European Journal of Medicinal Chemistry 46 (2011) 3142–3148

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Preliminary communication

Design, synthesis and antifungal activities of novel 1,2,4-triazole derivatives

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ARTICLE INFO

Article history:
Received 15 September 2009
Received in revised form
27 January 2011
Accepted 16 February 2011
Available online 24 February 2011

Keywords:
Synthesis
Antifungal activity
1,2,4-Triazole
Piperazine

ABSTRACT

A series of novel 1,2,4-triazole derivatives with a 4-(4-substitutedphenyl) piperazine side chain were designed and synthesized based on the structure of lanosterol 14α-demethylase (CYP51). Their antifungal activities against eight human pathogenic fungi were evaluated *in vitro* by measuring the minimal inhibitory concentrations. Nearly all tested compounds were found to be more potent against *Candida albicans* than control drug fluconazole. Noticeably, the MIC_{80} value of compounds **6**,**7**,**9**,**14** and **29** is 16 times lower than that of voriconazole against *C. albicans*. The activities of compounds **7** and **21** against *Cryptococcus neoformans in vitro* are comparable to that of voriconazole with a MIC_{80} value of 0.0156 μg/mL. Moreover, the molecular model for the binding between compound **7** and the active site of CACYP51 was provided based on the computational docking results.

1. Introduction

During the past two decades, the growing population of immuno-compromised patients due to organ transplantation, tuberculosis, AIDS and cancer chemotherapy has resulted in an increase in severe fungal infections. In many cases, it is not the AIDS or cancer itself but the mycoses that are lethal to these patients [1,2]. Azole compounds (e.g. fluconazole, voriconazole and itraconazole) which act by competitive inhibition of the lanosterol 14α-demethylase (CYP51) are an important class of antifungal agents as they have fungistatic, orally effective and broad-spectrum activities against most yeasts and filamentous fungi, which now become the most rapidly expanding group of antifungal compounds. However, their clinical application value has been limited by their relatively high risk of toxicity, the emergence of drug resistance, pharmacokinetic deficiencies and/or insufficiencies in their antifungal activities. Despite recent developments [3–6], there is still an urgent need for authentically genuinely broad-spectrum and low-toxicity antifungal agents.

CYP51 is a member of the cytochrome P450 super family and a key enzyme in the biosynthesis of ergosterol, which catalyzes the oxidative removal of the lanosterol 14α-methyl group to give $\Delta^{14,15}$-desaturated intermediates in fungal ergosterol biosynthesis. Recent studies showed that typical azole inhibitors were able to fit the putative active site of CYP51 by a combination of heme coordination, hydrogen bonding, π–π stacking and hydrophobic interactions [7–9]. Ji's study [9] indicated that in the active site of CYP51 the 1,2,4-triazole ring in the scaffold of 1,2,4-triazole antifungal agent was positioned perpendicularly to the porphyrin plane with a ring nitrogen atom (N-4 of 1,2,4-triazole) coordinated to the heme iron of CYP51 and was of key importance for the antifungal activity. The halogenated phenyl group was deep in the same hydrophobic binding cleft in the active site of the target enzyme CYP51 and long chains of some antifungals such as itraconazole and ketoconazole surpassed the active site and interacted with residues in the substrate access channel. Based on these properties of the active site of CYP51, it provides us an attempt to design new triazole derivatives to find potent systemic antifungal agents that have a broad antifungal spectrum but with less potential to develop drug resistance.

In our previous research [10–12], we designed and synthesized a series of novel 1-(1*H*-1,2,4- triazole-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanols containing a 1,2,4-triazole ring, a difluorogenatedphenyl group, a hydroxyl group and a long side chain connected by a 4-(4-substitutedphenyl) piperazine linker. Their minimal inhibitory concentration (MIC) value indicates that it is very helpful to introduce 4-(4-substitutedphenyl) piperazine as a side chain linker to adjust the physicochemical properties of the whole target molecule to avoid the dissatisfying side effects and/or improve

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doi:10.1016/j.ejmech.2011.02.042

the pharmacokinetic and pharmacodynamic behavior. Hereby in our present work, we designed, synthesized some analogous amides of alkyl carboxylic acids and evaluated their antifungal activities against eight human pathogenic fungi *in vitro*. The structures of this series of compounds are shown in Scheme 1 and all compounds are racemates.

2. Chemistry

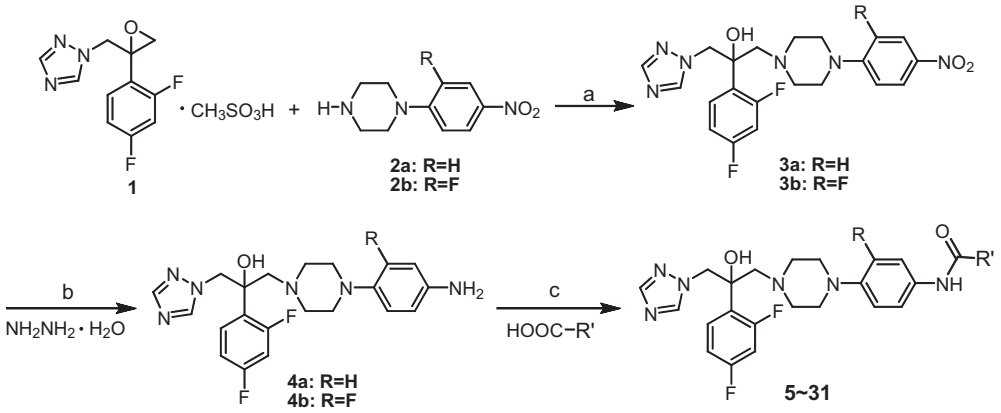
The general synthetic route of target compounds 1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluoro -phenyl)-3-[(4-substitutedphenyl)-piperazin-1-yl]-2-propanols (5–31) is outlined in Scheme 1. The important intermediate oxirane 1, compounds **2a** and **2b** were synthesized by known procedures [10–13]. Compounds **3a** and **3b** were obtained as racemates via ring-opening reactions of oxirane 1 with compounds **2a** and **2b**. Good yields were obtained when the nucleophilic reactions were performed in a protic solvent ethanol in the presence of triethylamine as a base at 80 °C. The nitro group on the phenyl ring of compounds **3a** and **3b** was reduced to an amino group in the presence of Ranney Ni and 85% hydrazine hydrate. In the presence of 4-dimethylaminopyridine (DMAP) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (EDCI) in dichloromethane, the anilines 4a and 4b were converted to target compounds 5–31 by reacting with various alkyl carboxylic acids at ambient temperature.

3. Antifungal assay

The *in vitro* minimal inhibitory concentrations (MICs) of the target compounds were determined by the micro-broth dilution method according to the methods defined by the National Committee for Clinical Laboratory Standards [14]. Fungi strains for testing: *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*, *Cryptococcus neoformans, Aspergillus fumigatus*, *Trichophyton rubrum*, *Fonsecaea compacta*, *Microsporum gypseum* were provided by Shanghai Changhai Hospital. *C. albicans, C. neoformans* and *C. parapsilosis* are ATCC standard strains, others are clinic isolates. *C. albicans* (ATCCY0109), *C. neoformans* (ATCCBLS108) and *C. parapsilosis* (ATCC0306392) were quality controlled strains, and tested in each assay. Fluconazole (FCZ), itraconazole (ICZ), ketoconazole (KCZ), voriconazole (VCZ) and amphotericin B (AMB) obtained from their respective manufacturers served as the positive control. The drug MIC_{80} was defined as the first well with an approximate 80% reduction in growth compared to the growth of the drug-free well. 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 *Candida albicans*, 72 h for *Cryptococcus neoformans* and at 7 days for filamentous fungi. The results of antifungal assays are summarized in Table 1. These data are the mean of three replicate tests performed with each antifungal compound.

4. Results and discussion

The results of antifungal activities *in vitro* showed that all the title compounds were active against all fungi tested to some extent. Among the compounds tested, most of them showed higher activity against *C. albicans* than fluconazole, itraconazole and amphotericin B *in vitro*. Noticeably, the MIC_{80} value of compounds **6**,**7**,**9**,**14**,**29** is 16 times lower than that of voriconazole against *C. albicans in vitro*. The activities of compounds **8**, **11**–**13**, **15**, **16**, **22**, **24**, **26**, **27** and **31** are



Conditions: (a)CH_3CH_2OH,Et_3N,80 ºC,5h; (b)Ranney Ni,NH_2NH_2 H_2O,CH_3CH_2OH,80 ºC,3.5h; (c)DMAP,EDCI,CH_2Cl_2,8h.

Compd.	R	R'	Compd.	R	R'	Compd.	R	R'
5	H	CH_2Cl	14	H	$CH_2(CH_2)_4CH_3$	23	F	CH_2CH_3
6	H	CF_2Cl	15	H	$CH_2(CH_2)_5CH_3$	24	F	$CH_2CH_2CH_3$
7	H	CF_3	16	H	$CH_2(CH_2)_7CH_3$	25	F	$CH(CH_3)_2$
8	H	CH_2CH_3	17	H	$CH_2(CH_2)_9CH_3$	26	F	$CH_2(CH_2)_2CH_3$
9	H	$CH_2CH_2CH_3$	18	H	$CH_2(CH_2)_{13}CH_3$	27	F	$C(CH_3)_3$
10	H	$CH(CH_3)_2$	19	F	CH_3	28	F	$CH_2(CH_2)_3CH_3$
11	H	$CH_2(CH_2)_2CH_3$	20	F	CH_2Cl	29	F	$CH_2(CH_2)_4CH_3$
12	H	$CH_2(CH_2)_3CH_3$	21	F	CF_2Cl	30	F	$CH_2(CH_2)_5CH_3$
13	H	$C(CH_3)_3$	22	F	CF_3	31	F	CH_2Ph

Scheme 1. Synthetic route of the title compounds.

Table 1
Antifungal Activities of The Title Compounds *in vitro* (MIC_{80} μg/mL).[a]

compd.	C. alb.	C. par.	C. tro.	C. neo.	A. fum.	T. rub.	F. com.	M. gyp.
5	0.0039	0.0156	0.0156	0.25	4	0.0625	0.0625	0.0625
6	0.00097	0.0039	0.0039	0.0625	1	0.0156	0.0625	0.0039
7	0.00097	0.0039	0.00097	0.0156	1	0.0156	0.0156	0.0039
8	0.0156	0.0156	0.0156	1	4	0.0625	0.25	0.25
9	0.00097	0.0156	0.0625	0.25	4	0.0625	0.25	0.0625
10	0.0039	0.0156	0.0156	1	4	0.25	0.25	0.0625
11	0.0156	0.0625	0.0625	0.25	1	0.0625	0.25	0.25
12	0.0156	0.25	0.25	1	>64	0.0625	1	0.0625
13	0.0156	0.0156	0.0156	0.25	16	0.0039	1	0.0156
14	0.00097	0.0156	0.0156	0.0625	>64	0.0039	0.0625	0.0039
15	0.0156	0.0625	0.0625	0.0625	1	0.0625	1	0.0156
16	0.0156	1	0.25	0.0625	1	0.0625	1	0.0156
17	0.0625	0.25	1	0.0625	1	0.0625	0.25	0.0156
18	0.25	1	1	16	>64	0.25	4	0.25
19	0.0625	0.0625	0.0625	1	4	0.25	0.25	1
20	0.0039	0.0156	0.0156	0.0625	1	0.0625	0.0625	0.0156
21	64	0.0039	0.0039	0.0156	1	0.0039	0.0156	0.0039
22	0.0156	0.0039	0.0039	0.0625	1	0.0156	0.25	>64
23	0.0625	0.0625	0.0625	1	4	0.0625	1	0.25
24	0.0156	0.0156	0.0156	0.25	1	0.0156	0.25	0.0156
25	0.0625	0.25	4	16	>64	0.0625	1	0.0625
26	0.0156	0.25	0.25	1	1	0.25	1	0.25
27	0.0156	0.0156	0.0156	0.25	64	0.0156	0.0625	0.0156
28	0.0039	0.25	0.0625	0.0625	1	0.0156	0.25	0.25
29	0.00097	0.0625	0.0625	0.0625	1	0.0156	0.25	0.0625
30	0.0625	0.0625	0.0625	0.25	1	0.0039	0.25	0.0625
31	0.0156	0.0625	0.0625	1	64	0.0039	0.0625	0.0156
FCZ	4	1	1	1	64	0.25	16	0.25
ICZ	1	0.25	0.25	1	1	0.0156	0.25	0.0156
KCZ	0.0625	0.0625	0.0625	0.0625	1	0.0625	0.0625	0.0039
VCZ	0.0156	1	0.25	0.0156	>64	0.0039	0.0156	0.0039
AMB	1	0.0156	0.0625	1	4	1	16	0.0039

[a] Abbreviations: *C. alb.*, *Candida albicans*; *C. par.*, *Candida paropsilosis*; *C. tro.*, *Candida tropicalis*; *C. neo.*, *Cryptococcus neoformans*; *A. fum.*, *Aspergillus fumigatus*; *T. rub.*, *Trichophyton rubrum*; *F. com.*, *Fonsecaea compacta*; *M. gyp.*, *Microsporum gypseum*; FCZ, fluconazole; ICZ, itraconazole; KCZ, ketoconazole; VCZ, voriconazole; AMB, amphotericin B.

comparable to that of voriconazole *in vitro* against *C. albicans* with the MIC_{80} value of 0.0156 μg/ml. The MIC_{80} value of compound 7 is 64 times lower than that of amphotericin B against *C. tropicalis in vitro*. Compounds 7, 21 exhibited the same activities against *C. neoformans* as voriconazole (with the MIC_{80} values of 0.0156 μg/mL).

Fluconazole is not effective against *A. fumigatus*, while our compounds exhibit moderate activity. For example, compounds **5**, **8**–**10**, **19**, **23** exhibited the same activities against *A. fumigatus* as amphotericin B (with the MIC_{80} values of 4 μg/mL). Compounds **6**, **7**, **11**, **15**–**17**, **20**–**22**, **24**, **26**, **28**–**30** exhibited the same activities against *A. fumigatus* as itraconazole and ketoconazole (with the MIC_{80} values of 1 μg/mL). The result is encouraging because it has been known that *A. fumigatus* possesses an intrinsic mechanism resistant to triazole antifungal agents.

Moreover, our compounds also showed excellent activity against dermatophytes (i.e. *T. rubrum* and *M. gypseum*). Compound **13**,**14**,**21**,**30**,**31** exhibited the same activities against *T. rubrum* as voriconazole (with the MIC_{80} values of 0.0039 μg/mL). Compounds **6**, **7**, **14**, **21** showed the same activity against *M. gypseum* as ketoconazole, voriconazole and amphotericin B (with the MIC_{80} values of 0.0039 μg/mL). Compound **7** showed the highest activity with broad antifungal spectrum, which is a good candidate for further evaluation.

The results of preliminary antifungal assays indicated that the introduction of fluorine atom to the phenyl group of side chain did not improve the antifungal activities effectively. However, the length of alkyl side chain is essential to their antifungal activities. Compounds with a short or moderate-length side chain present higher antifungal activities than those with longer side chains. Compared with the aromatic analogues studied previously [12], the introduction of an aliphatic side chain resulted in a better improvement of the antifungal activity, suggesting that the hydrophobic interactions of the aliphatic group with CYP51 were important for its binding affinity.

Although Sheng's study [15] indicated that the piperazinyl group is not the best linker for the design of azole antifungal side chain, according to our preliminary *in vitro* antifungal assay we still think that the piperazinyl group is a good choice for the new candidate design. Up to now, the crystal structure of CYP51 from *C. albicans* is unclear, so we can just clarify our design by using computational docking method based on the homonology modeling structure of CYP51.

In previous research, the molecular docking results indicated that the azole compound binds to the active site of CACYP51 through the formation of a coordination bond with iron of heme group. The difluorophenyl group is located in the hydrophobic binding cleft lined with Phe126, Ile304, Met306, Gly307 and Gly308. The piperazinyl side chain is oriented into substrate access channel 2 (FG loop) and forms hydrophobic and *van der waals* interactions with surrounding hydrophobic residues such as Tyr64, Gly65, Leu87, Leu88, Met92, Ala117, Tyr118, Pro230, Ile231, Phe233, Val234, Leu376, His377, Ser378, Ile379, Phe380, Met508. Furthermore, the phenyl group attached to the piperazinyl of the side chain interacts with the phenyl group of Phe380 through the formation of π−π face-to-edge interaction.

To clarify the binding mode of our synthesized compounds in this paper, compound **7** was docked into the active site of CACYP51 by the Builder module within Insight II 2000 software package (Fig. 1). The compound **7** docking result revealed that the triazole group, the difluorophenyl group and the piperazinyl side chain can bind to the active site of CACYP51 through the former binding mode.

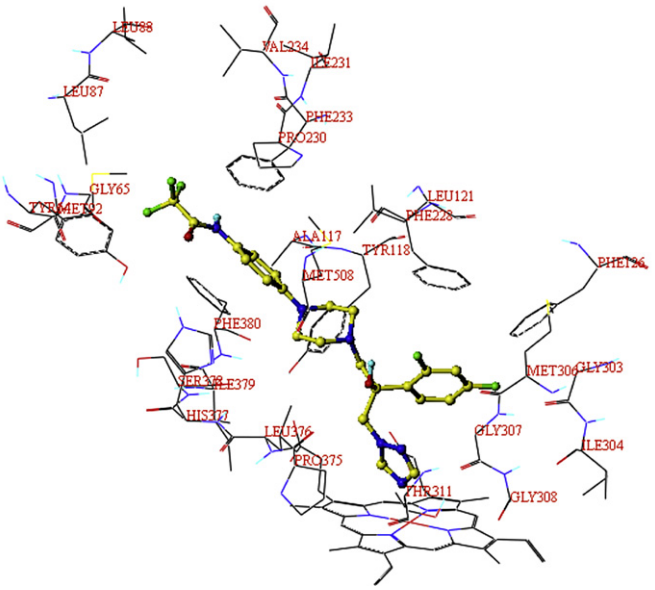


Fig. 1. Computed binding geometry of the new inhibitor 7 in the active site of CACYP51.

5. Conclusion

On the basis of the active site of CACYP51, a series of novel triazole derivatives with a 4-(4-substitutedphenyl) piperazine side chain have been successfully designed and synthesized as antifungal agents. The *in vitro* antifungal activities of all title compounds were evaluated against eight human pathogenic fungi which are often encountered clinically. Compared with their aromatic analogues, our present results clearly showed that the introduction of aliphatic side chain with a proper length greatly enhanced the antifungal activity of these title compounds against Candida species and the introduction of fluorine atom to the phenyl group of side chain is not necessary to improve their antifungal activities. The obtained results demonstrated that our effort which maintains the pharmacophores (a 1,2,4-triazole ring, a difluorogenated phenyl group and a hydroxyl group), substituted one triazole ring of fluconazole with a 4-(4-substitutedphenyl) piperazine linking a series of aliphatic side chain is encouraging. This observation was explainable by a molecular model resulting from the computational docking simulation. The piperazinyl side chain of the compound **7** is oriented into substrate access channel 2 (FG loop) and forms hydrophobic and *van der waals* interactions with surrounding hydrophobic residues. The phenyl group of the side chain can interacts with the phenyl group of Phe380 through the formation of π–π face-to-edge interaction. 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

Melting points were measured on a Yamato MP-21 melting-point apparatus and are uncorrected. Infrared spectra were recorded in potassium bromide disks on a HITACHI 270-50 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ with a Bruker AC-300P spectrometer, using TMS as internal standard. Elemental analysis was undertaken with an Italian MOD 1106 analyzer at the Analysis Center of Shanghai Institute of Pharmaceutical Industry. Mass spectra were recorded on an Agilent 1100 HPLC-MS. 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.

The important intermediates *1-[4-(4-amino-phenyl)-piperazin-1-yl]-2-(2,4-difluorophenyl)-3-(1H- 1,2,4-triazol-1-yl)-propan-2-ol (4a) and 2-(2,4-difluorophenyl)-1-[4-(2-fluoro-4-amino-phenyl) -piperazin-1-yl]-3-(1H-1,2,4-triazol-1-yl)-propan-2-ol* (**4b**) were prepared according to an established procedure [10,11].

6.1. General procedure for the preparation of title compounds 5–31

To a stirred mixture of **4a** or **4b** (0.001 mol), DMAP (100 mg) and EDCI (200 mg) in 50 mL dichloromethane under 0 °C and alkyl carboxylic acid (0.001 mol)was added and stirred for 8–12 h. The reaction was monitored by TLC (dichloromethane/methanol, 1/20–1/10, v/v). After filtration, the filtrate was evaporated under reduced pressure. The residue was then extracted with ethyl acetate (50 mL × 3). The extract was washed with saturated NaCl solution (20 mL × 3), dried over anhydrous Na_2SO_4 and evaporated. The residue was crystallized from absolute alcohol to afford the title compounds **5**–**31**.

The title compounds **5**–**31** were characterized as follows.

6.2. Data for 2-chloro-N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl] piperazin-1-yl}phenyl)acetamide (5)

Yield: 78%; m.p. 77–80 °C; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 7.58–6.79 (m, 7H, Ar–H), 4.56 (d, 1H, J = 15 Hz, triazole–CH_2), 4.54 (d, 1H, J = 15 Hz, triazole–CH_2), 4.16 (s, 2H, –CH_2–), 3.04–2.49 (m, 8H, piperazine-H), 3.16 (d, 1H, J = 15 Hz, CH_2–piperazine), 2.69 (d, 1H, J = 13.8 Hz, CH_2–piperazine). EIMS, *m/z*: 491 (M + 1). IR (KBr): 3265,3193,3128,3051,2952, 2825,1664,1614,1514,1271,1139,1014,848 cm^{-1}. Anal. calcd for $C_{23}H_{25}ClF_2N_6O_2$: C, 56.27; H, 5.13; N, 17.12. Found: C, 56.43; H, 5.15; N, 17.08.

6.3. Data for 2-chloro-N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl] piperazin-1-yl}phenyl)-2,2-difluoroacetamide (6)

Yield: 68%; m.p. 176–178 °C; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 8.01–6.79 (m, 7H, Ar–H), 5.16 (1H, s,OH), 4.61 (d, 1H, J = 14.4 Hz, triazole–CH_2), 4.49 (d, 1H, J = 14.4 Hz, triazole–CH_2), 3.06–2.50 (m, 8H, piperazine-H), 3.16 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.70 (d, 1H, J = 13.5 Hz, CH_2–piperazine). EIMS, *m/z*: 527 (M + 1). IR (KBr): 3271,3112,2826,1716,1616,1537,1309,1139,1007 cm^{-1}. Anal. calcd for $C_{23}H_{23}ClF_4N_6O_2$: C, 52.43; H, 4.40; N, 15.95. Found: C, 52.63; H, 4.52; N, 15.68.

6.4. Data for N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} phenyl)-2,2,2-trifluoroacetamide (7)

Yield: 74%; m.p. 103–105 °C; ^{1}HNMR ($CDCl_3$): 8.16 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 8.48–6.79 (m, 7H, Ar–H), 4.60 (d, 1H, J = 14.1 Hz, triazole–CH_2), 4.54 (d, 1H, J = 14.1 Hz, triazole–CH_2), 2.97–2.51 (m, 8H, piperazine-H), 3.18 (d, 1H, J = 13.8 Hz, CH_2–piperazine), 2.69 (d, 1H, J = 13.8 Hz, CH_2–piperazine). EIMS, *m/z*: 511 (M + 1). IR (KBr): 3118,2947,2828,2359,1710,1548,1422,1211,1186,1138,965 cm^{-1}. Anal. calcd for $C_{23}H_{23}F_5N_6O_2$: C, 54.12; H, 4.54; N, 16.46. Found: C, 53.98; H, 4.68; N, 16.57.

*6.5. Data for N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} phenyl)propionamide (**8**)*

Yield: 82%; m.p. 147–149 °C [10]; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 7.61–6.77 (m, 7H, Ar–H), 5.20 (1H, s,OH), 4.60 (d, 1H, J = 14.4 Hz, triazole–CH_2), 4.49 (d, 1H, J = 14.4 Hz, triazole–CH_2), 3.02–2.49 (m, 8H, piperazine-H), 3.16 (d, 1H, J = 12.3 Hz, CH_2–piperazine), 2.69 (d, 1H, J = 12.3 Hz, CH_2–piperazine), 2.39–2.31 (q, 2H, –CH_2–), 1.25–1.20 (t, 3H, –CH_3). EIMS, m/z: 471 (M + 1). IR (KBr): 3278,3118,3066,2966,2880,2825,1655, 1603,1543,1514,1453, 1205,1137 cm^{-1}. Anal. calcd for $C_{24}H_{28}F_2N_6O_2$: C, 61.26; H, 6.00; N, 17.86. Found: C, 61.11; H, 5.93; N, 17.82.

*6.6. Data for N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} phenyl)butanamide (**9**)*

Yield: 80%; m.p. 163–165 °C [10]; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 7.61–6.78 (m, 7H, Ar–H), 4.57 (d, 1H, J = 14.1 Hz, triazole–CH_2), 4.49 (d, 1H, J = 14.1 Hz, triazole–CH_2), 3.01–2.49 (m, 8H, piperazine-H), 3.16 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.69 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.31–2.26 (t, 2H, –CH_2–), 1.77–1.70 (m, 2H, –CH_2–), 1.01–0.96 (t, 3H, –CH_3). EIMS, m/z: 485 (M + 1). IR (KBr): 3351,3133, 3071,2962, 2869,2834,1655,1617,1594, 1515,1498,1454,1276 cm^{-1}. Anal. calcd for $C_{25}H_{30}F_2N_6O_2$: C, 61.97; H, 6.24; N, 17.34. Found: C, 61.82; H, 6.32; N, 17.18.

*6.7. Data for N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} phenyl)isobutanamide (**10**)*

Yield: 76%; m.p. 128–130 °C; ^{1}HNMR ($CDCl_3$): 8.16 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 7.61–6.78 (m, 7H, Ar–H), 4.60 (d, 1H, J = 14.4 Hz, triazole–CH_2), 4.49 (d, 1H, J = 14.4 Hz, triazole–CH_2), 3.01–2.49 (m, 8H, piperazine-H), 3.16 (d, 1H, J = 12.6 Hz, CH_2–piperazine), 2.69 (d, 1H, J = 12.6 Hz, CH_2–piperazine), 2.46–2.42 (m, H, –CH–), 1.24–1.21 (d, 6H, –CH_3). EIMS, m/z: 485 (M + 1). IR (KBr): 3443,3271,3113,3062,2972,2936,2875, 2811,1658,1604, 1546,1513,1498 cm^{-1}. Anal. calcd for $C_{25}H_{30}F_2N_6O_2$: C, 61.97; H, 6.24; N, 17.34. Found: C, 61.91; H, 6.28; N, 17.39.

*6.8. Data for N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} phenyl)pentanamide (**11**)*

Yield: 77%; m.p. 191–193 °C; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 7.57–6.77 (m, 7H, Ar–H), 5.21(1H, s,OH), 4.58 (d, 1H, J = 14.4 Hz, triazole–CH_2), 4.50 (d, 1H, J = 14.4 Hz, triazole–CH_2), 2.99–2.49 (m, 8H, piperazine-H), 3.15 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.69 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.33–2.28 (t, 2H, –CH_2–), 1.71–1.65 (m, 2H, –CH_2–), 1.41–1.26 (m, 2H, –CH_2–), 0.95–0.90 (t, 3H, –CH_3). EIMS, m/z: 499 (M + 1). IR (KBr): 3351,3133,3070,2955,2834,1655,1617,1594, 1515,1454,1389,1141 cm^{-1}. Anal. calcd for $C_{26}H_{32}F_2N_6O_2$: C, 62.64; H, 6.47; N, 16.86. Found: C, 62.46; H, 6.39; N, 16.79.

*6.9. Data for N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} phenyl)hexanamide (**12**)*

Yield: 67%; m.p. 199–201 °C; ^{1}HNMR ($CDCl_3$): 8.16 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 7.61–6.78 (m, 7H, Ar–H), 4.58 (d, 1H, J = 14.4 Hz, triazole–CH_2), 4.50 (d, 1H, J = 14.4 Hz, triazole–CH_2), 3.00–2.50 (m, 8H, piperazine-H), 3.17 (d, 1H, J = 14.4 Hz, CH_2–piperazine), 2.70 (d, 1H, J = 14.4 Hz, CH_2–piperazine), 2.33–2.28 (t, 2H, –CH_2–), 1.73–1.68 (m, 2H, –CH_2–), 1.36–1.23 (m, 4H, –CH_2–), 0.92–0.87 (t, 3H, –CH_3). EIMS, m/z: 513 (M + 1). IR (KBr): 3342,3132,2957, 2931,2859, 2829,1654,1616,1596, 1532,1415,1139 cm^{-1}. nal. calcd for $C_{27}H_{34}F_2N_6O_2$: C, 63.26; H, 6.69; N, 16.40. Found: C, 63.38; H, 6.58; N, 16.58.

*6.10. Data for N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} phenyl)pivalamide (**13**)*

Yield: 63%; m.p. 129–131 °C; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 7.61–6.77 (m, 7H, Ar–H), 4.60 (d, 1H, J = 14.4 Hz, triazole–CH_2), 4.49(d, 1H, J = 14.4 Hz, triazole–CH_2), 3.02–2.49 (m, 8H, piperazine-H), 3.16 (d, 1H, J = 14.4 Hz, CH_2–piperazine), 2.69 (d, 1H, J = 14.4 Hz, CH_2–piperazine), 1.29 (s, 9H, –CH_3). EIMS, m/z: 499 (M + 1). IR (KBr): 3374,3135, 2954,2836,1671,1615,1519,1497,1393,1154 cm^{-1}. Anal. calcd for $C_{26}H_{32}F_2N_6O_2$: C, 62.64; H, 6.47; N, 16.86. Found: C, 62.53; H, 6.31; N, 16.93.

*6.11. Data for N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} phenyl)heptanamide (**14**)*

Yield: 62%; m.p. 169–171 °C; ^{1}HNMR ($CDCl_3$): 8.16 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 7.57–6.77 (m, 7H, Ar–H), 4.58 (d, 1H, J = 14.4 Hz, triazole–CH_2), 4.50 (d, 1H, J = 14.4 Hz, triazole–CH_2), 2.99–2.49 (m, 8H, piperazine-H), 3.15 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.69(d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.32–2.27 (t, 2H, –CH_2–), 1.71–1.66 (m, 2H, –CH_2–), 1.30–1.26 (m, 6H, –CH_2–), 0.89–0.85 (t, 3H, –CH_3). EIMS, m/z: 527 (M + 1). IR (KBr): 3405,3324,2955,2927, 2851,2826,1653,1513,1140 cm^{-1}. Anal. calcd for $C_{28}H_{36}F_2N_6O_2$: C, 63.86; H, 6.89; N, 15.96. Found: C, 63.71; H, 6.73; N, 16.05.

*6.12. Data for N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} phenyl)octanamide (**15**)*

Yield: 66%; m.p. 96–98 °C; ^{1}HNMR ($CDCl_3$): 8.19 (s, 1H, triazoleC_3–H), 7.81 (s, 1H, triazoleC_5–H), 7.60–6.77 (m, 7H, Ar–H), 4.60 (d, 1H, J = 14.4 Hz, triazole–CH_2), 4.54 (d, 1H, J = 14.4 Hz, triazole–CH_2), 3.00–2.49 (m, 8H, piperazine-H), 3.16 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.69 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.35–2.27 (t, 2H, –CH_2–), 1.71–1.65 (m, 2H, –CH_2–), 1.34–1.26 (m, 8H, –CH_2–), 0.89–0.85 (t, 3H, –CH_3). EIMS, m/z: 541 (M + 1). IR (KBr): 3396, 3134,2920,2851,1674,1514,1498,1139 cm^{-1}. Anal. calcd for $C_{29}H_{38}F_2N_6O_2$: C, 64.42; H, 7.08; N, 15.54. Found: C, 64.32; H, 7.13; N, 15.29.

*6.13. Data for N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} phenyl)decanamide (**16**)*

Yield: 71%; m.p. 117–119 °C; ^{1}HNMR ($CDCl_3$): 8.16 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 7.57–6.75 (m, 7H, Ar–H), 4.58 (d, 1H, J = 14.4 Hz, triazole–CH_2), 4.50 (d, 1H, J = 14.4 Hz, triazole–CH_2), 2.91–2.50 (m, 8H, piperazine-H), 3.17 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.69 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.33–2.28 (t, 2H, –CH_2–), 1.70–1.63 (m, 2H, –CH_2–), 1.29–1.25 (m, 12H, –CH_2–), 0.89–0.84 (t, 3H, –CH_3). EIMS, m/z: 569 (M + 1). IR (KBr): 3333, 2927,2853,1670,1512,1272,1139 cm^{-1}. Anal. calcd for $C_{31}H_{42}F_2N_6O_2$: C, 65.47; H, 7.44; N, 14.78. Found: C, 65.33; H, 7.35; N, 14.62.

*6.14. Data for N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} phenyl)dodecanamide (**17**)*

Yield: 70%; m.p. 88–90 °C; ^{1}HNMR ($CDCl_3$): 8.16 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 7.58–6.76 (m, 7H, Ar–H), 4.55 (d, 1H, J = 14.4 Hz, triazole–CH_2), 4.49 (d, 1H, J = 14.4 Hz, triazole–CH_2), 2.92–2.51 (m, 8H, piperazine–H), 3.17 (d, 1H,

J = 13.5 Hz, CH_2–piperazine), 2.70 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.33–2.28 (t, 2H, –CH_2–), 1.71–1.64 (m, 2H, –CH_2–), 1.30–1.25 (m, 18H, –CH_2–), 0.89–0.85 (t, 3H, –CH_3). EIMS, m/z: 597 (M + 1). IR (KBr): 3306,2919, 2851,1665, 1516,1417,1254,1138 cm^{-1}. Anal. calcd for $C_{33}H_{46}F_2N_6O_2$: C, 66.42; H, 7.77; N, 14.08. Found: C, 66.28; H, 7.89; N, 13.99.

6.15. Data for N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} phenyl)palmitamide (**18**)

Yield: 63%; m.p. 71–73 °C; ^{1}HNMR ($CDCl_3$): 8.16 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 7.57–6.78 (m, 7H, Ar–H), 4.57 (d, 1H, J = 14.4 Hz, triazole–CH_2), 4.50 (d, 1H, J = 14.4 Hz, triazole–CH_2), 3.01–2.49 (m, 8H, piperazine-H), 3.16 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.68 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.33–2.28 (t, 2H, –CH_2–), 1.72–1.67 (m, 2H, –CH_2–), 1.29–1.24 (m, 24H, –CH_2–), 0.89–0.85 (t, 3H, –CH_3). EIMS, m/z: 653 (M + 1). IR (KBr): 3302, 2919,2850,1653, 1516,1417,1272,1138 cm^{-1}. Anal. calcd for $C_{37}H_{54}F_2N_6O_2$: C, 68.07; H, 8.34; N, 12.87. Found: C, 67.95; H, 8.16; N, 12.69.

6.16. Data for N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} -3-fluoro-phenyl) acetamide (**19**)

Yield: 81%; m.p. 104–106 °C; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.79 (s, 1H, triazoleC_5–H), 7.58–6.78 (m, 6H, Ar–H), 5.21(1H, s,OH), 4.58 (d, 1H, J = 14.25 Hz, triazole–CH_2), 4.50 (d, 1H, J = 14.25 Hz, triazole–CH_2), 2.92–2.51 (m, 8H, piperazine-H), 3.16 (d, 1H, J = 13.45 Hz, CH_2–piperazine), 2.71 (d, 1H, J = 13.45 Hz, CH_2–piperazine), 2.14 (s, 3H, $-CH_3$). EIMS, m/z: 475 (M + 1). IR (KBr): 3456,3117,2828,1669,1608,1515,1271,1254,1138,1015 cm^{-1}. Anal. calcd for $C_{23}H_{25}F_3N_6O_2$: C, 58.22; H, 5.31; N, 17.71. Found: C, 58.09; H, 5.23; N, 17.87.

6.17. Data for 2-chloro-N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl] piperazin-1-yl}-3-fluoro-phenyl)acetamide (**20**)

Yield: 75%; m.p. 91–93 °C; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 7.57–6.80 (m, 6H, Ar–H), 5.21(1H, s,OH), 4.58 (d, 1H, J = 14.3 Hz, triazole–CH_2), 4.50 (d, 1H, J = 14.3 Hz, triazole–CH_2), 4.16 (s, 2H, $-CH_2-$), 2.94–2.51 (m, 8H, piperazine-H), 3.16 (d, 1H, J = 13.45 Hz, CH_2–piperazine), 2.71 (d, 1H, J = 13.45 Hz, CH_2–piperazine). EIMS, m/z: 509 (M + 1). IR (KBr): 3483,3255,2950,2830,1683,1617,1514,1419, 1225,1138 cm^{-1}. Anal. calcd for $C_{23}H_{24}ClF_3N_6O_2$: C, 54.28; H, 4.75; N, 16.51. Found: C, 54.13; H, 4.68; N, 16.49.

6.18. Data for 2-chloro-N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl] piperazin-1-yl}-3-fluoro-phenyl)-2,2-difluoroacetamide (**21**)

Yield: 77%; m.p. 117–119 °C; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 7.60–6.79 (m, 6H, Ar–H), 4.60 (d, 1H, J = 14.1 Hz, triazole–CH_2), 4.49 (d, 1H, J = 14.1 Hz, triazole–CH_2), 2.97–2.52 (m, 8H, piperazine-H), 3.18 (d, 1H, J = 13.2 Hz, CH_2–piperazine), 2.70 (d, 1H, J = 13.2 Hz, CH_2–piperazine). EIMS, m/z: 545 (M + 1). IR (KBr): 3542,3115,2947,2829,1706,1658,1515,1274,1179, 1137 cm^{-1}. Anal. calcd for $C_{23}H_{22}ClF_5N_6O_2$: C, 50.70; H, 4.07; N, 15.42. Found: C, 50.58; H, 4.13; N, 15.29.

6.19. Data for N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} -3-fluoro-phenyl)-2,2,2-trifluoroacetamide (**22**)

Yield: 88%; m.p. 169–171 °C; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 7.61–6.78 (m, 6H, Ar–H), 5.16 (1H, s,OH), 4.61 (d, 1H, J = 14.1 Hz, triazole–CH_2), 4.49 (d, 1H, J = 14.1 Hz, triazole–CH_2), 3.06–2.50 (m, 8H, piperazine-H), 3.16 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.74 (d, 1H, J = 13.5 Hz, CH_2–piperazine). EIMS, m/z: 529 (M + 1). IR (KBr): 3275,3117,2829,1716,1617,1540,1454,1114 cm^{-1}. Anal. calcd for $C_{23}H_{22}F_6N_6O_2$: C, 52.27; H, 4.20; N, 15.90. Found: C, 52.09; H, 4.28; N, 16.03.

6.20. Data for N-(4-{4-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} -3-fluoro-phenyl) propionamide (**23**)

Yield: 80%; m.p. 98–100 °C; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.79 (s, 1H, triazoleC_5–H), 7.57–6.78 (m, 6H, Ar–H), 5.21(1H, s,OH), 4.58 (d, 1H, J = 14.25 Hz, triazole–CH_2), 4.50 (d, 1H, J = 14.25 Hz, triazole–CH_2), 2.92–2.50 (m, 8H, piperazine-H), 3.15 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.70 (d, 1H, J = 13.5 Hz, CH_2–piperazine), 2.37–2.33 (q, 2H, –CH_2–), 1.24–1.21 (t, 3H, –CH_3). EIMS, m/z: 489 (M + 1). IR (KBr): 3274,3115,2828,1664,1606,1514, 1421,1224,1138 cm^{-1}. Anal. calcd for $C_{24}H_{27}F_3N_6O_2$: C, 59.01; H, 5.57; N, 17.20. Found: C, 58.93; H, 5.48; N, 16.99.

6.21. Data for N-(4-{4-[2-(2,4-difluoro-phenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} -3-fluoro-phenyl) butanamide (**24**)

Yield: 78%; m.p. 113–115 °C; ^{1}HNMR ($CDCl_3$): 8.16 (s, 1H, triazoleC_3–H), 7.80 (s, 1H, triazoleC_5–H), 7.58–6.76 (m, 6H, Ar–H), 4.58 (d, 1H, J = 14.4 Hz, triazole–CH_2), 4.50 (d, 1H, J = 14.4 Hz, triazole–CH_2), 2.93–2.51 (m, 8H, piperazine-H), 3.17 (d, 1H, J = 12.6 Hz, CH_2–piperazine), 2.70 (d, 1H, J = 12.6 Hz, CH_2–piperazine), 2.32–2.27 (t, 2H, –CH_2–), 1.77–1.67 (m, 2H, –CH_2–), 1.01–0.96 (t, 3H, –CH_3). EIMS, m/z: 503 (M + 1). IR (KBr): 3443,3271, 3110, 2963,2826,1661,1604,1513,1137 cm^{-1}. Anal. calcd for $C_{25}H_{29}F_3N_6O_2$: C, 59.75; H, 5.82; N, 16.72. Found: C, 59.68; H, 5.79; N, 16.77.

6.22. Data for N-(4-{4-[2-(2,4-difluoro-phenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} -3-fluoro-phenyl) isobutanamide (**25**)

Yield: 79%; m.p. 126–128 °C; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.79 (s, 1H, triazoleC_5–H), 7.56–6.78 (m, 6H, Ar–H), 4.57 (d, 1H, J = 14.3 Hz, triazole–CH_2), 4.50 (d, 1H, J = 14.3 Hz, triazole–CH_2), 2.92–2.51 (m, 8H, piperazine-H), 3.16 (d, 1H, J = 13.42 Hz, CH_2–piperazine), 2.71 (d, 1H, J = 13.42 Hz, CH_2–piperazine), 2.48–2.45 (m, H, –CH–), 1.25–1.22 (d, 6H, $-CH_3$). EIMS, m/z: 503 (M + 1). IR (KBr): 3443,3272,3112,2829,1664,1606,1498, 1254,1137 cm^{-1}. Anal. calcd for $C_{25}H_{29}F_3N_6O_2$: C, 59.75; H, 5.82; N, 16.72. Found: C, 59.62; H, 5.86; N, 16.82.

6.23. Data for N-(4-{4-[2-(2,4-difluoro-phenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} -3-fluoro-phenyl) pentanamide (**26**)

Yield: 76%; m.p. 176–178 °C; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.79 (s, 1H, triazoleC_5–H), 7.58–6.76 (m, 6H, Ar–H), 5.23(1H, s,OH), 4.58 (d, 1H, J = 14.3 Hz, triazole–CH_2), 4.50 (d, 1H, J = 14.3 Hz, triazole–CH_2), 2.91–2.51 (m, 8H, piperazine-H), 3.15 (d, 1H, J = 13.4 Hz, CH_2–piperazine), 2.70 (d, 1H, J = 13.4 Hz,

CH_2–piperazine), 2.32–2.29 (t, 2H, –CH_2–), 1.70–1.64 (m, 2H, –CH_2–), 1.41–1.25 (m, 2H, –CH_2–), 0.93–0.90 (t, 3H, –CH_3). EIMS, *m/z*: 517 (M + 1). IR (KBr): 3352,2957,2820,1662,1597,1531,1509,1138 cm^{-1}. Anal. calcd for $C_{26}H_{31}F_3N_6O_2$: C, 60.45; H, 6.05; N, 16.27. Found: C, 60.29; H, 5.98; N, 16.41.

*6.24. Data for N-(4-{4-[2-(2,4-difluoro-phenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} -3-fluoro-phenyl) pivalamide (**27**)*

Yield: 78%; m.p. 115–117 °C; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.79 (s, 1H, triazoleC_5–H), 7.58–6.78 (m, 6H, Ar–H), 4.57 (d, 1H, *J* = 14.25 Hz, triazole–CH_2), 4.50 (d, 1H, *J* = 14.25 Hz, triazole–CH_2), 2.92–2.50 (m, 8H, piperazine-H), 3.15 (d, 1H, *J* = 13.6 Hz, CH_2–piperazine), 2.70 (d, 1H, *J* = 13.6 Hz, CH_2–piperazine), 1.28 (s, 9H, –CH_3). EIMS, *m/z*: 517 (M + 1). IR (KBr): 3258,2968,2827,1648,1616,1513,1419,1272,1137 cm^{-1}. Anal. calcd for $C_{26}H_{31}F_3N_6O_2$: C, 60.45; H, 6.05; N, 16.27. Found: C, 60.39; H, 6.12; N, 16.18.

*6.25. Data for N-(4-{4-[2-(2,4-difluoro-phenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} -3-fluoro-phenyl) hexanamide (**28**)*

Yield: 72%; m.p. 182–184 °C; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.79 (s, 1H, triazoleC_5–H), 7.58–6.77 (m, 6H, Ar–H), 4.57 (d, 1H, *J* = 14.24 Hz, triazole–CH_2), 4.50 (d, 1H, *J* = 14.24 Hz, triazole–CH_2), 2.91–2.50 (m, 8H, piperazine-H), 3.15 (d, 1H, *J* = 13.47 Hz, CH_2–piperazine), 2.70 (d, 1H, *J* = 13.47 Hz, CH_2–piperazine), 2.32–2.29 (t, 2H, –CH_2–), 1.71–1.68 (m, 2H, –CH_2–), 1.34–1.33 (m, 4H, –CH_2–), 0.91–0.88 (t, 3H, –CH_3). EIMS, *m/z*: 531 (M + 1). IR (KBr): 3354,2957,2932,2857,1662,1617,1529,1509,1421, 1138 cm^{-1}. Anal. calcd for $C_{27}H_{33}F_3N_6O_2$: C, 61.12; H, 6.27; N, 15.84. Found: C, 61.05; H, 6.15; N, 15.63.

*6.26. Data for N-(4-{4-[2-(2,4-difluoro-phenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} -3-fluoro-phenyl) heptanamide (**29**)*

Yield: 74%; m.p. 160–162 °C; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.79 (s, 1H, triazoleC_5–H), 7.56–6.77 (m, 6H, Ar–H), 4.58 (d, 1H, *J* = 14.27 Hz, triazole–CH_2), 4.50 (d, 1H, *J* = 14.27 Hz, triazole–CH_2), 2.91–2.51 (m, 8H, piperazine-H), 3.15 (d, 1H, *J* = 13.47 Hz, CH_2–piperazine), 2.70 (d, 1H, *J* = 13.47 Hz, CH_2–piperazine), 2.32–2.29 (t, 2H, –CH_2–), 1.72–1.67 (m, 2H, –CH_2–), 1.35–1.30 (m, 6H, –CH_2–), 0.89–0.86 (t, 3H, –CH_3). EIMS, *m/z*: 545 (M + 1). IR (KBr): 3356,2931,2851,1663,1597,1529,1508,1421,1385, 1138 cm^{-1}. Anal. calcd for $C_{28}H_{35}F_3N_6O_2$: C, 61.75; H, 6.48; N, 15.43. Found: C, 61.58; H, 6.59; N, 15.48.

*6.27. Data for N-(4-{4-[2-(2,4-difluoro-phenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} -3-fluoro-phenyl) octanamide (**30**)*

Yield: 75%; m.p. 122–124 °C; ^{1}HNMR ($CDCl_3$): 8.15 (s, 1H, triazoleC_3–H), 7.79 (s, 1H, triazoleC_5–H), 7.58–6.77 (m, 6H, Ar–H), 4.58 (d, 1H, *J* = 14.3 Hz, triazole–CH_2), 4.50 (d, 1H, *J* = 14.3 Hz, triazole–CH_2), 2.91–2.50 (m, 8H, piperazine-H), 3.15 (d, 1H, *J* = 13.55 Hz, CH_2–piperazine), 2.70 (d, 1H, *J* = 13.55 Hz, CH_2–piperazine), 2.32–2.29 (t, 2H, –CH_2–), 1.71–1.66 (m, 2H, –CH_2–), 1.32–1.27 (m, 8H, –CH_2–), 0.88–0.85 (t, 3H, –CH_3). EIMS, *m/z*: 559 (M + 1). IR (KBr): 3301,2929,2854,1661,1598,1511,1422,1139 cm^{-1}. Anal. calcd for $C_{29}H_{37}F_3N_6O_2$: C, 62.35; H, 6.68; N, 15.04. Found: C, 62.45; H, 6.57; N, 15.23.

*6.28. Data for N-(4-{4-[2-(2,4-difluoro-phenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]piperazin-1-yl} -3-fluoro-phenyl)-2-phenylacetamide (**31**)*

Yield: 76%; m.p. 183–185 °C; ^{1}HNMR ($CDCl_3$): 8.14 (s, 1H, triazoleC_3–H), 7.79 (s, 1H, triazoleC_5–H), 7.55–6.74 (m, 11H, Ar–H), 5.21(1H, s,OH), 4.57 (d, 1H, *J* = 14.3 Hz, triazole–CH_2), 4.49 (d, 1H, *J* = 14.3 Hz, triazole–CH_2), 4.70 (s, 2H, –CH_2–), 2.89–2.49 (m, 8H, piperazine-H), 3.14 (d, 1H, *J* = 13.45 Hz, CH_2–piperazine), 2.69 (d, 1H, *J* = 13.45 Hz, CH_2–piperazine). EIMS, *m/z*: 551 (M + 1). IR (KBr): 3344,3027,2953,2817,1664,1599,1508,1453, 1384,1137 cm^{-1}. Anal. calcd for $C_{29}H_{29}F_3N_6O_2$: C, 63.26; H, 5.31; N, 15.26. Found: C, 63.09; H, 5.25; N, 15.43.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant No. 30300437 and 20772153), the Eleventh Five Year Military Medicine and Public Health Research Projects (Grant No. 06MB206) and by Shanghai Leading Academic Discipline Project (Project No. B906).

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