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ORIGINAL ARTICLE

# Synthesis and biological evaluation of a series of 1,4-disubstituted 1,2,3-triazole derivatives as possible antimicrobial agents

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**Abstract** Three series of novel compounds derived from 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylic acid bearing piperazine carboxamides, (5-(substituted phenyl)-1,3,4-oxadiazol-2-yl) and (5-(alkylthio)-1,3,4-oxadiazol-2-yl) substitutions at the 4-position were synthesized. Synthesized compounds were characterized by $^{1}$H NMR, $^{13}$C NMR and mass spectral analysis and evaluated for their antimicrobial activities. Interestingly, most of the compounds exhibit moderate to good activities against tested Gram-positive, Gram-negative bacterial strains as well as fungal strains.


## 1. Introduction

1,2,3-Triazole is a well known important heterocycle both in synthetic as well as medicinal chemistry due to its simple synthesis via click chemistry approach and a wide range of biological activities. Simple copper catalyzed 1,3-dipolar cycloadditions of substituted azides and alkynes afford regioselective 1,4-disubstitued 1,2,3-triazoles with high yields. 1,2,3-Triazole with high dipole moment, considerable stability and capability for hydrogen bonding make it a favorable binder of biomolecular targets. 1,2,3-Triazole derivatives were reported to exhibit various biological activities such as antidiabetic [1], antitubercular [2,3], anti-inflammatory [4], antifungal [5–7], antiviral [8,9] and antibacterial [10,11]. Several drugs like carboxyamidotriazole, cefatrizine, and tazobactam bear 1,2,3-triazole in their structure. Moreover, Rufinamide, the amide of 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylic acid is an antiepileptic drug, which is used in the treatment of partial seizures and drop attacks associated with the Lennox–Gastaut syndrome [12].

Piperazines are considered as a useful and effective scaffold in drug design as they exhibit a wide range of biological activities such as FAAH and MAGL inhibitors [13], human histamine $H_4$ antagonist [14], and cannabinoid ligands [15]. Recently, piperazine bearing 1,2,3-triaozles are reported as potential anticancer, antiproliferative agents [16,17]. On the other hand, 1,3,4-oxadiazole is also a significant heterocycle that exhibit activities such as antimicrobial [18–23], anti-inflammatory, analgesic [24,25], antitubercular [26–28], anticonvulsant [29], antidiabetic [30] and anticancer [31]. In view of these findings and in continuation of our earlier attempts for the design and synthesis

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of novel azole containing heterocycles as possible antimicrobial and anti-inflammatory agents [32,33], we report herein the synthesis and antimicrobial evaluation of a series of piperazine carboxamide and 1,3,4-oxadiazole derivatives of 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylic acid as possible antimicrobial agents.

## 2. Experimental

### *2.1. Materials and measurements*

All chemicals used were of laboratory grade and used without further purification. Melting points of compounds were determined in open capillary tubes in a silicon oil bath using a Veego melting point apparatus and are uncorrected. Purity of compounds was monitored by TLC on silica $F_{254}$ coated aluminum plates (Merck) as adsorbent and U.V. light and iodine as visualizing agents. $^1$H and $^{13}$C NMR spectra were recorded on Varian mercury TH-300 operating at 300 MHz ($^1$H NMR) and 75 MHz ($^{13}$C NMR) using $CDCl_3$ and DMSO-$d_6$ as solvents and TMS as an internal standard (Chemical shift in ppm). The High Resolution Mass Spectra were recorded on Waters QT micro-mass analyzer.

### *2.2. Preparation methods*

#### *2.2.1. Synthesis of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid (**3**)*

Yield 85%, mp: 165–168 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 5.72 (s, 2H, Ar-$CH_2$), 7.14–7.21 (m, 2H, Ar-H), 7.49–7.54 (m, 1H, Ar-H), 8.74 (s, 1H, triazole-H), 13.40 (s, 1H, –COOH).

#### *2.2.2. General procedure for the synthesis of (1-(2,6-difluorobenzyl)-1H-1,2,3-triazol-4-yl)(4-substituted piperazin-1-yl)methanone (**4a–k**)*

To a cooled solution of 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylic acid (**3**) (1.0 mol) in DMF (10 mL) was added HOBt (1.1 mol) followed by corresponding piperazine (1.1 mol) TEA (2.1 mol) and EDC·HCl (1.1 mol). The reaction mixture was left overnight with stirring. The mixture was then poured onto crushed ice; the product was filtered and washed with water. The crude products (**4a–k**) were purified by column chromatography using hexane:EtOAc (9:1) as eluent.

*2.2.2.1. (1-(2,6-Difluorobenzyl)-1H-1,2,3-triazol-4-yl)(4-Bocpiperazin-1-yl)methanone (**4a**).* Yield 95%, mp: 168–169 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.47(s, 9H, –$C(CH_3)_3$), 3.51 (s, 4H, piperazine-H), 3.72 (t, 2H, piperazine-H), 4.27 (t, 2H, piperazine-H), 5.65 (s, 2H, Ar-$CH_2$), 6.99 (t, 2H, Ar-H), 7.35-7.45 (m, 1H, Ar-H), 8.11 (s, 1H, triazole-H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 28.3, 41.5, 42.5, 46.4, 80.2, 110.0, 111.7, 112.0, 128.3, 131.8, 144.4, 154.5, 159.7, 162.9.

*2.2.2.2. (1-(2,6-Difluorobenzyl)-1H-1,2,3-triazol-4-yl)(4-(2-methoxyphenyl)piperazin-1-yl) methanone (**4b**).* Yield 89%, mp: 121–122 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.11 (s, 4H, piperazine-H), 3.86 (s, 3H, –$OCH_3$), 3.93 (s, 2H, piperazine-H), 4.45 (s, 2H, piperazine-H), 5.62 (s, 2H, Ar-$CH_2$), 6.90–7.05 (m, 6H, Ar-H), 7.37–7.43 (m, 1H, Ar-H), 8.15 (s, 1H, triazole-H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 41.4, 42.8, 46.8, 50.7, 51.2, 55.4, 110.1, 111.2, 111.7, 112.0, 118.4, 121.0, 123.4, 128.2, 131.7, 140.7, 144.6, 152.2, 159.6, 163.0.

*2.2.2.3. (1-(2,6-Difluorobenzyl)-1H-1,2,3-triazol-4-yl)(4-(4-chlorophenyl)piperazin-1-yl)methanone (**4c**).* Yield 90%, mp: 149–151 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.20 (t, 4H, piperazine-H), 3.90 (t, 2H, piperazine-H), 4.45 (t, 2H, piperazine-H), 5.65 (s, 2H, Ar-$CH_2$), 6.84 (d, 2H, Ar-H), 6.98 (t, 2H, Ar-H), 7.21 (d, 2H, Ar-H), 7.34-7.43 (m, 1H, Ar-H), 8.11 (s, 1H, triazole-H); LC–MS $[M+H]^+$: 418.1179.

*2.2.2.4. (1-(2,6-Difluorobenzyl)-1H-1,2,3-triazol-4-yl)(4-p-tolylpiperazin-1-yl)methanone (**4d**).* Yield 95%, mp: 147–149 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.27 (s, 3H, –$CH_3$), 3.20 (s, 4H, piperazine-H), 3.92 (s, 2H, piperazine-H), 4.46 (s, 2H, piperazine-H), 5.66 (s, 2H, Ar-$CH_2$), 6.88 (s, 2H, Ar-H), 6.98 (t, 2H, Ar-H), 7.09 (d, 2H, Ar-H), 7.34–7.41 (m, 1H, Ar-H), 8.12 (s, 1H, triazole-H).

*2.2.2.5. (1-(2,6-Difluorobenzyl)-1H-1,2,3-triazol-4-yl)(4-(4-nitrophenyl)piperazin-1-yl)methanone (**4e**).* Yield 85%, mp: 170–172 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.52 (t, 4H, piperazine-H), 3.92 (t, 2H, piperazine-H), 4.51 (t, 2H, piperazine-H), 5.66 (s, 2H, Ar-$CH_2$), 6.83 (d, 2H, Ar-H), 6.99 (t, 2H, Ar-H), 7.34–7.44 (m, 1H, Ar-H), 8.14 (s, 1H, triazole-H), 8.15 (d, 2H, Ar-H); LC–MS $[M+H]^+$: 429.1465.

*2.2.2.6. (1-(2,6-Difluorobenzyl)-1H-1,2,3-triazol-4-yl)[4-(2-(trifluoromethyl)phenyl)piperazin-1-yl] methanone (**4f**).* Yield 89%, mp: 155–158 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.29 (t, 4H, piperazine-H), 3.92 (t, 2H, piperazine-H), 4.48 (t, 2H, piperazine-H), 5.65 (s, 2H, Ar-$CH_2$), 6.98 (t, 2H, Ar-H), 7.06–7.12 (m, 3H, Ar-H), 7.33–7.41 (m, 2H, Ar-H), 8.12 (s, 1H, triazole-H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 41.5, 42.4, 46.2, 48.9, 49.4, 110.1, 111.7, 112.0, 112.6, 116.5, 119.2, 122.3, 125.3, 128.3, 129.6, 131.7, 131.7, 144.4, 151.1, 159.6, 163.0; LC–MS $[M+H]^+$: 452.1576.

*2.2.2.7. (1-(2,6-Difluorobenzyl)-1H-1,2,3-triazol-4-yl)(4-(3,4-dichlorophenyl)piperazin-1-yl) methanone (**4g**).* Yield 92%, mp: 145–147 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.22 (t, 4H, piperazine-H), 3.89 (s, 2H, piperazine-H), 4.46 (s, 2H, piperazine-H), 5.65 (s, 2H, Ar-$CH_2$), 6.75 (dd, 1H, Ar-H), 6.96–7.01 (m, 2H, Ar-H), 7.27–7.30 (m, 2H, Ar-H), 7.36–7.41 (m, 1H, Ar-H), 8.12 (s, 1H, triazole-H); LC–MS $[M+H]^+$: 452.0840.

*2.2.2.8. (1-(2,6-Difluorobenzyl)-1H-1,2,3-triazol-4-yl)(4-benzylpiperazin-1-yl)methanone (**4h**).* Yield 87%, mp: 140–142 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.47–2.52 (m, 4H, piperazine-H), 3.52 (s, 2H, Ar-$CH_2$), 3.75 (t, 2H, piperazine-H), 4.27 (t, 2H, piperazine-H), 5.63 (s, 2H, Ar-$CH_2$), 6.97 (t, 2H, Ar-H), 7.28-7.40 (m, 7H, Ar-H), 8.07 (s, 1H, triazole-H).

*2.2.2.9. (1-(2,6-Difluorobenzyl)-1H-1,2,3-triazol-4-yl)(4-(4-chlorobenzyl)piperazin-1-yl)methanone (**4i**).* Yield 91%, mp: 165–168 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.43 (t, 4H, piperazine-H), 3.74 (s, 2H, piperazine-H), 4.23 (s, 2H, Ar-$CH_2$), 4.25 (s, 2H, piperazine-H), 5.61 (s, 2H, Ar-$CH_2$), 6.95 (t, 2H, Ar-H), 7.16–7.41 (m, 5H, Ar-H), 8.05 (s, 1H, triazole-H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 41.4, 42.7, 46.7, 51.5, 52.3, 75.1, 110.0, 111.8, 127.3, 127.8, 128.0, 128.7, 129.1, 131.7, 132.7, 140.7, 141.5, 144.6, 159.5, 163.0.