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Design, synthesis, and biological evaluation of novel triazole derivatives as inhibitors of cytochrome P450 14α-demethylase

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ABSTRACT

Based on the results of computational docking to the active site of the cytochrome P450 14α-demethylase (CYP51), a series of 1-(1*H*-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanols as analogs of fluconazole were designed, synthesized, and evaluated as antifungal agents. The MIC_{80} values indicate that compounds **1a**–**n** exhibited higher activity against nearly all fungi tested except *Aspergillus fumigatus* than fluconazole, while compounds **2a**–**f**, **3a**–**f** showed no activity or only moderate activity against all fungi tested. Noticeably, the MIC value of compounds **1a**, **1b** and **1g** is 64 times lower than that of fluconazole against *Microsporum gypseum in vitro*. And compounds **1a**, **1b** and **2b** showed 128 times higher activity (with the MIC_{80} value of 0.0039 μg/mL) than that of fluconazole against *Candida albicans* and also showed higher activity than that of the other positive controls. Computational docking experiments indicated that the inhibition of CYP51 involves a coordination bond with iron of the heme group, the hydrophilic H-bonding region, the hydrophobic region, and the narrow hydrophobic cleft. In addition, the activity of the compounds would be enhanced when the side chains were shorter.

1. Introduction

In recent years, life-threatening systemic fungal infections have become increasingly common, especially in the immunocompromised hosts suffering from tuberculosis, cancer or AIDS and in organ transplant cases [1,2]. Several clinical drugs, such as azoles, amphotericin B, 5-fluorocytosine, and caspofungin, have been developed to reduce the impact of fungal diseases. Among those, azoles, especially triazole antifungal agents, were used widely and efficiently. For example, fluconazole, voriconazole and itraconazole (Fig. 1), presently play a leading role in the treatment of invasive fungal infections. These antifungal drugs act by inhibiting CYP51, a necessary enzyme in the biosynthesis of ergosterol, through a mechanism in which the heterocyclic nitrogen atom (N-4 of triazole) binds to the heme iron atom [3]. However, the increasing administration of antifungal agents has led to the development of fungal resistance. Survey reveals genetic mutations that result in resistance to clinically used drugs, especially fluconazole, may also result in resistance to new structurally related azoles such as voriconazole and ravuconazole [4–6]. The emergence of resistance shows the need of the discovery of new antifungal compounds which have broader antifungal spectra and higher therapeutic indexes than fluconazole. And we could also study more about the structure–activity for the inhibition of CYP51.

CYP51 is a member of the cytochrome P450 superfamily, which catalyzes the oxidative removal of the 14α-methyl group of (C-32) lanosterol via three successive monooxygenation reactions to give $\delta^{14,15}$-desaturated intermediates in ergosterol biosynthesis. The first two of these reactions are conventional cytochrome P450 hydroxylations that produce the 14-hydroxymethyl and 14-carboxyaldehyde derivatives of lanosterol [7,8]. In the final step, the 14-aldehyde group is eliminated as formic acid with concomitant introduction of a $\delta^{14,15}$ double bond [9–11]. The crystal structure of CYP51 of fungi has not been obtained. Ji et al. constructed a 3D model of *Candida albicans* CYP51. In general, the active site of CYP51 for ligand binding can be divided into four subsites: a coordination bond with iron of the heme group, the hydrophilic H-bonding region, the hydrophobic region, and the narrow hydrophobic cleft formed by the residues in the helix B'-meander 1 loop and

Abbreviations: *C. alb*, *Candida albicans*; *Cry. neo*, *Cryptococcus neoformans*; *C. par*, *Candida parapsilosis*; *C. tro*, *Candida tropicalis*; *T. rub*, *Trichophyton rubrum*; *C. kri*, *Candida Krusei*; *M. gyp*, *Microsporum gypseum*; *A. fum*, *Aspergillus fumigatus*; ICZ, itraconazole; KCZ, ketoconazole; FCZ, fluconazole; VCZ, voriconazole; AMB, amphotericin B; TRB, terbinafine.

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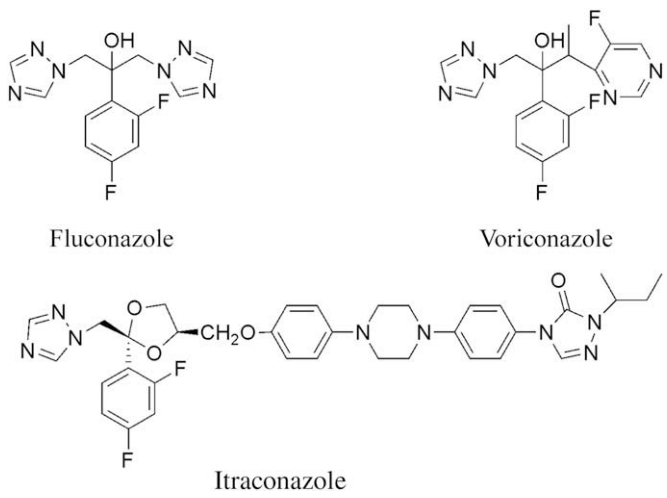


Fig. 1. Triazole antifungal agents used in clinical therapy.

N-terminus of helix I [12]. The analysis of the binding between fluconazole and CYP51 was shown in Fig. 2. Fluconazole binds to the active site of CYP51 via coordination of the N atom of the triazole nucleus with iron of the heme group. The difluorophenyl group is located in the hydrophobic binding cleft lined with Ala114, Phe126, Leu139, Met140, Phe145, Ile304, Met306 and Gly307. Several residues lined with Leu121, Thr122, Phe228, Thr311, Pro375, Leu376, His377, Ser378, Met508, Val509 and Val510 were observed to form indirect nonbonding interactions with another triazolyl ring.

Researches indicated that the triazole ring, the difluorophenyl group and the hydroxyl group were the pharmacophores of antifungal agents. But the side chains located in the narrow hydrophobic cleft were also important. We intended to alter the side chains to find potent systemic antifungal agents with a broad antifungal spectrum and less potential to develop resistance.

Based on the above results, we designed a series of 1-(1*H*-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanols (Fig. 3) containing a triazole ring, a difluorophenyl group, a hydroxyl group and a side chain. In the design, the N atom of the triazole was coordinated to iron atom of the heme, and the 2,4-difluorophenyl group could be located into the hydrophobic pocket. The side chain was designed to be oriented to the narrow hydrophobic cleft.

2. Chemistry

Compounds **1a–n** were prepared according to a very efficient and straightforward synthetic route outlined in Scheme 1. And compounds **2a–f** and **3a–f** were synthesized according to Scheme 2. After the key intermediate oxirane **7** was synthesized by a known procedure [13], the title compound **8** was synthesized by ring-open reaction of oxirane **7** with allylamine, and then was formed by adding the HCl gas. In the presence of KI and K_2CO_3 in acetonitrile at room temperature, the compound **8** was converted to the target compounds by reacting with various substituted benzyl bromide.

3. Pharmacology

The *in vitro* antifungal activities of all title compounds were evaluated against eight human pathogenic fungi, *C. albicans*, *Cryptococcus neoformans*, *Candida parapsilosis*, *Candida tropicalis*, *Trichophyton rubrum*, *Candida Krusei*, *Microsporum gypseum*, *Aspergillus fumigatus*, which are often encountered clinically, and were compared with fluconazole, itraconazole, ketoconazole, voriconazole, amphotericin B and terbinafine. *C. albicans* and *Cry. neoformans* were provided by Shanghai Changzheng Hospital; *C. parapsilosis*, *C. tropicalis*, *T. rubrum*, *C. Krusei*, *M. gypseum*, and *A. fumigatus* were provided by Shanghai Changhai Hospital. *C. albicans* and *Cry. neoformans* were purchased from ATCC, and other strains were clinic isolates. *C. albicans* (ATCC76615) and *Cry. neoformans* (ATCC32609) were used as the quality-controlled strains, and tested in each assay. Fluconazole (FLC), itraconazole (ICZ), ketoconazole (KCZ), voriconazole (VCZ), amphotericin B (AMB) and

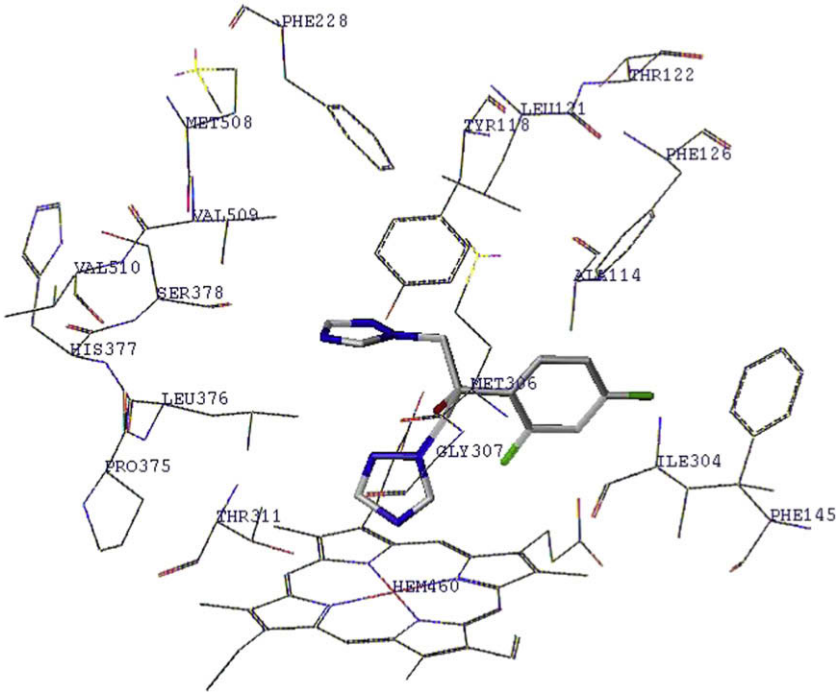


Fig. 2. Computed binding geometry of the clinical used inhibitor fluconazole in the active site of CYP51.

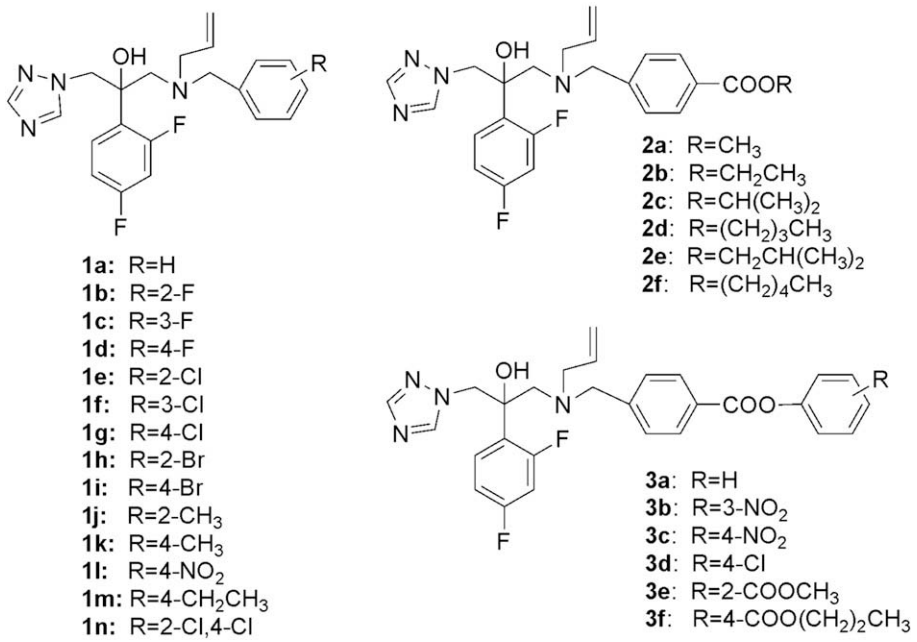


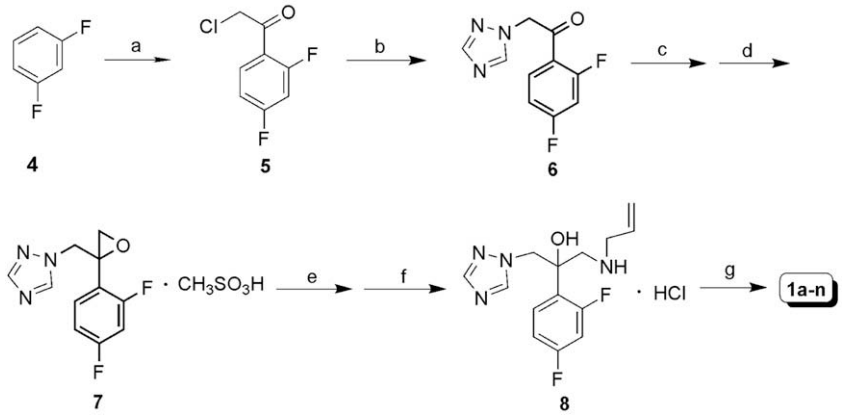
Fig. 3. All the compounds we designed and synthesized.

terbinafine (TRB) served as the positive control were obtained from their respective manufacturers.

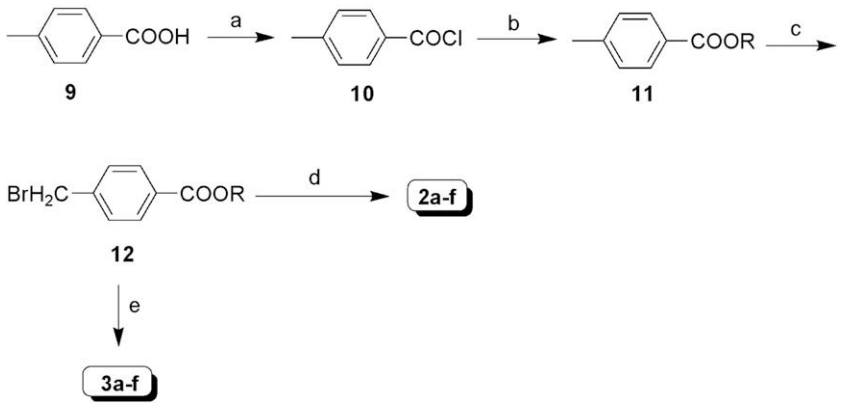
The *in vitro* minimal inhibitory concentrations (MICs) of the compounds were determined by the micro-broth dilution method in 96-well microtestplates according to the methods defined by the National Committee for Clinical Laboratory Standards (NCCLS) [14]. The MIC_{80} was defined as the first well with an approximate 80% reduction in growth compared to the growth of the drug-free well. For assays, the title compounds to be tested were dissolved in dimethyl sulfoxide (DMSO), serially diluted in growth medium, inoculated and incubated at 35 °C. Growth MIC was determined at 24 h for *C. albicans* and at 72 h for *Cry. neoformans*. The results of assays are summarized in Table 1. The data points form the mean of replicates. All of our susceptibility tests were performed three times by each antifungal agents.

4. Results and discussion

The MIC_{80} values indicate that compounds **1a**–**n** exhibited higher activity against nearly all fungi tested except *A. fumigatus* than fluconazole, while compounds **2a**–**f**, **3a**–**f** showed no activity or only moderate activity against nearly all fungi tested. Noticeably, the MIC value of compounds **1a**, **1b** and **1g** is 64 times lower than that of fluconazole against *M. gypseum in vitro*. And compounds **1a**, **1b** and **2b** showed 128 times higher activity (with the MIC_{80} value of 0.0039 μg/mL) than that of fluconazole against *C. albicans* and also showed higher activities than that of the other positive controls. These results clearly indicated that the substituted benzyl side chain greatly enhanced the antifungal activity of these analogs against *Candida* species, and that the amine side chain showed higher activity as it is shortened. In addition, despite the positive controls itraconazole and voriconazole showing cross-resistance to fluconazole-resistant strains of *C. albicans*, our target compounds **1a**–**n**, **2a**, **2b** and **3b** displayed certain extent of activities against these fluconazole-resistant strains. The *trichophyton* species *T. rubrum* was found to be much less sensitive to these derivatives, as indicated by their MIC_{80} values showing moderate to no activity. Because of the intrinsic mechanism resistant to triazole antifungals, the antifungal agents showed no activity to *A. fumigatus*.



Scheme 1. Synthesis of the benzyl derivatives **1a**–**n**. Conditions: (a) $ClCH_2COCl$, $AlCl_3$, 50 °C, 5 h, in 87% yield; (b) $C_6H_5CH_3$, $NaHCO_3$, 1*H*-1,2,4-triazole, reflux, 5 h, in 87% yield; (c) $C_6H_5CH_3$, $(CH_3)_3SOI$, NaOH, centylmethylammonium bromide, 60 °C, 3 h, in 86% yield; (d) CH_3SO_3H, 0 °C, 1 h, in 89% yield; (e) CH_3CH_2OH, Et_3N, allylamine, reflux, 6 h; (f) $HCl_{(g)}$, in 80–90% yield; (g) CH_3CN, KI, K_2CO_3, substituted benzyl bromide, rt, 5–6 h, in 50–70% yield.



Scheme 2. Synthesis of the *para*-benzoate derivatives **2a–f**, **3a–f**. Conditions: (a) $SOCl_2$, reflux, 4–5 h, in 95% yield; (b) alcohol or substituted phenol, CH_2Cl_2, Et_3N, 0–5 °C, 5–6 h, in 75–80% yield; (c) *N*-bromosuccimide, peroxybenzoic acid, CCl_4, reflux, 12 h,, in 70–78% yield; (d/e) compound **8**, CH_3CN, KI, K_2CO_3, rt, 5–8 h, in 40–60% yield.

To explain the results, we proposed a likely binding mode for **1b** to the active site of CYP51 based on computational docking results (Fig. 4). As usual, the triazole interacts with iron of the heme group, while the 2,4-difluorophenyl group in the designed compound could be placed into the hydrophobic pocket formed by Ala114, Phe126, Leu139, Met140, Phe145, Ile304, Met306 and Gly307 and the 2-chlorobenzyl group would generate π–π stacking interactions with the Tyr118. The latter two groups also incorporate to adjust the overall physical–chemical properties of the molecules and orientation of aromatic rings. In addition, the *N*-substituted group of the linker would be oriented to interact with a hydrophobic pocket formed by Leu121, Thr122, Phe228, Thr311, Pro375, Leu376, His377, Ser378, Met508, Val509 and Val510.

The side chains of the compounds **1a–n** we designed were rather short but the activity was very good. One reason was that the allyl group could improve the flexibility of the molecule making the phenyl group more easily lock its proper position, and the allyl group could form additional van der Waals interactions with the surrounding Ala117, Leu376, and Ile379. In addition, all of the side chains were of the pharmacophores, and the spatial orientations of the pharmacophores were just oriented in the hydrophobic pocket. The side chains of inhibitors were not the determinants for activity, but were very important. They played a role in adjusting the physico-chemical properties of the whole molecule to avoid some dissatisfying side effects and improve their pharmacokinetic and pharmacodynamic behaviors.

Table 1
Antifungal activities of the title compounds *in vitro* (MIC_{80}, μg/mL).

Compound	*C. alb*	*Cry. neo*	*C. par*	*C. tro*	*T. nru*	*C. kru*	*M. gyp*	*A. fum*
1a	0.0039	0.0625	0.0625	0.0625	0.25	0.0625	0.0039	>64
1b	0.0039	0.0625	0.0156	0.0625	0.25	0.0156	0.0039	>64
1c	0.0156	0.0625	0.0625	0.0625	0.25	0.0625	0.0156	>64
1d	0.0156	0.0625	0.0625	0.0625	1	0.0625	0.0156	>64
1e	0.0156	0.25	0.0625	0.25	1	0.0625	0.0625	>64
1f	0.0156	0.25	0.25	0.0625	1	0.0625	0.0625	>64
1g	0.25	0.25	0.25	0.25	0.25	0.0625	0.0625	16
1h	0.0625	0.25	0.25	0.0625	0.25	0.25	0.0156	>64
1i	0.0625	0.25	0.25	0.25	0.25	0.0625	0.0625	4
1g	0.0156	0.0625	0.0625	0.0625	0.0625	0.0625	0.0039	>64
1k	0.0156	0.0625	0.25	0.25	1	0.0625	0.0156	>64
1l	0.0156	0.25	0.0625	0.25	0.25	0.0625	0.0156	>64
1m	0.25	0.25	1	0.0156	1	0.25	0.0625	>64
1n	1	1	0.25	0.25	1	0.25	1	16
2a	0.0625	0.25	0.25	0.0625	0.25	0.0625	0.0156	>64
2b	0.0039	1	1	0.25	0.25	0.0625	0.25	>64
2c	0.25	1	1	1	1	0.25	0.0156	>64
2d	0.25	1	1	1	1	1	1	>64
2e	1	1	0.25	1	0.0625	1	0.25	>64
2f	1	1	1	1	0.25	1	1	>64
3a	1	1	1	1	16	1	1	>64
3b	0.25	1	0.25	0.0625	4	4	1	>64
3c	0.25	1	1	1	4	1	0.25	>64
3d	1	16	1	4	4	4	0.25	>64
3e	0.0625	>64	4	16	64	16	4	>64
3f	1	4	0.25	0.25	1	4	1	>64
ICZ	0.0625	0.125	0.125	0.125	0.125	0.5	0.0625	0.5
KCZ	0.0156	0.0625	0.0625	0.0625	0.0625	0.25	0.0156	1
FCZ	0.5	1	1	1	4	4	0.25	>64
VCZ	0.0156	0.0156	0.0039	0.0039	0.0625	0.0625	0.0039	0.25
AMB	2	2	2	2	2	2	2	64
TRB	4	1	0.25	0.0625	0.0625	16	4	0.0625

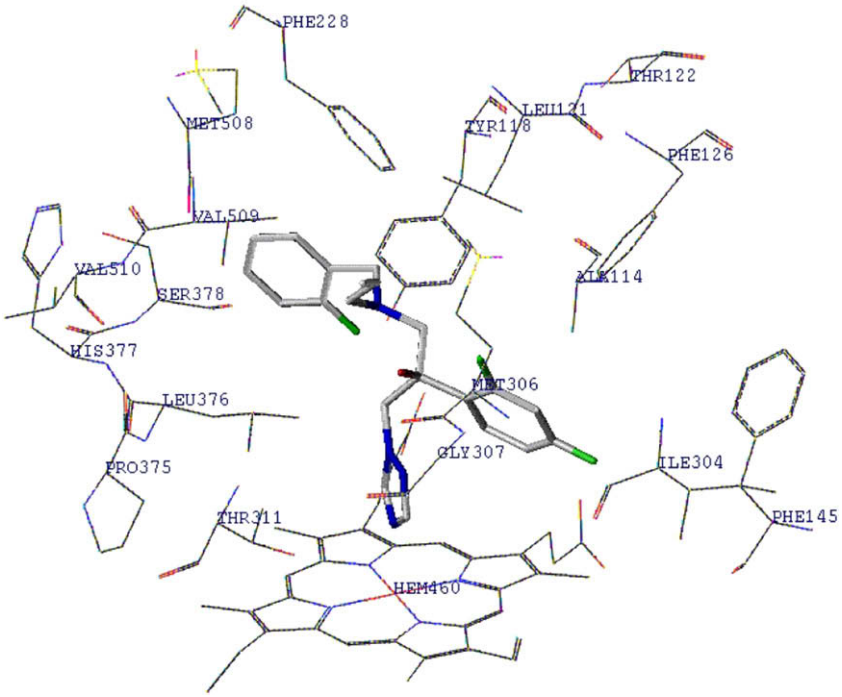


Fig. 4. Computed binding geometry of the new inhibitor **1b** in the active site of CYP51.

5. Conclusion

In conclusion, a series of 1-(1*H*-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanols as analogs of fluconazole were synthesized and their antifungal activities were screened for eight human pathogenic fungi. The compounds **1a**–**n** exhibited higher and broader spectrum antifungal activities with high activity against nearly all fungi tested except *A. fumigatus*. The obtained results indicated that for antifungal activity of these novel triazole derivatives it is very helpful to introduce the allyl group and the substituted benzyl bromide as side chains to interact with a hydrophobic pocket and also generate π–π stacking interactions with the Tyr118. Further evaluations are necessary to determine the antifungal activities of these title compounds *in vivo* and help us to optimize these new leading compounds.

6. Experimental part

In our studies, we constructed a 3D model of *C. albicans* CYP51 on the basis of Ji et al. [15]. All the molecular modeling calculations were performed using SYBYL 6.9 version. And the structures of the compounds were assigned with Gasteiger–Hückle partial atomic charges. Energy minimization was performed using the Tripos force field, Powell optimization method, and MAXIMIN2 minimizer with a convergence criterion 0.001 Kcal/mol Å. Simulated annealing was then performed. The system was heated to 1000 K for 1.0 ps and then annealed to 250 K for 1.5 ps. The annealing function was exponential; 50 such cycles of annealing were run and the resulting 50 conformers were optimized using methods described above. The lowest energy conformation was selected. All the other parameters were default values.

Melting points were measured on a Yamato MP-21 melting-point apparatus and are uncorrected. Infrared spectra were recorded using potassium bromide disks on a HITACHI270-50 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ unless otherwise indicated with a Bruker AC-300P spectrometer, using TMS as internal standard. The HPLC–MS were recorded on Agilent 1100 series LC–MS. The solvents and reagents were used as-received or dried prior to use as needed.

6.1. (1H-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-(allylamine)-propan-2-ols muriate (8)

To a stirred mixture of 1-[2-(2,4-difluorophenyl)-2,3-epoxypropyl]-1*H*-1,2,4-triazole methanesulfonate **7** (3.33 g, 10 mmol), CH_3CH_2OH (50 mL), $N(C_2H_5)_3$ (5 mL), and allylamine (0.89 g, 15 mmol) were added and was refluxed at 80–90 °C for 6 h. The reaction was monitored by TLC. After filtration, the filtrate was evaporated under reduced pressure. Water (50 mL) was added to the residue, which was then extracted with ethylacetate (80 mL × 3). The extract was washed with saturated NaCl solution (30 mL × 3), dried over anhydrous Na_2SO_4 and evaporated. The residue was dissolved with 20 mL ethylacetate, then added HCl gas to the solution. 1-(1*H*-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-(allylamine)-propan-2-ols muriate was separated from ethylacetate to afford **8** (2.63 g, 79.5%).

6.2. General procedure for the preparation of the compounds 1a–n

To a stirred mixture of 1-(1*H*-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-(allyl-mine)-propan-2-ols muriate (**8**, 1.0 mmol) and CH_3CN (25 mL), KI (0.5 mmol), K_2CO_3 (2.5 mmol), substituted benzyl bromide (1.2 mmol) were added and stirred for 5–6 h. The reaction was monitored by TLC. After filtration, the filtrate was evaporated under reduced pressure. Then the compounds **1a**–**n** were separated and purified readily by chromatography on silica gel.

6.3. General procedure for the preparation of the compounds 2a–f, 3a–f

4-Methylbenzoic acid (**9**, 1.36 g, 10.0 mmol) and thionyl chloride (10 mL) were added and stirred for 4–5 h until no gas released. Then evaporated the reagent under reduced pressure to afford compound **10** (1.47 g, 95.0%). The compound **10** (1.47 g, 9.5 mmol) was dropped in 25 mL CH_2Cl_2 which dissolved alcohol or substituted phenol (19.0 mmol) and Et_3N at 0 ~ 5 °C for 5 ~ 6 h to afford compound **11** (75–80%). The compound **11** (5.0 mmol), *N*-bromosuccimide

(6.0 mmol), peroxybenzoic acid (0.2 mmol) and CCl_4 (20 mL) were added and refluxed for 12 h to afford compound **12** (70–78%). To a stirred mixture of compound **8** (0.3420 g, 1.0 mmol), and CH_3CN (25 mL), KI (0.5 mmol), K_2CO_3 (2.5 mmol), the compound **12** (1.2 mmol) were added and stirred for 5–8 h. The reaction was monitored by TLC. After filtration, the filtrate was evaporated under reduced pressure. Then the compounds **2a**–**f**, **3a**–**f** were separated and purified readily by chromatography on silica gel.

The title compounds were characterized as follows.

*6.3.1. 1-(1*H*-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-[*N*-allyl-N-benzyl-amino]-2-propanol (**1a**)*

Mp: 67.2–68.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (1H, s, triazole-H), 7.73 (1H, s, triazole-H), 6.76–7.63 (8H, m, Ar-H), 5.63–5.72 (1H, m, $CH^*{=}CH_2$), 5.61 (1H, br, OH), 4.98–5.12 (2H, m, $CH{=}CH^*_2$), 4.39–4.50 (2H, dd, J = 14.4 Hz, triazole–CH_2–), 3.35–3.57 (2H, dd, J = 13.2 Hz, Ar–CH_2–), 2.99–3.16 (2H, m, CCH_2N), 2.82–2.89 (2H, m, $NCH^*_2CH{=}CH_2$); IR (KBr): 3250, 3110, 3080, 2975, 1645, 1520, 1450, 1263, 990, 910; LC–MS, m/z: 385.1 $(M+H)^+$.

*6.3.2. 1-(1*H*-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-[*N*-allyl-N-(2-fluorobenzyl)-amino]-2-propanol (**1b**)*

Mp: 77.0–78.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (1H, s, triazole-H), 7.69 (1H, s, triazole-H), 6.71–7.57 (7H, m, Ar-H), 5.58–5.66 (1H, m, $CH^*{=}CH_2$), 5.13 (1H, br, OH), 4.95–5.07 (2H, m, $CH{=}CH^*_2$), 4.35–4.48 (2H, dd, J = 14.4 Hz, triazole–CH_2–), 3.43–3.58 (2H, dd, J = 13.2 Hz, Ar–CH_2–), 2.83–2.98 (2H, m, CCH_2N), 2.78–2.82 (2H, m, $NCH^*_2CH{=}CH_2$); IR (KBr): 3215, 3108, 3070, 2990, 1640, 1510, 1475, 1230, 980, 908; LC–MS, m/z: 403.1 $(M+H)^+$.

*6.3.3. 1-(1*H*-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-[*N*-allyl-N-(3-fluorobenzyl)-amino]-2-propanol (**1c**)*

Mp: 72.6–74.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (1H, s, triazole-H), 7.73 (1H, s, triazole-H), 6.73–7.61 (7H, m, Ar-H), 5.60–5.69 (1H, m, $CH^*{=}CH_2$), 5.02 (1H, br, OH), 4.98–5.12 (2H, m, $CH{=}CH^*_2$), 4.40–4.98 (2H, dd, J = 14.4 Hz, triazole–CH_2–), 3.36–3.55 (2H, dd, J = 13.2 Hz, Ar–CH_2–), 2.98–3.18 (2H, m, CCH_2N), 2.82–2.88 (2H, m, $NCH^*_2CH{=}CH_2$); IR (KBr): 3220, 3106, 3082, 2995, 1638, 1543, 1462, 1217, 992, 905; LC–MS, m/z: 403.1 $(M+H)^+$.

*6.3.4. 1-(1*H*-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-[*N*-allyl-N-(4-fluorobenzyl)-amino]-2-propanol (**1d**)*

Mp: 69.3–71.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (1H, s, triazole-H), 7.72 (1H, s, triazole-H), 6.74–7.60 (7H, m, Ar-H), 5.59–5.68 (1H, m, $CH^*{=}CH_2$), 5.02 (1H, br, OH), 4.97–5.11 (2H, m, $CH{=}CH^*_2$), 4.39–4.51 (2H, dd, J = 14.4 Hz, triazole–CH_2–), 3.33–3.52 (2H, dd, J = 13.6 Hz, Ar–CH_2–), 2.96–3.17 (2H, m, CCH_2N), 2.80–2.86 (2H, m, $NCH^*_2CH{=}CH_2$); IR (KBr): 3230, 3145, 3073, 2990, 1647, 1550, 1477, 1240, 990, 915; LC–MS, m/z: 403.1 $(M+H)^+$.

*6.3.5. 1-(1*H*-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-[*N*-allyl-N-(2-chlorobenzyl)-amino]-2-propanol (**1e**)*

Mp: 72.4–73.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (1H, s, triazole-H), 7.72 (1H, s, triazole-H), 6.73–7.56 (7H, m, Ar-H), 5.69–5.77 (1H, m, $CH^*{=}CH_2$), 5.13 (1H, br, OH), 4.96–5.10 (2H, m, $CH{=}CH^*_2$), 4.33–4.48 (2H, dd, J = 14.0 Hz, triazole–CH_2–), 3.55–3.70 (2H, dd, J = 13.2 Hz, Ar–CH_2–), 2.97–3.24 (2H, m, CCH_2N), 2.82–3.23 (2H, m, $NCH^*_2CH{=}CH_2$); IR (KBr): 3285, 3153, 3080, 2950, 1645, 1527, 1440, 1235, 987, 905; LC–MS, m/z: 419.1 $(M+H)^+$.

*6.3.6. 1-(1*H*-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-[*N*-allyl-N-(3-chlorobenzyl)-amino]-2-propanol (**1f**)*

Mp: 76.0–77.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (1H, s, triazole-H), 7.74 (1H, s, triazole-H), 6.73–7.60 (7H, m, Ar-H), 5.60–5.69 (1H, m, $CH^*{=}CH_2$), 5.10 (1H, br, OH), 4.98–5.12 (2H, m, $CH{=}CH^*_2$), 4.40–4.53 (2H, dd, J = 14.0 Hz, triazole–CH_2–), 3.35–3.53 (2H, dd, J = 13.6 Hz, Ar–CH_2–), 2.98–3.17 (2H, m, CCH_2N), 2.83–2.88 (2H, m, $NCH^*_2CH{=}CH_2$); IR (KBr): 3215, 3108, 3073, 2950, 1654, 1553, 1432, 1270, 994, 897; LC–MS, m/z: 419.1 $(M+H)^+$.

*6.3.7. 1-(1*H*-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-[*N*-allyl-N-(4-chlorobenzyl)-amino]-2-propanol (**1g**)*

Mp: 74.4–75.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (1H, s, triazole-H), 7.74 (1H, s, triazole-H), 6.74–7.59 (7H, m, Ar-H), 5.59–5.70 (1H, m, $CH^*{=}CH_2$), 5.10 (1H, br, OH), 4.98–5.12 (2H, m, $CH{=}CH^*_2$), 4.40–4.53 (2H, dd, J = 14.4 Hz, triazole–CH_2–), 3.34–3.52 (2H, dd, J = 13.6 Hz, Ar–CH_2–), 2.97–3.17 (2H, m, CCH_2N), 2.81–2.88 (2H, m, $NCH^*_2CH{=}CH_2$); IR (KBr): 3295, 3180, 3074, 2955, 1648, 1527, 1435, 1258, 993, 905; LC–MS, m/z: 419.1 $(M+H)^+$.

*6.3.8. 1-(1*H*-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-[*N*-allyl-N-(2-bromobenzyl)-amino]-2-propanol (**1h**)*

Mp: 67.3–68.8 °C; ^{1}H NMR(400 MHz, $CDCl_3$) δ: 7.97 (1H, s, triazole-H), 7.71 (1H, s, triazole-H), 6.72–7.54 (7H, m, Ar-H), 5.70–5.77 (1H, m, $CH^*{=}CH_2$), 5.03 (1H, br, OH), 4.94–5.12 (2H, m, $CH{=}CH^*_2$), 4.30–4.46 (2H, dd, J = 14.4 Hz, triazole–CH_2–), 3.54–3.68 (2H, dd, J = 13.6 Hz, Ar–CH_2–), 2.98–3.23 (2H, m, CCH_2N), 2.81–2.87 (2H, m, $NCH^*_2CH{=}CH_2$); IR (KBr): 3256, 3090, 3045, 2997, 1650, 1533, 1457, 1235, 989, 908; LC–MS, m/z: 463.0 $(M+H)^+$.

*6.3.9. 1-(1*H*-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-[*N*-allyl-N-(4-bromobenzyl)-amino]-2-propanol (**1i**)*

Mp: 78.5–80.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (1H, s, triazole-H), 7.73 (1H, s, triazole-H), 6.73–7.58 (7H, m, Ar-H), 5.58–5.67 (1H, m, $CH^*{=}CH_2$), 5.12 (1H, br, OH), 4.97–5.09 (2H, m, $CH{=}CH^*_2$), 4.39–4.52 (2H, dd, J = 14.4 Hz, triazole–CH_2–), 3.32–3.49 (2H, dd, J = 13.2 Hz, Ar–CH_2–), 2.82–3.16 (2H, m, CCH_2N), 2.80–3.00 (2H, m, $NCH^*_2CH{=}CH_2$); IR (KBr): 3255, 3175, 3077, 2990, 1648, 1536, 1455, 1220, 998, 905; LC–MS, m/z: 463.0 $(M+H)^+$.

*6.3.10. 1-(1*H*-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-[*N*-allyl-N-(2-methylbenzyl)-amino]-2-propanol (**1j**)*

Mp: 70.8–72.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (1H, s, triazole-H), 7.71 (1H, s, triazole-H), 6.71–7.53 (7H, m, Ar-H), 5.70–5.72 (1H, m, $CH^*{=}CH_2$), 4.97–5.12 (2H, m, $CH{=}CH^*_2$), 4.93 (1H, br, OH), 4.29–4.41 (2H, dd, J = 14.0 Hz, triazole–CH_2–), 3.37–3.60 (2H, dd, J = 13.6 Hz, Ar–CH_2–), 2.99–3.17 (2H, m, CCH_2N), 2.81–2.88 (2H, m, $NCH^*_2CH{=}CH_2$), 2.23 (3H, s, Ar–CH_3); IR (KBr): 3285, 3108, 3080, 2975, 1668, 1545, 1430, 1286, 998, 895; LC–MS, m/z: 399.1 $(M+H)^+$.

*6.3.11. 1-(1*H*-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-[*N*-allyl-N-(4-methylbenzyl)-amino]-2-propanol (**1k**)*

Mp: 63.1–64.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (1H, s, triazole-H), 7.72 (1H, s, triazole-H), 6.73–7.58 (7H, m, Ar-H), 5.35–5.77 (1H, m, $CH^*{=}CH_2$), 5.22 (1H, br, OH), 4.96–5.10 (2H, m, $CH{=}CH^*_2$), 4.37–4.48 (2H, dd, J = 14.4 Hz, triazole–CH_2–), 3.29–3.50 (2H, dd, J = 13.2 Hz, Ar–CH_2–), 2.96–3.17 (2H, m, CCH_2N), 2.81–2.87 (2H, m, $NCH^*_2CH{=}CH_2$), 2.32 (3H, s, Ar–CH_3); IR (KBr): 3245, 3118, 3075, 2996, 1645, 1535, 1466, 1230, 990, 910; LC–MS, m/z: 399.1 $(M+H)^+$.

*6.3.12. 1-(1*H*-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-[*N*-allyl-N-(4-nitrobenzyl)-amino]-2-propanol (**1l**)*

Mp: 95.5–97.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (1H, s, triazole-H), 7.75 (1H, s, triazole-H), 6.73–8.13 (7H, m, Ar-H), 5.61–5.71 (1H, m, $CH^*{=}CH_2$), 5.00 (1H, br, OH), 5.00–5.15 (2H, m, $CH{=}CH^*_2$), 4.45–4.58 (2H, dd, J = 14.4 Hz, triazole–CH_2–), 3.54–3.69 (2H, dd, J = 14.4 Hz, Ar–CH_2–), 2.99–3.19 (2H, m, CCH_2N), 2.86–2.91 (2H, m, $NCH^*_2CH{=}CH_2$); IR (KBr): 3215, 3108, 3073, 2950, 1645, 1553, 1432, 1280, 994, 897; LC–MS, m/z: 430.1 $(M+H)^+$.

*6.3.13. 1-(1H-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-[N-allyl-N-(4-ethylbenzyl)-amino]-2-propanol (**1m**)*

Mp: 87.7–89.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (1H, s, triazole-H), 7.72 (1H, s, triazole-H), 6.71–7.54 (7H, m, Ar-H), 5.63–5.69 (1H, m, $CH^*{=}CH_2$), 5.10 (1H, br, OH), 4.97–5.12 (2H, m, $CH{=}CH_2^*$), 4.30–4.48 (2H, dd, $J = 14.4$ Hz, triazole–CH_2–), 3.47–3.61 (2H, dd, $J = 14.0$ Hz, Ar–CH_2–), 2.96–3.20 (2H, m, CCH_2N), 2.81–2.94 (2H, m, $NCH_2^*CH{=}CH_2$); 2.57–2.67 (2H, q, Ar–$CH_2^*CH_3$), 1.12–1.23 (3H, t, Ar–$CH_2CH_3^*$); IR (KBr): 3254, 3175, 3030, 2990, 1683, 1544, 1445, 1296, 986, 905; LC–MS, *m*/*z*: 413.1 $(M + H)^+$.

*6.3.14. 1-(1H-1,2,4-Triazole-1-yl)-2-(2,4-difluorophenyl)-3-[N-allyl-N-(2,4-dichlorobenzyl)-amino]-2-propanol (**1n**)*

Mp: 83.6–85.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (1H, s, triazole-H), 7.73 (1H, s, triazole-H), 6.71–7.52 (6H, m, Ar-H), 5.64–5.73 (1H, m, $CH^*{=}CH_2$), 5.00 (1H, br, OH), 4.96–5.12 (2H, m, $CH{=}CH_2^*$), 4.33–4.48 (2H, dd, $J = 14.4$ Hz, triazole–CH_2–), 3.53–3.63 (2H, dd, $J = 13.6$ Hz, Ar–CH_2–), 2.96–3.20 (2H, m, CCH_2N), 2.81–2.94 (2H, m, $NCH_2^*CH{=}CH_2$); IR (KBr): 3246, 3123, 3055, 2997, 1640, 1563, 1426, 1208, 1002, 910; LC–MS, *m*/*z*: 453.1 $(M + H)^+$.

*6.3.15. Methyl-4-({allyl[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazole-1-yl)-propyl]-amino}-methyl)-benzoate (**2a**)*

Mp: 66.4–68.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (1H, s, triazole-H), 7.95 (1H, s, triazole-H), 6.72–7.93 (7H, m, Ar-H), 5.60–5.68 (1H, m, $CH^*{=}CH_2$), 5.13 (1H, br, OH), 4.98–5.10 (2H, m, $CH{=}CH_2^*$), 4.41–4.52 (2H, dd, $J = 14.0$ Hz, triazole–CH_2–), 3.91 (3H, s, OCH_3), 3.43–3.60 (2H, dd, $J = 13.6$ Hz, Ar–CH_2–), 2.98–3.19 (2H, m, CCH_2N), 2.83–2.89 (2H, m, $NCH_2^*CH{=}CH_2$); IR (KBr): 3255, 3118, 3075, 2985, 1735, 1645, 1535, 1466, 1230, 987, 905; LC–MS, *m*/*z*: 443.1 $(M + H)^+$.

*6.3.16. Ethyl-4-({allyl[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazole-1-yl)-propyl]-amino}-methyl)-benzoate (**2b**)*

Mp: 60.4–62.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (1H, s, triazole-H), 7.95 (1H, s, triazole-H), 6.72–7.94 (7H, m, Ar-H), 5.61–5.68 (1H, m, $CH^*{=}CH_2$), 5.13 (1H, br, OH), 4.98–5.10 (2H, m, $CH{=}CH_2^*$), 4.41–4.52 (2H, dd, $J = 14.0$ Hz, triazole–CH_2–), 4.34–4.40 (2H, dd, $J = 14.0$ Hz, OCH_2–), 3.44–3.59 (2H, dd, $J = 13.6$ Hz, Ar–CH_2–), 2.99–3.19 (2H, m, CCH_2N), 2.83–2.90 (2H, m, $NCH_2^*CH{=}CH_2$), 1.37–1.40 (3H, t, CH_3); IR (KBr): 3235, 3145, 3053, 2990, 1760, 1648, 1555, 1477, 1240, 980, 912; LC–MS, *m*/*z*: 457.1 $(M + H)^+$.

*6.3.17. Isopropyl-4-({allyl[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazole-1-yl)-propyl]-amino}-methyl)-benzoate (**2c**)*

Mp: 58.3–59.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (1H, s, triazole-H), 7.94 (1H, s, triazole-H), 6.72–7.92 (7H, m, Ar-H), 5.61–5.66 (1H, m, $CH^*{=}CH_2$), 5.13 (1H, br, OH), 5.21–5.27 (1H, m, OCH), 4.98–5.12 (2H, m, $CH{=}CH_2^*$), 4.42–4.52 (2H, dd, $J = 14.4$ Hz, triazole–CH_2–), 3.44–3.58 (2H, dd, $J = 13.6$ Hz, Ar–CH_2–), 2.98–3.19 (2H, m, CCH_2N), 2.82–2.90 (2H, m, $NCH_2^*CH{=}CH_2$), 1.36–1.37 (6H, d, $J = 6.0$ Hz, $2 \times CH_3$); IR (KBr): 3262, 3208, 3096, 2998, 1744, 1677, 1580, 1477, 1220, 988, 915; LC–MS, *m*/*z*: 471.1 $(M + H)^+$.

*6.3.18. Butyl-4-({allyl[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazole-1-yl)-propyl]-amino}-methyl)-benzoate (**2d**)*

Mp: 43.1–45.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (1H, s, triazole-H), 7.95 (1H, s, triazole-H), 6.72–7.93 (7H, m, Ar-H), 5.61–5.68 (1H, m, $CH^*{=}CH_2$), 5.12 (1H, br, OH), 4.98–5.10 (2H, m, $CH{=}CH_2^*$), 4.42–4.52 (2H, dd, $J = 14.0$ Hz, triazole–CH_2–), 4.30–4.33 (2H, t, OCH_2–), 3.43–3.59 (2H, dd, $J = 13.6$ Hz, Ar–CH_2–), 2.98–3.19 (2H, m, CCH_2N), 2.82–2.89 (2H, m, $NCH_2^*CH{=}CH_2$), 1.73–1.82 (2H, m, $OCH_2CH_2^*CH_2CH_3$), 1.32–1.46 (2H, m, $OCH_2CH_2CH_2^*CH_3$), 0.98–1.20 (3H, t, CH_3); IR (KBr): 3250, 3135, 3065, 2988, 1730, 1643, 1552, 1450, 1263, 987, 895; LC–MS, *m*/*z*: 485.1 $(M + H)^+$.

*6.3.19. Isobutyl-4-({allyl[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazole-1-yl)-propyl]-amino}-methyl)-benzoate (**2e**)*

Mp: 67.3–68.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (1H, s, triazole-H), 7.95 (1H, s, triazole-H), 6.72–7.93 (7H, m, Ar-H), 5.63–5.65 (1H, m, $CH^*{=}CH_2$), 5.12 (1H, br, OH), 4.98–5.09 (2H, m, $CH{=}CH_2^*$), 4.41–4.52 (2H, dd, $J = 14.4$ Hz, triazole–CH_2–), 4.09–4.10 (2H, d, $J = 6.4$ Hz, OCH_2–), 3.43–3.59 (2H, dd, $J = 13.6$ Hz, Ar–CH_2–), 2.98–3.18 (2H, m, CCH_2N), 2.82–2.89 (2H, m, $NCH_2^*CH{=}CH_2$), 2.04–2.11 (1H, m, OCH_2CH^*), 1.01–1.02 (6H, d, $J = 6.8$ Hz, $2 \times CH_3$); IR (KBr): 3285, 3102, 3040, 2975, 1738, 1668, 1545, 1430, 1286, 992, 915; LC–MS, *m*/*z*: 485.1 $(M + H)^+$.

*6.3.20. Pentyl-4-({allyl[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazole-1-yl)-propyl]-amino}-methyl)-benzoate (**2f**)*

Mp: 65.3–68.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (1H, s, triazole-H), 7.95 (1H, s, triazole-H), 6.72–7.93 (7H, m, Ar-H), 5.61–5.68 (1H, m, $CH^*{=}CH_2$), 5.12 (1H, br, OH), 4.98–5.10 (2H, m, $CH{=}CH_2^*$), 4.42–4.52 (2H, dd, $J = 14.0$ Hz, triazole–CH_2–), 4.30–4.33 (2H, t, OCH_2–), 3.43–3.59 (2H, dd, $J = 13.6$ Hz, Ar–CH_2–), 2.98–3.19 (2H, m, CCH_2N), 2.82–2.89 (2H, m, $NCH_2^*CH{=}CH_2$), 1.71–1.79 (2H, m, $OCH_2CH_2^*CH_2CH_2CH_3$), 1.43–1.53 (2H, m, $OCH_2CH_2CH_2^*CH_2CH_3$), 1.26–1.33 (2H, m, $OCH_2CH_2CH_2CH_2^*CH_3$), 0.96–1.00 (3H, t, CH_3); IR (KBr): 3265, 3158, 3074, 2996, 1735, 1645, 1531, 1435, 1245, 990, 905; LC–MS, *m*/*z*: 499.1 $(M + H)^+$.

*6.3.21. Phenyl-4-({allyl[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazole-1-yl)-propyl]-amino}-methyl)-benzoate (**3a**)*

Mp: 72.2–73.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (1H, s, triazole-H), 7.75 (1H, s, triazole-H), 6.74–8.11 (12H, m, Ar-H), 5.62–5.72 (1H, m, $CH^*{=}CH_2$), 5.15 (1H, br, OH), 5.00–5.15 (2H, m, $CH{=}CH_2^*$), 4.44–4.55 (2H, dd, $J = 14.4$ Hz, triazole–CH_2–), 3.49–3.64 (2H, dd, $J = 14.0$ Hz, Ar–CH_2–), 3.02–3.49 (2H, m, CCH_2N), 2.86–2.92 (2H, m, $NCH_2^*CH{=}CH_2$); IR (KBr): 3245, 3150, 3054, 2998, 1738, 1645, 1531, 1423, 1210, 995, 905; LC–MS, *m*/*z*: 505.1 $(M + H)^+$.

*6.3.22. 3-Nitrophenyl-4-({allyl[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-amino}-methyl)-benzoate (**3b**)*

Mp: 74.5–75.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (1H, s, triazole-H), 7.76 (1H, s, triazole-H), 6.77–8.17 (11H, m, Ar-H), 5.48–5.79 (1H, m, $CH^*{=}CH_2$), 5.13 (1H, br, OH), 5.02–5.17 (2H, m, $CH{=}CH_2^*$), 4.39–4.52 (2H, dd, $J = 14.0$ Hz, triazole–CH_2–), 3.50–3.65 (2H, dd, $J = 14.0$ Hz, Ar–CH_2–), 2.99–3.42 (2H, m, CCH_2N), 2.80–2.95 (2H, m, $NCH_2^*CH{=}CH_2$); IR (KBr): 3236, 3177, 3056, 2996, 1745, 1638, 1531, 1435, 1245, 992, 898; LC–MS, *m*/*z*: 550.1 $(M + H)^+$.

*6.3.23. 4-Nitrophenyl-4-({allyl[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-amino}-methyl)-benzoate (**3c**)*

Mp: 82.3–84.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (1H, s, triazole-H), 7.76 (1H, s, triazole-H), 6.74–8.34 (11H, m, Ar-H), 5.63–5.73 (1H, m, $CH^*{=}CH_2$), 5.12 (1H, br, OH), 5.01–5.16 (2H, m, $CH{=}CH_2^*$), 4.43–4.57 (2H, dd, $J = 14.0$ Hz, triazole–CH_2–), 3.52–3.68 (2H, dd, $J = 14.4$ Hz, Ar–CH_2–), 2.92–3.22 (2H, m, CCH_2N), 2.87–2.90 (2H, m, $NCH_2^*CH{=}CH_2$); IR (KBr): 3283, 3135, 3066, 2985, 1740, 1665, 1542, 1446, 1220, 996, 912; LC–MS, *m*/*z*: 550.1 $(M + H)^+$.

*6.3.24. 4-Chlorophenyl-4-({allyl[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-amino}-methyl)-benzoate (**3d**)*

Mp: 85.2–86.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (1H, s, triazole-H), 7.75 (1H, s, triazole-H), 6.74–8.09 (11H, m, Ar-H), 5.62–5.71 (1H, m, $CH^*{=}CH_2$), 5.20 (1H, br, OH), 5.00–5.15 (2H, m, $CH{=}CH_2^*$), 4.43–4.55 (2H, dd, $J = 14.4$ Hz, triazole–CH_2–), 3.49–3.65 (2H, dd, $J = 14.0$ Hz, Ar–CH_2–), 3.00–3.21 (2H, m, CCH_2N), 2.85–2.91 (2H, m, $NCH_2^*CH{=}CH_2$); IR (KBr): 3265, 3102, 3030, 2995,

1738, 1668, 1545, 1443, 1286, 982, 896; LC–MS, *m*/*z*: 539.1 $(M+H)^+$.

*6.3.25. Methyl-2-[4-({allyl[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-amino}-methyl)-benzoyloxy]-benzoate (**3e**)*

Mp: 99.3–101.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (1H, s, triazole-H), 7.75 (1H, s, triazole-H), 6.74–8.13 (11H, m, Ar-H), 5.63–5.70 (1H, m, $CH^*{=}CH_2$), 5.20 (1H, br, OH), 5.00–5.14 (2H, m, $CH{=}CH_2^*$), 4.44–4.55 (2H, dd, $J = 14.4$ Hz, triazole–CH_2–), 3.78 (3H, s, OCH_3), 3.49–3.64 (2H, dd, $J = 14.0$ Hz, Ar–CH_2–), 3.02–3.21 (2H, m, CCH_2N), 2.86–2.93(2H, m, $NCH_2^*CH{=}CH_2$); IR (KBr): 3265, 3198, 3066, 2998, 1734, 1657, 1580, 1477, 1230, 990, 915; LC–MS, *m*/*z*: 563.1 $(M+H)^+$.

*6.3.26. 4-(Propoxycarbonyl)-phenyl-[4-({allyl[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]amino}methyl)]benzoate (**3f**)*

Mp: 90.4–91.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (1H, s, triazole-H), 7.76 (1H, s, triazole-H), 6.74–8.14 (11H, m, Ar-H), 5.64–5.71 (1H, m, $CH^*{=}CH_2$), 5.12 (1H, br, OH), 5.01–5.16 (2H, m, $CH{=}CH_2^*$), 4.44–4.56 (2H, dd, $J = 14.0$ Hz, triazole–CH_2–), 4.29–4.32 (2H, t, OCH_2), 3.51–3.66 (2H, dd, $J = 13.6$ Hz, Ar–CH_2–), 3.02–3.51 (2H, m, CCH_2N), 2.86–2.92 (2H, m, $NCH_2^*CH{=}CH_2$), 1.76–1.85 (2H, m, $OCH_2CH_2^*$), 1.02–1.06 (3H, t, CH_3); IR (KBr): 3245, 3214, 3096, 2985, 1735, 1657, 1570, 1477, 1220, 978, 910; LC–MS, *m*/*z*: 591.1 $(M+H)^+$.

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References

[1] S.K. Fridkin, W.R. Jarvis, Clin. Microbiol. Rev. 9 (1996) 499–511.
[2] J.R. Wingard, H. Leather, Biol. Blood Marrow Transplant. 10 (2004) 73–90.
[3] N.H. Georgopapadakou, T.J. Walsh, Antimicrob. Agents Chemother. 40 (1996) 279.
[4] M.A. Pfaller, S.A. Messer, R.J. Hollis, R.N. Jones, Antimicrob. Agents Chemother. 45 (2001) 2862.
[5] L. Jeu, F.J. Piacenti, A.G. Lyakhovetskiy, H.B. Fung, Clin. Ther. 25 (2003) 1321.
[6] G.I. Lepesheva, N.G. Zaitseva, W.D. Nes, W. Zhou, M. Arase, J. Liu, G.C. Hill, M.R. Waterman, J. Biol. Chem. 281 (2006) 3577–3585.
[7] J.M. Trzaskos, R.T. Fischer, M.F. Favata, J. Biol. Chem. 261 (1986) 16937.
[8] Y. Aoyama, Y. Yoshida, Y. Sonoda, Y. Sato, J. Biol. Chem. 262 (1987) 1239.
[9] Y. Aoyama, Y. Yoshida, Y. Sonoda, Y. Sato, J. Biol. Chem. 264 (1989) 18502.
[10] R.T. Fischer, J.M. Trzaskos, R.L. Magolda, S.S. Ko, C.S. Brosz, B. Larsen, J. Biol. Chem. 266 (1991) 6124.
[11] A.Z. Shyadehi, D.C. Lamb, S.L. Kelly, D.E. Kelly, W.H. Schunck, J.N. Wright, D. Corina, M. Akhtar, J. Biol. Chem. 271 (1996) 12445.
[12] C.Q. Sheng, W.N. Zhang, H.T. Ji, Chin. Chem. Lett. 15 (2004) 404.
[13] K. Richardson, US Patent 4404216, 1983.
[14] National Committee for Clinical Laboratory Standards, Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts Approved standard. Document M27–A2, National Committee for Clinical Laboratory Standards, Wayne, PA, 2002.
[15] H.T. Ji, W.N. Zhang, Y.J. Zhou, M. Zhang, J. Zhu, L.Y. Song, J.G. Lü, J. Zhu, J. Med. Chem. 43 (2000) 2493.