98	−10.66
Fluconazole	0.84	−9.88

Conclusion

In conclusion, we have synthesized a series of 1,2,4-triazole, benzotriazole, imidazole, and benzimidazole derivatives. These compounds were evaluated against some yeasts and molds. Among the synthesized compounds, compounds **3**, **9**, and **10** showed antifungal activity against all tested microorganism and compounds **12**, **13**, and **14** did not show any antifungal effect against the investigated fungi in range 0.0312 to 256 μg/mL. Some compounds like **9** and **10** had antifungal activity against tested clinical species of *Candida* which were resistant to fluconazole as well as itraconazole. Furthermore, there is no correlation found between FDE and log*p* with antifungal activity.

Experimental

All solvents and reagents were purchased from Sigma or Merck Chemical Companies. The products were purified by column chromatography techniques. NMR spectra were recorded on a Brucker Avance DPX 250 MHZ instrument. Mass spectra were recorded on a Hewlett-Packard GC-MS.

Molecular Docking

The ligands were drawn in the Hyperchem 7.5. The geometry was optimized through the molecular dynamic method AMBER and semi-empirical method AM1. The protein was obtained from Protein Data Bank (1E9X) and then water molecules were removed from the protein for docking.

The Autodock software version 3.0.5 was used for the molecular docking process. The grids were constructed around the proteins. The Lamarckian Genetic Algorithm method was used for the global optimum binding position search. A number of 100 cycles of calculation were used in order to get a final binding position as accurate as possible. All the compounds as well as fluconazole were docked into the active site of 14α-demethylase. The complex of ligand-receptor was viewed by Accelry's Discovery Studio Visualizer. The docking procedure was run and the maximum negative final docking energy (FDE) was calculated (Table 2).

Table 3. *In-vitro* antifungal activities of compounds **1–16** against standard species of *Candida*.

Compound	Tested fungi (MIC 90% and MFC μg/mL)											
	C. albicans		***C. tropicalis***		***C. glabrata***		***C. parapeilosis***		***C. kruzei***		***C. dubliniensis***	
	MIC	**MFC**	**MIC**	**MFC**	**MIC**	**MFC**	**MIC**	**MFC**	**MIC**	**MFC**	**MIC**	**MFC**
1	32	>256	1	256	0.5	256	64	128	>256	>256	8	256
2	32	64	0.5	64	0.5	128	256	>256	256	256	4	64
3	64	128	16	256	16	128	64	>256	>256	>256	4	256
4	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
5	32	32	>256	>256	32	256	64	256	>256	>256	NT	NT
6	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
7	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
8	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
9	1	64	1	32	0.5	0.5	0.5	16	0.5	2	0.5	1
10	0.5	0.5	2	32	0.5	2	8	32	0.5	0.5	0.5	16
11	>256	>256	256	128	128	256	>256	>256	>256	>256	128	256
12	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
13	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
14	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
15	16	>256	>256	>256	>256	>256	>256	>256	>256	>256	128	>256
16	64	–	64	64	64	256	128	128	128	128	32	256
Fluconazole	>256	>256	32	>256	4	>256	2	16	16	>256	1	>256
Itraconazole	>256	>256	>256	>256	0.06	>256	0.03	0.25	0.03	0.06	>256	>256

NT = not tested

Table 4. *In-vitro* antifungal activities of compounds **1–16** against clinical species of *Candida*.

Compound	Tested fungi (MIC 90% and MFC μg/mL)									
	C. albicans		***C. tropicalis***		***C. parapeilosis***		***C. albicans*** (resistant to fluconazole and itraconazole)		***C. tropicalis*** (resistant to fluconazole and itraconazole)	
	MIC	**MFC**	**MIC**	**MFC**	**MIC**	**MFC**	**MIC**	**MFC**	**MIC**	**MFC**
1	8	256	16	>256	64	>256	8	>256	>256	>256
2	0.5	128	8	256	256	256	0.5	256	256	256
3	4	256	8	256	256	256	>256	>256	>256	>256
4	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
5	32	64	64	256	NT	NT	NT	NT	NT	NT
6	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
7	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
8	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
9	0.5	0.5	1	64	0.5	128	0.5	32	64	256
10	0.5	16	4	32	2	32	8	64	4	4
11	>256	>256	>256	>256	256	256	>256	>256	>256	>256
12	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
13	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
14	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
15	64	256	64	>256	>256	>256	256	>256	>256	>256
16	64	128	64	256	128	>256	32	>256	128	128
Fluconazole	2	>256	4	>256	0.25	0.5	R	R	R	R
Itraconazole	0.03	>256	1	>256	0.125	0.25	R	R	R	R

NT = not tested
R = resistant

General procedures for the synthesis of compounds

Four millimoles of azole compound (1, 2, 4-triazole, 1,2,3-benzotriazole, imidazole or benzimidazole) and 3 mmol of aryl or alkyl halide were added to a solution of tetraethyl ammonium iodide (0.065 g, 0.25 mmol), anhydrous potassium carbonate (0.55 g, 4 mmol), and sodium hydroxide (0.16 g, 4 mmol) in acetonitrile and then stirred for 24–48 h at reflux temperature. Then, the reaction mixture was filtered and the solid washed with aceto-

Table 5. *In-vitro* antifungal activities of compounds **1–16** against *Aspergillus* and *Dermatophytes*.

Compound	Tested fungi (MIC μg/mL)					
	A. fumigatus	***A. flavus***	***T. mentagrophytes***	***T. mentagrophytes***	***M. canis***	***M. gypseum***
	MIC	**MIC**	**MIC**	**MIC**	**MIC**	**MIC**
1	32	64	16	4	1	64
2	32	256	**32**	16	0.5	64
3	128	256	**32**	64	8	64
4	>256	>256	>256	>256	8	>256
5	256	>256	>256	64	2	>256
6	>256	>256	>256	>256	8	>256
7	>256	>256	>256	>256	2	>256
8	>256	256	>256	256	16	>256
9	0.5	0.5	1	0.5	1	0.5
10	4	0.5	0.5	0.5	1	8
11	>256	128	128	64	32	>256
12	>256	>256	>256	>256	>256	>256
13	>256	>256	>256	>256	>256	>256
14	>256	>256	>256	>256	>256	>256
15	>256	>256	32	64	8	>256
16	64	128	128	128	64	128
Fluconazole	4	NT	NT	NT	NT	NT
Griseofulvin	NT	NT	5	1	0.6	8

NT = not tested

nitrile. The solvent was evaporated *in vacuo* and the residue was washed with water and dichloromethane. The organic layer was dried over Na_2SO_4 and then evaporated *in vacuo*.

*1-(Diphenylmethyl)-1H-1,2,4-triazole (**1**)*

The reaction time was 24 h (55%, mp: 52°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.00 (s, 1H, triazole), 7.89 (s, 1H, triazole), 7.08–7.39 (m, 10H, phenyl), 6.74 (s, 1H CH). MS (*m*/*z* %) 235 (M^+, 100), 165 (100), 89 (51), 77 (100), 51 (74). Anal. calcd. for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86; Found: C, 76.41; H, 5.21; N, 17.1.

*1-[(4-Chlorophenyl)(phenyl)methyl]-1H-1,2,4-triazole (**2**)*

This compound was synthesized after 24 h (40%, mp: 55°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.00 (s, 1H, triazole), 7.9 (s, 1H, triazole), 7.02–7.45 (m, 9H, phenyl), 6.7 (s, 1H, CH). MS (*m*/*z* %) 271 (M + 2, 31), 269 (M^+, 100), 201 (100), 165 (100), 152 (16), 89 (5), 77 (31), 51(9). Anal. calcd. for $C_{15}H_{12}ClN_3$: C, 66.79; H, 4.48; N, 15.58; Found: C, 67.31; H, 4.58; N, 15.29.

*1,2-Diphenyl-2-(1H-1,2,4-triazol-1-yl)ethanone (**3**)*

The reaction time was 24 h (40%, mp: 55°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.06 (s, 1H, triazole), 7.69 (s, 1H, triazole), 7.23–7.54 (m, 10H, phenyl), 7.17 (s, 1H CH). MS (*m*/*z* %) 263 (M^+, 12.5), 174 (12), 105 (100), 77 (100), 51 (24). Anal. calcd. for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96; Found: C, 73.21; H, 5.15; N, 14.1.

*1,1′-(Chloromethylene)bis(4-methoxybenzene) (**4a**)*

This product obtained from the reaction of 500 mg 4,4′-dimethoxy benzhydrol and 10 mL thionyl chloride in the presence of pyridine under reflux condition. The time of reaction was 16 h and the yield was 50% with mp: 58°C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.82–7.26 (m, 8H, phenyl), 6.26 (s, 1H, CH), 3.78 and 3.89 (2s, 6H, OCH_3). MS (*m*/*z* %) 264 (M + 2, 4), 262 (M^+, 12), 227 (100), 197 (14), 153 (12), 77 (16). Anal. calcd. for $C_{15}H_{15}ClO_2$: C, 68.57; H, 5.75; Found: C, 69.01; H, 6.15.

*1-[bis(4-Methoxyphenyl)methyl]-1H-1,2,4-triazole (**4**)*

This compound was synthesized from 2 mmol (523 mg) **4a** and 3 mmol (207.21 mg) triazole according the general procedure. The reaction time was 24 h (30%, mp: 57°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.78 (s, 1H, triazole), 7.77 (s, 1H, triazole), 6.8–7.23 (m, 8H, phenyl), 5.26 (s, 1H, CH), 3.76–3.86 (s, 6H, OCH_3). MS (*m*/*z* %) 295 (M^+, 100), 265 (100), 233 (100), 228 (14), 197 (15), 167 (9), 31 (11). Anal. calcd. for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23; Found: C, 69.81; H, 5.10; N, 14.09.

*2-{4-[(4-Chlorophenyl)(phenyl)methyl]piperazino}-1-ethanol (**5a**)*

This product obtained after 20 h (60%, mp: 61°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.2–7.36 (m, 9H, phenyl), 4.21 (s, 1H, CH), 3.58–3.6 (t, 3H, OH and CH_2), 2.54 (t, 2H, N–CH_2), 2.18–2.42 (m, 8H, piperazine). MS (*m*/*z* %) 332 (M + 2, 31), 330 (M^+, 100), 312 (17), 271 (20), 256 (19), 203 (100). 179 (12), 165 (100), 129 (100), 86 (43), 74 (36), 42 (40). Anal. calcd. for $C_{19}H_{23}ClN_2O$: C, 68.97; H, 7.01; N, 8.47; Found: C, 68.91; H, 5.71; N, 8.12.

*1-(2-Chloroethyl)-4-[(4-chlorophenyl)(phenyl)methyl]-piperrazine (**5b**)*

This product obtained from reaction between 2 mmole (661 mg) **5a** and 15 mL thionyl chloride in the presence of pyridine under reflux condition. The time of reaction was 16 h and the yield was 30%. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.2–7.36 (m, 9H, phenyl), 4.27 (s, 1H, CH), 3.58–3.59 (t, 2H, CH_2Cl), 2.54 (t, 2H, CH_2N), 2.18–2.42 (m, 8H, piperazine). MS (*m*/*z* %) 353 (M + 4, 1.7), 351(M + 2, 10) 349 (M^+, 16), 312 (74), 285 (14), 256 (13), 202(100), 179 (16), 125 (21), 165 (100), 147 (100), 84 (42), 70 (16) 42 (28). Anal. calcd. for $C_{19}H_{22}Cl_2N_2$: C, 65.33; H, 6.35; N, 8.02; Found: C, 64.81; H, 5.83; N, 7.97.

*1-[(4-Chlorophenyl)(phenyl)methyl]-4-[2-1H-1,2,4-triazole-1-yl)ethyl]piperazine (**5**)*

This product obtained from the reaction of 1 mmol (349 mg) **5b** and 2 mmol (139 mg) 1,2,4-triazole according to the general procedure. The reaction time was 24 h and the yield was 30% (mp: 67°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.17 (s, 1H, triazole), 7.91 (s, 1H, triazole), 7.20–7.71 (m, 9H, phenyl), 4.19 (s, 1H, CH), 4.24–4.30 (t, 2H, CH_2N-triazole), 2.78–2.81 (t, 2H, CH_2N-piperazine), 2.50 (m, 8H, piperazine). MS (*m*/*z* %) 383 (M + 2, 19), 381 (M^+, 67), 201 (100), 179 (100), 166 (100), 150 (19), 111 (42), 97 (44) 83 (46), 68 (29), 42 (44). Anal. calcd. for $C_{21}H_{24}ClN_5$: C, 66.04; H, 6.33; N, 18.34; Found: C, 66.28; H, 6.17; N, 18.03.

*1-(Diphenylmethyl)-1H-1,2,3-benzotriazole (**6**)*

This compound was synthesized after 48 h (49%, mp: 67°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.22–7.40 (m, 14H, H-Ar), 7.10 (s, 1H, CH). MS (*m*/*z* %) 285 (M^+, 42), 167 (100), 139 (13), 89 (10), 77 (59), 64 (20), 51 (26), 39 (14). Anal. calcd. for $C_{19}H_{15}N3$: C, 79.98; H, 5.30; N, 14.75; Found: C, 80.15; H, 5.84; N, 15.00.

*1-[(4-Chlorophenyl)(phenyl)methyl]-1H-1,2,3-benzotriazole (**7**)*

This compound was synthesized after 48 h (48%, mp: 66°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.15–8.11 (m, 13H, H-Ar), 7.11 (s, 1H, CH). MS (*m*/*z* %) 321 (M + 2, 30), 319 (M^+, 100), 201 (100), 165 (80), 152 (41), 127 (18), 115 (12), 89 (10), 77 (42), 63 (16), 51 (14). Anal. calcd. for $C_{19}H_{14}ClN_3$: C, 71.36; H, 4.41; N, 13.14; Found: C, 71.21; H, 4.13; N, 13.01.

*2-(1H-1,2,3-Benzotriazol-1-yl)-1,2-diphenylethanone (**8**)*

This compound was synthesized after 48 h (48%, mp: 66°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.15–8.11 (m, 13H, H-Ar), 7.11 (s, 1H, CH). MS (*m*/*z* %) 319 (M^+, 100), 201 (100), 165 (80), 152 (41), 127 (18), 115 (12), 89 (10), 77 (42), 63 (16), 51 (14). Anal. calcd. for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41; Found: C, 76.14; H, 4.22; N, 12.99.

*1-(Diphenylmethyl)-1H-imidazole (**9**)*

This compound was synthesized after 24 h (66.6%, mp: 55°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.37 (s, 1H, N–CH–N-imidazole), 7.35–7.06 (m, 10H, phenyl), 6.82 (s, 1H, imidazole), 6.49 (s, 1H, imidazole), 5.42 (s, 1H, CH). MS (*m*/*z* %) 234 (M^+, 100), 168 (80), 77 (80), 51 (20). Anal. calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96; Found: C, 82.65; H, 5.83; N, 11.73.

*1-[(4-Chlorophenyl)(phenyl)methyl]-1H-imidazole (**10**)*

This compound was synthesized after 24 h (50%, mp: 56°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.37 (s, 1H, N–CH–N-imidazole), 7.34–7.01 (m, 9H, phenyl), 6.98 (s, 1H, imidazole), 6.76 (s, 1H, imidazole), 6.46 (s, 1H, CH). MS (m/z %) 270 (M + 2, 13), 268 (M^+, 43), 201 (100), 166 (80), 77 (29), Anal. calcd. for $C_{16}H_{13}ClN_2$: C, 71.51; H, 4.88; N, 10.42; Found: C, 71.55; H, 4.71; N, 10.17.

*2-(1H-imidazol-1-yl)-1,2-diphenylethanone (**11**)*

The time of reaction was 24 h (46.6%, mp = 62°C). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.97 (s, 1H, N–CH–N–imidazole), 7.94–2354 (m, 10H, phenyl), 7.07 (s, 1H, imidazole), 5.94 (s, 1H, imidazole), 5.88 (s, 1H, CH). MS (*m*/*z* %) 262 (M^+, 13), 194 (2), 105 (100), 77 (42), 51 (4). Anal. calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68; Found: C, 77.12; H, 5.18; N, 10.11.

*1-[bis(4-Methoxyphenyl)methyl]-1H-imidazole(**12**)*

This compound was synthesized from 3 mmol (787.5 mg) **4a** and 4 mmol (272.3 mg) imidazole according the general procedure. The reaction time was 24 h (40%, mp: 57°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.78 (s, 1H, N–CH–N–imidazole), 7.77–6.92 (m, 8H, phenyl), 6.83 (s, 1H, imidazole), 6.8 (s, 1H, imidazole), 5.26 (s, 1H, CH), 3.86–3.76 (s, 6H, OCH_3). MS (*m*/*z* %) 294 (M^+, 15), 232 (100), 227 (100), 196 (41), 165 (16), 67 (31), Anal. calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52; Found: C, 73.06; H, 6.81; N, 9.09.

*1-[(4-Chlorophenyl)phenylmethyl]4-(ethylimidazole)-piperazine (**13**)*

This product obtained from the reaction of 1 mmol (349 mg) **5b** and 2 mmol (136 mg) imidazole according to the general procedure. The reaction time was 24 h and the yield was 40% (mp: 65°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.77 (1H, N–CH–N-imidazole), 7.70 (s, 1H, imidazole), 7.03–7.51 (m, 9H, phenyl), 6.98 (s, 1H, imidazole), 4.19 (s, 1H, CH-diphenyl), 4.00–4.03 (t, 2H, CH_2N-triazole), 2.68–2.70 (t, 2H, CH_2N-piperazine), 1.00–2.50 (m, 8H, piperazine). MS (*m*/*z* %) 382 (M + 2, 14), 380 (M^+, 47), 345 (10), 313 (13), 201 (100), 181 (100), 167 (42), 111 (100), 97 (38). Anal. calcd. for $C_{22}H_{25}ClN_4$: C, 69.37; H, 6.62; N, 14.71; Found: C, 69.10; H, 5.81; N, 14.00.

*1-(Diphenylmethyl)-1H-benzimidazole(**14**)*

This compound was synthesized after 38 h (53%, mp: 67°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.84 (s, 1H, N–CH–N), 7.15–7.62 (m, 14H, HAr), 6.76 (s, 1H, CH). MS (*m*/*z* %) 284 (M^+, 100), 168 (100), 90 (32), 77 (31), 51 (18). Anal. calcd. for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85; Found: C, 83.92; H, 5.47; N, 9.73.

*1-[(4-Chlorophenyl)(phenyl)methyl]-1H-benzimidazole(**15**)*

This compound was synthesized after 36 h (56.6%, mp: 66°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.83 (s, 1H, N–CH–N), 7.15–7.62(m, 13H, HAr), 6.73 (s, 1H, CH). MS (*m*/*z* %) 320 (M + 2, 30), 318 (M^+, 100), 201 (100), 168 (50), 90 (31), 77 (16). Anal. calcd. for $C_{20}H_{15}ClN_2$: C, 75.35; H, 4.74; N, 8.79; Found: C, 75.18; H, 4.23; N, 8.51.

*2-(1H-Benzimidazol-1-yl)-1,2-diphenylethanone(**16**)*

This compound was synthesized after 36 h (66.6%, mp: 70°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.11 (s, 1H, N–CH–N), 7.30–7.72 (m, 14H, HAr), 7.26 (s, 1H, CH). MS (*m*/*z* %) 312 (M^+, 100), 207 (100), 194 (30), 105 (100), 77 (86), 51 (36). Anal. calcd. for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97; Found: C, 80.16; H, 4.95; N, 8.65.

Antifungal Assay

Microorganisms were obtained from the Mycology and Parasitology Departments of Shiraz University of Medical Sciences, southern Iran. Sabouraud dextrose agar (SDA), potato dextrose agar (PDA), oat meal, and RPMI 1640 were used for agar dilution and macrodilution methods. The clinical isolates of fungi including *Candida albicans*, *Candida tropicalis*, and *Candida parapeilosis* were purified and subcultured on SC, SCC, and PDA media before testing. The stock solution of compounds was prepared in DMSO at a concentration of 200 mg/ml. The compounds were diluted in solid and broth media to obtain final concentration from 0.0312 to 256 μg/mL, using PDA and RPMI 1640 media. The inocula of the molds and yeasts were prepared from 1-10 days mature colonies grown. Fluconazole and itraconazole or griseofulvin were used as positive and the solvents of the compounds as negative blanks.

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