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Short communication

# Design, synthesis, and antifungal activity of triazole and benzotriazole derivatives

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# ABSTRACT

This study describes the design, synthesis and evaluation of a novel series of 1.2.4-triazole and benzotriazole derivatives as inhibitors of cytochrome P450 14a-demethylase (14DM). The chemical structures of the new compounds were confirmed by elemental and spectral (<sup>1</sup>H NMR, <sup>13</sup>C NMR, Mass) analyses. Compounds were designed by a generating virtual library of compounds and docking them into the enzyme active site. Furthermore, they were found to have in vitro activity against Microsporum canis, Trichophyton mentagrophyte, Trichophyton rubrum, Epidermophyton floccosum, and Candida albicans comparable to fluconazole and clotrimazole.

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# 1. Introduction

The incidence of systemic fungal infections has been increasing dramatically due to an increase in the number of immunocompromised hosts. Patients undergoing anticancer chemotherapy, organ transplants or long treatment with antimicrobial agents and patients with AIDS are immunosuppressed and very susceptible to life threatening systemic fungal infections like candidiasis, cryptococcosis and aspergillosis. In recent years the developments of resistance to currently available antifungal azoles in *Candida* spp., as well as clinical failures in the treatment of fungal infections have been reported [1–4]. Triazole may be considered as a bioisostere of imidazole which is incorporated into the structures of many antifungal compounds [5]. With the aim of obtaining new antifungal compounds, we synthesized a series of triazole and benzotriazole derivatives.

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 [6]. The key interactions in the active site are these components: (i) the amidine nitrogen atom (N-3 in the imidazoles, N-4 in the triazoles) to bind to the heme iron of enzyme; (ii) aromatic rings; (iii) the large nonpolar portion of molecule [7].

Antifungal azoles, fluconazole with triazole ring and clotrimazole with imidazole ring are strong inhibitors of lanosterol 14 $\alpha$ -demethylase (cytochrome P-45014 $\alpha$ -DM) which have been widely used in antifungal chemotherapy. The fungicides containing triazole have high prevention and cure against fungi and have the function to increase the yield [8].

In this study a series of new 1,2,4-triazole and benzotriazoles related to clotrimazole and fluconazole were synthesized and then the compounds docked in the active site of  $14\alpha$ -demethylase using Autodock program. In addition we investigated the activity of the compounds against Microsporum canis, Trichophyton mentagrophyte, Trichophyton rubrum, Epidermophyton floccosum, and Candida albicans.

# 2. Chemistry

Triazole or benzotriazole rings, trityl moiety or alkyl halide, potassium bicarbonate, tetraethylammonium iodide (TEAI) and NaOH in acetonitrile (30-40 ml) were refluxed for 24-90 h. Then the reaction mixture was filtered and the solid washed with acetonitrile and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The filtered evaporated in vacuo and the crude product was purified by column chromatography using chloroform-ethanol for triazole derivatives and dichloromethane-ethyl acetate for benzotriazole derivatives to get the final compounds. The yield of reaction was 81-90%. The synthetic route to these compounds is shown in Scheme 1 for triazole derivatives and in Scheme 2 for benzotriazole derivatives.





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Scheme 1. Synthesis of 1,2,4-triazole derivatives.

There are several reports on alkylation of 1,2,4-triazole and 1,2,3benzotriazole [9–12]. 1,2,4-Triazoles can be alkylated on N<sub>1</sub> or N<sub>4</sub> and 1,2,3-benzotriazoles on N<sub>1</sub> or N<sub>2</sub>. The controlled, regioselective alkylation of them, is difficult. Our strategy was a modification of these methods to get N<sub>1</sub>-substituted of the azoles in higher yield. Therefore, we applied the acetonitrile as solvent, tetra ethyl ammonium iodide, anhydrous potassium carbonate, and sodium hydroxide as catalysts.

# 3. Modeling studies

The compounds were drawn in the hyperchem 7 and minimized using the AM1 method with a gradient cut-off of 0.01 Kcal/mol. The protein was obtained from Protein Data Bank (1E9X) and then water molecules were removed from the protein for docking. All the compounds as well as fluconazole were docked into the active site of  $14\alpha$ -demethylase using Autodock 3.0.5.

# 4. Antifungal assays

Microorganisms were obtained from the Mycology and Parasitology Department of the Shiraz University of Medical Sciences. Sabouraud dextrose agar (SDA), potato dextrose agar (PDA) and RPMI 1640 were used for agar dilution and macrodilution methods. The clinical isolates of fungi including *M. canis*, *T. mentagrophytes*, *T. rubrum*, *E. floccosum* and *C. albicans* 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 1000– 5000 µg/ml. The compounds were diluted in solid and broth media to obtain final concentration from 0.0625 to 4 µg/ml, using PDA and RPMI 1640 media. The inocula of the molds and yeast were prepared from 2- to 7-day mature colonies grown. Fluconazole and clotrimazole were used as positive and the solvents of the compounds as negative blanks.

#### 5. Results and discussion

#### 5.1. Modeling

We chose a number of different possibilities for the components in the compounds to interact with the active site of  $14\alpha$ demethylase. It is also important to select compounds which have drug-like properties. All the compounds have a molecular weight



Scheme 2. Synthesis of 1,2,3-benzotriazole derivatives.

 Table 1

 Docking results of synthesized compounds into the active site of MT-CvtP51 (1E9X)

Compound	Final docked energy (Kcal/mol)	log p	Molecular weight
1	-5.17	4.43	311
2	-6.55	4.68	341
3	-2.25	4.93	371
4	-4.37	5.38	361
5	-5.41	5.12	391
6	-2.87	4.87	421
7	-7.29	4.43	139
8	-8.73	4.45	181
9	-7.26	1.45	189
10	-9.77	3.03	231
Fluconazole	-10.55	0.84	306

ranging from 139 to 421 and the log *p* range of the molecules was between 1.4 and 5.3 (Table 1). The compounds were drawn in the hyperchem 7. 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. Docking score showed that these compounds docked to the active site of the enzyme comparable to fluconazole (Table 1). All new azole compounds plus fluconazole were characterized by a docking mode in the active site of the cytochrome P450 14 $\alpha$ -sterol demethylase. Trityl triazole derivatives (compounds 1-3) had more negative docking energy in comparison with trityl benzotriazole derivatives (compounds **4–6**). But alkyl derivatives (compounds **7–10**) docked to the active site of the enzyme with the most negative docking energy. There is some correlation between antifungal activity and docking energy. Thus for example compounds 8 and 9 show potent growth inhibition and have good docking energy. In other compounds there was a lower correlation between docking energy and growth inhibition as in antifungal assays. In these cases there are factors such as penetration that may be important.

# 5.2. Antifungal assays

The clinical isolates of fungi including *M. canis*, *T. mentagrophytes*, *T. rubrum*, *E. floccosum* and *C. albicans* 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 1000–5000 µg/ml. Agar dilution assay and macrodilution method were used to establish the minimum inhibitory concentration (MIC) of synthetic derivatives [13,14]. The compounds were diluted in solid and broth media to obtain final concentration from 0.0625 to 64 µg/ml, using PDA and RPMI 1640 media. The inocula of the molds and yeast were prepared from 2- to 7-day mature colonies grown.

Fluconazole and clotrimazole were used as positive and the solvents of the compounds as negative blanks. The results are

 Table 2

 Minimum inhibitory concentrations (MICs) of the synthesized compounds

Compound	T. mentagrophyte	C. albicans	T. rubrum	M. canis	E. floccosum
	MIC (µg/ml)	MIC (µg/ml)	MIC (µg/ml)	MIC (µg/ml)	MIC (µg/ml)
1	32	-	64	64	1
2	16	-	32	32	8
3	32	-	8	64	16
4	-	64	64	-	64
5	64	-	64	-	64
6	64	-	32	-	-
7	64	-	64	64	64
8	16	16	16	16	8
9	32	32	32	16	16
10	64	-	64	64	32
Clotrimazole	0.05	4	0.5	.065	4
Fluconazole	1	32	32	16	0.25

shown in Table 2. As shown in Table 2 all the compounds tested showed antifungal activity against *T. rubrum*. The structural activity study shows that antifungal activity is dependent on the heterocyclic moiety as well as on the nature of the substituents. The maximum inhibition was observed in compound **1** with the lowest MIC (1  $\mu$ g/ml) against *E. floccosum*. Compound **1** has smaller size than the other compounds and may be attributed to the better penetration into fungi cell. The benzotriazoles compounds **4**, **5**, and **6** had low antifungal activity. The activity was decreased by the presence of methoxy group on the triazoles and benzotriazoles moiety (compounds **2**, **3**, **5**, and **6**). Compounds **8** and **9** also possessed great inhibitory effect on tested fungus.

# 6. Conclusion

In conclusion 10 new compounds related to clotrimazole and fluconazole were synthesized and the major products were purified using column chromatography and then the structures of them were confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR and MS spectroscopies and elemental analysis. These compounds showed similar antifungal activity against some fungi to fluconazole and there was a correlation between docking energy and growth inhibition for some compounds.

# 7. 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.

# 7.1. General procedure for the synthesis of compounds

Four millimoles of 1,2,4-triazole (0.276 g) or 1,2,3-benzotriazole (0.476 g), 3 mmol of trityl moiety or alkyl halide were added to a solution of tetra ethyl 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 24–90 h at reflux temperature. After completion of the reaction, the suspension was filtered and the solid washed with acetonitrile ( $3 \times 10 \text{ ml}$ ) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The filtered evaporated by rotary evaporator. The product was purified by column chromatography using chloroform–ethanol as eluent to get the final compounds (Schemes 1 and 2).

#### 7.1.1. 1-Trityl-1H-1,2,4-triazole (1)

The time of reaction was 37 h (90%, mp = 204). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 8.06 (s, 1H, triazole), 8.03 (s, 1H, triazole), 7.36 (s, 6H, phenyls), 7.2–7.2 (m, 9H phenyls). <sup>13</sup>C NMR  $\delta$  (ppm): 142.5, 139.8, 131.2, 127.4, 125.5, 74.2. MS (*m*/*z* %) 311(M<sup>+</sup>, 100), 243 (100), 165 (55), 77 (28), 51 (12). Anal. Calcd for C<sub>21</sub>H<sub>17</sub>N<sub>3</sub>: C, 81.02; H, 5.46; N, 13.5; Found: C, 80.21; H, 5.65; N, 13.1.

#### 7.1.2. (4-Methoxyphenyl)(diphenyl)1H-1,2,4,-triazole-1ylmethane (**2**)

This product was synthesized after 27 h (87%, mp = 248). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 8.05 (s, 1H, triazole), 7.99 (s, 1H, triazole), 7.25–7.33 (m, 6H, phenyls), 6.81–7.15 (m, 8H, phenyls), 3.8 (s, 3H, OCH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  (ppm): 154.2, 141.5, 139.2, 131.5, 125.8, 122.1, 119.7, 74.3, 50.2. MS (*m*/*z* %) 341(M<sup>+</sup>, 50), 273 (100), 242 (5), 195 (12), 165 (24), 77 (23), 51 (7). Anal. Calcd for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>O<sub>1</sub>: C, 77.41; H, 5.57; N, 12.31; Found: C, 76.71; H, 5.35; N, 12.01.

# 7.1.3. 1-[Di(4-methoxyphenyl)(phenyl) methyl]-1H-1,2, 4-triazole (**3**)

The reaction completed after 24 h (83%, mp = 268). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 7.93 (s, 1H, triazole), 7.88 (s, 1H, triazole), 7.21 (s, 4H, phenyls), 7.18 (s, 2H, phenyls), 6.68–7.12 (m, 7H, phenyls), 3.69 (s, 3H, OCH<sub>3</sub>), 3.66 (s, 3H, OCH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  (ppm): 151.2, 140.1, 139.4, 130.8, 128.5, 124.5, 74.1, 52.3. MS (*m*/*z* %) 371 (M<sup>+</sup>, 45), 303 (100), 271 (12), 243 (100), 195 (15), 165 (10), 77 (50), 51 (7). Anal. Calcd for C<sub>23</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>: C, 74.39; H, 5.66; N, 11.32; Found: C, 72.29; H, 5.95; N, 10.98.

# 7.1.4. 1-Trityl-1H-1,2,3-benzotriazole (4)

This compound was synthesized after 63 h (90%, mp = 215). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 7.8 (d, 1H, J Hz = 6.4, benzotriazole), 7.2–7.3 (m, 6H, phenyls), 6.8–7.1 (m, 2H, benzimidazole and 9H, phenyls), 6.3 (d, 1H, *J* = 11.2 Hz, benzotriazole). <sup>13</sup>C NMR  $\delta$  (ppm): 151.6, 142.8, 135.9, 131.7, 125.7, 123.5, 121.4, 118.4, 81.7. MS (*m*/*z* %) 361(M<sup>+</sup>, 1), 243 (100), 165 (55), 77 (15), 51 (8). Anal. Calcd for C<sub>25</sub>H<sub>19</sub>N<sub>3</sub>: C, 76.72; H, 5.26; N, 11.63; Found: C, 77.91; H, 5.580; N, 11.29.

#### 7.1.5. 1H-1,2,3-Benzotriazol-1-yl(4-methoxyphenyl)diphenylmethane (5)

This compound was synthesized after 42 h (85%, mp = 220). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 7.3 (d, 1H, J Hz = 6.0, benzotriazole), 7.07–7.2 (m, 3H, benzotriazole and 9H, phenyls), 6.75–6.86 (m, 5H, phenyls), 3.7 (d, 3H, *J* = 8 Hz, OCH3). <sup>13</sup>C NMR  $\delta$  (ppm): 154.3, 150.2, 144.0, 131.1, 127.9, 119.9, 115.4, 79.8, 55.1. MS (*m*/*z* %) 391 (M<sup>+</sup>, 1), 273 (100), 243 (60), 195 (23), 165 (60), 77 (100), 51 (40). Anal. Calcd for C<sub>26</sub>H<sub>21</sub>N<sub>3</sub>O<sub>1</sub>: C, 79.79; H, 5.37; N, 10.74; Found: C, 77.71; H, 5.15; N, 10.31.

# 7.1.6. 1H-1,2,3,-Benzotriazol-1-yl[di(4methoxyphenyl)]phenylmethane (**6**)

This compound was synthesized after 24 h (81%, mp = 222). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 8.1 (d, 1H, *J* = 7.4 Hz, benzotriazole), 7.3–7.5 (m, 1H, benzotriazole and 6H, phenyls), 6.8–6.9 (d, 2H, *J* = 8 Hz, benzotriazole), 6.4–6.6 (m, 7H, phenyls), 3.7 (d, 6H, *J* = 7.1 Hz, (OCH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C NMR  $\delta$  (ppm): 155.7, 141.5, 139.8, 135.6, 132.8, 129.8, 119.5, 119.1, 81.2, 51.1. MS (*m*/*z* %) 421 (M<sup>+</sup>, 14), 303 (100), 273 (6), 243 (100), 165 (13), 77 (54), 51 (16). Anal. Calcd for C<sub>27</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>: C, 76.95; H, 5.46; N, 9.97; Found: C, 75.55; H, 5.63; N, 9.27.

#### 7.1.7. 1-Pentyl-1H-1,2,4,-triazole (7)

This compound was synthesized after 90 h (85%). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 8.03 (s, 1H, triazole), 7.84 (s, 1H, triazole) 4–4.22 (t, 2H, J = 4 Hz, N–CH<sub>2</sub>) 1.65–1.94 (m, 2H, N–CH<sub>2</sub>–CH<sub>2</sub>), 1.11–1.42 (m, 4H (–CH<sub>2</sub>–)<sub>2</sub>), 0.72–0.92 (t, 3H, J = 8 Hz, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  (ppm): 148.5, 52.8, 31.2, 29.7, 21.3, 15.8. MS (m/z%) 139 (M<sup>+</sup>, 14), 126 (17), 111 (15), 97 (15), 83 (20), 69 (35), 55 (50), 43 (100). Anal. Calcd for C<sub>7</sub>H<sub>13</sub>N<sub>3</sub>: C, 60.43; H, 9.35; N, 30.21; Found: C, 60.71; H, 9.15; N, 29.81.

# 7.1.8. 1-Octyl-1H-1,2,4,-triazole (8)

This compound was synthesized after 90 h (90%). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 8.04 (s, 1H, triazole), 7.92 (s, 1H, triazole) 4.07–4.24

(t, 2H, J = 6.8 Hz, N–CH<sub>2</sub>) 1.8–2 (m, 2H, N–CH<sub>2</sub>–CH<sub>2</sub>), 1.1–1.3 (m, 10H (–CH<sub>2</sub>–)<sub>5</sub>), 0.79–0.93 (t, 3H, J = 5.8 Hz, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  (ppm): 144.5, 51.4, 31.2, 30.2, 29.8, 26.5, 26.1, 22.4. MS (m/z %) 181(M<sup>+</sup>, 30), 152 (10), 97 (15), 97 (40), 83 (80), 70 (100), 55 (80), 41 (100). Anal. Calcd for C<sub>10</sub>H<sub>19</sub>N<sub>3</sub>: C, 66.29; H, 10.46; N, 23.2; Found: C, 65.45; H, 9.87; N, 22.74.

#### 7.1.9. 1-Pentyl-1H-1,2,3-benzotriazole (9)

This compound was synthesized after 42 h (83%, mp = 271.5). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 7.9–8 (d, 2H, *J* = 6.8, benzotriazole), 7.1–7.3 (d, 2H, *J* = 7.8 Hz, benzotriazole), 4.4 (t, 2H, *J* = 8 Hz, N–CH<sub>2</sub>), 1.8 (m, 4H (–CH<sub>2</sub>–)<sub>2</sub>), 0.7 (t, 3H, *J* = 8.1 Hz, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  (ppm): 145.5, 131.1, 126.8, 125.7, 118.4, 110.1, 50.5, 30.7, 22.1, 15.1. MS (*m*/*z* %) 189 (M<sup>+</sup>, 73), 174 (6), 161 (21), 146 (31), 132 (58), 118 (50), 91 (100), 66 (45), 43 (100). Anal. Calcd for C<sub>11</sub>H<sub>15</sub>N<sub>3</sub>: C, 69.84; H, 7.93; N, 22.22; Found: C, 68.73; H, 6.54; N, 21.77.

#### 7.1.10. 1-Octyl-1H-1,2,3,-benzotriazole (10)

This compound was synthesized after 72 h (81%, mp = 309.7). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm): 8.4–8.7 (m, 2H, benzotriazole), 7.9–8.1 (m, 2H, benzotriazole), 5.4 (t, 2H, *J* = 7.1 Hz, N–CH<sub>2</sub>), 2.8 (m, 2H, N–CH<sub>2</sub>–CH<sub>2</sub>–), 2.1(m, 8H, (–CH<sub>2</sub>–)<sub>4</sub>), 1.6 (m 2H, CH<sub>2</sub>–CH<sub>3</sub>), 0.7 (t, 3H, *J* = 7.1, CH<sub>3</sub>). <sup>13</sup>C NMR  $\delta$  (ppm): 141.5, 135.7, 129.3, 121.1, 115.7, 95.0, 86.2, 55.4, 51.9, 33.2, 20.1, 12.5. MS (*m*/*z* %) 231 (M+, 23), 202 (7), 188 (10), 174 (18), 160 (12), 146 (42), 132 (77), 119 (35). Anal. Calcd for C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>: C, 72.72; H, 9.09; N, 18.18; Found: C, 71.71; H, 8.99; N, 17.91.

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