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Preliminary communication

Design, synthesis and molecular docking studies of novel triazole as antifungal agent

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ABSTRACT

In order to meet the urgent need for novel antifungal agents with improved activity and broader spectrum, a series of 1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[(4-substituted trifluoromethyl phenyl)-piperazin-1-yl]-propan-2-ols were designed, synthesized and evaluated as antifungal agents. The MIC_{80} values indicate that the compounds **7a**–**7q**, **8a**–**8d** showed higher antifungal activities against *Candida albicans* than **5a**–**5i**, **6a**–**6j**. Moreover, the molecular model for the binding between compound **5a**, **7a** and the active site of CACYP51 was provided based on the computational docking results, and the structure–activity relationship was analyzed.

1. Introduction

The incidence of infections caused by fungi pathogenic has increased significantly over the years [1]. Many fungal infections are caused by opportunistic pathogens that may be endogenous (*Candida* infections) or acquired from the environment (*Cryptococcus*, *Aspergillus* infections). However, besides these known fungal species, new emerging fungal pathogens appear every year as the cause of morbidity and life-threatening infections in the immunocompromised hosts [1,2]. Nowadays, numerous antifungal drugs with various structures and scaffolds are known and available. These drugs are amphotericin B [3], 5-fluorocytosine, azoles (such as fluconazole and itraconazole) [4], and echinocandins (such as caspofungin and micafungin) [5]. However, their clinical uses have been limited by the emergence of drug resistance, high risk of toxicity, insufficiencies in their antifungal activity and undesirable side effects [6,7]. Hence, there is still a need to develop and extend the safe and efficient chemotherapeutic agents with potent broad spectrum antifungal activities [7].

One of the most common classes of antifungal agents are azoles. For over a decade, azoles have been a mainstay of the antifungal armamentarium. These antigugal drugs act by inhibiting CYP51, a necessary enzyme in the biosynthesis of ergosterol, through a mechanism in which the heterocyclic nitrogen atom (N-4 of triazole) binds to the heme iron atom [8]. As a member of the cytochrome P450 superfamily, CYP51 catalyzes the oxidative removal of the 14α-methyl group of (C-32) lanosterol via three successive monooxygenation reactions to give $\triangle^{14,15}$-desaturated intermediates in ergosterol biosynthesis. The first two of these reactions are conventional cytochrome P450 hydroxylations that produce the 14-hydroxymethyl and 14-carboxyaldehyde derivatives of lanosterol [9,10]. In the final step, the 14-aldehyde group is eliminated as formic acid with concomitant introduction of a $\triangle^{14,15}$ double bond [11–13].

Unfortunately, the broad use of azoles has led to development of severe resistance, which significantly reduced their efficacy [14,15]. The emergence of resistance shows the need of the discovery of new antifungal compounds which have broader antifungal spectra and higher therapeutic indexes than fluconazole. And we could also study more about the structure–activity for the inhibition of CYP51.

Researches indicated that the structurally and functionally important regions, such as the heme group, the hydrophilic H-bonding region, the narrow hydrophobic cleft- substrate access

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channel 2 (FG loop), and the active site have been recognized accurately. The binding mode of azoles with CACYP51 has been investigated by flexible molecular docking [16–19]. The molecular modeling, which gives the utilization of structural information of fungal CYP51s can accelerate the discovery of novel antifungal agents. In our previous research, we introduced the phenyl group and fluorophenyl group to the piperazinyl of the side chain, most of the compounds exhibited higher activity against nearly all fungi tested. In this paper, we introduce the trifluoromethyl phenyl group following the conclusion of the previous and the strategy of structure-based rational drug design.

2. Chemistry

The general synthetic methodology for the preparation of title compounds 1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[(4-substituted trifluoromethyl phenyl)-piperazin-1-yl]-propan-2-ols (**5a**–**5i**, **6a**–**6j**, **7a**–**7q**, **8a**–**8d**) is outlined in Scheme 1. As a key intermediate of our designed triazole antifungals, the oxirane compound **1** was synthesized by the reported procedure [10]. And compound **2** were synthesized according to the literature [20]. 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 (4-dimethylaminopyridine) and EDCI (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide HCl) in dichloromethane at room temperature, the aniline **4** was converted to title compounds by reacting with various acids. All the new compounds (**5a**–**5i**, **6a**–**6j**, **7a**–**7q**, **8a**–**8d**) described above were characterized by IR, LC-MS and NMR spectroscopic analysis.

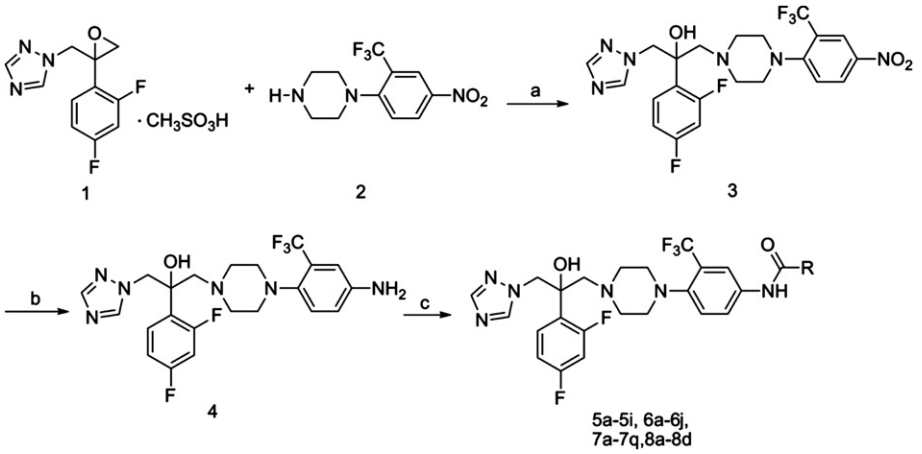
3. Pharmacology

The *in vitro* antifungal activities of all title compounds were evaluated against eight human pathogenic fungi, *Candida albicans*, *Cryptococcus neoformans*, *Candida parapsilosis*, *Candida tropicalis*, *Trichophyton rubrum*, *Fonsecaea compacta*, *Microsporum gypseum*, *Aspergillus fumigatus*, which are often encountered clinically, and were compared with fluconazole, itraconazole, voriconazole. *C. albicans* and *C. neoformans* were provided by Shanghai Changzheng Hospital; *C. parapsilosis*, *C. tropicalis*, *T. rubrum*, *F. compacta*, *M. gypseum*, and *A. fumigatus* were provided by Shanghai Changhai Hospital. *C. albicans* and *C. neoformans* were purchased from ATCC, and other strains were clinic isolates. *C. albicans* (ATCCY0109) and *C. neoformans* (ATCCBLS108) were used as the quality-controlled strains, and tested in each assay. Fluconazole (FLC), itraconazole (ICZ), voriconazole (VCZ) served as the positive control were obtained from their respective manufacturers.

The *in vitro* minimal inhibitory concentrations (MICs) of the compounds were determined by the micro-broth dilution method in 96-well microtestplates according to the methods defined by the National Committee for Clinical Laboratory Standards (NCCLS) [21]. The MIC_{80} was defined as the first well with an approximate 80% reduction in growth compared to the growth of the drug-free well. For assays, the title compounds to be tested were dissolved in dimethyl sulfoxide (DMSO), serially diluted in growth medium, inoculated and incubated at 35 °C. Growth MIC was determined at 24 h for *C. albicans* and at 72 h for *C. neoformans*. Fluconazole (FLC), itraconazole (ICZ) and voriconazole (VCZ) served as the positive control were obtained from their respective manufacturers. The results of assays are summarized in Table 1. The data points from the mean of replicates. All of our susceptibility tests were performed three times by each antifungal agent.

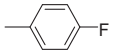
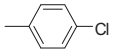
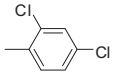
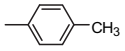
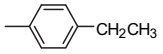
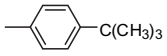
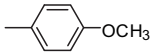
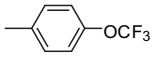
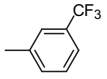
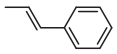
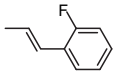
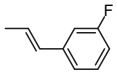
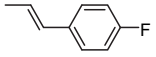
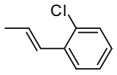
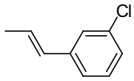
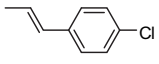
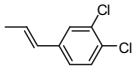
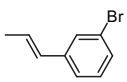
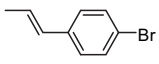
4. Results and discussion

The results of antifungal activities *in vitro* showed that all the compounds showed only moderate activity or no activity against nearly all fungi tested. Only several compounds exhibited excellent activity against *C. albicans*. Among the compounds tested, **5a**, **6j**, **7a**, **7b**, **7d**, **7e**, **7p**, **8a**, **8b** and **8c** showed higher activity against *C. albican* than FCZ and ICZ. The series of **7a**–**7q** and **8a**–**8d** showed no activity against nearly all fungi tested except *C. albicans*, *C. neoformans* and *A. fumigatus*. And the series of **5a**–**5i** and **6a**–**6j** exhibited moderate activity against nearly all fungi tested. Noticeably, the MIC_{80} values indicate that the compounds **7a**–**7q**, **8a**–**8d** showed higher antifungal activities against *C. albicans* than **5a**–**5i**, **6a**–**6j**. Compound **7a** showed 16 times higher activity (with the MIC_{80} value of 0.00097 μg/mL) than that of voriconazole against *C. albicans*. And compound **7d**, **7p** showed the same activity (with the MIC_{80} value of 0.0156 μg/mL) as that of voriconazole against *C. albicans*. Besides, the series of **6a**–**6j**, **7a**–**7q** and **8a**–**8d** exhibited higher activity against *A. fumigatus* than **5a**–**5i**. Compounds **7g**, **7i**, **7j**, **8a** and **8c** exhibited the same activities against *A. fumigatus* as voriconazole (with the MIC_{80} value of 1 mg/mL). The MIC_{80} value of compound **6d** is four times lower than that of itraconazole (with the MIC_{80} value of 0.25 mg/mL) against *A. fumigatus in vitro*.



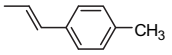
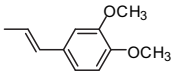
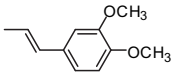
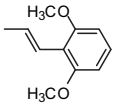
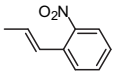
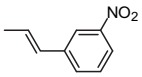
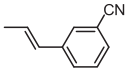
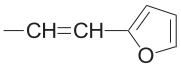
Scheme 1. Reagents and conditions: (a) CH_3CH_2OH, Et_3N, 80 °C, 5 h; (b) Raney Ni, $NH_2NH_2{\bullet}H_2O$, CH_3CH_2OH, 80 °C, 3.5 h; (c) Various acids, DMAP, EDCI, CH_2Cl_2, 8 h.

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

Compd	R	*C. alb.*	*C. par.*	*C. tro.*	*C. neo.*	*T. rub.*	*F. com.*	*M. gyp.*	*A. fum.*
5a	CH_3	0.0625	0.25	0.25	0.25	1	1	1	>64
5b	CH_2CH_3	0.25	1	0.25	1	1	4	1	16
5c	$CH_2CH_2CH_3$	1	0.25	1	1	4	4	1	>64
5d	$CH(CH_3)_2$	0.25	0.25	1	1	1	4	1	64
5e	$CH_2(CH_2)_2CH_3$	1	0.25	1	4	4	4	4	>64
5f	$C(CH_3)_3$	0.25	1	1	1	4	4	0.25	>64
5g	$CH_2(CH_2)_3CH_3$	1	1	4	1	4	16	4	64
5h	$CH_2(CH_2)_4CH_3$	1	4	4	1	4	16	4	>64
5i	$CH_2(CH_2)_5CH_3$	0.25	4	16	16	4	4	0.25	>64
6a		1	0.25	1	0.25	1	4	1	4
6b		4	0.25	1	16	4	4	1	4
6c		4	0.25	1	>64	4	4	0.25	4
6d		0.25	–	–	0.25	–	–	–	0.25
6e		1	0.25	1	1	4	16	1	64
6f		0.25	–	–	0.0625	–	–	–	4
6g		4	0.25	1	0.25	4	4	4	>64
6h		1	1	1	1	1	16	1	4
6i		16	4	4	16	16	16	4	64
6j		0.0625	–	–	0.0625	–	–	–	16
7a		0.00097	–	–	0.25	–	–	–	4
7b		0.0625	–	–	0.25	–	–	–	4
7c		0.25	–	–	0.25	–	–	–	16
7d		0.0156	–	–	0.25	–	–	–	4
7e		0.0625	–	–	0.25	–	–	–	4
7f		0.25	–	–	0.25	–	–	–	4
7g		1	–	–	0.25	–	–	–	1
7h		0.25	–	–	0.25	–	–	–	4
7i		0.25	–	–	0.25	–	–	–	1
7j		1	–	–	0.25	–	–	–	1

(*continued on next page*)

Table 1 (*continued*)

Compd	R	*C. alb.*	*C. par.*	*C. tro.*	*C. neo.*	*T. rub.*	*F. com.*	*M. gyp.*	*A. fum.*
7k		0.25	–	–	1	–	–	–	4
7l		1	–	–	1	–	–	–	4
7m		0.25	–	–	1	–	–	–	>64
7n		0.25	–	–	0.25	–	–	–	>64
7o		0.25	–	–	0.0625	–	–	–	4
7p		0.0156	–	–	0.25	–	–	–	4
7q		0.25	–	–	0.25	–	–	–	4
8a		0.0625	–	–	0.25	–	–	–	1
8b		0.0625	–	–	0.25	–	–	–	4
8c		0.0625	–	–	0.25	–	–	–	1
8d		0.25	–	–	0.25	–	–	–	4
FCZ		4	1	1	1	0.25	16	0.25	64
ICZ		1	0.25	0.25	1	0.0156	0.25	0.0156	1
VCZ		0.0156	1	0.25	0.0156	0.0039	0.0156	0.0039	>64

[a] Abbreviations: *C. alb.*, *C. albicans*; *C. par.*; *C. parapsilosis*; *C. tro.*, *C. tropicalis*; *C. neo.*, *C. neoformans*; *T. rub.*, *T. rubrum*; *F. com.*, *F. compacta*; *M. gyp.*, *M. gypseum*; *A. fum.*, *A. fumigatus*; FCZ: fluconazole; ICZ: itraconazole; VCZ: voriconazole.

In our previous research, the molecular docking result indicated that the 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 $\pi-\pi$ face-to-edge interaction.

To clarify the binding mode of our synthesized compounds in this paper, compound **5a** and **7a** were docked into the active site of CACYP51 respectively by the Builder module within InsightII 2000 software package (Fig. 1). The compound **7a** docking result revealed that the triazole group and the difluorophenyl group can bind to the active site of CACYP51 through the former binding mode. Although the side chain of the compound **5a** is also oriented into the substrate access channel 2, the amide side chain were too short to form hydrophobic and van der waals interactions with surrounding

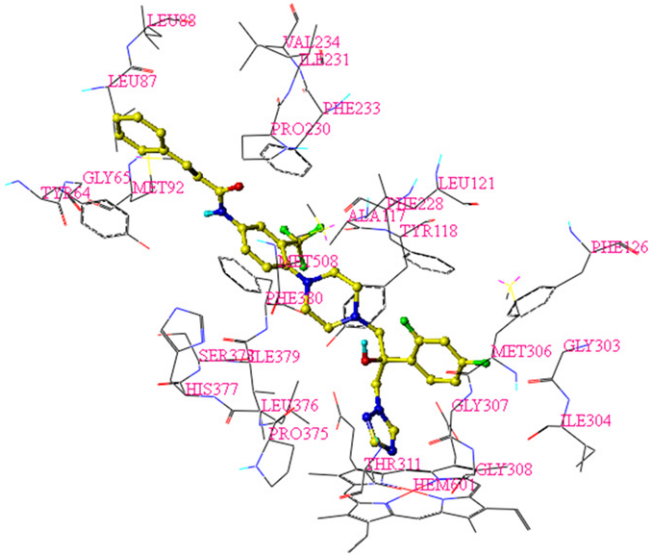


Fig. 1. Computed binding geometry of the new inhibitors **5a** and **7a** in the active site of CACYP51.

hydrophobic residues. From the figure we can see the difluorophenyl group of compound **5a** diverged from the hydrophobic binding cleft slightly. That is because the big trifluoromethyl group attached to the piperazinyl of the side chain and the short side chain blocks the compounds combinding with the active site compatibly. And the trifluoromethyl phenyl group of the side chain can interact with the phenyl group of Phe380 through the formation of $\pi-\pi$ face-to-edge interaction.

5. Conclusion

In summary, a series of 1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluoro-phenyl)-3-[(4-substituted trifluoromethyl phenyl)-piperazin-1-yl]-propan-2-ols were successfully designed and synthesized. *In vitro* antifungal activity assay indicated that the trifluoromethyl phenyl group of the side chain greatly influences the antifungal activity of these analogs against *Candida* species. This observation was explainable by a molecular model resulting from the computational docking simulation. The piperazinyl side chain of the compound **7a** is oriented into substrate access channel 2 (FG loop) and forms hydrophobic and *van der waals* interactions with surrounding hydrophobic residues. The trifluoromethyl phenyl group of the side chain can interacts with the phenyl group of Phe380 through the formation of $\pi-\pi$ 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

In our studies, the 3D structures of the designed azoles were built by the Builder module within InsightII 2000 software package. Then, the flexible ligand docking procedure in the Affinity module within InsightII was used to define the lowest energy position for the substrate using a Monte Carlo docking protocol. All the atoms within a defined radius (8 Å) of the substrate were allowed to move. The solvation grid supplied with the affinity Program was used. If the resulting substrate/enzyme system was within a predefined energy tolerance of the previous structure, the system was subjected to minimization. The resulting structure was accepted on the basis of energy check, which used the Metropolis criterion, and also a check of RMS distance of the new structure versus the structure found so far. The final conformation were obtained through a simulation annealing procedure from 500 to 300 K, and then 5000 rounds of energy minimization were performed to reach a convergence, where the resulting interaction energy values were used to define a rank order.

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 HITACHI270-50 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO unless otherwise indicated with a Bruker AC-300P spectrometer, using TMS as internal standard. The HPLC-MS were recorded on Agilent 1100 series LC/MS. The solvents and reagents were used as received or dried prior to use as needed.

6.1. 1-[4-nitro-2-(trifluoromethyl)phenyl]piperazine (**2**)

To a stirred mixture of 1-chloro-4-nitro-2-(trifluoromethyl) benzene (33.9 g, 150 mmol) and CH_3CN (300 mL), piperazine anhydrous (26.94 g, 300 mmol) was added and reflux for 10 h. The reaction was monitored by TLC. After filtration, the filtrate was evaporated under reduced pressure. Water (60 mL) was added to the residue, which was then extracted with ethyl acetate (80 mL × 3). The extract was washed with saturated NaCl solution (30 mL × 3), dried over anhydrous Na_2SO_4 and concentrated. The residue was crystallized to afford a white solid **2** 32.2 g, in 78% yield: m.p. 51–53 °C.

6.2. 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, 0.005 mol), C_2H_5OH (30 mL) and $N(C_2H_5)_3$ (3 mL), 1-[4-nitro-2-(trifluoromethyl) phenyl]piperazine (**2**) (1.65 g, 0.006 mol) was added and 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 C_2H_5OH to afford a white solid **3** 1.92 g, in 75% yield: m.p. 115–117 °C. ^{1}H NMR (DMSO-d_6): 6.80–8.48 (6H, m, Ar-H), 7.81, 8.13 (2H, ss, triazole–H), 4.51–4.60 (2H, dd, J = 15 Hz, triazole–CH_2–), 2.50–3.01 (8H, m, piperazine–H), 2.73–3.17 (2H, dd, J = 15 Hz, CH_2–piperazine–), 5.10 (1H, s, OH). IR (KBr): 3200, 2940, 2893, 1605, 1514, 1338, 1257, 1136, 918 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{22}H_{21}F_5N_6O_3$, 512.2, found $[M + H]^+$ 513.3.

6.3. 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[4-(4-amino-2-(trifluoromethyl)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**) (2.56 g, 0.005 mol), C_2H_5OH (30 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** 2.00 g, in 83% yield: m.p. 161–163 °C. ^{1}H NMR (DMSO-d_6): 6.75–7.60 (6H, m, Ar-H), 7.78, 8.16 (2H, ss, triazole–H), 4.52–4.54 (2H, dd, J = 15 Hz, triazole–CH_2–), 2.44–2.72 (8H, m, piperazine–H), 2.70–3.16 (2H, dd, J = 15 Hz, CH_2–piperazine–), 5.28 (1H, s, OH), 3.52 (2H, s, NH_2). IR (KBr): 3404, 3212, 3117, 3053, 2950, 2835, 1616, 1514, 1274, 1139, 965 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{22}H_{21}F_5N_6O_3$, 482.2, found $[M + H]^+$ 483.3.

6.4. General procedure for the target compound **5a**–5i, **6a**–6j, **7a**–7q, **8a**–8d

To a stirred mixture of 1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[4-(4-amino-2-(trifluoromethyl)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 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.

6.5. The title compounds were characterized as follows

*6.5.1. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-acetamide (**5a**)*

Mp: 168–170 °C; Yield: 81%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.78–7.78 (6H, m, Ar-H), 7.79, 8.16 (2H, ss, triazole–H), 4.53–4.54 (2H, dd, triazole–CH_2–), 2.46–2.76 (8H, m, piperazine–H), 2.74–3.17 (2H, dd, CH_2–piperazine–), 2.17 (s, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.51, 150.42, 146.94, 144.89, 136.37, 129.75, 126.27, 126.10, 125.63, 124.97, 123.43, 122.01, 116.89, 110.80, 110.54, 104.09, 103.72, 103.38, 74.54, 63.61, 55.70, 54.61, 53.25, 23.89. IR (KBr): 3420, 3302, 3186, 3069, 2947, 2827, 1694, 1616, 1547, 1503, 1232, 1135 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{24}H_{25}F_5N_6O_2$, 524.2, found $[M + H]^+$ 525.3.

*6.5.2. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-propionamide (**5b**)*

Mp: 173–175 °C; Yield: 71%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.78–7.76 (6H, m, Ar-H), 7.79, 8.16 (2H, ss, triazole–H), 4.53–4.54 (2H, dd, triazole–CH_2–), 2.46–2.77 (8H, m, piperazine–H), 2.68–3.17 (2H, dd, CH_2–piperazine–), 2.35–2.42 (q, 2H, –CH_2–), 1.21–1.24 (t, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.21, 150.42, 146.86, 144.89, 136.43, 129.78, 126.27, 125.62, 124.96, 123.43, 116.90, 110.82, 110.56, 103.73, 74.61, 63.61, 55.69, 54.61, 53.26, 29.44, 9.51. IR (KBr): 3420, 3300, 3186, 3066, 2977, 2943, 2848, 1685, 1616, 1550, 1504, 1271, 1135 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{25}H_{27}F_5N_6O_2$, 538.2, found $[M + H]^+$ 539.3.

*6.5.3. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-butyramide (**5c**)*

Mp: 189–191 °C; Yield: 68%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.78–7.63 (m, 6H, Ar-H), 7.79, 8.16 (ss, 2H, triazole–H), 4.53–4.54 (s, 2H, triazole–CH_2), 2.47–2.77 (m, 8H, piperazine–H), 2.71–3.17 (d, 2H, CH_2–piperazine), 2.30–2.35 (t, 2H, –CH_2–), 1.71–1.78 (m, 2H, –CH_2–), 0.97–1.01 (t, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.35, 150.42, 146.90, 144.87, 136.38, 129.76, 126.29, 126.01, 125.63, 124.95, 123.45, 116.93, 110.82, 110.54, 104.08, 103.73, 103.37, 74.59, 74.52, 63.61, 55.71, 54.61, 53.25, 18.45, 13.52. IR (KBr): 3301, 3254, 3184, 3110, 3065, 2875, 1688, 1616, 1551, 1505, 1383, 1134, 1017 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{26}H_{29}F_5N_6O_2$, 552.2, found $[M + H]^+$ 553.3.

*6.5.4. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-isobutyramide (**5d**)*

Mp: 189–191 °C; Yield: 69%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.78–7.79 (m, 6H, Ar-H), 7.80, 8.16 (ss, 2H, triazole–H), 4.53–4.55 (s, 2H, triazole–CH_2), 2.50–2.76 (m, 8H, piperazine–H), 2.69–3.18(d, 2H, CH_2–piperazine), 2.45–2.48 (m, H, –CH–), 1.22–1.26 (d, 6H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.50, 150.40, 146.90, 144.90, 136.58, 129.81, 126.37, 126.19, 125.99, 125.63, 124.88, 123.57, 117.08, 110.78, 110.51, 104.05, 103.69, 103.34, 74.61, 74.54, 63.66, 55.72, 54.61, 53.28, 34.93, 19.37. IR (KBr): 3310, 3120, 3166, 2969, 2879, 2823, 1672, 1616, 1540, 1502, 1273, 1137 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{26}H_{29}F_5N_6O_2$, 552.2, found $[M + H]^+$ 553.3.

*6.5.5. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-pentanamide (**5e**)*

Mp: 168–170 °C; Yield: 78%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.78–7.76 (m, 6H, Ar-H), 7.79, 8.17 (ss, 2H, triazole–H), 4.53–4.54 (s, 2H, triazole–CH_2), 2.48–2.77 (m, 8H, piperazine–H), 2.71–3.18 (d, 2H, CH_2–piperazine), 2.32–2.37 (t, 2H, –CH_2–), 1.67–1.72 (m, 2H, –CH_2–), 1.35–1.43 (m, 2H, –CH_2–), 0.91–0.96 (t, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.54, 150.37, 146.86, 144.79, 136.49, 129.82, 126.35, 126.28, 125.65, 124.87, 123.44, 122.32, 117.01, 110.87, 110.50, 104.08, 103.65, 103.33, 74.54, 63.65, 55.73, 54.62, 53.27, 36.30, 30.84, 23.82, 13.79. IR (KBr): 3255, 3185, 3116, 3066, 2960, 2934, 2875, 1689, 1616, 1550, 1504, 1271, 1134 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{27}H_{31}F_5N_6O_2$, 566.2, found $[M + H]^+$ 567.4.

*6.5.6. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-pivalamide (**5f**)*

Mp: 99–101 °C; Yield: 76%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.78–7.76 (m, 6H, Ar-H), 7.79, 8.17 (ss, 2H, triazole–H), 4.53–4.54 (s, 2H, triazole–CH_2), 2.50–2.78 (m, 8H, piperazine–H), 2.69–3.18 (d, 2H, CH_2–piperazine), 1.30 (s, 9H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.92, 150.46, 146.60, 144.56, 136.59, 129.86, 126.34, 126.19, 125.99, 125.61, 124.88, 123.53, 117.08, 110.78, 110.51, 104.05, 103.69, 103.34, 74.61, 74.54, 63.66, 55.72, 54.61, 53.28, 34.93, 19.22. IR (KBr): 3374, 3123, 2965, 2875, 2824, 1669, 1617, 1503, 1383, 1273, 1137 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{27}H_{31}F_5N_6O_2$, 566.2, found $[M + H]^+$ 567.3.

*6.5.7. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-hexanamide (**5g**)*

Mp: 107–109 °C; Yield: 72%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.78–7.76 (m, 6H, Ar-H), 7.79,8.17 (ss, 2H, triazole–H), 4.53–4.54 (s, 2H, triazole–CH_2), 2.48–3.19 (m, 8H, piperazine–H), 3.14–3.19 (d, 2H, CH_2–piperazine), 2.31–2.36 (t, 2H, –CH_2–), 1.68–1.73 (m, 2H, –CH_2–), 1.26–1.37 (m, 4H, –CH_2–), 0.87–0.92 (t, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.54, 150.39, 146.86, 144.89, 136.49, 129.80, 126.35, 126.18, 125.65, 124.87, 123.44, 122.02, 117.01, 110.77, 110.50, 104.04, 103.68, 103.33, 74.54, 63.65, 55.73, 54.61, 53.27, 36.30, 30.84, 24.71, 21.88, 13.79. IR (KBr): 3420, 3307, 3261, 3119, 3066, 2957, 2933, 2859, 1693, 1616, 1542, 1503, 1383, 1136, 1013 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{28}H_{33}F_5N_6O_2$, 580.3, found $[M + H]^+$ 581.4.

*6.5.8. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-heptanamide (**5h**)*

Mp: 83–85 °C; Yield: 71%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.77–7.63 (m, 6H, Ar-H), 7.79,8.16 (ss, 2H, triazole–H), 4.53–4.54 (s, 2H, triazole–CH_2), 2.47–2.76 (m, 8H, piperazine–H), 2.70–3.18 (d, 2H, CH_2–piperazine), 2.32–2.37 (t, 2H, –CH_2–), 1.65–1.73 (m, 2H, –CH_2–), 1.29–1.38 (m, 6H, –CH_2-), 0.86–0.91 (t, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.56, 150.39, 146.85, 144.91, 136.53, 129.84, 126.37, 125.99, 125.63, 124.93, 123.46, 116.91, 110.77, 110.51, 104.05, 103.68, 103.33, 74.56, 63.70, 55.70, 54.62, 53.28, 36.34, 31.04, 28.30, 24.99, 21.98, 13.91. IR (KBr): 3310, 3121, 3065, 2957, 2931, 2856, 2824, 1670, 1617, 1541, 1503, 1383, 1136, 1057 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{29}H_{35}F_5N_6O_2$, 594.3, found $[M + H]^+$ 595.4.

*6.5.9. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-octanamide (**5i**)*

Mp: 62–64 °C; Yield: 65%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.78–7.63 (m, 6H, Ar-H), 7.79,8.17 (ss, 2H, triazole–H), 4.53–4.54 (s, 2H, triazole–CH_2), 2.47–2.76 (m, 8H, piperazine–H), 2.70–3.17 (d, 2H, CH_2–piperazine), 2.31–2.36 (t, 2H, –CH_2–), 1.68–1.73 (m, 2H, –CH_2–), 1.26–1.37 (m, 8H, –CH_2–), 0.85–0.89 (t, 3H, –CH_3); ^{13}C

NMR (75 MHz, $CDCl_3$) δ: 171.52, 150.44, 146.78, 144.96, 136.52, 129.84, 126.34, 125.88, 125.60, 124.95, 123.42, 116.87, 110.68, 110.59, 104.05, 103.68, 103.37, 74.56, 63.70, 55.73, 54.62, 53.24, 36.34, 31.04, 28.28, 24.99, 22.33, 21.98, 13.94. IR (KBr): 3307, 3120, 3064, 2955, 2929, 2855, 1670, 1616, 1541, 1502, 1383, 1136, 1013 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{30}H_{37}F_5N_6O_2$, 608.3, found $[M + H]^+$ 609.4.

*6.5.10. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-benzamide (**6a**)*

Mp: 173–175 °C; Yield: 78%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.82–7.88 (11H, m, Ar-H), 7.79, 8.15 (2H, ss, triazole–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.49–2.80 (8H, m, piperazine–H), 2.70–3.19 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.61, 163.21, 157.28, 150.44, 147.54, 144.89, 136.22, 134.49, 131.76, 129.76, 128.40, 127.66, 126.29, 125.91, 125.55, 124.74, 122.07, 118.41, 110.84, 110.55, 104.10, 103.75, 103.39, 74.54, 63.62, 55.73, 54.62, 53.27. IR (KBr): 3295, 3110, 3075, 3015, 2951, 2888, 2813, 2750, 1668, 1615, 1541, 1505, 1384, 1135, 1042 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{29}H_{27}F_5N_6O_2$, 586.2, found $[M + H]^+$ 587.3.

*6.5.11. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-4-fluorobenzamide (**6b**)*

Mp: 204–206 °C; Yield: 75%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.79–7.90 (10H, m, Ar-H), 7.79, 8.16 (2H, ss, triazole–H), 4.53–4.54 (2H, dd, triazole–CH_2–), 2.48–2.79 (8H, m, piperazine–H), 2.70–3.19 (2H, dd, CH_2–piperazine–), 5.30 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.55, 163.32, 157.26, 150.44, 147.61, 144.82, 136.68, 133.17, 129.63, 129.35, 128.43, 126.35, 126.13, 125.95, 125.48, 124.79, 122.07, 118.45, 110.80, 110.54, 104.33, 103.21, 103.16, 74.67, 74.58, 63.69, 55.76, 54.66, 53.27. IR (KBr): 3294, 3113, 3078, 3016, 2949, 2887, 2847, 2821, 2753, 1669, 1607, 1547, 1506, 1384, 1164, 1041 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{29}H_{26}F_6N_6O_2$, 604.2, found $[M + H]^+$ 605.3.

*6.5.12. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-4-chlorobenzamide (**6c**)*

Mp: 201–203 °C; Yield: 76%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.79–7.89 (10H, m, Ar-H), 7.79, 8.16 (2H, ss, triazole–H), 4.49–4.59 (2H, dd, triazole–CH_2–), 2.49–2.80 (8H, m, piperazine–H), 2.70–3.19 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.47, 163.39, 157.28, 150.44, 147.66, 144.89, 136.68, 133.16, 129.61, 129.30, 128.46, 126.31, 126.13, 125.95, 125.68, 124.79, 122.05, 118.45, 110.83, 110.55, 104.09, 103.74, 103.38, 74.60, 74.54, 63.63, 55.75, 54.63, 53.27. IR (KBr): 3289, 3253, 3189, 3136, 3077, 2952, 2843, 2750, 1672, 1614, 1548, 1504, 1384, 1135, 1041 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{29}H_{26}ClF_5N_6O_2$, 620.2, found $[M + H]^+$ 621.3.

*6.5.13. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-2,4-dichlorobenzamide (**6d**)*

Mp: 193–195 °C; Yield: 80%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.79–7.97 (9H, m, Ar-H), 7.80, 8.17 (2H, ss, triazole–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.45–2.80 (8H, m, piperazine–H), 2.70–3.19 (2H, dd, CH_2–piperazine–), 5.36 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.18, 159.92, 150.40, 147.84, 146.30, 144.88, 135.83, 131.26, 130.35, 129.79, 127.43, 126.34, 126.17, 125.69, 124.20, 121.95, 117.69, 110.79, 110.53, 104.06, 103.70, 103.35, 74.61, 74.53, 63.65, 55.75, 54.81, 54.58, 53.25. IR (KBr): 3420, 3254, 3121, 2954, 2883, 2823, 1670, 1616, 1541, 1501, 1456, 1383, 1137, 1050 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{29}H_{25}Cl_2F_5N_6O_2$, 654.1, found $[M + H]^+$ 655.2.

*6.5.14. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-4-methylbenzamide (**6e**)*

Mp: 174–176 °C; Yield: 74%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.79–7.97 (10H, m, Ar-H), 7.79,8.15 (2H, ss, triazole–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.48–2.79 (8H, m, piperazine–H), 2.70–3.19 (2H, dd, CH_2–piperazine–), 2.43 (3H, s, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.40, 159.94, 150.43, 147.41, 144.88, 141.83, 136.28, 131.58, 129.75, 128.92, 127.68, 126.27, 126.10, 125.88, 125.51, 124.69, 122.07, 118.37, 110.81, 110.56, 104.10, 103.75, 103.38, 74.60, 74.53, 63.62, 55.71, 54.62, 53.26, 20.98. IR (KBr): 3291, 3131, 3078, 2955, 2884, 2815, 1669, 1615, 1541, 1505, 1420, 1383, 1137, 1041 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{30}H_{29}F_5N_6O_2$, 600.2, found $[M + H]^+$ 601.3.

*6.5.15. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-4-ethylbenzamide (**6f**)*

Mp: 98–100 °C; Yield: 71%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.84–7.86 (10H, m, Ar-H), 7.80, 8.18 (2H, ss, triazole–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.48–2.84 (8H, m, piperazine–H), 2.69–3.17 (2H, dd, CH_2–piperazine–), 2.69–2.77 (2H, m, CH_2), 1.25–1.30 (3H, t, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.40, 159.88, 150.37, 147.92, 147.34, 144.82, 136.25, 131.83, 129.70, 129.16, 127.71, 126.21, 126.07, 125.83, 125.63, 124.73, 122.00, 118.20, 110.75, 110.49, 104.03, 103.68, 103.32, 74.54, 74.48, 63.57, 55.64, 54.56, 53.21, 28.01, 15.26. IR (KBr): 3417, 3274, 3117, 2962, 2876, 2819, 1652, 1615, 1541, 1499, 1384, 1186, 1015 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{31}H_{31}F_5N_6O_2$, 614.2, found $[M + H]^+$ 615.3.

*6.5.16. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-4-isopropylbenzamide (**6g**)*

Mp: 101–103 °C; Yield: 70%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.79–7.90 (10H, m, Ar-H), 7.79, 8.16 (2H, ss, triazole–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.50–2.81 (8H, m, piperazine–H), 2.72–3.18 (2H, dd, CH_2–piperazine–), 1.36 (9H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.62, 155.04, 150.42, 147.41, 144.88, 136.31, 131.74, 129.76, 129.12, 127.52, 126.27, 126.10, 125.89, 125.69, 125.51, 124.80, 118.21, 110.81, 110.54, 104.09, 103.73, 74.60, 74.53, 63.62, 55.72, 54.61, 53.26, 34.66, 30.88. IR (KBr): 3420, 3124, 2963, 2907, 2870, 2824, 1653, 1615, 1539, 1504, 1384, 1136, 1013 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{33}H_{35}F_5N_6O_2$, 642.3, found $[M + H]^+$ 643.4.

*6.5.17. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-4-methoxybenzamide (**6h**)*

Mp: 139–141 °C; Yield: 68%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.79–7.87 (10H, m, Ar-H), 7.79, 8.16 (2H, ss, triazole–H), 4.53–4.54 (2H, dd, triazole–CH_2–), 2.48–2.79 (8H, m, piperazine–H), 2.70–3.19(2H, dd, CH_2–piperazine–), 3.87 (3H, s, $-OCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.98, 162.08, 159.95, 150.45, 147.30, 144.90, 136.45, 129.64, 126.49, 126.30, 125.92, 125.73, 125.54, 124.76, 124.66, 122.11, 118.32, 113.63, 110.83, 110.57, 104.11, 103.76, 103.38, 74.61, 63.64, 55.73, 55.40, 54.65, 53.29. IR (KBr): 3432, 3284, 3245, 3185, 3129, 3069, 2951, 2821, 1673, 1607, 1577, 1504, 1383, 1175, 1022 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{30}H_{29}F_5N_6O_3$, 616.2, found $[M + H]^+$ 617.3.

*6.5.18. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-4-(trifluoromethoxy)-benzamide (**6i**)*

Mp: 177–179 °C; Yield: 75%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.79–7.91 (10H, m, Ar-H), 7.79, 8.15 (2H, ss, triazole–H), 4.49–4.54 (2H, dd, triazole–CH_2–), 2.48–2.79 (8H, m, piperazine–H),

2.70–3.19 (2H, dd, CH_2–piperazine–), 5.33 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.04, 152.44, 147.86, 144.89, 135.63, 135.30, 131.83, 129.73, 129.57, 129.07, 128.38, 126.37, 126.15, 125.93, 125.58, 124.86, 124.23, 122.09, 118.58, 110.82, 110.54, 104.09, 103.77, 103.30, 74.62, 63.63, 55.73, 54.61, 53.27. IR (KBr): 3394, 3113, 3078, 3026, 2949, 2887, 2847, 2811, 2753, 1660, 1607, 1547, 1511, 1384, 1134, 1028 cm^{-1} LC-MS, *m*/*z* Calcd. for $C_{30}H_{26}F_8N_6O_3$, 670.2, found $[M + H]^+$ 671.3.

*6.5.19. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(trifluoromethyl)-benzamide (**6j**)*

Mp: 109–111 °C; Yield: 79%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.80–8.12 (10H, m, Ar-H), 7.80, 8.17 (2H, ss, triazole–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.49–2.81 (8H, m, piperazine–H), 2.70–3.19 (2H, dd, CH_2–piperazine–), 5.32 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.04, 150.44, 147.85, 144.89, 135.83, 135.33, 131.83, 129.73, 129.47, 129.04, 128.30, 126.30, 126.14, 125.93, 125.56, 124.86, 124.23, 122.04, 118.58, 110.82, 110.55, 104.09, 103.74, 103.38, 74.62, 63.63, 55.72, 54.60, 53.27. IR (KBr): 3289, 3120, 3070, 2957, 2884, 2823, 2678, 1663, 1616, 1599, 1500, 1384, 1164, 1012 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{30}H_{26}F_8N_6O_2$, 654.2, found $[M + H]^+$ 655.3.

*6.5.20. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-cinnamamide (**7a**)*

Mp: 193–195 °C; Yield: 71%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.52–7.92 (11H, m, Ar-H), 7.81, 8.18 (2H, ss, triazole–H), 6.85, 7.56 (2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.47–2.77 (8H, m, piperazine–H), 2.70–3.18 (2H, dd, CH_2-piperazine-); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.73, 160.32, 159.87, 150.43, 147.25, 144.90, 140.57, 136.38, 134.58, 129.87, 129.00, 127.78, 126.30, 125.72, 123.71, 122.02, 121.87, 117.22, 110.82, 110.55, 104.10, 103.74, 103.38, 74.62, 74.56, 63.66, 55.73, 54.63, 53.26. IR (KBr): 3420, 3300, 3120, 3062, 2952, 2884, 2823, 1669, 1598, 1510, 1300, 1178, 1015 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{31}H_{29}F_5N_6O_2$, 612.2, found $[M + H]^+$ 613.3.

*6.5.21. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(2-fluorophenyl)-acrylamide (**7b**)*

Mp: 142–144 °C; Yield: 73%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.68–7.84 (10H, m, Ar-H), 7.81,8.18 (2H, ss, triazole–H), 6.85, 7.56 (2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.48–2.78 (8H, m, piperazine–H), 2.69–3.18 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.23, 158.21, 156.95, 154.43, 154.27, 147.43, 144.42, 141.88, 133.14, 130.54, 129.38, 128.22, 126.76, 124.78, 123.28, 122.74, 120.76, 118.99, 114.32, 107.81, 107.55, 101.09, 100.72, 100.37, 71.61, 71.54, 60.63, 52.73, 51.41, 50.35. IR (KBr): 3374, 3116, 3061, 2953, 2882, 2820, 1670, 1617, 1549, 1499, 1383, 1135, 1014 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{31}H_{28}F_6N_6O_2$, 630.2, found $[M + H]^+$ 631.3.

*6.5.22. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(3-fluorophenyl)-acrylamide (**7c**)*

Mp: 145–147 °C; Yield: 75%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.50–7.90 (10H, m, Ar-H), 7.81, 8.18 (2H, ss, triazole–H), 6.82, 7.57 (2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.40–2.79 (8H, m, piperazine–H), 2.72–3.18 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.08, 160.84, 160.71, 160.55, 150.43, 147.35, 144.89, 139.20, 137.24, 134.24, 130.97, 129.77, 126.32, 125.74, 125.03, 123.47, 122.00, 117.29, 116.34, 110.82, 110.55, 104.09, 103.73, 103.37, 74.61, 74.54, 63.64, 55.74, 54.62, 53.25. IR (KBr): 3420, 3299, 3121, 3066, 2952, 2884, 2823, 1683, 1616, 1584, 1541, 1501, 1383, 1321, 1137, 1012 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{31}H_{28}F_6N_6O_2$, 630.2, found $[M + H]^+$ 631.3.

*6.5.23. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(4-fluorophenyl)-acrylamide (**7d**)*

Mp: 179–181 °C; Yield: 74%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.43–7.90 (10H, m, Ar-H), 7.81, 8.18 (2H, ss, triazole–H), 6.82, 7.56 (2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.47–2.78 (8H, m, piperazine–H), 2.70–3.19 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.52, 160.68, 159.90, 157.25, 150.43, 147.29, 144.87, 139.19, 134.32, 133.51, 129.74, 128.40, 126.46, 125.72, 125.02, 123.68, 122.60, 121.97, 117.22, 110.74, 110.53, 104.07, 103.71, 103.36, 74.53, 63.60, 55.71, 54.64, 53.20. IR (KBr): 3420, 3245, 3195, 3129, 3056, 2952, 2881, 2829, 1672, 1630, 1601, 1544, 1505, 1383, 1326, 1180, 1012 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{31}H_{28}F_6N_6O_2$, 630.2, found $[M + H]^+$ 631.3.

*6.5.24. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(2-chlorophenyl)-acrylamide (**7e**)*

Mp: 146–148 °C; Yield: 76%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.53–8.17 (10H, m, Ar-H), 7.80, 8.18 (2H, ss, triazole–H), 6.82,7.56 (2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.48–2.78 (8H, m, piperazine–H), 2.71–3.19 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.20, 157.54, 156.95, 154.43, 154.27, 147.43, 144.42, 141.88, 133.14, 130.54, 129.38, 128.22, 126.76, 124.78, 123.28, 122.74, 120.76, 118.99, 114.32, 107.81, 107.55, 101.09, 100.72, 100.37, 71.61, 71.54, 60.63, 52.73, 51.61, 50.25. IR (KBr): 3395, 3117, 3056, 2953, 2881, 2820, 1655, 1616, 1550, 1499, 1384, 1323, 1180, 1015 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{31}H_{28}ClF_5N_6O_2$, 646.2, found $[M + H]^+$ 647.3.

*6.5.25. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(3-chlorophenyl)-acrylamide (**7f**)*

Mp: 159–161 °C; Yield: 70%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.51–7.90 (10H, m, Ar-H), 7.80, 8.18 (2H, ss, triazole–H), 6.82, 7.56 (2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.48–2.78 (8H, m, piperazine–H), 2.71–3.15 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.34, 160.53, 160.12, 157.26, 150.42, 147.32, 144.87, 138.88, 136.87, 133.75, 130.70, 129.77, 126.83, 126.27, 126.12, 124.96, 123.70, 121.98, 117.34, 110.80, 110.53, 104.06, 103.71, 103.35, 74.58, 74.51, 63.62, 55.75, 54.61, 53.24. IR (KBr): 3395, 3108, 3057, 2948, 2883, 2820, 1668, 1624, 1551, 1499, 1383, 1321, 1181, 1015 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{31}H_{28}ClF_5N_6O_2$, 646.2, found $[M + H]^+$ 647.3.

*6.5.26. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(4-chlorophenyl)-acrylamide (**7g**)*

Mp: 202–204 °C; Yield: 77%; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.48–7.89 (10H, m, Ar-H), 7.81, 8.18 (2H, ss, triazole–H), 6.83, 7.57(2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.48–2.83 (8H, m, piperazine–H), 2.69–3.19 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.47, 160.68, 159.93, 157.25, 150.43, 147.29, 144.87, 139.19, 134.32, 133.51, 129.74, 128.40, 126.46, 125.72, 125.02, 123.68, 122.60, 121.97, 117.22, 110.79, 110.53, 104.07, 103.71, 103.36, 74.53, 63.60, 55.71, 54.60, 53.23. IR (KBr): 3420, 3246, 3115, 3057, 2952, 2883, 2826, 2756, 1673, 1629, 1542, 1503, 1383, 1318, 1143, 1012 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{31}H_{28}ClF_5N_6O_2$, 646.2, found $[M + H]^+$ 647.3.

*6.5.27. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(2,3-dichlorophenyl)-acrylamide (**7h**)*

Mp: 147–149 °C; Yield: 69%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.40–7.74 (9H, m, Ar-H), 7.81,8.19 (2H, ss, triazole–H), 6.83,7.57(2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.49–2.79 (8H, m, piperazine–H), 2.68–3.19 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.22, 160.68, 159.93, 157.25, 150.42, 147.36, 144.88, 139.37, 135.50, 132.00, 129.66, 128.03, 126.29, 125.71, 125.02, 123.74, 122.85, 121.97, 117.27, 110.81, 110.53, 104.07, 103.71, 103.36, 74.53, 63.60, 55.71, 54.60, 53.24. IR (KBr): 3419, 3274, 3116, 3059, 2951, 2883, 2823, 1684, 1617, 1542, 1500, 1384, 1319, 1134, 1012 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{31}H_{27}Cl_2F_5N_6O_2$, 680.2, found $[M + H]^+$ 681.3.

*6.5.28. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(3-bromophenyl)-acrylamide (**7i**)*

Mp: 168–170 °C; Yield: 68%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.50–7.86 (10H, m, Ar-H), 7.81,8.18 (2H, ss, triazole–H), 6.83,7.57(2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.41–2.79 (8H, m, piperazine–H), 2.71–3.19 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.33, 160.70, 160.54, 157.27, 150.43, 147.31, 144.87, 138.79, 136.22, 132.24, 129.24, 126.52, 126.30, 126.16, 125.62, 125.43, 122.30, 121.99, 117.31, 110.82, 110.55, 104.07, 103.71, 103.36, 74.56, 74.50, 63.63, 55.77, 54.63, 53.25. IR (KBr): 3404, 3264, 3109, 3060, 2947, 2883, 2820, 1669, 1617, 1548, 1499, 1383, 1320, 1179, 1014 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{31}H_{28}BrF_5N_6O_2$, 690.1, found $[M + H]^+$ 691.3.

*6.5.29. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(4-bromophenyl)-acrylamide (**7j**)*

Mp: 183–185 °C; Yield: 71%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.50–7.90 (10H, m, Ar-H), 7.81,8.18 (2H, ss, triazole–H), 6.83,7.57 (2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.47–2.78 (8H, m, piperazine–H), 2.70–3.19 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.42, 160.32, 160.21, 157.46, 150.36, 147.23, 144.81, 139.19, 136.18, 133.80, 131.87, 129.20, 126.20, 126.03, 125.65, 123.00, 122.65, 121.92, 117.17, 110.76, 110.48, 104.02, 103.67, 103.31, 74.53, 74.47, 63.56, 55.65, 54.55, 53.18. IR (KBr): 3420, 3256, 3113, 3062, 2951, 2882, 2824, 1678, 1628, 1541, 1502, 1383, 1318, 1137, 1010 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{31}H_{28}BrF_5N_6O_2$, 690.1, found $[M + H]^+$ 691.3.

*6.5.30. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(4-methyl)-acrylamide (**7k**)*

Mp: 176–178 °C; Yield: 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.45–7.90 (10H, m, Ar-H), 7.87, 8.18 (2H, ss, triazole–H), 6.83, 7.57(2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.48–2.79 (8H, m, piperazine–H), 2.73–3.18 (2H, dd, CH_2–piperazine–), 2.38 (3H, s, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.86, 160.70, 159.95, 157.26, 150.42, 147.17, 144.87, 139.70, 136.41, 131.84, 129.58, 127.74, 126.48, 126.27, 125.36, 124.99, 122.02, 120.77, 117.25, 110.81, 110.54, 104.08, 103.72, 103.37, 74.59, 74.52, 63.63, 55.73, 54.62, 53.25, 20.93. IR (KBr): 3353, 3123, 3024, 2947, 2881, 2819, 1655, 1617, 1549, 1383, 1318, 1225, 1181, 1016 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{32}H_{31}F_5N_6O_2$, 626.2, found $[M + H]^+$ 627.4.

*6.5.31. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(3,4-dimethoxyphenyl)-acrylamide (**7l**)*

Mp: 191–193 °C; Yield: 72%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.38–7.73 (9H, m, Ar-H), 7.80, 8.18 (2H, ss, triazole–H), 6.83, 7.44 (2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 3.92, 3.93(6H, ss, $-OCH_3$), 2.47–2.79 (8H, m, piperazine–H), 2.72–3.18 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.11, 160.73, 160.17, 160.00, 157.41, 150.47, 148.98, 144.92, 140.75, 136.60, 129.81, 127.40, 126.33, 125.69, 125.00, 123.59, 121.93, 119.48, 117.20, 110.57, 110.02, 104.11, 103.76, 103.40, 74.62, 74.56, 63.68, 55.77, 55.38, 54.68, 53.30. IR (KBr): 3445, 3123, 3063, 2996, 2944, 2813, 1669, 1622, 1599, 1549, 1501, 1383, 1314, 1225, 1136, 1026 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{33}H_{33}F_5N_6O_4$, 672.3, found $[M + H]^+$ 673.5.

*6.5.32. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(2,6-dimethoxyphenyl)-acrylamide (**7m**)*

Mp: 109–111 °C; Yield: 65%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.64–7.99 (9H, m, Ar-H), 7.80, 8.18 (2H, ss, triazole–H), 6.83, 7.33 (2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 3.80, 3.85(6H, ss, $-OCH_3$), 2.49–2.81 (8H, m, piperazine–H), 2.71–3.17 (2H, dd, CH_2–piperazine–); IR (KBr): 3299, 3120, 3067, 3000, 2949, 2833, 1682, 1618, 1540, 1499, 1383, 1316, 1136, 1013 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{33}H_{33}F_5N_6O_4$, 672.3, found $[M + H]^+$ 673.4.

*6.5.33. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(2-nitrophenyl)-acrylamide (**7n**)*

Mp: 175–177 °C; Yield: 75%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.42–8.12 (10H, m, Ar-H), 7.80, 8.18 (2H, ss, triazole–H), 6.83, 7.57 (2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.48–2.79 (8H, m, piperazine–H), 2.71–3.19 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.24, 162.86, 160.71, 157.29, 150.44, 148.25, 147.50, 144.89, 136.05, 130.43, 129.86, 128.75, 126.14, 125.77, 125.01, 124.72, 123.80, 121.99, 117.43, 110.82, 110.56, 104.08, 103.72, 103.37, 74.60, 74.54, 63.64, 55.76, 54.63, 53.25. IR (KBr): 3420, 3274, 3112, 3058, 2948, 2882, 2825, 1674, 1616, 1571, 1516, 1501, 1384, 1320, 1227, 1137, 1011 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{31}H_{28}F_5N_7O_4$, 657.2, found $[M + H]^+$ 658.4.

*6.5.34. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(3-nitrophenyl)-acrylamide (**7o**)*

Mp: 208–210 °C; Yield: 77%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.66–8.44 (10H, m, Ar-H), 7.81, 8.18 (2H, ss, triazole–H), 6.83, 7.58(2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.48–2.79 (8H, m, piperazine–H), 2.70–3.19 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.04, 162.74, 160.55, 157.29, 150.43, 148.18, 147.37, 144.87, 136.12 130.42, 129.77, 126.28, 126.11, 125.74, 125.59, 124.73, 123.92, 121.96, 117.19, 110.81, 110.54, 104.07, 103.71, 103.36, 74.60, 74.53, 63.63, 55.74, 54.62, 53.23. IR (KBr): 3420, 3251, 3101, 3047, 2956, 2881, 2828, 1682, 1636, 1615, 1534, 1500, 1384, 1351, 1225, 1132, 1010 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{31}H_{28}F_5N_7O_4$, 657.2, found $[M + H]^+$ 658.4.

*6.5.35. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(4-nitrophenyl)-acrylamide (**7p**)*

Mp: 229–231 °C; Yield: 81%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.57–8.11 (10H, m, Ar-H), 7.80, 8.17 (2H, ss, triazole–H), 6.83, 7.56 (2H, ss, C=C–H), 5.36 (1H, s, OH), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.48–2.79 (8H, m, piperazine–H), 2.70–3.19 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.04, 162.94, 160.73, 157.41, 150.47, 147.65, 147.48, 144.86, 136.01, 129.74, 128.77, 126.29, 126.06, 125.57, 125.07, 124.09, 123.76, 121.95, 117.35, 110.80, 110.54, 104.08, 103.72, 103.36, 74.60, 74.53, 63.61, 55.70, 54.59, 53.22. IR (KBr): 3445, 3110, 3058, 2950, 2885, 2826, 1682, 1617, 1600, 1541, 1501, 1384, 1315, 1223, 1138, 1013 cm^{-1}. LC-MS, *m/z* Calcd. for $C_{31}H_{28}F_5N_7O_4$, 657.2, found $[M + H]^+$ 658.3.

*6.5.36. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(3-cyanophenyl)-acrylamide (**7q**)*

Mp: 183–185 °C; Yield: 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.58–7.90 (10H, m, Ar-H), 7.81, 8.18 (2H, ss, triazole–H), 6.83, 7.56(2H, ss, C=C–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.48–2.79 (8H, m, piperazine–H), 2.70–3.19 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.55, 160.70, 160.54, 157.42, 150.43, 147.40, 144.87, 138.31, 136.12, 135.93, 130.12, 129.76, 126.31, 126.11, 125.25, 125.02, 124.29, 123.76, 121.98, 117.31, 110.82, 110.54, 104.08, 103.73, 103.37, 74.60, 74.52, 63.64, 55.76, 54.83, 53.24. IR (KBr): 3339, 3125, 3072, 2944, 2885, 2823, 2234, 1685, 1635, 1617, 1600, 1514, 1501, 1384, 1318, 1226, 1133, 1012 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{32}H_{28}F_5N_7O_2$, 637.2, found $[M + H]^+$ 638.4.

*6.5.37. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-furan-2-carboxamide (**8a**)*

Mp: 193–195 °C; Yield: 76%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.57–7.93 (9H, m, Ar-H), 7.80, 8.17 (2H, ss, triazole–H), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.48–2.79 (8H, m, piperazine–H), 2.70–3.19 (2H, dd, CH_2–piperazine–), 5.36 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.42, 160.58, 157.46, 150.45, 147.59, 147.30, 144.91, 135.66, 129.80, 126.36, 125.30, 124.77, 122.05, 118.45, 115.07, 110.84, 110.57, 104.09, 103.73, 103.38, 74.59, 74.52, 63.66, 55.77, 54.65, 53.27. IR (KBr): 3252, 3116, 3076, 3015, 2951, 2889, 2817, 2750, 1681, 1615, 1541, 1506, 1384, 1325, 1225, 1137, 1016 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{27}H_{25}F_5N_6O_3$, 576.2, found $[M + H]^+$ 577.3.

*6.5.38. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-nicotinamide (**8b**)*

Mp: 163–165 °C; Yield: 81%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.79–9.10 (10H, m, Ar-H), 7.88, 8.22 (2H, ss, triazole–H), 5.36 (1H, s, OH), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.44–2.81 (8H, m, piperazine–H), 2.71–3.19 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.14, 160.11, 157.43, 150.43, 148.74, 147.78, 144.90, 140.27, 135.95, 130.20, 126.31, 125.94, 124.86, 122.04, 118.44, 117.71, 110.81, 110.56, 104.09, 103.74, 103.38, 74.55, 63.66, 55.74, 54.83, 53.47, 53.27. IR (KBr): 3385, 3298, 3252, 3122, 3065, 3051, 2950, 2883, 2822, 1679, 1617, 1554, 1502, 1384, 1319, 1224, 1136, 1015 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{28}H_{26}F_5N_7O_2$, 587.2, found $[M + H]^+$ 588.3.

*6.5.39. N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-isonicotinamide (**8c**)*

Mp: 169–171 °C; Yield: 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.80–8.83 (10H, m, Ar-H), 7.80, 8.17 (2H, ss, triazole–H), 4.49–4.55 (2H, dd, triazole–CH_2–), 2.48–2.81 (8H, m, piperazine–H), 2.70–3.19 (2H, dd, CH_2–piperazine–), 5.35 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.02, 160.71, 157.44, 150.44, 147.99, 144.89, 141.49, 135.64, 129.78, 126.31, 126.15, 125.57, 125.20, 122.01, 121.53, 118.58, 110.83, 110.56, 104.09, 103.74, 103.38, 74.62, 74.55, 63.63, 55.73, 54.60, 53.25. IR (KBr): 3293, 3110, 3075, 2949, 2886, 2821, 1673, 1616, 1595, 1542, 1383, 1322, 1237, 1135, 1016 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{28}H_{26}F_5N_7O_2$, 587.2, found $[M + H]^+$ 588.3.

*6.5.40. (E)-N-(4-{4-[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl]-piperazin-1-yl}-3-(trifluoromethyl)-phenyl)-3-(furan-2-yl)-acrylamide (**8d**)*

Mp: 212–214 °C; Yield: 85%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.38–7.55 (9H, m, Ar-H), 7.80, 8.18 (2H, ss, triazole–H), 6.83, 7.55 (2H, ss, C=C–H), 5.36 (1H, s, OH), 4.54–4.55 (2H, dd, triazole–CH_2–), 2.47–2.78 (8H, m, piperazine–H), 2.75–3.17 (2H, dd, CH_2–piperazine–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.56, 160.71, 157.44, 150.78, 147.24, 145.31, 144.88, 136.29, 129.77, 127.68, 126.07, 125.62, 125.10, 118.85, 117.14, 114.88, 112.60, 110.83, 110.57, 104.11, 103.74, 103.39, 74.61, 74.54, 63.62, 55.70, 54.61, 53.25. IR (KBr): 3420, 3299, 3120, 2944, 2884, 2825, 2755, 1734, 1685, 1634, 1542, 1384, 1320, 1215, 1135, 1013 cm^{-1}. LC-MS, *m*/*z* Calcd. for $C_{29}H_{27}F_5N_6O_3$, 602.2, found $[M + H]^+$ 603.4.

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