European Journal of Medicinal Chemistry 45 (2010) 6020–6026

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Novel conformationally restricted triazole derivatives with potent antifungal activity

Wenya Wang, Shengzheng Wang, Yang Liu, Guoqiang Dong, Yongbing Cao, Zhenyuan Miao, Jianzhong Yao, Wannian Zhang*, Chunquan Sheng**

Department of Medicinal Chemistry, School of Pharmacy, Second Military Medical University, 325 Guohe Road, Shanghai 200433, People's Republic of China

ARTICLE INFO

Article history:
Received 29 July 2010
Received in revised form
29 September 2010
Accepted 29 September 2010
Available online 7 October 2010

Keywords:
Azole
Rational design
Conformationally restricted analogues
Molecular docking
Antifungal activity

ABSTRACT

In continuation of our work on azole antifungal agents, a series of new conformationally restricted triazole derivatives possessing benzylpiperidin-4-yl methyl amino side chains were designed and synthesized. All the new azoles showed moderate to excellent *in vitro* antifungal activity against most of the tested pathogenic fungi. Several compounds (such as **12e**, **12f**, **12h** and **12n**) showed higher antifungal activity against *Candida albicans* than fluconazole. Moreover, compounds **12g**–**i** also showed good activity against *Aspergillus fumigatus* with their MIC_{80} on the level of 1 μg/mL. Flexible molecular docking was used to analyze the binding mode of the designed compounds. They interact with CACYP51 through hydrophobic and *van der Waals* interactions.

1. Introduction

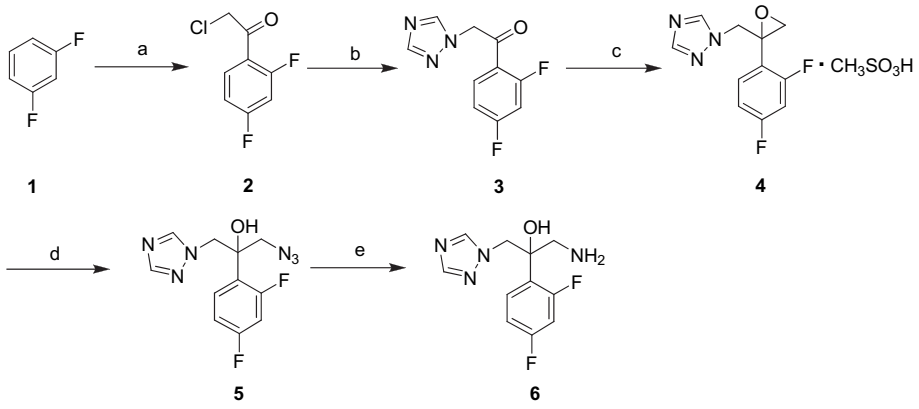
During the past two decades, the incidence of life-threatening invasive and systemic fungal infections has increased significantly in the immunocompromised patients due to AIDS, organ transplantation and chemotherapy [1]. Serious fungal infections are caused mostly by *Candida albicans* (*C. albicans*) [2], *Cryptococcus neoformans* (*C. neoformans*) and *Aspergillus fumigatus* (*A. fumigatus*) [3]. For the treatment of these infections, only four major classes of antifungal agents are available in clinical use. These are azoles (such as fluconazole and itraconazole) [4], polyene macrolides (amphotericin B) [5], flucytosine (5-fluorocytosine) and echinocandins (such as caspofungin and micafungin) [6]. Among them, azoles are the most widely used antifungal agents in clinic because of their generally broad antifungal spectrum, high potency and low toxicity [4]. Unfortunately, massive use of azoles has led to the emergence of severe resistance [7], showing an urgent need of searching for new azoles. Second generation azole antifungal drugs, such as voriconazole [8], posaconazole [9], ravuconazole [10] and albaconazole [11,12], are available in the market or are currently under clinical trials.

Azole antifungals have been shown to competitively inhibit lanosterol 14α-demethylase (CYP51), leading to block fungal biosynthesis of ergosterol which is a key constituent of the fungal cell membrane, thereby preventing fungal growth [13]. Due to membrane associated proteins, it is difficult to solve the crystal structures of eukaryotic CYP51s. In our previous studies, our group has constructed three-dimensional (3D) models of CYP51 from *C. albicans* (CACYP51), *C. neoformans* (CNCYP51) and *A. fumigatus* (AFCYP51) using homology modeling methods [14–16] on the basis of the crystal coordinates of CYP51 from *Mycobacterium tuberculosis* (MTCYP51) [17,18]. The binding modes of azoles were investigated by flexible molecular docking [16,19] and site-directed mutagenesis [20]. The results from molecular modeling provided important information for rational inhibitor design and led to the discovery of novel azole and non-azole CYP51 inhibitors [19,21–26].

Recently, we have designed and synthesized a series of novel azoles with substituted phenoxyalkyl C-3 side chains [23–25]. These compounds showed excellent *in vitro* antifungal activity against most of the tested pathogenic fungi, representing a promising lead for further optimization. In order to extend their structure–activity relationships (SARs), a series of new conformationally restricted triazole derivatives possessing benzylpiperidin-4-yl side chains were designed and synthesized, which revealed potent antifungal activity and broad spectrum. The binding mode of the azoles was investigated by molecular docking.

* Corresponding author. Tel./fax: +86 21 81870243.
** Corresponding author. Tel./fax: +86 21 81871233.
E-mail addresses: zhangwnk@hotmail.com (W. Zhang), shengcq@hotmail.com (C. Sheng).

0223-5234/$ – see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2010.09.070



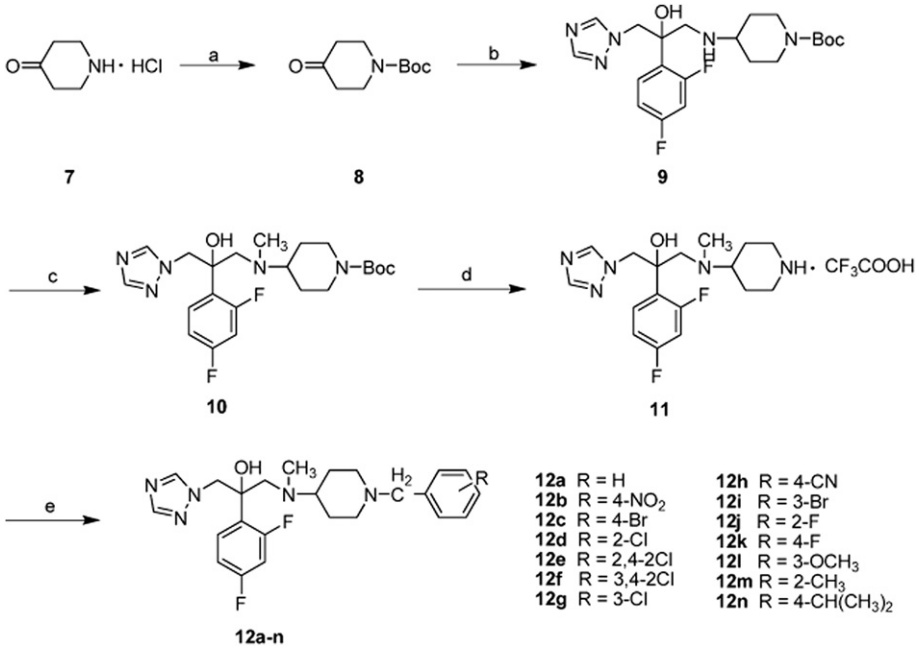
Scheme 1. Reagents and conditions: a. $ClCH_2COCl$, $AlCl_3$, CH_2Cl_2, 40 °C, 3 h, 50%; b. triazole, K_2CO_3, CH_2Cl_2, r.t., 24 h, 70.0%; c. $(CH_3)_3SOI$, NaOH, toluene, 60 °C, 3 h, 62.3%; d. NaN_3, NH_4Cl, MeOH, reflux, 8 h, 98%; e. H_2, Pd–C, EtOH, 4 h, 99.1%.

2. Chemistry

We have reported the synthetic procedure (Scheme 1) of the key intermediate **6** with the total yield of 21.2% [24]. Piperidin-4-one hydrochloride **7** was treated with excess di-*tert*-butyl dicarbonate in the presence of *N*,*N*-diisopropylethylamine (DIEA) in 1,4-dioxane/H_2O (4:1) to give compound **8**. Starting from compound **8**, 2-(2,4-difluorophenyl)-1-{methyl[1-(*tert*-butoxycarbonyl) piperidin-4-yl]amino}-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (compound **10**) was synthesized via two steps of reductive amination. First, intermediate **6** was reacted with *tert*-butyl 4-oxopiperidine-1-carboxylate (compound **8**) and sodium cyanoborohydride in methanol at room temperature to give **9**. Then compound **9** was reacted with formaldehyde according to the same protocol described for **9** to afford **10**. Compound **10** was subsequently treated with trifluoroacetic acid at room temperature over night to afford **11**. The target compounds **12a**–**n** were obtained as racemates by treating compound **11** with various substituted benzyl bromide or chloride in the presence of K_2CO_3 in methanol with moderate to high yields (Scheme 2).

3. Pharmacology

In vitro antifungal activity was measured by means of the minimum inhibitory concentration (MIC) using the serial dilution method in 96-well microtest plates. Fluconazole was used as the reference drug. Test fungal strains were obtained from the ATCC or were clinical isolates. The MIC determination was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) recommendations with RPMI 1640 (Sigma) buffered with 0.165 M MOPS (Sigma) as the test medium. The MIC value was defined as the lowest concentration of test compounds that resulted in a culture with turbidity less than or equal to 80% inhibition when compared with the growth of the control. Test compounds were dissolved in DMSO serially diluted in growth medium. The yeasts were incubated at 35 °C and the dermatophytes at 28 °C.



Scheme 2. Reagents and conditions: a. Boc_2O, DIEA, 1,4-dioxane-H_2O, r.t., 24 h, 80.2%; b. **6**, $NaBH_3CN$, AcOH/MeOH, r.t., 16 h, 99.0%; c. formaldehyde, $NaBH_3CN$, AcOH/MeOH, r.t., 24 h, 92.6%; d. CF_3COOH, CH_2Cl_2, 12 h, 95.1%; e. substituted benzyl bromide, K_2CO_3, MeOH, r.t., 16 h, 45.5%–81.2%.

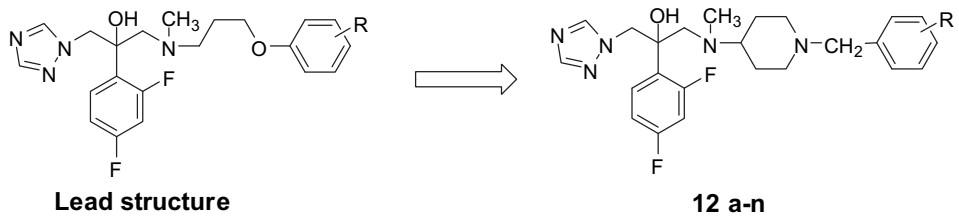


Fig. 1. Design rationale of the new azoles with benzylpiperidin-4-yl side chains.

Growth MIC was determined at 24 h for *Candida* species, at 72 h for *C. neoformans*, and at 7 days for filamentous fungi.

4. Results and discussion

4.1. Design rationale

As a part of our continual effort in azoles optimization, we have designed a series of novel azoles with substituted phenoxyalkyl C-3 side chains [24–26]. *In vitro* antifungal assay indicated that they displayed excellent antifungal activity with broad spectrum, which could serve as a good starting point for the discovery of novel antifungal agents. Therefore, the extension of SARs of these potent antifungal azoles is of great importance. We chose the *N*-methyl derivative (Fig. 1) as a starting point. In the present study, *N*-methyl group was retained as the linker, and the propoxy group was replaced by the piperidin-4-yl group to restrict the conformation of the C3-side chain and form stronger hydrophobic and *van der Waals* interactions with CACYP51. Then a series of conformationally restricted triazole derivatives was designed. In order to validate the binding mode of the designed compounds, compound **12n**, a representative derivative, was docked into the active site of CACYP51 using the Affinity module within Insight II 2000 software package [27]. Fig. 2 shows that compound **12n** binds to the active site of CACYP51 with an extended conformation, which is similar to that in our reported docking models [19,24–26]. The triazolyl ring, difluorophenyl group and C2 hydroxyl group are essential pharmacophoric elements of the azole antifungal agents. The triazolyl ring of the compounds binds to CACYP51 through the formation of a coordination bond with iron of heme group. The difluorophenyl group is located in a hydrophobic pocket and interacts with Phe126, Met306 and Phe145. The *N*-methyl group forms hydrophobic and *van der Waals* interactions with Tyr118. The piperidyl group interacts with the surrounding hydrophobic residues lined with Ile379 and Val509. The terminal benzyl group binds to substrate access channel 2 [19] (FG loop) through the hydrophobic and *van der Waals* interactions with Leu461, Leu376, Leu403, Met372, and Met374.

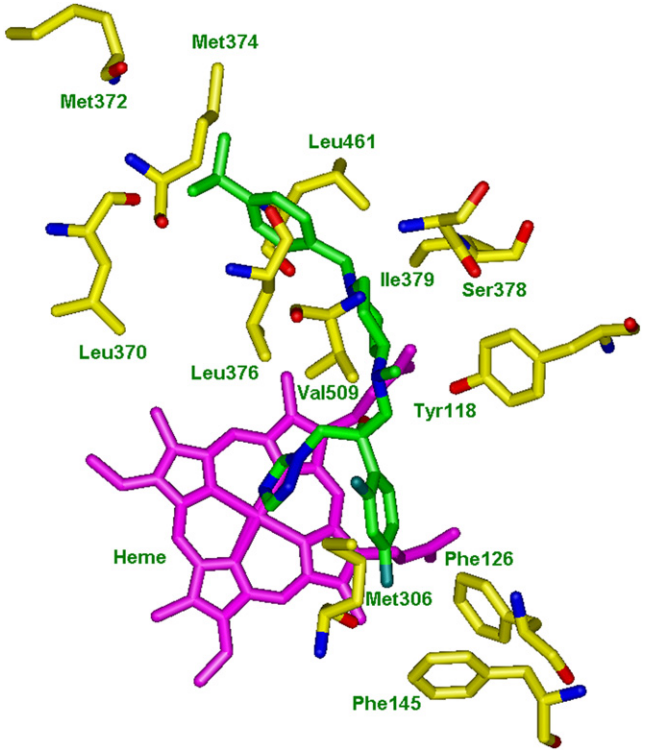


Fig. 2. The docking conformation of compound **12n** in the active site of CACYP51. Important residues interacting with the compounds are shown.

4.2. In vitro antifungal activity

In vitro antifungal activity of the synthesized compounds is listed in Table 1. The MIC_{80} values of all the targeted compounds were determined against seven important fungal pathogens (such as *C. albicans*, *C. neoformans* and *A. fumigatus*) and compared with fluconazole. The assay indicated that the synthesized compounds **12a**–**n** showed moderate to excellent activity against all the tested fungal pathogens. Most of the compounds were more potent than fluconazole. In general, compounds **12e**–**i** exhibited potent antifungal activity and a broad spectrum. On the *C. albicans* strain, the most common cause of life-threatening fungal infections, most of the compounds showed higher antifungal activity than fluconazole ($MIC_{80} = 0.25$ μg/mL) with their MIC_{80} values on the level of 0.0625 μg/mL. In particular, compound **12n** displayed the highest activity ($MIC_{80} = 0.0156$ μg/mL), which was 16 fold more potent than fluconazole. Moreover, these compounds also revealed excellent inhibitory activity against other *Candida* spp., such as *C. tropicalis*, *Candida parapsilosis* and *Candida kefyr* with their MIC_{80} values in the range of 1–0.0625 μg/mL. For the dermatophytes

Table 1
Antifungal *in vitro* activity of the compounds (MIC_{80}, μg mL^{-1}).[a]

Compd	*C. alb.*	*C. neo.*	*C. tro.*	*C. par.*	*C. kef.*	*T. rub.*	*A. fum.*
12a	0.25	1	1	0.25	1	1	64
12b	0.0625	0.25	0.25	0.0625	1	0.25	4
12c	0.0625	0.25	0.25	0.0625	1	0.25	4
12d	0.25	0.25	0.25	0.0625	1	1	4
12e	0.0625	0.25	0.0625	0.0625	0.25	0.25	4
12f	0.0625	0.25	0.0625	0.0625	0.25	0.25	4
12g	0.0625	0.0625	0.25	0.0625	1	0.25	1
12h	0.0625	0.0625	0.25	0.25	0.0625	0.0625	1
12i	0.0625	0.25	0.0625	0.0625	0.25	0.25	1
12j	0.25	0.25	0.25	0.25	0.25	1	16
12k	0.25	0.25	0.25	0.25	0.25	1	16
12l	0.25	0.25	0.25	0.25	0.25	1	64
12m	0.0625	0.25	0.25	0.25	0.25	1	64
12n	0.0156	0.25	0.25	0.25	0.25	0.25	16
FLZ	0.25	0.0625	1	0.25	1	1	>64

[a] Abbreviations: *C. alb. Candida albicans*; *C. neo. Cryptococcus neoformans*; *C. tro. Candida tropicalis*; *C. par. Candida parapsilosis*; *C. kef. Candida kefyr*; *T. rub. Trichophyton rubrum*; *A. fum. Aspergillus fumigatus*; FLZ: Fluconazole.

(*e.g.*, *T. rubrum*), most compounds showed higher activity than fluconazole. Especially, the MIC_{80} value of compound **12h** is 0.0625 μg/mL, indicating that it is 16 fold more potent than fluconazole. However, most of the compounds were inferior to fluconazole against *C. neoformans* ($MIC_{80} = 0.0625$ μg/mL) with their MIC_{80} values on the level of 0.25 μg/mL and only compounds **12g** and **12h** were comparable to that of fluconazole. Interestingly, fluconazole is not effective against *A. fumigatus*, while most of our synthesized compounds show moderate antifungal activity. For example, the MIC_{80} values of compounds **12g**–**i** are 1 μg/mL. Among the synthesized azoles, compounds **12h** and **12n** exhibited strong *in vitro* antifungal activity with broad antifungal spectrum, which were worthy of further evaluation.

4.3. Structure–activity relationships

According to the *in vitro* antifungal activity data, preliminary SARs of the synthesized compounds were obtained. Compared with compound **12a**, the introduction of various substitutent groups on the terminal benzyl group could significantly improve the antifungal activity. The electrostatic property of the substitutions had little effect on the antifungal activity. For the type of the substitutions, halogen, nitro, cyano and *iso*-propyl are favorable for the antifungal activity (*e.g.*, compounds **12g**, **12b**, **12h** and **12n**). Among the halogen substituted derivatives, fluorine substituted compounds (**12j**–**k**) are less active than bromine or chlorine substituted compounds (*e.g.*, compounds **12c**, **12g** and **12i**). In comparison with the mono-chlorine substituted compounds (**12d** and **12g**), the di-substituted derivatives (**12e**–**f**) showed improved antifungal activity. For the position of halogen, the 4-substituted and 3-substituted derivatives exhibit higher inhibitory activity than 2-substituted derivatives. When the halogen was replaced by alkyl group, such as methyl and methoxy group, similar antifungal activity was observed. The good antifungal activity of **12h** and **12n** highlighted the importance of the hydrophobic and *van der Waals* interactions of the substituent with CACYP51. In addition, 4-cyano, 3-choloro and 3-bromo derivatives displayed the highest inhibitory activity against *A. fumigatus* which was not sensitive to fluconazole.

5. Conclusion

In conclusion, a series of conformationally restricted triazole derivatives with substituted benzylpiperidin-4-yl methyl amino side chains was rational designed and synthesized. Flexible molecular docking studies revealed that the designed compounds interacted with CACYP51 mainly through hydrophobic and *van der Waals* interactions. Most of the synthesized compounds showed good antifungal activity against both systemic pathogenic fungi and dermatophytes. Several compounds were found to be more potent than fluconazole. Compounds **12g**–**i** were most potent against *A. fumigatus* with their MIC_{80} value on the level of 1 μg/mL. In particular, compounds **12h** and **12n** exhibited strong antifungal activity and broad spectrum, suggesting that they are promising leads for further structural optimization.

6. Experimental protocols

6.1. General procedure for the synthesis of compounds

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 500 spectrometer with TMS as an internal standard and $CDCl_3$ as solvent. Chemical shifts (δ values) and coupling constants (J values) are given in ppm and Hz, respectively. ESI mass spectra were performed on an API-3000 LC–MS spectrometer. High-resolution mass spectrometry measurements were performed on a Kratos-concept mass spectrometer under electron impact ionization (EI) conditions. TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical, China). Silica gel column chromatography was performed with Silica gel 60G (Qindao Haiyang Chemical, China). Commercial solvents were used without any pretreatment.

6.1.1. Chemical synthesis of tert-butyl 4-oxopiperidine-1-carboxylate (**8**)

DIEA (32.31 g, 0.25 mol, 2.5 equiv) was added to a solution of piperidin-4-one hydrochloride **7** (13.5 g, 0.10 mol, 1.0 equiv) in 200 mL 1,4-dioxane and H_2O (v/v, 4/1). Subsequently, di-*tert*-butyl dicarbonate (32.74 g, 0.15 mol, 1.5 equiv) was added dropwise to the reaction mixture over 1 h, and the resulting solution was stirred at room temperature for 24 h. Then the solvent was evaporated under reduced pressure, and the residue was poured into a 5% citric acid solution, then extracted with dichloromethane (100 mL × 3). The organic layer was separated, dried with anhydrous Na_2SO_4, and concentrated to give crude solid, which was recrystallized from cyclohexane to afford **8** as white needle: 15.96 g, (80.2%, yield). ^{1}H NMR δ (ppm): 3.60 (t, 4H, $J = 6.2$ Hz, piperidin-2,6-CH_2), 2.34 (t, 4H, $J = 6.2$ Hz, piperidin-3,5-CH_2), 1.43 (s, 9H, $C(CH_3)_3$). MS (ESI) m/z: 200 (M + 1).

6.1.2. Chemical synthesis of 2-(2,4-difluorophenyl)-1-[1-(tert-butoxycarbonyl)piperidin-4-yl]amino-3-(1H-1,2,4-triazol-1-yl) propan-2-ol (**9**)

Compound **8** (3.0 g, 0.015 mol, 1 equiv) was added to a solution of intermediate **6** (3.8 g, 0.015 mol, 1 equiv) in methanol 100 mL and acetic acid 2.0 mL. Then sodium cyanoborohydride (1.1 g, 0.018 mol, 1.2 equiv) was added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 16 h and the reaction was almost completed. The solvent was evaporated under reduced pressure, and the residue was diluted with 25 mL H_2O, extracted with dichloromethane (30 mL × 3). The organic layer was separated, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give **9** as yellow oil: 6.5 g, (99.0%, yield). The product was used in the next step without further purification.

6.1.3. Chemical synthesis of 2-(2,4-difluorophenyl)-1-{methyl[1-(tert-butoxycarbonyl)piperidin-4-yl]amino}-3-(1H-1,2,4-triazol-1-yl)propan-2-ol (**10**)

Formaldehyde (1.2 mL, 0.015 mol, 1 equiv) was added to a solution of compound **9** (6.6 g, 0.015 mol, 1 equiv) in methanol 100 mL and acetic acid 2.0 mL. Then sodium cyanoborohydride (1.1 g, 0.018 mol, 1.2 equiv) was added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 h and the reaction was almost completed. The solvent was evaporated under reduced pressure, and the residue was diluted with 25 mL H_2O, extracted with dichloromethane (30 mL × 3). The organic layer was separated, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH, 100:5, v/v) to give **10** as yellow oil: 6.3 g, (92.6%, yield). ^{1}H NMR δ (ppm): 8.16 (s, 1H, $TriazC_3$–H), 7.80 (s, 1H, $TriazC_5$–H), 6.78–7.60 (m, 3H, Ar–H), 5.30 (s, 1H, OH), 4.50 (d, 2H, $J = 14.2$ Hz, C_1–HaHb), 4.11 (br, 2H, piperidin-2-CH_2), 3.02 (d, 1H, $J = 13.3$ Hz, C_3–Ha), 2.72 (d, 1H, $J = 13.5$ Hz, C_3–Hb), 2.51 (br, 2H, piperidin-6-CH_2), 2.25 (br, 1H, piperidin-4-CH), 1.97 (s, 3H, NCH_3), 1.57–1.59 (m, 2H, piperidin-3-CH_2), 1.45 (s, 9H, $C(CH_3)_3$), 1.22–1.25 (m, 2H, piperidin-5-CH_2). MS (ESI) m/z: 452 (M + 1).

6.1.4. Chemical synthesis of 2-(2,4-difluorophenyl)-1-[methyl (piperidin-4-yl)]amino-3-(1H-1,2,4-triazol-1-yl)propan-2-ol trifluoroacetate (**11**)

Trifluoroacetic acid (2.32 g, 0.020 mol, 4 equiv) was added to a solution of **10** (2.26 g, 0.005 mol, 1 equiv) in dichloromethane

(50 mL), and the resulting solution was stirred at room temperature for 24 h. Then the solution was evaporated to dryness under reduced pressure to give **11** as yellow oil: 2.21 g, (95.1%, yield). The product was used in the next step without any further purification.

*6.1.5. Chemical synthesis of 3-[(1-benzylpiperidin-4-yl)(methyl) amino]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**12a**)*

A suspension of **11** (0.46 g, 1.0 mmol, 1 equiv), benzyl bromide (0.26 g, 1.5 mmol, 1.5 equiv) and anhydrous K_2CO_3 (0.83 g, 6 mmol, 6 equiv) in methanol (15 mL) was stirred at room temperature for 16 h. Then the mixture was filtrated, and the filtrate was concentrated under reduced pressure. The residue was diluted with 10 mL H_2O and extracted with dichloromethane (20 mL × 3). The organic layer was separated, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 100:2, v/v) to give **12a** as yellow oil: 0.20 g (45.5%, yield). IR (KBr, cm^{-1}): 3424, 2942, 2855, 1617, 1500, 1454, 1272, 1137, 1049, 963. ^1H NMR δ (ppm): 8.16 (s, 1H, TriazC$_3$—H), 7.78 (s, 1H, TriazC$_5$—H), 6.77—7.56 (m, 8H, Ar—H), 5.30 (s, 1H, OH), 4.50 (d, 2H, J = 14.2 Hz, C$_1$—HaHb), 3.48 (br, 2H, Ar—C$\underline{H}_2$), 3.01 (d, 1H, J = 13.8 Hz, C$_3$—Ha), 2.90 (br, 2H, piperidin-2-CH_2), 2.81 (d, 1H, J = 13.8 Hz, C$_3$—Hb), 2.13 (s, 1H, piperidin-4-CH), 1.97 (s, 3H, NCH_3), 1.86 (br, 2H, piperidin-6-CH_2), 1.57—1.60 (m, 2H, piperidin-3-CH_2), 1.25 (br, 2H, piperidin-5-CH_2). ^{13}C NMR δ (ppm): 162.60, 158.89, 150.85, 144.66, 138.11, 129.35, 129.02, 128.14, 127.00, 111.35, 104.11, 71.11, 62.76, 58.56, 56.58, 52.91, 39.17, 28.40, 27.56. HRMS (m/z): calcd. for $C_{24}H_{29}F_2N_5O$: 441.2340; found: 441.2352.

The target compounds **12c**—**n** were synthesized according to the same protocol described for **12a**.

*6.1.6. Chemical synthesis of 3-{[1-(4-nitrobenzyl)piperidin-4-yl] (methyl)amino]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl) propan-2-ol (**12b**)*

A suspension of **11** (0.30 g, 0.64 mmol, 1 equiv), 4-nitrobenzyl chloride (0.16 g, 0.96 mmol, 1.5 equiv) and triethylamine (1 mL) in methanol 15 mL was stirred at room temperature for 16 h. Then the solvent was evaporated and the residue was diluted with 10 mL H_2O and extracted with dichloromethane (20 mL × 3). The organic layer was separated, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH 100:2, v/v) to give **12b** as yellow oil: 0.15 g (48.4%, yield). IR (KBr, cm^{-1}): 3455, 2923, 2853, 1616, 1520, 1462, 1273, 1138, 1049, 964. ^1H NMR δ (ppm): 8.15—8.18 (m, 2H, Ar—H,TriazC$_3$—H), 7.80 (s, 1H, TriazC$_5$—H), 6.78—7.59 (m, 6H, Ar—H), 5.30 (s, 1H, OH), 4.50 (d, 2H, J = 14.2 Hz, C$_1$—HaHb), 3.51 (br, 2H, Ar—C$\underline{H}_2$), 3.01 (d, 1H, J = 13.0 Hz, C$_3$—Ha), 2.82 (br, 2H, piperidin-2-CH_2), 2.80 (d, 1H, J = 13.0 Hz, C$_3$—Hb), 2.20 (br, 1H, piperidin-4-CH), 1.98 (s, 3H, NCH_3), 1.87 (br, 2H, piperidin-6-CH_2), 1.58 (br, 2H, piperidin-3-CH_2), 1.25 (br, 2H, piperidin-5-CH_2). HRMS (m/z): calcd. for $C_{24}H_{28}F_2N_6O_3$: 486.2191; found: 486.2177.

*6.1.7. 3-{[1-(4-Bromobenzyl)piperidin-4-yl](methyl)amino]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**12c**)*

Pale yellow solid: 0.25 g (75.8%, yield), mp 126—127 °C. IR (KBr, cm^{-1}): 3436, 2924, 2854, 1610, 1492, 1466, 1270, 1136, 1059, 959. ^1H NMR δ (ppm): 8.16 (s, 1H, TriazC$_3$—H), 7.79 (s, 1H, TriazC$_5$—H), 6.77—7.57 (m, 7H, Ar—H), 5.30 (s, 1H, OH), 4.49 (d, 2H, J = 14.1 Hz, C$_1$—HaHb), 3.37 (br, 2H, Ar—C$\underline{H}_2$), 3.00 (d, 1H, J = 13.4 Hz, C$_3$—Ha), 2.82 (br, 2H, piperidin-2-CH_2), 2.80 (d, 1H, J = 13.4 Hz, C$_3$—Hb), 2.12 (br, 1H, piperidin-4-CH), 1.97 (s, 3H, NCH_3), 1.80 (br, 2H, piperidin-6-CH_2), 1.47—1.55 (m, 2H, piperidin-3-CH_2), 1.36—1.39 (m, 2H, piperidin-5-CH_2). HRMS (m/z): calcd. for $C_{24}H_{28}BrF_2N_5O$: 519.1445; found: 519.1434.

*6.1.8. 3-{[1-(2-Chlorobenzyl)piperidin-4-yl](methyl)amino]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**12d**)*

Pale yellow solid: 0.23 g (76.7%, yield), mp 78—79 °C. IR (KBr, cm^{-1}): 3406, 2942, 2854, 1612, 1501, 1468, 1270, 1137, 1047, 961. ^1H NMR δ (ppm): 8.17 (s, 1H, TriazC$_3$—H), 7.79 (s, 1H, TriazC$_5$—H), 6.80—7.57 (m, 7H, Ar—H), 5.30 (s, 1H, OH), 4.50 (d, 2H, J = 14.2 Hz, C$_1$—HaHb), 3.54 (br, 2H, Ar—C$\underline{H}_2$), 3.00 (d, 1H, J = 13.7 Hz, C$_3$—Ha), 2.90—2.99 (m, 2H, piperidin-2-CH_2), 2.82 (d, 1H, J = 13.7 Hz, C$_3$—Hb), 2.12—2.18 (m, 1H, piperidin-4-CH), 1.97 (s, 3H, NCH_3), 1.91—1.94 (m, 2H, piperidin-6-CH_2), 1.57—1.60 (m, 2H, piperidin-3-CH_2), 1.39—1.45 (m, 2H, piperidin-5-CH_2). ^{13}C NMR δ (ppm): 162.65, 158.92, 150.88, 144.72, 136.08, 134.14, 130.48, 129.35, 128.01, 126.93, 126.54, 111.40, 104.15, 71.10, 62.77, 58.93, 58.43, 56.56, 53.07, 39.28, 28.63, 27.61. HRMS (m/z): calcd. for $C_{24}H_{28}ClF_2N_5O$: 475.1590; found: 475.1600.

*6.1.9. 3-{[1-(2,4-Dichlorobenzyl)piperidin-4-yl](methyl)amino]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**12e**)*

Pale yellow solid: 0.25 g (78.1%, yield), mp 101—102 °C. IR (KBr, cm^{-1}): 3404, 2930, 2854, 1612, 1494, 1466, 1270, 1139, 1053, 960. ^1H NMR δ (ppm): 8.17 (s, 1H, TriazC$_3$—H), 7.80 (s, 1H, TriazC$_5$—H), 6.78—7.58 (m, 6H, Ar—H), 5.30 (s, 1H, OH), 4.50 (d, 2H, J = 14.3 Hz, C$_1$—HaHb), 3.49 (br, 2H, Ar—C$\underline{H}_2$), 3.00 (d, 1H, J = 13.8 Hz, C$_3$—Ha), 2.99 (br, 2H, piperidin-2-CH_2), 2.82 (d, 1H, J = 13.8 Hz, C$_3$—Hb), 2.12—2.15 (m, 1H, piperidin-4-CH), 1.97 (s, 3H, NCH_3), 1.91—1.93 (m, 2H, piperidin-6-CH_2), 1.45—1.50 (m, 2H, piperidin-3-CH_2), 1.25—1.41 (m, 2H, piperidin-5-CH_2). ^{13}C NMR δ (ppm): 162.71, 158.91, 150.92, 144.77, 134.67, 132.95, 131.25, 129.37, 129.11, 126.90, 111.44, 104.20, 71.13, 62.71, 58.39, 56.54, 53.07, 39.30, 28.65, 27.60. HRMS (m/z): calcd. for $C_{24}H_{27}Cl_2F_2N_5O$: 509.1561; found: 509.1570.

*6.1.10. 3-{[1-(3,4-Dichlorobenzyl)piperidin-4-yl](methyl)amino]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**12f**)*

Yellow oil: 0.26 g (71.2%, yield). IR (KBr, cm^{-1}): 3432, 2925, 2855, 1617, 1500, 1467, 1272, 1136, 1050, 963. ^1H NMR δ (ppm): 8.16 (s, 1H, TriazC$_3$—H), 7.80 (s, 1H, TriazC$_5$—H), 6.78—7.60 (m, 6H, Ar—H), 5.30 (s, 1H, OH), 4.50 (d, 2H, J = 14.2 Hz, C$_1$—HaHb), 3.37 (br, 2H, Ar—C$\underline{H}_2$), 3.00 (d, 1H, J = 13.1 Hz, C$_3$—Ha), 2.82 (br, 2H, piperidin-2-CH_2), 2.80 (d, 1H, J = 13.1 Hz, C$_3$—Hb), 2.12 (br, 1H, piperidin-4-CH), 1.98 (s, 3H, NCH_3), 1.82 (br, 2H, piperidin-6-CH_2), 1.57 (br, 2H, piperidin-3-CH_2), 1.44—1.47 (m, 2H, piperidin-5-CH_2). HRMS (m/z): calcd. for $C_{24}H_{27}Cl_2F_2N_5O$: 509.1561; found: 509.1573.

*6.1.11. 3-{[1-(3-Chlorobenzyl)piperidin-4-yl](methyl)amino]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**12g**)*

Yellow oil: 0.24 g (80.0%, yield). IR (KBr, cm^{-1}): 3429, 2943, 2856, 1617, 1500, 1467, 1272, 1137, 1049, 964. ^1H NMR δ (ppm): 8.16 (s, 1H, TriazC$_3$—H), 7.80 (s, 1H, TriazC$_5$—H), 6.77—7.58 (m, 7H, Ar—H), 5.30 (s, 1H, OH), 4.50 (d, 2H, J = 14.2 Hz, C$_1$—HaHb), 3.42 (br, 2H, Ar—C$\underline{H}_2$), 3.01 (d, 1H, J = 14.1 Hz, C$_3$—Ha), 2.83 (br, 2H, piperidin-2-CH_2), 2.80 (d, 1H, J = 14.1 Hz, C$_3$—Hb), 2.13 (br, 1H, piperidin-4-CH), 1.98 (s, 3H, NCH_3), 1.84 (br, 2H, piperidin-6-CH_2), 1.57—1.60 (m, 2H, piperidin-3-CH_2), 1.40—1.48 (m, 2H, piperidin-5-CH_2). HRMS (m/z): calcd. for $C_{24}H_{28}ClF_2N_5O$: 475.1950; found: 475.1963.

*6.1.12. 3-{[1-(4-Cyanobenzyl)piperidin-4-yl](methyl)amino]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**12h**)*

Yellow oil: 0.13 g (46.4%, yield). IR (KBr, cm^{-1}): 3424, 2922, 2853, 1615, 1501, 1460, 1273, 1138, 1049, 963. ^1H NMR δ (ppm): 8.17 (s, 1H, TriazC$_3$—H), 7.80 (s, 1H, TriazC$_5$—H), 6.78—7.60 (m, 7H, Ar—H), 5.30 (s, 1H, OH), 4.50 (d, 2H, J = 14.1 Hz, C$_1$—HaHb), 3.47 (br, 2H, Ar—C$\underline{H}_2$), 3.01 (d, 1H, J = 13.0 Hz, C$_3$—Ha), 2.83 (br, 2H, piperidin-2-CH_2), 2.80 (d, 1H, J = 13.0 Hz, C$_3$—Hb), 2.14 (br, 1H, piperidin-4-CH), 1.98 (s, 3H, NCH_3), 1.86 (br, 2H, piperidin-6-CH_2), 1.58 (br, 2H, piperidin-3-CH_2), 1.39—1.49 (m, 2H, piperidin-5-CH_2). ^{13}C NMR

δ (ppm): 162.66, 158.85, 150.88, 144.76, 144.20, 132.06, 129.19, 126.81, 118.87, 111.44, 110.88, 104.18, 71.15, 62.56, 62.14, 58.40, 56.46, 53.05, 39.20, 28.44, 27.47. HRMS (*m*/*z*): calcd. for $C_{25}H_{28}F_2N_6O$: 466.2293; found: 466.2279.

*6.1.13. 3-{[1-(3-Bromobenzyl)piperidin-4-yl](methyl)amino}-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**12i**)*

Yellow oil: 0.23 g (69.7%, yield). IR (KBr, cm^{-1}): 3431, 2925, 2855, 1617, 1500, 1465, 1272, 1137, 1049, 963. ^1H NMR δ (ppm): 8.16 (s, 1H, TriazC$_3$—H), 7.80 (s, 1H, TriazC$_5$—H), 6.78–7.57 (m, 7H, Ar—H), 4.49 (d, 2H, $J = 14.2$ Hz, C$_1$—HaHb), 3.39 (br, 2H, Ar—C$\underline{H}_2$), 3.01 (d, 1H, $J = 13.7$ Hz, C$_3$—Ha), 2.83 (br, 2H, piperidin-2-CH$_2$), 2.80 (d, 1H, $J = 13.7$ Hz, C$_3$—Hb), 2.10 (br, 1H, piperidin-4-CH), 1.97 (s, 3H, NCH$_3$), 1.82 (br, 2H, piperidin-6-CH$_2$), 1.57 (br, 2H, piperidin-3-CH$_2$), 1.40–1.50 (m, 2H, piperidin-5-CH$_2$). HRMS (*m*/*z*): calcd. for $C_{24}H_{28}BrF_2N_5O$: 519.1445; found: 519.1429.

*6.1.14. 3-{[1-(2-Fluorobenzyl)piperidin-4-yl](methyl)amino}-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**12j**)*

Yellow oil: 0.21 g (72.4%, yield). IR (KBr, cm^{-1}): 3432, 2943, 2858, 1689, 1498, 1454, 1273, 1136, 1084, 965. ^1H NMR δ (ppm): 8.16 (s, 1H, TriazC$_3$—H), 7.78 (s, 1H, TriazC$_5$—H), 6.77–7.56 (m, 7H, Ar—H), 5.30 (s, 1H, OH), 4.49 (d, 2H, $J = 14.2$ Hz, C$_1$—HaHb), 3.53 (br, 2H, Ar—C$\underline{H}_2$), 2.99 (d, 1H, $J = 13.7$ Hz, C$_3$—Ha), 2.88 (br, 2H, piperidin-2-CH$_2$), 2.80 (d, 1H, $J = 13.7$ Hz, C$_3$—Hb), 2.15 (br, 1H, piperidin-4-CH), 1.96 (s, 3H, NCH$_3$), 1.84–1.89 (m, 2H, piperidin-6-CH$_2$), 1.57–1.60 (m, 2H, piperidin-3-CH$_2$), 1.42–1.50 (m, 2H, piperidin-5-CH$_2$). HRMS (*m*/*z*): calcd. for $C_{24}H_{28}F_3N_5O$: 459.2246; found: 459.2233.

*6.1.15. 3-{[1-(4-Fluorobenzyl)piperidin-4-yl](methyl)amino}-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**12k**)*

Yellow oil: 0.20 g (69.0%, yield). IR (KBr, cm^{-1}): 3428, 2925, 2855, 1613, 1505, 1452, 1272, 1136, 1052, 963. ^1H NMR δ (ppm): 8.16 (s, 1H, TriazC$_3$—H), 7.79 (s, 1H, TriazC$_5$—H), 6.78–7.57 (m, 7H, Ar—H), 5.30 (s, 1H, OH), 4.49 (d, 2H, $J = 14.2$ Hz, C$_1$—HaHb), 3.39 (br, 2H, Ar—C$\underline{H}_2$), 3.00 (d, 1H, $J = 13.7$ Hz, C$_3$—Ha), 2.82 (br, 2H, piperidin-2-CH$_2$), 2.79 (d, 1H, $J = 13.7$ Hz, C$_3$—Hb), 2.12 (br, 1H, piperidin-4-CH), 1.97 (s, 3H, NCH$_3$), 1.80 (br, 2H, piperidin-6-CH$_2$), 1.56 (br, 2H, piperidin-3-CH$_2$), 1.37–1.40 (m, 2H, piperidin-5-CH$_2$). HRMS (*m*/*z*): calcd. for $C_{24}H_{28}F_3N_5O$: 459.2246; found: 459.2260.

*6.1.16. 2-(2,4-Difluorophenyl)-3-{[1-(3-methoxybenzyl)piperidin-4-yl](methyl)amino}-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**12l**)*

Yellow oil: 0.15 g (50.0%, yield). IR (KBr, cm^{-1}): 3435, 2926, 2855, 1614, 1497, 1460, 1270, 1138, 1047, 964. ^1H NMR δ (ppm): 8.16 (s, 1H, TriazC$_3$—H), 7.79 (s, 1H, TriazC$_5$—H), 6.77–7.56 (m, 7H, Ar—H), 4.49 (d, 2H, $J = 14.2$ Hz, C$_1$—HaHb), 3.80 (s, 3H, OCH$_3$), 3.41 (br, 2H, Ar—C$\underline{H}_2$), 2.99 (d, 1H, $J = 13.9$ Hz, C$_3$—Ha), 2.86 (br, 2H, piperidin-2-CH$_2$), 2.81 (d, 1H, $J = 13.7$ Hz, C$_3$—Hb), 2.15 (br, 1H, piperidin-4-CH), 1.97 (s, 3H, NCH$_3$), 1.81 (br, 2H, piperidin-6-CH$_2$), 1.41–1.47 (m, 2H, piperidin-3-CH$_2$), 1.25 (br, 2H, piperidin-5-CH$_2$). HRMS (*m*/*z*): calcd. for $C_{25}H_{31}F_2N_5O_2$: 471.2446; found: 471.2442.

*6.1.17. 3-{[1-(2-Methylbenzyl)piperidin-4-yl](methyl)amino}-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**12m**)*

Yellow oil: 0.17 g (58.6%, yield). IR (KBr, cm^{-1}): 3432, 2925, 2855, 1616, 1499, 1461, 1272, 1138, 1048, 963. ^1H NMR δ (ppm): 8.16 (s, 1H, TriazC$_3$—H), 7.78 (s, 1H, TriazC$_5$—H), 6.79–7.57 (m, 7H, Ar—H), 5.29 (s, 1H, OH), 4.49 (d, 2H, $J = 14.2$ Hz, C$_1$—HaHb), 3.37 (br, 2H, Ar—C$\underline{H}_2$), 2.99 (d, 1H, $J = 13.8$ Hz, C$_3$—Ha), 2.83–2.86 (m, 2H, piperidin-2-CH$_2$), 2.81 (d, 1H, $J = 13.8$ Hz, C$_3$—Hb), 2.32 (s, 3H, Ar—C$\underline{H}_3$), 2.13 (br, 1H, piperidin-4-CH), 1.96 (s, 3H, NCH$_3$), 1.82–1.84 (m, 2H, piperidin-6-CH$_2$), 1.45 (br, 2H, piperidin-3-CH$_2$), 1.32–1.38 (m, 2H, piperidin-5-CH$_2$). ^{13}C NMR δ (ppm): 163.63, 159.01, 150.93, 144.70, 137.29, 136.65, 130.17, 129.55, 129.38, 126.90, 125.40, 111.39, 104.11, 71.13, 62.95, 60.52, 58.50, 56.56, 53.08, 39.23, 28.73, 27.64, 19.10. HRMS (*m*/*z*): calcd. for $C_{25}H_{31}F_2N_5O$: 455.2497; found: 455.2779.

*6.1.18. 3-{[1-(4-Isopropylbenzyl)piperidin-4-yl](methyl)amino}-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**12n**)*

Pale yellow solid: 0.14 g (46.7%, yield), mp 75–76 °C. IR (KBr, cm^{-1}): 3432, 2923, 2854, 1612, 1498, 1464, 1269, 1135, 1053, 960. ^1H NMR δ (ppm): 8.15 (s, 1H, TriazC$_3$—H), 7.78 (s, 1H, TriazC$_5$—H), 6.77–7.56 (m, 7H, Ar—H), 5.30 (s, 1H, OH), 4.49 (d, 2H, $J = 14.1$ Hz, C$_1$—HaHb), 3.49 (br, 1H, Ar—CH(CH$_3$)$_2$), 3.41 (br, 2H, Ar—C$\underline{H}_2$), 3.00 (d, 1H, $J = 13.7$ Hz, C$_3$—Ha), 2.87–2.92 (m, 2H, piperidin-2-CH$_2$), 2.81 (d, 1H, $J = 13.7$ Hz, C$_3$—Hb), 2.12 (br, 1H, piperidin-4-CH), 1.97 (s, 3H, NCH$_3$), 1.81 (br, 2H, piperidin-6-CH$_2$), 1.55–1.58 (m, 2H, piperidin-3-CH$_2$), 1.41–1.48 (m, 2H, piperidin-5-CH$_2$), 1.23–1.26 (m, 6H, —CH(C$\underline{H}_3$)$_2$). HRMS (*m*/*z*): calcd. for $C_{27}H_{35}F_2N_5O$: 483.2810; found: 483.2822.

6.2. Flexible docking analysis

The 3D structures of the designed azoles were built by the Builder module within Insight II 2000 software package. Then, the flexible ligand docking procedure in the Affinity module within Insight II was used to define the lowest energy position for the substrate using a Monte Carlo docking protocol. The detailed docking parameters were from our previous studies [19].

Acknowledgement

This work was supported by the National Natural Science Foundation of China (Grant No. 30930107), Shanghai Rising-Star Program (Grant No. 09QA1407000) and Shanghai Leading Academic Discipline Project (Project No. B906).

References

[1] N.H. Georgopapadakou, T.J. Walsh, Antimicrob. Agents Chemother. 40 (1996) 279–291.
[2] K.A. Marr, Oncology (Williston Park) 18 (2004) 9–14.
[3] R.P. Vonberg, P. Gastmeier, J. Hosp. Infect. 63 (2006) 246–254.
[4] D.J. Sheehan, C.A. Hitchcock, C.M. Sibley, Clin. Microbiol. Rev. 12 (1999) 40–79.
[5] H.A. Gallis, R.H. Drew, W.W. Pickard, Rev. Infect. Dis. 12 (1990) 308–329.
[6] D.W. Denning, J. Antimicrob. Chemother. 49 (2002) 889–891.
[7] I.A. Casalinuovo, P. Di Francesco, E. Garaci, Eur. Rev. Med. Pharmacol. Sci. 8 (2004) 69–77.
[8] L.B. Johnson, C.A. Kauffman, Clin. Infect. Dis. 36 (2003) 630–637.
[9] R. Herbrecht, Int. J. Clin. Pract. 58 (2004) 612–624.
[10] S. Arikan, J.H. Rex, Curr. Opin. Investig. Drugs 3 (2002) 555–561.
[11] J. Capilla, C. Yustes, E. Mayayo, B. Fernandez, M. Ortoneda, F.J. Pastor, J. Guarro, Antimicrob. Agents Chemother. 47 (2003) 1948–1951.
[12] J. Bartroli, E. Turmo, M. Alguero, E. Boncompte, M.L. Vericat, L. Conte, J. Ramis, M. Merlos, J. Garcia-Rafanell, J. Forn, J. Med. Chem. 41 (1998) 1869–1882.
[13] D.C. Lamb, D.E. Kelly, K. Venkateswarlu, N.J. Manning, H.F. Bligh, W.H. Schunck, S.L. Kelly, Biochemistry 38 (1999) 8733–8738.
[14] C. Sheng, Z. Miao, H. Ji, J. Yao, W. Wang, X. Che, G. Dong, J. Lu, W. Guo, W. Zhang, Antimicrob. Agents Chemother. 53 (2009) 3487–3495.
[15] C. Sheng, W. Zhang, M. Zhang, Y. Song, H. Ji, J. Zhu, J. Yao, J. Yu, S. Yang, Y. Zhou, J. Lu, J. Biomol. Struct. Dyn. 22 (2004) 91–99.
[16] H. Ji, W. Zhang, Y. Zhou, M. Zhang, J. Zhu, Y. Song, J. Lu, J. Med. Chem. 43 (2000) 2493–2505.
[17] A.N. Eddine, J.P. von Kries, M.V. Podust, T. Warrier, S.H. Kaufmann, L.M. Podust, J. Biol. Chem. 283 (2008) 15152–15159.
[18] L.M. Podust, T.L. Poulos, M.R. Waterman, Proc. Natl. Acad. Sci. U.S.A. 98 (2001) 3068–3073.
[19] C. Sheng, W. Zhang, H. Ji, M. Zhang, Y. Song, H. Xu, J. Zhu, Z. Miao, Q. Jiang, J. Yao, Y. Zhou, J. Lu, J. Med. Chem. 49 (2006) 2512–2525.
[20] S.H. Chen, C.Q. Sheng, X.H. Xu, Y.Y. Jiang, W.N. Zhang, C. He, Biol. Pharm. Bull. 30 (2007) 1246–1253.
[21] H. Ji, W. Zhang, M. Zhang, M. Kudo, Y. Aoyama, Y. Yoshida, C. Sheng, Y. Song, S. Yang, Y. Zhou, J. Lu, J. Zhu, J. Med. Chem. 46 (2003) 474–485.
[22] Y. Xu, C. Sheng, W. Wang, X. Che, Y. Cao, G. Dong, S. Wang, H. Ji, Z. Miao, J. Yao, W. Zhang, Bioorg. Med. Chem. Lett. 20 (2010) 2942–2945.
[23] C. Sheng, W. Wang, X. Che, G. Dong, S. Wang, H. Ji, Z. Miao, J. Yao, W. Zhang, ChemMedChem 5 (2010) 390–397.

[24] W. Wang, C. Sheng, X. Che, H. Ji, Z. Miao, J. Yao, W. Zhang, Arch. Pharm. (Weinheim) 342 (2009) 732–739.
[25] W. Wang, C. Sheng, X. Che, H. Ji, Y. Cao, Z. Miao, J. Yao, W. Zhang, Bioorg. Med. Chem. Lett. 19 (2009) 5965–5969.
[26] X. Che, C. Sheng, W. Wang, Y. Cao, Y. Xu, H. Ji, G. Dong, Z. Miao, J. Yao, W. Zhang, Eur. J. Med. Chem. 44 (2009) 4218–4226.
[27] Insight II 2000: Accelrys Inc, 10188 Telesis Court, Suite 100, San Diego, CA 92121. Phone: (858) 799-5000. Fax: (858) 799-5100. Website: http://www.accelrys.com/.