Design, synthesis, and antifungal activities of novel triazole derivatives containing the benzyl group

Abstract: In previous studies undertaken by our group, a series of 1-(1H-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanols (1a–r), which were analogs of fluconazole, was designed and synthesized by click chemistry. In the study reported here, the in vitro antifungal activities of all the target compounds were evaluated against eight human pathogenic fungi. Compounds 1a, 1q, and 1r showed the more antifungal activity than the others.

Keywords: triazole, synthesis, antifungal activity, CYP51

Introduction

In the past three decades, deep fungal infections have sharply escalated due to the employment of clinical antitumor drugs and immunosuppressants; the widespread application of broad-spectrum antibiotics, cancer chemotherapy, radiotherapy, peritoneal dialysis, organ transplantation; and immune deficiency disorders, especially AIDS.1,2 Currently, aspergillosis, cryptococcosis, and candidiasis are three major clinical fungal infections in immunocompromised individuals.3,4 Azole nitrogen compounds have been progressively getting people’s attention, mainly because of their superiority in antifungal therapy but also for their contribution in the treatment of various microbes.5 Azoles (fluconazole, itraconazole, voriconazole, and posaconazole, Figure 1) are one very significant class of compounds for treating deep fungal infections in the clinical context.6 One of the principal problems in the treatment of Candida albicans infections is the spread of antifungal drug resistance, mainly in patients chronically subjected to antimycotic therapy such as HIV-infected people.7,8

More recently, there has been a development in the number of antifungal drugs available. Five major classes of antifungal compounds are currently in clinical use: polyenes, azole derivatives, allylamines, thiocarbamates, and fluoropyrimidines.9–12 In spite of this growing list of antifungal agents in the process of being studied, treatment of fungal diseases remains unsatisfactory. The limitations of current antifungal drugs, increased incidence of systemic fungal infections, and rapid development of drug resistance have emphasized the need for the discovery of new antifungal agents with a new mode of action and fewer side effects.4,10,13–15

In particular, azole drugs are very important antifungal agents widely used in the clinical context.16 Azoles exert antifungal activity through the inhibition of cytochrome P450 14α-demethylase (CYP51), which is crucial in the process of biosynthesis of ergosterol. The CYP51 enzyme contains an iron protoporphyrin unit located in its active site, which catalyzes the oxidative removal of the 14α-methyl group of lanosterol by typical monoxygenase activity.17 Azole antifungal agents bind to the iron of the porphyrin and cause blockade of the fungal ergosterol biosynthesis pathway.
by preventing the access of the natural substrate lanosterol to the active site of the enzyme.\textsuperscript{18}

In previous research by our group,\textsuperscript{19–27} numerous studies on the structure–activity relationships (SAR) of antifungal azoles were undertaken, and these studies led to new compounds endowed with better biological and pharmacological properties. These studies indicated that the triazole ring, the difluorophenyl group, and the hydroxyl group are the pharmacophores of antifungal agents. We focused our attention on installing various substituted benzyl groups of the side chain by click chemistry.

According to the results of these studies, we designed a series of 1-\(\text{H}-1,2,4\)-triazole-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanols (1a–r, Figure 2) containing a triazole ring, a difluorophenyl group, a hydroxyl group, and a side chain containing a piperazine group. In our design, we systematically altered the structure of fluconazole as a platform and tried to insert a 1,2,3-triazole group into the side chain.

**Chemistry**

The general synthetic methodology for the preparation of the title compounds (1a–r) is outlined in Figure 3. Compound 3 was synthesized by ring-open reaction of oxirane 2 with benzyamine. Then, compound 3 was transformed into compound 4 by reacting with propargyl bromide in the presence of KI and K\(_2\)CO\(_3\) in acetonitrile. The target compounds were obtained by using click chemistry\textsuperscript{28} with various substituted benzyl azides.

**Pharmacology**

The in vitro antifungal activities of all the target compounds were evaluated against eight human pathogenic fungi – \textit{C. albicans} 14053, \textit{C. albicans} 20352, \textit{Candida parapsilosis}, \textit{Cryptococcus neoformans}, \textit{Candida glabrata}, \textit{Aspergillus fumigatus}, \textit{Trichophyton rubrum}, and \textit{Microsporum gypseum}—which are often encountered clinically, and were compared with itraconazole (ICZ), voriconazole (VCZ), and fluconazole (FCZ). All eight human pathogenic fungi were provided by Shanghai Changzheng Hospital; FCZ, ICZ, and VCZ, which 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 micro test plates according to the methods defined by the National Committee for Clinical Laboratory Standards.\textsuperscript{29} The MIC80 was defined as the first well containing an approximate 80% reduction in growth compared with
Novel triazole derivatives containing the benzyl group

Figure 3 Synthesis of the target compounds 1a–r.
Notes: Conditions: (a) Et,N, benzylamine, EtOH, Et,N, reflux, 5 hours, 72%; (b) propargyl bromide, KI, K₂CO₃, CH₃CN, rt, 5–6 hours, 81%; (c) NaN₃, substituted benzyl bromide, dimethyl sulfoxide, CuSO₄.5H₂O, sodium ascorbate, rt, 12 hours, 60%–70%.

Materials and methods
Melting points (MPs) were measured on a YRT-3 Melting Point Tester (Tianda Tianfa Technology Co., LTD, Tianjin, People’s Republic of China) and are presented uncorrected. Proton nuclear magnetic resonance (¹H NMR) spectra are recorded in CDCl₃, unless otherwise indicated, with an Avance II 300 spectrometer (Bruker Corporation, Billerica, MA, USA), using tetramethysilane as the internal standard. Electrospray ionization-mass spectrometry (ESI-MS) spectra were obtained using an API 3000 liquid chromatography–mass spectrometry spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). Thin-layer chromatography analysis was carried out on GF254 silica gel plates (Qingdao Haiyang Chemical Co Ltd, Qingdao, People’s Republic of China). Column chromatography was performed with silica gel 60 G (Qingdao Haiyang Chemical Co Ltd). The solvents and reagents were used as received or dried prior to use, as needed.

Compound 3: 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-(benzylamino)-2-propanol
To a stirred mixture of 1-[2-(2,4-difluorophenyl)-2,3-epoxypropyl]-1H-1,2,4-triazole methanesulphonate (2) (16.5 g, 0.05 mol), C₂H₅OH (200 mL) and N(C₂H₅)₃ (30 mL), benzylamine (6.42 g, 0.06 mol) were added and heated at 70°C–80°C for 5 hours. The reaction was monitored by thin layer chromatography. After filtration, the filtrate was evaporated under reduced pressure. Water was added to the residue, which was then extracted with ethyl acetate. The extract was washed with saturated NaCl solution, dried over anhydrous Na₂SO₄, and evaporated. The residue was separated and purified readily by chromatography on silica gel to afford Compound 3 (12.4 g, 72% yield).

Compound 4: 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-(N-benzyl-N-propargyl amino)-2-propanol
To a stirred mixture, Compound 3 (3.44 g, 0.01 mol), propargyl bromide (2.36 g, 0.02 mol), KI (166 mg, 0.001 mol), K₂CO₃ (3.45 g, 0.025 mol), and CH₃CN (50 mL) was stirred at room temperature for 6 hours. The reaction was monitored by thin layer chromatography. When the reaction was completed, the solid was filtrated, washed with CH₃CN, then the filtrate was concentrated in a vacuum. Column chromatography of the residue afforded Compound 4 as an oil (3.09 g, 81% yield).

General procedure for the preparation of Compounds 1a–r
A mixture of NaN₃ (100 mg, 1.4 mmol), 2-fluorobenzyl bromide (200 mg, 1.2 mmol), and DMSO (15 mL) was stirred at room temperature for 6 hours. Then, to this was added Compound 4 (229 mg, 0.6 mmol), sodium ascorbate (20 mg), CuSO₄.5H₂O (25 mg), and H₂O (1 mL). The mixture
Table 1  Antifungal activities of the title compounds in vitro (80% minimal inhibitory concentration μg/mL)

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<th>C. albicans</th>
<th>Candida parapsilosis</th>
<th>Cryptococcus neoformans</th>
<th>Candida glabrata</th>
<th>Aspergillus fumigatus</th>
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was stirred at room temperature for 2 hours, then NH4H2O was added carefully, then extracted with ethyl acetate. The organic layer was acidified with dilute hydrochloric acid, then the pH of the aqueous layer was adjusted to about 7.0 by saturation with sodium bicarbonate, then the solution was extracted with ethyl acetate, washed with water, NaHCO3 and NaCl solutions, dried with Na2SO4, and concentrated in a vacuum to afford Compound 1a (212 mg, 69% yield; MP, 92.0°C–94.0°C; 1H NMR [300 MHz, CDCl3] δ: 8.06 [1H, s, triazole-H], 7.72 [1H, s, triazole-H], 7.63–7.56 [1H, m, Ar], 7.39–7.12 [8H, m, Ar-H, triazole-H], 6.83–6.69 [2H, m, Ar-H], 5.60 [2H, s, Ar-CH2-], 4.50–4.36 [2H, m, CH2], 3.72–3.38 [4H, m, -CH2-N-CH2-], 3.28–2.90 [2H, m, CH2], 13C NMR [75 MHz, CDCl3] δ: 163.2, 159.0, 151.1, 130.2, 130.0, 129.9, 129.8, 129.8, 129.7, 129.6, 129.6, 129.5, 129.5, 129.4, 128.5, 128.0, 116.2, 111.8, 104.4, 73.0, 59.7, 57.5, 56.0, 35.6, 49.2; ESI-MS, m/z calculated for C28H26F3N7O, 533.2, found [M+H]+ 534.5). (The characterization of Compounds b–r is presented in the “Supplementary materials” section).

**Results**

The in vitro antifungal activities are summarized in Table 1, along with the MIC values (in μg/mL) against different pathogenic fungi, in comparison with ICZ, VCZ, and FCZ. The results of the study of the antifungal activities in vitro show that all 18 target compounds (1a–r) were active against nearly all fungi tested to some extent, except against A. fumigatus and C. glabrata. The MIC80 value of Compounds 1a and 1h was four times lower than that of FCZ against C. albicans 14053 in vitro (with an MIC80 value of 0.25 μg/mL). The MIC80 value of Compounds 1a, 1q, and 1r was 256 times lower than that of ICZ and VCZ, respectively. As indicated that most of the compounds showed antifungal activities against 3,685 clinical isolates of Candida spp and Cryptococcus neoformans. The MIC80 value of Compounds 1a and 1h was four times lower than that of ICZ against Cryptococcus neoformans, and four times lower than that of FCZ against C. albicans. In vitro, and the same antifungal activity that was broad spectrum, which will be valuable to future investigations.

**Acknowledgments**

This work was supported by the National Key Basic Research Program of China (no 2013CB531602), the National Natural Science Foundation of China (no 81330083), the Creativity and Innovation Training Program of Second Military Medical University, and the Pharmaceutical Education Research Project of the Chinese Association of Higher Medical Education Professional Committee (grant no ZD201220).

Electronic supplementary information available: proton nuclear magnetic resonance and electrospray ionization-mass spectrometry spectral data of Compounds 1b–r.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**

Supplementary materials
The title compounds 1b–r were characterized as follows.

**Compound 1b**: 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-{(N-benzyl-N-[(1-(3-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl]amino)-2-propanol

Melting point (MP): 94.1°C–96.0°C; proton nuclear magnetic resonance (1H NMR) (300 MHz, CDCl$_3$) δ: 8.13 (1H, s, triazole-H), 7.77 (1H, s, triazole-H), 6.74–7.55 (1H, m, Ar), 7.37–7.12 (8H, m, Ar-H, triazole-H), 6.82–6.74 (2H, m, Ar-H), 5.46 (2H, s, Ar-CH$_2$ N-C$_6$H$_4$), 4.51–4.36 (2H, m, CH$_2$), 3.71–3.36 (4H, m, -CH$_2$N-C$_6$H$_4$), 3.27–2.91 (2H, m, CH$_2$); carbon-13 nuclear magnetic resonance (13C NMR) (75 MHz, CDCl$_3$) δ: 163.3, 159.1, 151.2, 130.3, 130.1, 129.9, 129.9, 129.7, 129.7, 129.6, 129.6, 129.5, 129.5, 129.4, 128.6, 128.1, 116.3, 111.9, 104.5, 73.1, 59.8, 57.6, 56.1, 35.7, 49.3; electrospray ionization-mass spectrometry (ESI-MS), m/z calculated for C$_{25}$H$_{26}$F$_2$N$_5$O, 533.2, found [M+H]$^+$ 534.3.

**Compound 1c**: 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-{(N-benzyl-N-[(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl]amino)-2-propanol (1c)

Melting point (MP): 94.1°C–96.0°C; 1H NMR (300 MHz, CDCl$_3$) δ: 8.11 (1H, s, triazole-H), 7.72 (1H, s, triazole-H), 7.69–7.57 (1H, m, Ar), 7.29–7.06 (8H, m, Ar-H, triazole-H), 6.84–6.69 (2H, m, Ar-H), 5.51 (2H, s, Ar-CH$_2$ N-C$_6$H$_4$), 4.60–4.36 (2H, m, CH$_2$), 3.67–3.34 (4H, m, -CH$_2$N-C$_6$H$_4$), 3.01–2.64 (2H, m, CH$_2$); 13C NMR (75 MHz, CDCl$_3$) δ: 163.1, 159.0, 151.0, 130.1, 130.0, 129.9, 129.9, 129.8, 129.7, 129.7, 129.7, 129.6, 129.6, 129.5, 129.4, 128.7, 128.0, 116.1, 111.7, 104.2, 73.2, 59.7, 57.5, 56.0, 35.5, 49.2; ESI-MS, m/z calculated for C$_{25}$H$_{26}$F$_2$N$_5$O, 533.2, found [M+H]$^+$ 534.4.

**Compound 1d**: 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-{(N-benzyl-N-[(1-(3-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl]amino)-2-propanol

Melting point (MP): 116.8°C–118.2°C; 1H NMR (300 MHz, CDCl$_3$) δ: 8.07 (1H, s, triazole-H), 7.75 (1H, s, triazole-H), 7.63–7.61 (1H, m, Ar-H), 7.57–7.51 (2H, m, Ar-H), 7.27–7.11 (8H, m, Ar-H, triazole-H), 6.82–6.70 (2H, m, Ar-H), 5.52 (2H, s, Ar-CH$_2$ N-C$_6$H$_4$), 4.51–4.36 (2H, m, CH$_2$), 3.73–3.40 (4H, m, -CH$_2$N-C$_6$H$_4$), 3.30–2.85 (2H, m, CH$_2$); 13C NMR (75 MHz, CDCl$_3$) δ: 163.5, 159.6, 151.4, 136.2, 134.8, 131.8, 131.8, 131.5, 130.5, 130.4, 130.3, 129.8, 129.7, 129.7, 129.2, 128.9, 128.8, 128.7, 128.3, 112.2, 104.8, 73.4, 62.1, 58.2, 53.2, 52.0, 48.0;
Compound 1h: 1-(1H,1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-{N-benzyl-N-[(1-(3-bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl]amino}-2-propanol

MP: 79.6°C; 1H NMR (300 MHz, CDCl₃) δ: 8.08 (1H, s, triazole-H), 7.69 (1H, s, triazole-H), 7.62–7.57 (1H, m, Ar-H), 7.35–7.20 (10H, m, Ar-H, triazole-H), 6.83–6.67 (2H, m, Ar-H), 5.56 (2H, s, Ar-CH₂), 4.58–4.12 (2H, m, CH₂), 3.70–3.20 (4H, m, -CH₂), 3.33–2.87 (2H, m, CH₂); 13C NMR (75 MHz, CDCl₃) δ: 164.1, 155.3, 138.3, 134.7, 130.1, 130.0, 129.9, 129.9, 129.8, 129.7, 129.6, 129.5, 129.4, 129.3, 129.2, 128.7, 128.6, 125.1, 111.8, 104.1, 72.3, 59.7, 57.3, 55.3, 54.0, 49.3, 22.3; ESI-MS, m/z calculated for C₂₅H₂₇BrF₂N,O 529.6, found [M+H]+ 530.6.

Compound 1i: 1-(1H,1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-{N-benzyl-N-[(1-(4-bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl]amino}-2-propanol

MP: 91.2°C–93.0°C; 1H NMR (300 MHz, CDCl₃) δ: 8.06 (1H, s, triazole-H), 7.71 (1H, s, triazole-H), 7.66–7.57 (1H, m, Ar-H), 7.29–7.16 (10H, m, Ar-H), 6.82–6.67 (2H, m, Ar-H), 5.50 (2H, s, Ar-CH₂), 4.51–4.35 (2H, m, CH₂), 3.72–3.45 (4H, m, -CH₂-N-CH₂), 3.33–2.90 (2H, m, CH₂), 2.85 (3H, s, Ar-CH₃); 13C NMR (75 MHz, CDCl₃) δ: 163.9, 155.7, 138.2, 134.5, 130.0, 130.0, 129.9, 129.9, 129.8, 129.7, 129.7, 129.6, 129.5, 129.4, 129.2, 128.5, 128.3, 125.3, 111.7, 104.5, 72.6, 59.5, 57.1, 54.1, 49.7, 22.6; ESI-MS, m/z calculated for C₂₅H₂₇BrF₂N,O 529.6, found [M+H]+ 530.6.

Compound 1l: 1-(1H,1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-{N-benzyl-N-[(1-(3-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl]amino}-2-propanol

MP: 92.6°C–94.1°C; 1H NMR (300 MHz, CDCl₃) δ: 8.07 (1H, s, triazole-H), 7.78 (1H, s, triazole-H), 7.70–7.58 (1H, m, Ar-H), 7.32–7.08 (10H, m, Ar-H, triazole-H), 6.83–6.69 (2H, m, Ar-H), 5.56 (2H, s, Ar-CH₂), 4.60–4.45 (2H, m, CH₂), 3.75–3.45 (4H, m, -CH₂-N-CH₂), 3.30–2.90 (2H, m, CH₂), 2.37 (3H, s, Ar-CH₃); 13C NMR (75 MHz, CDCl₃) δ: 163.5, 155.1, 138.1, 134.6, 130.0, 129.9, 129.9, 129.8, 129.7, 129.7, 129.6, 129.5, 129.4, 129.2, 128.8, 128.6, 125.3, 111.7, 104.3, 72.5, 59.8, 57.5, 55.8, 54.1, 49.8, 22.5; ESI-MS, m/z calculated for C₂₅H₂₇BrF₂N,O 529.6, found [M+H]+ 530.5.

Compound 1m: 1-(1H,1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-{N-benzyl-N-[(1-(2-cyanobenzyl)-1H-1,2,3-triazol-4-yl)methyl]amino}-2-propanol

MP: 91.1°C–92.1°C; 1H NMR (300 MHz, CDCl₃) δ: 8.07 (1H, s, triazole-H), 7.76 (1H, s, triazole-H), 7.65–7.63 (1H, m, Ar-H), 7.54–7.21 (10H, m, Ar-H, triazole-H), 6.85–6.71 (2H, m, Ar-H), 5.74 (2H, s, Ar-CH₂), 4.58–4.38 (2H, m, CH₂), 3.75–3.43 (4H, m, -CH₂-N-CH₂), 3.30–2.87 (2H, m, CH₂), 2.38 (3H, s, Ar-CH₃); 13C NMR (75 MHz, CDCl₃) δ: 163.7, 155.7, 138.2, 134.5, 130.0, 130.0, 129.9, 129.9, 129.8, 129.7, 129.7, 129.6, 129.5, 129.3, 129.3, 128.3, 125.3, 111.7, 104.5, 72.6, 59.5, 57.1, 55.1, 54.1, 49.7, 22.8; ESI-MS, m/z calculated for C₂₅H₂₇BrF₂N,O 529.6, found [M+H]+ 530.7.
Compound 1m: \(1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-\{\text{N-benzyl-N-}[(1-\text{cyanobenzyl})-1H-1,2,3-triazol-4-yl] \text{methyl} \} \text{amino}\} \text{-2-propanol}

**1H NMR (300 MHz, CDCl\(_3\))**: \(δ\) 8.08 (1H, s, triazole-H), 7.75 (1H, s, triazole-H), 7.66–7.63 (1H, m, Ar-H), 7.53–7.15 (10H, m, Ar-H, triazole-H), 6.84–6.72 (2H, m, Ar-H), 5.59 (2H, s, Ar-CH\(_2\)), 4.58–4.35 (2H, m, CH\(_2\)), 3.72–3.41 (4H, m, -CH\(_2\)-N-CH\(_2\)-), 3.30–2.82 (2H, m, CH\(_2\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(δ\): 163.3, 158.5, 152.3, 142.3, 133.2, 131.3, 130.1, 130.0, 129.9, 129.8, 129.7, 129.6, 129.3, 128.9, 128.7, 127.5, 127.4, 126.3, 118.4, 113.3, 112.0, 104.5, 73.7, 61.5, 58.3, 56.3, 53.6, 50.2; ESI-MS, m/z calculated for C\(_{29}\)H\(_{26}\)F\(_2\)N\(_3\)O 560.2, found \([M+1]^+\) 561.4.

Compound 1n: \(1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-\{\text{N-benzyl-N-}[(1-\text{cyanobenzyl})-1H-1,2,3-triazol-2-yl] \text{methyl} \} \text{amino}\} \text{-2-propanol}

**1H NMR (300 MHz, CDCl\(_3\))**: \(δ\) 8.08 (1H, s, triazole-H), 7.75 (1H, s, triazole-H), 7.66–7.63 (1H, m, Ar-H), 7.53–7.15 (10H, m, Ar-H, triazole-H), 6.84–6.72 (2H, m, Ar-H), 5.59 (2H, s, Ar-CH\(_2\)), 4.58–4.35 (2H, m, CH\(_2\)), 3.72–3.41 (4H, m, -CH\(_2\)-N-CH\(_2\)-), 3.30–2.82 (2H, m, CH\(_2\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(δ\): 163.3, 158.5, 152.3, 142.3, 133.2, 131.3, 130.1, 130.0, 129.9, 129.8, 129.7, 129.6, 129.3, 128.9, 128.7, 127.5, 127.4, 126.3, 118.4, 113.3, 112.0, 104.5, 73.7, 61.5, 58.3, 56.3, 53.6, 50.2; ESI-MS, m/z calculated for C\(_{29}\)H\(_{26}\)F\(_2\)N\(_3\)O 560.2, found \([M+1]^+\) 561.4.

Compound 1p: \(1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-\{\text{N-benzyl-N-}[(1-\text{cyanobenzyl})-1H-1,2,3-triazol-4-yl]-\text{methyl} \} \text{amino} \} \text{-2-propanol}

**1H NMR (300 MHz, CDCl\(_3\))**: \(δ\) 8.08 (1H, s, triazole-H), 7.75 (1H, s, triazole-H), 7.66–7.63 (1H, m, Ar-H), 7.53–7.15 (10H, m, Ar-H, triazole-H), 6.84–6.72 (2H, m, Ar-H), 5.59 (2H, s, Ar-CH\(_2\)), 4.58–4.35 (2H, m, CH\(_2\)), 3.72–3.41 (4H, m, -CH\(_2\)-N-CH\(_2\)-), 3.30–2.82 (2H, m, CH\(_2\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(δ\): 163.3, 158.5, 152.3, 142.3, 133.2, 131.3, 130.1, 130.0, 129.9, 129.8, 129.7, 129.6, 129.3, 128.9, 128.7, 127.5, 127.4, 126.3, 118.4, 113.3, 112.0, 104.5, 73.7, 61.5, 58.3, 56.3, 53.6, 50.2; ESI-MS, m/z calculated for C\(_{29}\)H\(_{26}\)F\(_2\)N\(_3\)O 560.2, found \([M+1]^+\) 561.4.