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Synthesis and antimicrobial activity of 2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)-N-phenylacetamide analogues

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Abstract: Regioselective synthesis of 2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)-N-phenylacetamide analogues **(7a-7j)** was carried out *via* click reaction of (prop-2-ynyloxy)benzene **(3a)**/ 1-chloro-4-(prop-2-ynyloxy)benzene **(3b)** with 2-azido-N-arylacetamides. The structures of synthesized triazoles were confirmed by using various analytical techniques like FT-IR, ^{1}H NMR, ^{13}C NMR and HRMS. The above synthesized amide-ether linked 1,4-disubstituted 1,2,3-triazoles **(7a-7j)** were assessed for *in vitro* antimicrobial potential against two Gram positive bacteria- *Bacillus subtilis*, *Staphylococcus aureus*, two Gram negative bacteria- *Escherichia coli*, *Pseudomonas aeruginosa*, and two fungal strains- *Candida albicans*, *Aspergillus niger*. Among synthesized molecules, compound **7d** displayed good antimicrobial efficacy against *S. aureus*, *C. albicans* and *A. niger*, while, compound **7i** exhibited good antibacterial potential against *S. aureus*.

Keywords: Click reaction, Disubstituted 1,2,3-triazoles, Antibacterial activity, Antifungal activity.

1. Introduction

Continuous increase in multi drug resistant microbes leads to hurdles in smooth treatment of infectious diseases in human beings caused by variety of pathogenic bacterial and fungal strains [1]. Despite of much progress in the medicinal chemistry, still, it remains a challenge for the synthetic chemists to design new broadly active molecules which can pose a tough fight to the drug resistant microorganisms [2]. 1,2,3-Triazoles are the moieties of keen interest for the researchers due to their good biocompatibility, aqueous solubility and capability to bind effectively with microbial proteins through hydrogen bonding [3]. Further, these compounds are also reported to have good biological spectrum [4] in terms of antiviral [5], bactericidal [6-7], fungicidal [8], micobactericidal [9], antiplasmodial [10], anticancer [11] and antihypertensive agents [12]. Overall, these features of substituted 1,2,3-triazoles add good flavour to explore their pharmacological actions in form of effective

antimicrobials.

Earlier, Huisgen's cycloaddition reaction between terminal alkynes and organic azides, at elevated temperature was employed for the preparation of disubstituted 1,2,3-triazoles [13]. The above process with limitation of poor selectivity in product formation, was independently improved by Sharpless [14] and Meldal [15] by using the fragrance of copper(I) catalyst in old classical Huisgen's method and resulting in the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles as sole product. This modified process is generally referred as one of the key click reaction in literature due to mind-blowing impact on researchers for good regioselectivity, simple reaction conditions and generation of non toxic by-products. Further, the click reaction have been also used for the synthesis [16-18] of various disubstituted 1,2,3-triazoles in the form of dendrimers [19], triazolophanes [20], peptides [21], nanotubes [22], liquid crystals [23], peptidomimetics [24] and ionic receptors [25].

So, keeping in view the above aspects and in continuation of our previous research work [26-33], here, we report the synthesis of 2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)-N-phenylacetamide analogues **(7a-7j)** through click reaction between (prop-2-ynyloxy) benzene **(3a)**/ 1-chloro-4-(prop-2-ynyloxy) benzene **(3b)** and 2-azido-*N*-arylacetamides. To the best of our knowledge, the amide-ether linked 1,4-disubstituted 1,2,3-triazoles synthesized in present case are unknown. The structural confirmation of synthesized triazoles was carried out by using spectroscopic techniques- FT-IR, ^{1}H NMR, ^{13}C NMR and HRMS. The synthesized triazoles were tested for *in-vitro* antimicrobial assay against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis*, *Candida albicans* and *Aspergillus niger*.

2. Materials and Methods

2.1 General

Chemicals used in the present research work were procured from Hi-Media, Sigma-Aldrich, CDH, Alfa-Aesar and Qualigens. The purification of solvents was carried out as per procedures reported in literature. Melting points of the synthesized compounds were determined by applying open capillary method using an electro-thermal apparatus, and are given in degree celsius. The progress of reactions and the purity of the products formed were checked by thin layer chromatography (TLC) using readymade silica gel plates, SIL G/UV$_{254}$, ALUGRAM, and examined under ultraviolet lamp. The structures of synthesized compounds were corroborated by using different spectral techniques- FT-IR, ^{1}H NMR, ^{13}C NMR and HRMS. The FT-IR spectra were scanned on Shimazdu IR Affinity-I FT-IR spectrophotometer in range of 400-4000 cm^{-1} using potassium bromide (KBr) powder. The NMR spectra were recorded at 400 (^{1}H NMR), and 100 (^{13}C NMR) MHz, respectively, on a commercial Bruker Avance II instrument, in deuterated dimethylsulphoxide-d_6 as solvent. The chemical shift value were noted in parts per million (δ ppm) using tetramethylsilane as an internal standard. The peak pattern is given as: *s* for singlet, *br s* for broad singlet, *d* for doublet, *m* for multiplet and coupling constant (*J*) values are given in Hertz (Hz). HRMS were recorded on Waters Micromass Q-Tof Micro (ESI) spectrophotometer.

2.2 Synthesis of (prop-2-ynyloxy)benzene (3a)/ 1-chloro-4-(prop-2-ynyloxy) benzene (3b):

A mixture of phenol **1a** (1.0 mmol)/ p-chlorophenol **1b** (1.0 mmol), propargyl bromide **2** (1.5 mmol) and potassium carbonate (3.0 mmol) in dry dimethylformamide, was stirred in round bottomed flask at 35-45 ºC for 5-8

h (Scheme 1) [34]. The progress of reaction was monitored by thin layer chromatography. After completion of reaction, the reaction mixture was neutralized by using 2N hydrochloric acid solution and the contents were further stirred for 5-10 minutes. The product was extracted with ethyl acetate (50 mL × 3) and the organic layer was washed with saturated brine solution. Then, the organic layer was dried using anhydrous sodium sulphate, filtered and finally evaporated to obtain required (prop-2-ynyloxy)benzene **(3a)**/ 1-chloro-4-(prop-2-ynyloxy)benzene **(3b)**, respectively.

2.3 Synthesis of 2-bromo-N-arylacetamides (6a-6e):

A solution of aromatic amines **4a-4e** (1.0 mmol) and triethylamine (3.0 mmol) in dry dichloromethane (15 ml) was taken in a round bottomed flask, and bromoacetyl bromide **5** (1.2 mmol) was added dropwise in the above solution in 10-15 minutes and the reaction mixture was stirred at 0-15 ºC for 4-6 h (Scheme 2) [35]. The progress of reaction was monitored by thin layer chromatography. After completion of reaction, 50 mL of dichloromethane was added to the reaction mixture, stirred the content and transferred into a separating funnel. The organic layer was washed with 2N hydrochloric acid, followed by saturated sodium bicarbonate solution and finally with brine solution. The organic layer was dried using anhydrous sodium sulphate, filtered and evaporated to obtain corresponding 2-bromo-N-arylacetamides **(6a-6e)**.

2.4 Synthesis of 2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)-N-phenylacetamide analogues (7a-7j):

For the synthesis of 2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)-N-phenylacetamide analogues, aqueous solution of sodium azide (3.0 mmol) was added to a stirred solution of 2-bromo-*N*-arylacetamides (1.0 mmol) **(6a-6e)** in dimethylformamide in round bottom flask. After one hour, (prop-2-ynyloxy)benzene **(3a)** (1.0 mmol)/ 1-chloro-4-(prop-2-ynyloxy) benzene **(3b)** (1.0 mmol), copper sulphate pentahydrate (0.1 mmol), sodium ascorbate (0.2 mmol) were added successively and the reaction contents were stirred at 55-60 ºC for 9-12 h (Scheme 3) [36]. The progress of reaction was monitored by thin layer chromatography. On completion of the reaction, cold water was added to the reaction mixture and filtered the precipitated solid. The solid product was washed with aqueous ammonia solution followed by washing with water. The crude products obtained above were purified by washing with ethyl acetate and dried under vacuum to get the desired target compounds **7a-7j**.

2.5 Characterization of the synthesized compounds

2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)-N-phenylacetamide (7a)

Appearance: white solid; Yield: 88%; m.p. 178-180 ºC; FTIR (KBr): 3265 (N-H str., amide), 3143 (C-H str., triazole ring), 3068, 2949, 1670 (C=O str., amide), 1598, 1548, 1483, 1249, 1045 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.18 (s, 2H, OCH_2), 5.36 (s, 2H, NCH_2), 6.97 (t, 1H, Ar-H, J = 8.0 Hz), 7.05-7.11 (m, 3H, Ar-H), 7.30-7.36 (m, 4H, Ar-H), 7.59 (d, 2H, Ar-H, J = 8.0 Hz), 8.27 (s, 1H, C-H triazole), 10.49 (s, 1H, N-H amide); ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.7, 61.3, 115.1, 119.7, 121.3, 124.3, 126.7 (C-5 triazole), 129.4, 130.0, 138.9, 143.0 (C-4 triazole), 158.5, 164.7 (C=O amide); HRMS m/z for $C_{17}H_{16}N_4O_2$: 308.9825 $[M+H]^+$.

N-(4-methoxyphenyl)-2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)acetamide (7b)

Appearance: white solid; Yield: 73%; m.p. 188-190 ºC; FTIR (KBr): 3275 (N-H str., amide), 3140 (C-H str., triazole ring), 3093, 2947, 1674 (C=O str., amide), 1598, 1550, 1506, 1246,

1043 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.73 (s, 3H, OCH_3), 5.17 (s, 2H, OCH_2), 5.33 (s, 2H, NCH_2), 6.91 (d, 2H, Ar-H, *J* = 8.0 Hz), 6.96 (t, 1H, Ar-H, *J* = 8.0 Hz), 7.06 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.31 (t, 2H, Ar-H, *J* = 8.0 Hz), 7.51 (d, 2H, Ar-H, *J* = 8.0 Hz), 8.26 (s, 1H, C-H triazole), 10.43 (s, 1H, N-H amide); ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.6, 55.6, 61.3, 114.5, 115.1, 121.2, 121.3, 126.7 (C-5 triazole), 130.0, 132.0, 143.0 (C-4 triazole), 156.0, 158.5, 164.1 (C=O amide); HRMS m/z for $C_{18}H_{18}N_4O_3$: 339.0030 $[M+H]^+$.

N-(4-bromophenyl)-2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)acetamide (7c)

Appearance: white solid; Yield: 68%; m.p. 210-212 ºC; FTIR (KBr): 3273 (N-H str., amide), 3128 (C-H str., triazole ring), 3057, 2922, 1683 (C=O str., amide), 1600, 1537, 1477, 1240, 1062 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.17 (s, 2H, OCH_2), 5.37 (s, 2H, NCH_2), 6.96 (t, 1H, Ar-H, *J* = 8.0 Hz), 7.06 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.31 (t, 2H, Ar-H, *J* = 8.0 Hz), 7.52-7.58 (m, 4H, Ar-H), 8.26 (s, 1H, C-H triazole), 10.63 (s, 1H, N-H amide); ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.7, 61.3, 115.1, 115.9, 121.3, 121.6, 126.7 (C-5 triazole), 130.0, 132.2, 138.2, 143.0 (C-4 triazole), 158.5, 164.9 (C=O amide); HRMS m/z for $C_{17}H_{15}BrN_4O_2$: 388.9021 $[M+2]^+$.

N-(4-nitrophenyl)-2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)acetamide (7d)

Appearance: white solid; Yield: 71%; m.p. 190-192 ºC; FTIR (KBr): 3259 (N-H str., amide), 3157 (C-H str., triazole ring), 3064, 2947, 1703 (C=O str., amide), 1624, 1577, 1506 (N-O str., asym., NO_2), 1469, 1344 (N-O str., sym., NO_2), 1238, 1062 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.18 (s, 2H, OCH_2), 5.46 (s, 2H, NCH_2), 6.96 (t, 1H, Ar-H, *J* = 8.0 Hz), 7.06 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.31 (t, 2H, Ar-H, *J* = 8.0 Hz), 7.84 (d, 2H, Ar-H, *J* = 8.0 Hz), 8.26 (d, 2H, Ar-H, *J* = 8.0 Hz), 8.28 (s, 1H, C-H triazole), 11.11 (s, 1H, N-H amide); ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.8, 61.3, 115.1, 119.5, 121.3, 125.6, 126.8 (C-5 triazole), 130.0, 143.1 (C-4 triazole), 145.0, 158.5, 165.8 (C=O amide); HRMS m/z for $C_{17}H_{15}N_5O_4$: 353.9808 $[M+H]^+$.

N-(naphthalen-1-yl)-2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)acetamide (7e)

Appearance: white solid; Yield: 75%; m.p. 204-206 ºC; FTIR (KBr): 3261 (N-H str., amide), 3147 (C-H str., triazole ring), 3062, 2943, 1664 (C=O str., amide), 1595, 1552, 1496, 1253, 1031 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.19 (s, 2H, OCH_2), 5.58 (s, 2H, NCH_2), 6.96 (t, 1H, Ar-H, *J* = 8.0 Hz), 7.07 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.32 (t, 2H, Ar-H, *J* = 8.0 Hz), 7.52-7.61 (m, 3H, Ar-H), 7.73-7.82 (m, 2H, Ar-H), 7.97 (d, 1H, Ar-H, *J* = 8.0 Hz), 8.18 (d, 1H, Ar-H, *J* = 8.0 Hz), 8.33 (s, 1H, C-H triazole), 10.48 (s, 1H, N-H amide); ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.6, 61.4, 115.1, 121.3, 122.0, 123.1, 126.1, 126.2, 126.5, 126.7 (C-5 triazole), 126.8, 128.0, 128.7, 130.0, 133.2, 134.2, 143.0 (C-4 triazole), 158.6, 165.6 (C=O amide); HRMS m/z for $C_{21}H_{18}N_4O_2$: 359.0233 $[M+H]^+$.

2-(4-((4-chlorophenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-N-phenylacetamide (7f)

Appearance: white solid; Yield: 76%; m.p. 196-198 ºC; FTIR (KBr): 3267 (N-H str., amide), 3145 (C-H str., triazole ring), 3078, 2947, 1670 (C=O str., amide), 1602, 1550, 1494, 1249, 1099, 1006 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.18 (s, 2H, OCH_2), 5.36 (s, 2H, NCH_2), 7.08-7.11 (m, 3H, Ar-H), 7.32-7.36 (m, 4H, Ar-H), 7.59 (d, 2H, Ar-H, *J* = 8.0 Hz), 8.27 (s, 1H, C-H triazole), 10.49 (s, 1H, N-H amide); ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.7, 61.7, 116.9, 119.7, 124.3, 125.0, 126.9 (C-5 triazole), 129.4, 129.7, 138.9, 142.6 (C-4 triazole), 157.4, 164.6 (C=O amide); HRMS m/z for $C_{17}H_{15}ClN_4O_2$: 342.9275 $[M+H]^+$.

2-(4-((4-chlorophenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-N-(4-methoxyphenyl)acetamide (7g)

Appearance: white solid; Yield: 73%; m.p. 202-

204 ºC; FTIR (KBr): 3265 (N-H str., amide), 3136 (C-H str., triazole ring), 3088, 2943, 1680 (C=O str., amide), 1602, 1500, 1485, 1456, 1240, 1103, 1026 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.72 (s, 3H, OCH_3), 5.18 (s, 2H, OCH_2), 5.32 (s, 2H, NCH_2), 6.91 (d, 2H, Ar-H, J = 8.0 Hz), 7.09 (d, 2H, Ar-H, J = 8.0 Hz), 7.35 (d, 2H, Ar-H, J = 8.0 Hz), 7.50 (d, 2H, Ar-H, J = 8.0 Hz), 8.26 (s, 1H, C-H triazole), 10.36 (s, 1H, N-H amide); ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.6, 55.6, 61.7, 114.5, 116.9, 121.2, 126.8 (C-5 triazole), 129.7, 132.0, 142.6 (C-4 triazole), 156.0, 157.4, 164.1 (C=O amide); HRMS m/z for $C_{18}H_{17}ClN_4O_3$: 372.9218 $[M+H]^+$.

N-(4-bromophenyl)-2-(4-((4-chlorophenoxy) methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (7h)
Appearance: white solid; Yield: 70%; m.p. 216-218 ºC; FTIR (KBr): 3253 (N-H str., amide), 3140 (C-H str., triazole ring), 3059, 2949, 1670 (C=O str., amide), 1593, 1544, 1492, 1240, 1101, 1006 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.18 (s, 2H, OCH_2), 5.37 (s, 2H, NCH_2), 7.09 (d, 2H, Ar-H, J = 8.0 Hz), 7.35 (d, 2H, Ar-H, J = 8.0 Hz), 7.52 (d, 2H, Ar-H, J = 8.0 Hz), 7.56 (d, 2H, Ar-H, J = 8.0 Hz), 8.27 (s, 1H, C-H triazole), 10.64 (s, 1H, N-H amide); ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.7, 61.7, 115.9, 116.9, 121.6, 125.0, 126.9 (C-5 triazole), 129.7, 132.2, 138.2, 142.7 (C-4 triazole), 157.4, 164.9 (C=O amide); HRMS m/z for $C_{17}H_{14}BrClN_4O_2$: 422.8661 $[M+2]^+$.

2-(4-((4-chlorophenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-N-(4-nitrophenyl)acetamide (7i)
Appearance: light brown solid; Yield: 76%; m.p. 206-208 ºC; FTIR (KBr): 3228 (N-H str., amide), 3155 (C-H str., triazole ring), 3097, 2956, 1695 (C=O str., amide), 1618, 1571, 1506 (N-O str., asym., NO_2), 1462, 1340 (N-O str., sym., NO_2), 1240, 1111, 1010 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.19 (s, 2H, OCH_2), 5.45 (s, 2H, NCH_2), 7.09 (d, 2H, Ar-H, J = 8.0 Hz), 7.35 (d, 2H, Ar-H, J = 8.0 Hz), 7.83 (d, 2H, Ar-H, J = 8.0 Hz), 8.26 (d, 2H, Ar-H, J = 8.0 Hz), 8.28 (s, 1H, C-H triazole), 11.11 (s, 1H, N-H amide); ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.8, 61.7, 117.0, 119.5, 125.0, 125.6,_126.9 (C-5 triazole), 129.7, 143.1 (C-4 triazole), 145.0, 157.4, 165.8 (C=O amide); HRMS m/z for $C_{17}H_{14}ClN_5O_4$: 387.8985 $[M+H]^+$.

2-(4-((4-chlorophenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-N-(naphthalen-1-yl)acetamide (7j)
Appearance: white solid; Yield: 78%; m.p. 202-204 ºC; FTIR (KBr): 3265 (N-H str., amide), 3140 (C-H str., triazole ring), 3064, 2974, 1666 (C=O str., amide), 1589, 1552, 1463, 1219, 1103, 1004 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.19 (s, 2H, OCH_2), 5.57 (s, 2H, NCH_2), 7.10 (d, 2H, Ar-H, J = 8.0 Hz), 7.35 (d, 2H, Ar-H, J = 8.0 Hz), 7.51-7.61 (m, 3H, Ar-H), 7.72 (d, 1H, Ar-H, J = 8.0 Hz), 7.81 (d, 1H, Ar-H, J = 8.0 Hz), 7.97 (d, 1H, Ar-H, J = 8.0 Hz), 8.17 (d, 1H, Ar-H, J = 8.0 Hz), 8.32 (s, 1H, C-H triazole), 10.46 (s, 1H, N-H amide); ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.6, 61.8, 117.0, 122.0, 123.1, 125.0, 126.1, 126.2, 126.5, 126.7 (C-5 triazole), 126.9, 128.0, 128.7, 129.7, 133.2, 134.2, 142.7 (C-4 triazole), 157.4, 165.6 (C=O amide); HRMS m/z for $C_{21}H_{17}ClN_4O_2$: 392.9634 $[M+H]^+$.

2.6 Antibacterial activity

The synthesized 2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)-N-phenylacetamide analogues **7a-7j** were assayed for *in-vitro* antibacterial activity against two Gram-positive bacteria *i.e. Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 7443) and two Gram-negative bacteria *i.e. Pseudomonas aeruginosa* (MTCC 424), *Escherichia coli* (MTCC 1652) by serial dilution method [37] using stock solutions of 400 and 2000 µg/mL. Double strength nutrient broth was used as a culture media and dimethylsulphoxide as solvent control. 1.0 mL nutrient broth was added in each of nine test tubes for study. To the first test-tube

1.0 mL solution of test compound (2000 µg/mL) was added to get the concentration of 1000 µg/mL. From this concentration, other dilutions were prepared by serial dilution procedure to get final concentrations of 500 µg/mL and 250 µg/mL. From second stock solution, 1.0 mL solution of test compound (400 µg/mL) was taken in fourth test tube, to get the concentration of 200 µg/mL. From the above solution, other concentrations i.e. 100 µg/mL, 50 µg/mL, 25 µg/mL, 12.5 and 6.25 µg/mL were prepared by serial dilution method. All the test tubes were inoculated aseptically by 0.1 mL of desired bacterial strain. The test samples containing microorganisms were then incubated at 37±1 °C for 24 h (*Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*) and 48 h (*Escherichia coli*) in BOD incubator and the results were recorded in minimum inhibitory concentrations (MIC) given in µmol/mL as reflacted in Table 1. Ciprofloxacin was used as standard drug.

2.7 Antifungal activity

Antifungal activity assay of synthesized compounds **7a-7j** was evaluated against two fungal strains *i.e. Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 1344) by serial dilution technique [37]. Stock solutions of 2000 and 400 µg/mL concentrations of test compounds were prepared in dimethylsulphoxide. Sabouraud dextrose broth played the role of fungal culture media. One mL of sterile culture media was added aseptically in each test tube followed by serial dilution with synthesized triazoles to get concentrations of 1000-6.25 µg/mL concentrations, same as followed in antibacterial study. Afterwards, the dilutions were inoculated with 0.1 mL of respective microorganism. The samples containing microorganisms were incubated at 25±1 °C for two and seven days in case of *Candida albicans* and *Aspergillus niger*, respectively. Fluconazole was used as a standard drug. Antifungal activity results are presented in minimum inhibitory concentration (MIC) in µmol/mL as highlighted in Table 2**.**

3. Results and Discussion

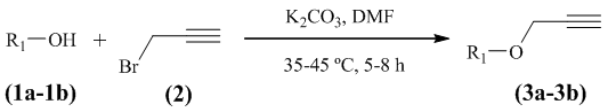
3.1 Chemistry

2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)-N-phenylacetamide analogues **(7a-7j)** were synthesized [36] *via* click reaction of (prop-2-ynyloxy)benzene **(3a)**/ 1-chloro-4-(prop-2-ynyloxy)benzene **(3b)** with 2-azido-*N*-arylacetamides (Scheme 3). 2-Azido-*N*-arylacetamides were prepared *in situ* by reacting aqueous sodium azide with corresponding 2-bromo-*N*-arylacetamides **(6a-6e)**.

(Prop-2-ynyloxy)benzene **(3a)** and 1-chloro-4-(prop-2-ynyloxy)benzene **(3b)** were synthesized [34] by reacting propargylbromide **(2)** with phenol **(1a)** and p-chloro-phenol **(1b)**, respectively, using potassium carbonate in dimethylformamide (Scheme 1).

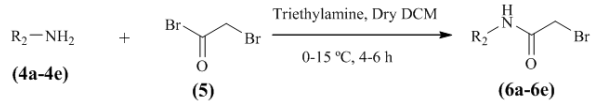
2-Bromo-*N*-arylacetamides **(6a-6e)** were synthesized [35] by treating various aromatic amines **(4a-4e)** with bromoacetylbromide **(5)** in dry dichloromethane, with triethylamine as base (Scheme 2).

Finally, the terminal alkynes *i.e.* (prop-2-ynyloxy)benzene **(3a)** and 1-chloro-4-(prop-2-ynyloxy)benzene **(3b)** were reacted with 2-bromo-*N*-substituted acetamides **(6a-6e)** using sodium azide, copper sulphate pentahydrate and sodium ascorbate in dimethylformamide-water to obtain required amide-ether linked 1,4-disubstituted 1,2,3-triazoles i.e. 2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)-N-phenylacetamide analogues, **7a-7e** and **7f-7j**, respectively, in the present case (Scheme 3).



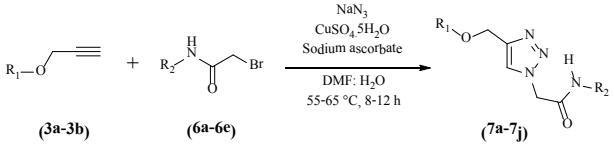
Compound	R_1
1a; 3a	C_6H_5
1b; 3b	4-ClC_6H_4

Scheme 1 Synthesis of (prop-2-ynyloxy) benzene **(3a)**/ 1-chloro-4-(prop-2-ynyloxy) benzene **(3b)**



Compound	R_2
4a; 6a	C_6H_5
4b; 6b	4-$CH_3OC_6H_4$
4c; 6c	4-BrC_6H_4
4d; 6d	4-$NO_2C_6H_4$
4e; 6e	α-$C_{10}H_7$ (α-Naphthyl)

Scheme 2 Synthesis of 2-bromo-*N*-arylacetamides **(6a-6e)**



Compound	R_1	R_2
7a	C_6H_5	C_6H_5
7b	C_6H_5	4-$CH_3OC_6H_4$
7c	C_6H_5	4-BrC_6H_4
7d	C_6H_5	4-$NO_2C_6H_4$
7e	C_6H_5	α-$C_{10}H_7$
7f	4-ClC_6H_4	C_6H_5
7g	4-ClC_6H_4	4-$CH_3OC_6H_4$
7h	4-ClC_6H_4	4-BrC_6H_4
7i	4-ClC_6H_4	4-$NO_2C_6H_4$
7j	4-ClC_6H_4	α-$C_{10}H_7$

Scheme 3 Synthesis of amide-ether linked 1,4-disubstituted 1,2,3-triazoles **(7a-7j)**

The synthesized 1,2,3-triazoles **(7a-7j)** were characterized by spectroscopic techniques like FTIR, ^{1}H NMR, ^{13}C NMR and high resolution mass spectrometry. In the FTIR spectra of the compound 2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)-N-phenylacetamide **(7a)**, a sharp absorption band appeared at 3265 cm^{-1} was due to N-H stretching vibrations of amide linkage, while, absorption band appeared at 3143 cm^{-1} was attributed to C-H stretching vibration of triazole ring. The C=O stretching vibrations of amide bond appeared at 1670 cm^{-1}. Presence of absorption bands in the region 1598-1483 cm^{-1} were appeared due to C=C stretching vibrations of aromatic rings.

The ^{1}H NMR spectrum of compound **7a**, displayed one singlet at δ 10.49 due to NH proton of amide functionality, whereas, signal due to triazolyl proton was appeared on δ 8.27. Two characteristic singlets appeared at δ 5.18 and δ 5.36 each integrating two protons were assigned to methylene groups attached to C-4 and N-1 of the triazole ring. A doublet displayed at δ 7.59 having coupling constant value of 8.0 Hz, was attributed to two aromatic protons attached to ortho position of anilide ring, while, the remaining eight aromatic protons of the molecule appeared in the region at δ 6.96-7.36 as multiplets.

In ^{13}C NMR spectrum of compound **7a**, signals due to C-4 and C-5 of the triazole moiety appeared at δ 143.0 and δ 126.7, respectively. The peak due to C=O amide was resonated at δ 164.7. The signals at δ 52.7 and δ 61.3 were assigned to two methylene carbon atoms attached to N-1 and C-4 of triazole ring, respectively. Aromatic carbon of phenoxy ring attached to oxygen of ether functionality was resonated at δ 158.5, while, aromatic carbon of anilide ring attached to nitrogen of amide functionality was displayed at δ 138.9, respectively.

The high resolution mass spectrum of the

compound **7a**, exhibited peak at *m/z* 308.9825 attributed to $[M+H]^+$ ions, which is in good agreement with calculated value.

Likewise, structures of remaining triazoles were also confirmed by spectroscopic techniques (FTIR, ^{1}H NMR, ^{13}C NMR and HRMS). The formation of compounds was confirmed by the presence of absorption bands in the region at 3275-3228 (N-H str., amide), 3157-3128 (C-H str., triazole ring) and 1703-1664 (C=O str., amide) cm^{-1} in FT-IR spectra. The presence of characteristic singlet in the region δ 5.17-5.19 (OCH_2), 5.32-5.58 (NCH_2), 8.26-8.33 (C-H triazole), 10.36-11.11 (N-H amide) ppm in ^{1}H NMR spectra, while, the peaks in ^{13}C NMR spectra at δ 52.6-52.8 (NCH_2), 61.3-61.8 (OCH_2), 126.7-126.9 (C-5 triazole ring), 142.6-143.1 (C-4 triazole ring), 164.1-165.8 (C=O amide) ppm also confirmed the formation of target compounds. The results obtained from high resolution mass spectral analysis were found to agree with their predicted values.

3.2 Antibacterial activity

The amide-ether linked 1,4-disubstituted 1,2,3-triazoles **7a-7j** were tested for antibacterial activity against four bacterial strains- *B. subtilis* (MTCC 441), *E. coli* (MTCC 1652), *S. aureus* (MTCC 7443), *P. aeruginosa* (MTCC 424) by using serial dilution method [37]. Ciprofloxacin was used as reference drug. The minimum inhibitory concentrations (MICs) are represented in µmol/mL as depicted in Table 1.

The inspection of antibacterial activity data revealed that the synthesized compounds displayed average to good activity against tested bacterial strains. Compound **7d** and **7i** exhibited good antibacterial potential against *S. aureus*, while, remaining compounds exhibited average antibacterial activity against tested bacterial strains.

3.3 Antifungal activity

Synthesized amide-ether linked 1,4-disubstituted 1,2,3-triazoles **7a-7j** were examined for antifungal assay against two fungal strains- *C. albicans* (MTCC 227), *A. niger* (MTCC 1344) by using serial dilution technique [37]. Fluconazole was used as reference drug. The results were recorded in terms of MIC in µmol/mL as shown in Table 2.

Table 1 Antibacterial assay of amide-ether linked 1,4-disubstituted 1,2,3-triazoles **7a-7j** (MIC in µmol/mL)

	Gram-positive bacteria		Gram-negative bacteria	
Compound	*Bacillus subtilis* (MTCC 441)	*Staphylococcus aureus* (MTCC 7443)	*Pseudomonas aeruginosa* (MTCC 424)	*Escherichia coli* (MTCC 1652)
7a	0.3243	0.6487	0.6487	0.8108
7b	0.5911	0.5911	0.5911	1.4777
7c	0.5165	0.6456	0.5165	0.6456
7d	0.1415	0.2830	0.1415	0.2830
7e	0.2790	0.5581	0.2790	1.3951
7f	0.7293	0.5835	0.5835	0.5835
7g	0.5365	0.6706	0.6706	1.3412
7h	1.1857	0.5929	0.5929	0.5929
7i	0.1289	0.2579	0.5158	0.2579
7j	0.5091	1.2728	1.2728	0.2546
Ciprofloxacin	0.0377	0.1509	0.0377	0.0754

Table 2 Antifungal assay of amide-ether linked of 1,4-disubstituted 1,2,3-triazoles **7a-7j** (MIC in µmol/mL)

Compound	*Candida albicans* (MTCC 227)	*Aspergillus niger* (MTCC 1344)
7a	0.1622	0.1622
7b	0.5911	0.5911
7c	0.5165	0.6456
7d	0.0708	0.0708
7e	0.6976	0.6976
7f	0.1459	0.1459
7g	0.5365	0.6706
7h	0.5929	1.1857
7i	0.2579	0.1289
7j	1.2728	1.2728
Fluconazole	0.0408	0.0816

The antifungal activity data revealed that the synthesized triazoles exhibited average to good activity against tested fungal strains. Compound **7d** appeared as good antifungal agent against both tested fungal strains, while, remaining compounds displayed average antifungal activity.

From the above results, it was observed that the presence of nitro group at p-position of anilide ring improved the antimicrobial potency against *S. aureus*, *C. albicans* and *A. niger*.

Conclusion

In the present case, regioselective synthesis of 2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)-N-phenylacetamide analogues **(7a-7j)** was carried out through click reaction of (prop-2-ynyloxy)benzene **(3a)**/ 1-chloro-4-(prop-2-ynyloxy)benzene **(3b)** with 2-azido-*N*-arylacetamides. The synthesized compounds were examined for antimicrobial assay against *B. subtilis*, *P. aeruginosa*, *E. coli*, *S. aureus*, *C. albicans* and *A. niger*. Compound **7d** appeared as good antimicrobial agent against *S. aureus, C. albicans* and *A. niger*, while, compound **7i** displayed good antibacterial potential against *S. aureus*. Remaining compounds exhibited average antimicrobial activity against tested microbial strains.

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