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Preliminary communication

Synthesis of novel triazole derivatives as inhibitors of cytochrome P450 14α-demethylase (CYP51)

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Abstract

A series of 1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[(4-substitutedphenyl)-piperazin-1-yl]-propan-2-ols have been designed and synthesized on the basis of the structure–activity relationships and antimycotic mechanism of azole antifungal agents. Their structures were confirmed by elemental analysis, IR, MS and ^{1}H NMR. Results of preliminary antifungal tests against eight human pathogenic fungi (*Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Trichophyton rubrum*, *Fonsecaea compacta*, and *Microsporum gypseum*) in vitro showed that all title compounds exhibited activity against fungi tested to some extent. Among the compounds tested, all compounds showed higher activity against *C. albicans* than fluconazole in vitro. Compounds **3**, **6**–**8**, **28**, **29**, and **32** exhibited the same activities against *C. albicans* as voriconazole (with the MIC value of 0.0152 μg/mL). Compounds **3**, **6**, and **7** showed higher activity against *C. parapsilosis* than all five positive controls.

Keywords: Triazole; Synthesis; Antifungal activity; CYP51

1. Introduction

Fungal infections have become an important complication and a major cause of morbidity and mortality in immunocompromised individuals suffering from tuberculosis, cancer or AIDS and in organ transplant cases [1,2]. Triazole antifungals (e.g. fluconazole and voriconazole) which act by inhibiting lanosterol cytochrome P450 14α-demethylase (CYP51) have now become the most rapidly expanding group of antifungal compounds. However, their clinical 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 a need for a genuinely broad-spectrum and low-toxicity antifungal agents.

CYP51 is a member of the cytochrome P450 superfamily, which catalyzes the oxidative removal of the 14α-methyl group of lanosterol to give $\Delta^{14,15}$-desaturated intermediates in ergosterol biosynthesis. During the catalytic cycle, a substrate undergoes three successive monooxygenation reactions resulting in the formation of 14-hydroxymethyl, 14-carboxaldehyde and 14-formyl derivatives followed by elimination of formic acid with concomitant introduction of a C14, C15 double bond. Ji et al. [7] built a homologous 3D model of CYP51 from *C. albicans* based on the crystal coordinates of all four known prokaryotic P450s. With this model they identified the

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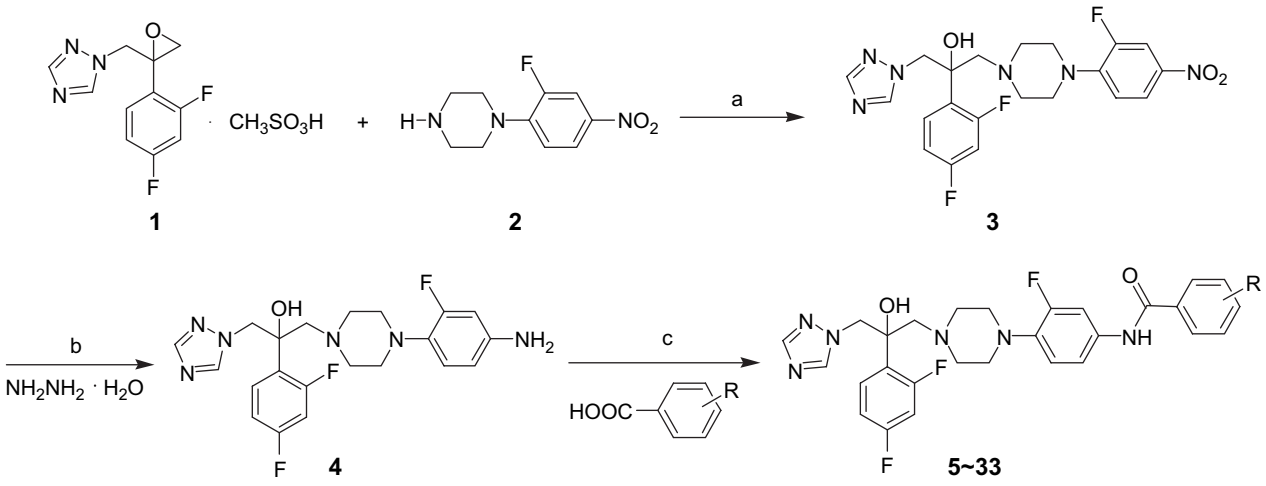
structurally and functionally important residues such as the heme binding residues, the residue interacting with the redox partner protein and/or involved in electron transfer, the residues lining the substrate access channel, and the substrate and inhibitor binding residues. Another 3D molecular model constructed by Lewis et al. [8] also showed that typical azole inhibitors were able to fit the putative active site of CYP51 by a combination of heme ligation, hydrogen bonding, π–π stacking and hydrophobic interactions within the heme environment of the enzymes.

Ji's study indicated that the triazole ring in the scaffold of triazole antifungals was positioned perpendicularly to the porphyrin plane with a ring nitrogen atom 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 the structure of the active site of CYP51 and the extensive investigation of the structure–activity relationships of azole antifungals, we herein designed a novel series of 1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[(4-substituted phenyl)-piperazin-1-yl]-propan-2-ols containing a triazole ring, a difluorogenated phenyl group and a long side chain, to find potent systemic antifungal agents that have a broad antifungal spectrum but with less potential to develop resistance. The N3 atom of triazole was designed to be coordinated to iron atom of the heme, the 2,4-difluorophenyl group could be located into the hydrophobic pocket and the 4-(4-substitutedphenyl)piperazine was chosen as side chains to interact with the residues of the narrow hydrophobic cleft and adjust the physico-chemical properties of the whole molecule to avoid the dissatisfying side effects and/or improve the pharmacokinetic and pharmacodynamic behavior. The structures of this series of compounds are shown in Scheme 1.

2. Chemistry

The general synthetic route of title compounds 1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluoro-phenyl)-3-[(4-substitutedphenyl)-



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

Compd.	R	Compd.	R	Compd.	R
5	-	15	3-methyl	25	4-pentyl
6	2-fluoro	16	4-methyl	26	2-methoxy
7	4- fluoro	17	3-trifluoromethyl	27	3-methoxy
8	2-chloro	18	2,4-dimethyl	28	4-methoxy
9	3-chloro	19	3,4-dimethyl	29	4-trifluoromethoxy
10	4-chloro	20	4-ethyl	30	3,4-dimethoxy
11	2,4-dichloro	21	4-propyl	31	3,4,5-trimethoxy
12	2-bromo	22	4-isopropyl	32	2-nitro
13	3-bromo	23	4-butyl	33	4-nitro
14	2-methyl	24	4-terbutyl		

Scheme 1. Synthetic route to the title compounds.

piperazin-1-yl]-propan-2-ols (**5**–**33**) is outlined in Scheme 1. The important intermediate oxirane **1** and compound **2** were synthesized with known procedures [9–12]. The title compound **3** was synthesized by ring-open reaction of oxirane **1** with compound **2**. The good yield was obtained when the reaction was performed in a protic solvent ethanol in the presence of triethylamine as a base at 80 °C. Then the nitro group on the phenyl ring of compound **3** was reduced to an amino group in the presence of Raney Ni and hydrazine hydrate. In the presence of DMAP and EDCI in dichloromethane at room temperature, the aniline **4** was converted to title compounds **5**–**33** by reacting with various benzoic acids.

3. Bioassays of antifungal activities

The in vitro minimal inhibitory concentrations (MICs) of the title compounds were determined by the micro-broth dilution method according to the methods defined by the National Committee for Clinical Laboratory Standards [13]. Fungi strains for testing *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Trichophyton rubrum*, *Fonsecaea compacta*, and *Microsporum gypseum* were provided through 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 *C. albicans*, 72 h for *C. neoformans* and at 7 days for filamentous fungi.

4. Results and discussion

The in vitro antifungal activities of all title compounds **3**–**33** were evaluated against eight human pathogenic fungi (*C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. neoformans*, *A. fumigatus*, *T. rubrum*, *F. compacta*, and *M. gypseum*) which are often encountered clinically and are summarized in Table 1. The MIC_{80} values (in μg/mL) against different pathogenic fungi, in comparison with fluconazole (FCZ), itraconazole (ICZ), ketoconazole (KCZ), voriconazole (VCZ) and amphotericin B (AMB) are given.

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, all compounds showed higher activity against *C. albicans* than fluconazole in vitro. Compounds **3**, **6**–**8**, **28**, **29**, and **32** exhibited the same activities against *C. albicans* as voriconazole (with the MIC value of 0.0152 μg/mL). Compounds **3**, **6**, and **7** showed higher activity against *C. parapsilosis* than all five positive controls. Compounds **5** and **30** showed higher activity against *C. tropicalis* than all five positive controls (with the MIC value of 0.0039 μg/mL). Compounds **3**, **4**, **6**, **7**, and **27** exhibited the same activities against *C. neoformans* as voriconazole (with the MIC value of 0.0152 μg/mL). Compounds **10**, **11**, and **28** exhibited higher activities against *A. fumigatus* than itraconazole and ketoconazole (with the MIC value of 0.25 μg/mL). The MIC values of compounds **10**, **11**, and **28** are four times lower than that of itraconazole and ketoconazole against *A. fumigatus* in vitro. Compound **12** exhibited the same activities against *T. rubrum* as voriconazole (with the MIC value of 0.0039 μg/mL). Compound **11** showed the same activity against *M. gypseum* as ketoconazole, voriconazole and amphotericin B (with the MIC value of 0.0039 μg/mL).

5. Conclusion

In conclusion, we have demonstrated the design and synthesis of a series of novel 1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluoro-phenyl)-3-[(4-substitutedphenyl)-piperazin-1-yl]-propan-2-ols. All the title compounds showed antifungal activities against all fungi tested to some extent. Some of the compounds were found to have excellent potency against a broad range of fungal pathogens including *A. fumigatus* in vitro. The obtained results indicated that for antifungal activity of these novel triazole derivatives it is very helpful to introduce the 4-(4-substitutedphenyl)piperazine as side chains to interact with the residues of the narrow hydrophobic cleft of CYP51 and adjust the physico-chemical properties of the whole title molecules. Further evaluations are necessary to determine the antifungal spectrum 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 $CDCl_3$ or DMSO-d_6 unless otherwise indicated 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. The solvents and reagents were used as received or were dried prior to use as needed.

*6.1. Preparation of 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[4-(2-fluoro-4-nitro-phenyl)-piperazin-1-yl]-propan-2-ol (**3**)*

To a stirred mixture of 1-[2-(2,4-difluorophenyl)-2,3-epoxypropyl]-1*H*-1,2,4-triazole methanesulfonate (**1**) (1.65 g,

Table 1
Antifungal activities of the title compounds in vitro (MIC_{80} μg/mL)[a]

Compound	*C. alb.*	*C. par.*	*C. tro.*	*C. neo.*	*A. fum.*	*T. rub.*	*F. com.*	*M. gyp.*
3	0.0152	0.0039	0.0152	0.0152	1	0.0152	0.0625	0.0152
4	0.25	0.25	4	0.0152	4	0.25	0.25	0.0625
5	0.0625	0.0152	0.0039	0.0625	1	0.0152	0.25	0.0152
6	0.0152	<0.0039	0.0152	0.0152	4	0.0152	0.0625	0.0625
7	0.0152	0.0039	0.0152	0.0152	1	0.25	0.0625	0.0152
8	0.0152	0.0152	0.0152	0.25	1	0.0152	0.0625	0.0152
9	0.25	0.0152	0.0625	0.25	4	0.0625	0.25	0.0625
10	0.0625	0.0152	0.0152	0.25	0.25	0.0625	0.0625	0.25
11	0.25	0.0152	0.0625	0.0625	0.25	0.0625	0.25	0.0039
12	0.0625	0.0152	0.0152	0.0625	1	0.0039	0.25	0.0625
13	0.0625	0.0625	0.0625	0.25	4	0.0625	0.25	0.25
14	0.0625	0.0152	0.0152	0.0625	1	0.0625	0.25	0.0152
15	0.0625	0.0152	0.0152	0.0625	1	0.0625	0.25	0.0152
16	0.0625	0.0152	0.0152	0.0625	1	0.0625	0.0625	1
17	0.25	0.0152	0.25	0.25	4	0.0625	0.25	0.0625
18	0.25	0.25	0.0625	0.0625	1	0.0625	0.25	0.0152
19	0.25	0.0152	0.0625	0.25	1	0.0625	0.25	0.0152
20	0.25	4	0.0625	0.0625	1	0.0625	0.0625	0.25
21	1	0.0625	1	1	4	0.25	0.25	0.25
22	1	0.25	0.25	0.0625	4	0.25	0.25	0.25
23	1	1	1	1	16	1	0.0625	0.0625
24	1	0.0625	0.25	0.25	4	4	0.25	0.25
25	0.25	0.25	4	0.25	4	1	1	1
26	0.0625	0.25	0.0152	0.0625	1	0.0625	0.25	0.0625
27	0.0625	0.0152	0.0152	0.0152	1	0.0152	0.25	0.25
28	0.0152	0.0152	0.0152	0.0625	0.25	0.25	0.25	0.25
29	0.0152	0.0625	0.0625	0.25	1	0.0625	0.0625	0.0625
30	0.0625	0.0625	0.0039	0.25	1	0.25	0.25	0.25
31	0.25	0.0625	0.0625	1	4	>64	4	1
32	0.0152	0.0625	0.0625	1	1	0.0152	1	0.0625
33	0.25	1	4	0.25	4	0.25	0.0625	0.0625
FCZ	4	1	1	1	64	0.25	16	0.25
ICZ	1	0.25	0.25	1	1	0.0152	0.25	0.0152
KCZ	0.0625	0.0625	0.0625	0.0625	1	0.0625	0.0625	0.0039
VCZ	0.0152	1	0.25	0.0152	>64	0.0039	0.0152	0.0039
AMB	1	0.0152	0.0625	1	4	1	16	0.0039

[a] Abbreviations: *C. alb.*, *Candida albicans*; *C. par.*, *Candida parapsilosis*; *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.

0.005 mol), CH_3CH_2OH (30 mL) and $N(C_2H_5)_3$ (3 mL), 1-(2-fluoro-4-nitro-phenyl)-piperazine (**2**) (1.35 g, 0.006 mol) was added and was heated at 70–80 °C for 5 h. The reaction was monitored by TLC. After filtration, the filtrate was evaporated under reduced pressure. Water (30 mL) was added to the residue, which was then extracted with ethyl acetate (80 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 DMF/H_2O to afford a white solid **3** in 78% yield: m.p. 165–167 °C. ^{1}H NMR (DMSO-d_6): 6.80–7.96 (6H, m, Ar–H), 7.93, 8.13 (2H, ss, triazole–H), 4.52–4.61 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.50–3.18 (8H, m, piperazine–H), 2.73–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.05 (1H, s, OH). EIMS, *m/z*: 463 (M + 1). IR (KBr): 3200, 2940, 2893, 1605, 1514, 1338, 1257, 1136, 918 cm^{-1}. Anal. calcd for $C_{21}H_{21}F_3N_6O_3$: C, 54.54; H, 4.58; N, 18.17. Found: C, 54.04; H, 4.55; N, 17.97.

6.2. Preparation of 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[4-(2-fluoro-4-amino-phenyl)-piperazin-1-yl]-propan-2-ol (**4**)

To a stirred mixture of 1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[4-(2-fluoro-4-nitro-phenyl)-piperazin-1-yl]-propan-2-ol (**3**) (2.31 g, 0.005 mol), CH_3CH_2OH (20 mL) and 85% hydrazine hydrate (8 mL), freshly prepared Raney Ni (0.5 g) was added and was heated at 70–80 °C for 3 h. The reaction was monitored by TLC. After filtration, the filtrate was evaporated under reduced pressure. Water (20 mL) was added to the residue, which was then extracted with ethyl acetate (60 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 ethyl acetate to afford a white solid **4** in 75% yield: m.p. 134–135°C. ^{1}H NMR (DMSO-d_6): 6.35–7.56 (6H, m, Ar–H), 7.79, 8.15 (2H, ss, triazole–H), 4.52–4.54 (2H, dd, $J = 15$ Hz, triazole–CH_2–),

2.49–2.84 (8H, m, piperazine–H), 2.69–3.14 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.28 (1H, s, OH), 3.52 (2H, s, NH_2). EIMS, *m/z*: 433 (M + 1). IR (KBr): 3404, 3212, 3117, 3053, 2950, 2835, 1616, 1514, 1274, 1139, 965 cm^{-1}. Anal. calcd for $C_{21}H_{23}F_3N_6O$: C, 58.33; H, 5.36; N, 19.43. Found: C, 58.17; H, 5.36; N, 19.19.

*6.3. General procedure for the preparation of title compounds **5–33***

To a stirred mixture of 1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[4-(2-fluoro-4-amino-phenyl)-piperazin-1-yl]-propan-2-ol (**4**) (0.001 mol) DMAP (100 mg) and EDCI (200 mg) in 50 mL dichloromethane under 0 °C and substituted benzoic acid (0.001 mol) were added and stirred for 8–12 h. The reaction was monitored by TLC. After filtration, the filtrate was evaporated under reduced pressure. The residue was then extracted with ethyl acetate (60 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 ethyl acetate to afford the title compounds **5–33**.

The title compounds **5–33** were characterized as follows.

*6.3.1. 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)-benzamide (**5**)*

Yield: 85.6%; m.p. 157–158 °C; ^{1}H NMR (DMSO-d_6): 6.83–7.84 (11H, m, Ar–H), 7.80, 8.15 (2H, ss, triazole–H), 4.50–4.58 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.95 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.23 (1H, s, OH). EIMS, *m/z*: 537 (M + 1). IR (KBr): 3375, 3122, 2949, 2820, 1655, 1527, 1425, 1272, 1139, 965 cm^{-1}. Anal. calcd for $C_{28}H_{27}F_3N_6O_2$: C, 62.68; H, 5.07; N, 15.66. Found: C, 62.68; H, 5.08; N, 15.54.

*6.3.2. 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-fluoro-benzamide (**6**)*

Yield: 87.4%; m.p. 179–180 °C; ^{1}H NMR (DMSO-d_6): 6.80–8.31 (10H, m, Ar–H), 7.77, 8.16 (2H, ss, triazole–H), 4.54–4.62 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.62–3.01 (8H, m, piperazine–H), 2.77–3.21 (2H, dd, $J = 15$ Hz, CH_2–piperazine–). EIMS, *m/z*: 555 (M + 1). IR (KBr): 3393, 3117, 2958, 2828, 1655, 1532, 1423, 1382, 1238, 1138, 1012, 965, 752 cm^{-1}. Anal. calcd for $C_{28}H_{26}F_4N_6O_2$: C, 60.64; H, 4.73; N, 15.15. Found: C, 60.72; H, 4.73; N, 15.04.

*6.3.3. 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)-4-fluoro-benzamide (**7**)*

Yield: 86.2%; m.p. 158–159 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.86 (10H, m, Ar–H), 7.80, 8.15 (2H, ss, triazole–H), 4.51–4.58 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.95 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.22 (1H, s, OH). EIMS, *m/z*: 555 (M + 1). IR (KBr): 3327, 3126, 2946, 2828, 1662, 1603, 1512, 1426, 1272, 1236, 1138, 1012, 966 cm^{-1}. Anal. calcd for $C_{28}H_{26}F_4N_6O_2$: C, 60.64; H, 4.73; N, 15.15. Found: C, 60.66; H, 4.79; N, 14.98.

*6.3.4. Data for 2-chloro-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)-benzamide (**8**)*

Yield: 85.5%; m.p. 87–89 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.92 (10H, m, Ar–H), 7.78, 8.14 (2H, ss, triazole–H), 4.50–4.58 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.95 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.23 (1H, s, OH). EIMS, *m/z*: 571 (M + 1). IR (KBr): 3311, 3070, 2954, 2833, 1704, 1673, 1601, 1513, 1324, 1139, 964 cm^{-1}. Anal. calcd for $C_{28}H_{26}ClF_3N_6O_2$: C, 58.90; H, 4.59; N, 14.72. Found: C, 58.82; H, 4.67; N, 14.81.

*6.3.5. Data for 3-chloro-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)-benzamide (**9**)*

Yield: 82.8%; m.p. 102–104 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.82 (10H, m, Ar–H), 7.79, 8.15 (2H, ss, triazole–H), 4.51–4.59 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.54–2.96 (8H, m, piperazine–H), 2.76–3.17 (2H, dd, $J = 15$ Hz, CH_2–piperazine–). EIMS, *m/z*: 571 (M + 1). IR (KBr): 3310, 3070, 2953, 2882, 2822, 1703, 1673, 1601, 1513, 1324, 1224, 1139, 964 cm^{-1}. Anal. calcd for $C_{28}H_{26}ClF_3N_6O_2$: C, 58.90; H, 4.59; N, 14.72. Found: C, 58.74; H, 4.72; N, 14.85.

*6.3.6. Data for 4-chloro-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)-benzamide (**10**)*

Yield: 87.5%; m.p. 188–190 °C; ^{1}H NMR (DMSO-d_6): 6.82–7.79 (10H, m, Ar–H), 7.80, 8.15 (2H, ss, triazole–H), 4.53–4.56 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.95 (8H, m, piperazine–H), 2.71–3.13 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.23 (1H, s, OH). EIMS, *m/z*: 571 (M + 1). IR (KBr): 3336, 3132, 2950, 2830, 1645, 1594, 1511, 1414, 1269, 1140, 1015, 966 cm^{-1}. Anal. calcd for $C_{28}H_{26}ClF_3N_6O_2$: C, 58.90; H, 4.59; N, 14.72. Found: C, 58.78; H, 4.59; N, 14.67.

*6.3.7. Data for 2,4-dichloro-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)-benzamide (**11**)*

Yield: 88.4%; m.p. 99–101 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.82 (9H, m, Ar–H), 7.80, 8.14 (2H, ss, triazole–H), 4.50–4.58 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–3.01 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.21 (1H, s, OH). EIMS, *m/z*: 605 (M + 1). IR (KBr): 3204, 3100, 2942, 2825, 1651, 1586, 1512, 1382, 1252, 1137, 965 cm^{-1}. Anal. calcd for $C_{28}H_{25}Cl_2F_3N_6O_2$: C, 55.55; H, 4.16; N, 13.88. Found: C, 55.38; H, 4.19; N, 13.74.

*6.3.8. Data for 2-bromo-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)-benzamide (**12**)*

Yield: 81.2%; m.p. 94–96 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.70 (10H, m, Ar–H), 7.78, 8.14 (2H, ss, triazole–H), 4.50–4.58 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.95 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.22 (1H, s, OH). EIMS, *m/z*: 615 (M + 1). IR (KBr): 3309, 3070, 2953, 2881, 2835, 1703, 1673, 1601, 1514, 1324, 1139, 964 cm^{-1}. Anal. calcd for $C_{28}H_{26}BrF_3N_6O_2$: C, 54.64; H, 4.26; N, 13.66. Found: C, 54.47; H, 4.35; N, 13.48.

*6.3.9. Data for 3-bromo-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)-benzamide (**13**)*

Yield: 83.6%; m.p. 126–128 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.97 (10H, m, Ar–H), 7.79, 8.15 (2H, ss, triazole–H), 4.51–4.59 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.53–2.96 (8H, m, piperazine–H), 2.72–3.17 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.23 (1H, s, OH). EIMS, *m/z*: 615 (M + 1). IR (KBr): 3276, 3108, 2946, 2821, 1655, 1601, 1511, 1428, 1249, 1139, 1011, 966 cm^{-1}. Anal. calcd for $C_{28}H_{26}BrF_3N_6O_2$: C, 54.64; H, 4.26; N, 13.66. Found: C, 54.40; H, 4.29; N, 13.52.

*6.3.10. 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-methyl-benzamide (**14**)*

Yield: 79.3%; m.p. 74–76 °C; ^{1}H NMR (DMSO-d_6): 6.83–7.57 (10H, m, Ar–H), 7.79, 8.15 (2H, ss, triazole–H), 4.53–4.55 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.94 (8H, m, piperazine–H), 2.74–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.22 (1H, s, OH), 2.49 (3H, s, $-CH_3$). EIMS, *m/z*: 551 (M + 1). IR (KBr): 3311, 2953, 2821, 1702, 1672, 1596, 1513, 1321, 1286, 1139, 965 cm^{-1}. Anal. calcd for $C_{29}H_{29}F_3N_6O_2$: C, 63.26; H, 5.31; N, 15.26. Found: C, 63.21; H, 5.41; N, 15.41.

*6.3.11. 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)-3-methyl-benzamide (**15**)*

Yield: 78.5%; m.p. 167–169 °C; ^{1}H NMR (DMSO-d_6): 6.82–7.75 (10H, m, Ar–H), 7.79, 8.15 (2H, ss, triazole–H), 4.51–4.59 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.53–2.96 (8H, m, piperazine–H), 2.72–3.17 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.23 (1H, s, OH), 2.42 (3H, s, $-CH_3$). EIMS, *m/z*: 551 (M + 1). IR (KBr): 3373, 3112, 2963, 2828, 1645, 1588, 1523, 1420, 1272, 1137, 1015, 966 cm^{-1}. Anal. calcd for $C_{29}H_{29}F_3N_6O_2$: C, 63.26; H, 5.31; N, 15.26. Found: C, 63.23; H, 5.28; N, 15.25.

*6.3.12. 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)-4-methyl-benzamide (**16**)*

Yield: 77.6%; m.p. 174–175 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.74 (10H, m, Ar–H), 7.80, 8.15 (2H, ss, triazole–H), 4.54–4.55 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.95 (8H, m, piperazine–H), 2.74–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.23 (1H, s, OH), 2.42 (3H, s, $-CH_3$). EIMS, *m/z*: 551 (M + 1). IR (KBr): 3355, 3137, 2947, 2822, 1655, 1513, 1269, 1140, 967 cm^{-1}. Anal. calcd for $C_{29}H_{29}F_3N_6O_2$: C, 63.26; H, 5.31; N, 15.26. Found: C, 63.22; H, 5.29; N, 15.20.

*6.3.13. 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)-3-trifluoromethyl-benzamide (**17**)*

Yield: 82.8%; m.p. 128–130 °C; ^{1}H NMR (DMSO-d_6): 6.83–8.09 (10H, m, Ar–H), 7.79, 8.15 (2H, ss, triazole–H), 4.51–4.59 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.54–2.96 (8H, m, piperazine–H), 2.72–3.17 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.22 (1H, s, OH). EIMS, *m/z*: 605 (M + 1). IR (KBr): 3279, 3109, 2952, 2826, 1741, 1659, 1616, 1512, 1426, 1335, 1250, 1139, 966 cm^{-1}. Anal. calcd for $C_{29}H_{26}F_6N_6O_2$: C, 57.62; H, 4.33; N, 13.90. Found: C, 57.51; H, 4.41; N, 13.89.

*6.3.14. 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)-2,4-dimethyl-benzamide (**18**)*

Yield: 76.8%; m.p. 92–93 °C; ^{1}H NMR (DMSO-d_6): 6.83–7.58 (9H, m, Ar–H), 7.79, 8.15 (2H, ss, triazole–H), 4.51–4.55 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.94 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.23 (1H, s, OH), 2.35 (6H, s, $-CH_3$), 2.46 (6H, s, $-CH_3$). EIMS, *m/z*: 565 (M + 1). IR (KBr): 3311, 3069, 2932, 2836, 1705, 1674, 1596, 1513, 1318, 1252, 1141, 966 cm^{-1}. Anal. calcd for $C_{30}H_{31}F_3N_6O_2$: C, 63.82; H, 5.53; N, 14.88. Found: C, 63.74; H, 5.62; N, 14.74.

*6.3.15. 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)-3,4-dimethyl-benzamide (**19**)*

Yield: 77.2%; m.p. 73–75 °C; ^{1}H NMR (DMSO-d_6): 6.80–7.74 (9H, m, Ar–H), 7.80, 8.15 (2H, ss, triazole–H), 4.51–4.55 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.95 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.23 (1H, s, OH), 2.32 (6H, s, $2CH_3$). EIMS, *m/z*: 565 (M + 1). IR (KBr): 3331, 3071, 2938, 2821, 1709, 1679, 1615, 1593, 1510, 1284, 1141, 966 cm^{-1}. Anal. calcd for $C_{30}H_{31}F_3N_6O_2$: C, 63.82; H, 5.53; N, 14.88. Found: C, 63.86; H, 5.57; N, 14.79.

*6.3.16. 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)-4-ethyl-benzamide (**20**)*

Yield: 74.5%; m.p. 165–167 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.76 (10H, m, Ar–H), 7.79,8.15 (2H, ss, triazole–H), 4.51–4.58 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.94 (8H, m, piperazine–H), 2.72–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 1.24–1.28 (3H, t, CH_3), 2.69–2.71 (2H, m, CH_2). EIMS, *m/z*: 565 (M + 1). IR (KBr): 3356, 3135, 2965, 2834, 1649, 1513, 1417, 1269, 1140, 1015, 966 cm^{-1}.

Anal. calcd for $C_{30}H_{31}F_3N_6O_2$: C, 63.82; H, 5.53; N, 14.88. Found: C, 63.94; H, 5.54; N, 14.92.

*6.3.17. 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)-4-propyl-benzamide (**21**)*

Yield: 70.8%; m.p. 166–167 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.75 (10H, m, Ar–H), 7.79, 8.15 (2H, ss, triazole–H), 4.51–4.58 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.94 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 0.93–0.96 (3H, t, CH_3), 2.63–2.66 (2H, m, CH_2), 1.64–1.68 (2H, m, CH_2), 5.23 (1H, s, OH). EIMS, *m/z*: 579 (M + 1). IR (KBr): 3356, 3049, 2947, 2836, 1650, 1511, 1417, 1269, 1138, 1015, 966 cm^{-1}. Anal. calcd for $C_{31}H_{33}F_3N_6O_2$: C, 64.35; H, 5.75; N, 14.52. Found: C, 64.29; H, 5.66; N, 14.41.

*6.3.18. 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)-4-isopropyl-benzamide (**22**)*

Yield: 71.8%; m.p. 160–161 °C; ^{1}H NMR (DMSO-d_6): 6.82–7.78 (10H, m, Ar–H), 7.75, 8.16 (2H, ss, triazole–H), 4.54 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.54–2.98 (8H, m, piperazine–H), 2.68–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 1.26–1.27 (6H, d, CH_3), 2.95–2.97 (1H, m, CH). EIMS, *m/z*: 579 (M + 1). IR (KBr): 3375, 3139, 2960, 2829, 1651, 1512, 1418, 1269, 1140, 1015, 966 cm^{-1}. Anal. calcd for $C_{31}H_{33}F_3N_6O_2$: C, 64.35; H, 5.75; N, 14.52. Found: C, 64.34; H, 5.77; N, 14.47.

*6.3.19. Data for 4-butyl-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)-benzamide (**23**)*

Yield: 72.5%; m.p. 139–141 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.75 (10H, m, Ar–H), 7.80, 8.15 (2H, ss, triazole–H), 4.51–4.58 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.94 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 0.91–0.94 (3H, t, CH_3), 2.65–2.71 (2H, m, CH_2), 1.32–1.39 (2H, m, CH_2), 1.58–1.64 (2H, m, CH_2). EIMS, *m/z*: 593 (M + 1). IR (KBr): 3377, 3134, 2933, 2825, 1655, 1513, 1424, 1249, 1139, 1015, 966 cm^{-1}. Anal. calcd for $C_{32}H_{35}F_3N_6O_2$: C, 64.85; H, 5.95; N, 14.18. Found: C, 65.01; H, 5.98; N, 14.06.

*6.3.20. Data for 4-tert-butyl-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)-benzamide (**24**)*

Yield: 71.3%; m.p. 187–188 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.78 (10H, m, Ar–H), 7.80, 8.15 (2H, ss, triazole–H), 4.54–4.55 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.95 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 1.34 (9H, s, CH_3). EIMS, *m/z*: 593 (M + 1). IR (KBr): 3283, 2961, 2828, 1663, 1607, 1513, 1271, 1133, 964 cm^{-1}. Anal. calcd for $C_{32}H_{35}F_3N_6O_2$: C, 64.85; H, 5.95; N, 14.18. Found: C, 64.76; H, 5.99; N, 14.09.

*6.3.21. 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)-4-pentyl-benzamide (**25**)*

Yield: 68.5%; m.p. 174–175 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.75 (10H, m, Ar–H), 7.79, 8.15 (2H, ss, triazole–H), 4.51–4.59 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.54–2.95 (8H, m, piperazine–H), 2.75–3.17 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 0.87–0.90 (3H, t, CH_3), 2.64–2.67 (2H, m, CH_2), 1.29–1.33 (4H, m, CH_2), 1.60–1.66 (2H, m, CH_2). EIMS, *m/z*: 607 (M + 1). IR (KBr): 3434, 3130, 2929, 2827, 1667, 1615, 1513, 1424, 1274, 1139, 1013, 967 cm^{-1}. Anal. calcd for $C_{33}H_{37}F_3N_6O_2$: C, 65.33; H, 6.15; N, 13.85. Found: C, 65.38; H, 6.19; N, 13.77.

*6.3.22. 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)-2-methoxy-benzamide (**26**)*

Yield: 70.2%; m.p. 165–167 °C; ^{1}H NMR (DMSO-d_6): 6.83–8.27 (10H, m, Ar–H), 7.80, 8.15 (2H, ss, triazole–H), 4.51–4.58 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.95 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.24 (1H, s, OH), 4.05 (3H, s, –OCH_3). EIMS, *m/z*: 567 (M + 1). IR (KBr): 3352, 3131, 2832, 1670, 1595, 1509, 1242, 1137, 1048, 963 cm^{-1}. Anal. calcd for $C_{29}H_{29}F_3N_6O_3$: C, 61.48; H, 5.16; N, 14.83. Found: C, 61.50; H, 5.24; N, 14.84.

*6.3.23. 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)-3-methoxy-benzamide (**27**)*

Yield: 68.8%; m.p. 149–151 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.71 (10H, m, Ar–H), 7.80, 8.15 (2H, ss, triazole–H), 4.51–4.58 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.95 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.23 (1H, s, OH), 3.86 (3H, s, –OCH_3). EIMS, *m/z*: 567 (M + 1). IR (KBr): 3445, 3394, 3135, 2951, 2827, 1663, 1594, 1424, 1258, 1139, 1041, 967 cm^{-1}. Anal. calcd for $C_{29}H_{29}F_3N_6O_3$: C, 61.48; H, 5.16; N, 14.83. Found: C, 61.61; H, 5.18; N, 14.68.

*6.3.24. 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)-4-methoxy-benzamide (**28**)*

Yield: 67.8%; m.p. 173–175 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.81 (10H, m, Ar–H), 7.80, 8.15 (2H, ss, triazole–H), 4.53–4.55 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.94 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.23 (1H, s, OH), 3.86 (3H, s, –OCH_3). EIMS, *m/z*: 567 (M + 1). IR (KBr): 3371, 3137, 2949, 2835, 1657, 1606, 1514, 1245, 1139, 968 cm^{-1}. Anal. calcd for $C_{29}H_{29}F_3N_6O_3$: C, 61.48; H, 5.16; N, 14.83. Found: C, 61.57; H, 5.16; N, 14.89.

*6.3.25. 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)-4-trifluoromethoxy-benzamide (**29**)*

Yield: 80.5%; m.p. 203–205 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.89 (10H, m, Ar–H), 7.80, 8.15 (2H, ss, triazole–H), 4.51–4.58 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.95 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.23 (1H, s, OH). EIMS, *m/z*: 621 (M + 1). IR (KBr): 3348, 3136, 2948, 2832, 1651, 1512, 1250, 1168, 967 cm^{-1}. Anal. calcd for $C_{29}H_{26}F_6N_6O_3$: C, 56.13; H, 4.22; N, 13.54. Found: C, 56.15; H, 4.25; N, 13.43.

*6.3.26. 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)-3,4-dimethoxy-benzamide (**30**)*

Yield: 68.9%; m.p. 168–169 °C; ^{1}H NMR (DMSO-d_6): 6.83–7.72 (9H, m, Ar–H), 7.80, 8.15 (2H, ss, triazole–H), 4.51–4.58 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.95 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.23 (1H, s, OH), 3.94 (6H, s, OCH_3). EIMS, *m/z*: 597 (M + 1). IR (KBr): 3369, 3111, 2955, 2828, 1647, 1583, 1514, 1383, 1223, 1137, 1019, 810 cm^{-1}. Anal. calcd for $C_{30}H_{31}F_3N_6O_4$: C, 60.40; H, 5.24; N, 14.09. Found: C, 60.51; H, 5.26; N, 13.98.

*6.3.27. 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)-3,4,5-trimethoxy-benzamide (**31**)*

Yield: 65.8%; m.p. 106–108 °C; ^{1}H NMR (DMSO-d_6): 6.81–7.76 (9H, m, Ar–H), 7.79, 8.15 (2H, ss, triazole–H), 4.51–4.60 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.56–2.99 (8H, m, piperazine–H), 2.74–3.19 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 3.89–3.91 (9H, m, OCH_3). EIMS, *m/z*: 627 (M + 1). IR (KBr): 3289, 2941, 2833, 1586, 1510, 1418, 1333, 1225, 1128, 1010, 966 cm^{-1}. Anal. calcd for $C_{31}H_{33}F_3N_6O_5$: C, 59.42; H, 5.31; N, 13.41. Found: C, 59.34; H, 5.37; N, 13.39.

*6.3.28. 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-nitro-benzamide (**32**)*

Yield: 78.6%; m.p. 167–169 °C; ^{1}H NMR (DMSO-d_6): 6.80–8.11 (10H, m, Ar–H), 7.76, 8.13 (2H, ss, triazole–H), 4.50–4.58 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.52–2.95 (8H, m, piperazine–H), 2.71–3.16 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.22 (1H, s, OH). EIMS, *m/z*: 582 (M + 1). IR (KBr): 3244, 3115, 2944, 2820, 1681, 1601, 1510, 1349, 1272, 1139, 1012, 965, 899 cm^{-1}. Anal. calcd for $C_{28}H_{26}F_3N_7O_4$: C, 57.83; H, 4.51; N, 16.86. Found: C, 57.86; H, 4.55; N, 16.77.

*6.3.29. 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)-4-nitro-benzamide (**33**)*

Yield: 80.8%; m.p. 133–135 °C; ^{1}H NMR (DMSO-d_6): 6.35–7.56 (10H, m, Ar–H), 7.79, 8.15 (2H, ss, triazole–H), 4.50–4.57 (2H, dd, $J = 15$ Hz, triazole–CH_2–), 2.49–2.84 (8H, m, piperazine–H), 2.69–3.14 (2H, dd, $J = 15$ Hz, CH_2–piperazine–), 5.28 (1H, s, OH). EIMS, *m/z*: 582 (M + 1). IR (KBr): 3403, 3211, 2951, 2835, 1616, 1514, 1275, 1165, 965 cm^{-1}. Anal. calcd for $C_{28}H_{26}F_3N_7O_4$: C, 57.83; H, 4.51; N, 16.86. Found: C, 57.74; H, 4.56; N, 16.79.

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