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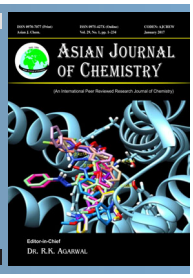

Synthesis and Microbicidal Activity of Substituted 1,2,3-Triazoles having Amide and Hydroxy Functionality

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A series of 1,4-disubstituted 1,2,3-triazoles was designed and synthesized from hydroxy terminal alkynes and 2-azido-*N*-substituted *N*-phenylpropanamides. All the synthesized substituted triazoles were characterized by spectral techniques (FT-IR, ^{1}H NMR, ^{13}C NMR, HRMS) and explored for *in vitro* antimicrobial activity against three Gram-negative bacteria *Escherichia coli*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*; one Gram-positive bacteria *Staphylococcus aureus* and two fungal strains *Candida albicans* and *Aspergillus niger*. The bioactive assay of synthesized triazoles reflected moderate to good antibacterial and antifungal efficacy.

Keywords: Click chemistry, Substituted 1,2,3-triazoles, Microbicidal activity.

INTRODUCTION

An antimicrobial is an agent that kills microorganisms or inhibits their growth. The search for new molecules with broad spectrum of antimicrobial properties is challenging task to researchers. In view of continuous enhancement of microbial infection in society, the triazole ring system possess appreciable biocompatibility and can play a pivotal role in designing new potent antimicrobials. Triazole moieties are found to show antimalarial [1,2], antioxidant [3], antitrypanosomal [4], anti-inflammatory [5,6], antibacterial [7-9], antifungal [10-12], antiproliferative [13], antiprotozoal [14], antituberculosis [15,16] and anticancer [17,18]. Further, 1,4-disubstituted 1,2,3-triazoles serve as effective bioactive molecule being stable to reaction conditions *i.e.*, oxidation, reduction, hydrolysis and participate in hydrogen bonding with biological system.

The dipolar [3+2] cycloaddition of organic azides and terminal alkynes is the usual method for the synthesis of 1,2,3-triazoles. This reaction was comprehensively studied by Huisgen and Padwa [19] yielding 1,4 and 1,5-disubstituted 1,2,3-triazoles variant of substituted 1,2,3-triazole. Later, Sharpless *et al.* [20] and Meldal [21] developed Cu(I) catalyzed azide-alkyne cycloaddition (CuAAC) through "Click Chemistry" concept results into formation of 1,4-disubstituted 1,2,3-triazoles.The "Click Chemistry" projected cycloaddition reactions are prime important due to its several advantages in form of regioselectivity, wide substrate scope, mild reaction conditions and excellent yields.

Here, we sought to synthesize 1,4-disubstituted 1,2,3-triazoles having amide and hydroxy functionality from the reaction of terminal alkynes and 2-azido-*N*-substituted *N*-phenylpropanamides (generated *in situ* from reaction of 2-bromo-*N*-substituted-*N*-phenylpropanamides and sodium azide). The synthesized triazoles were characterized by various spectroscopic techniques *viz.*, FT-IR, ^{1}H NMR, ^{13}C NMR, HRMS and evaluated for microbicidal activity against *Escherichia coli*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus niger.*

EXPERIMENTAL

All the chemicals and solvents were purchased from Sigma-Aldrich, Alfa Aesar and Hi-Media. The reactions were monitored by thin layer chromatography using *n*-hexane, ethyl acetate and chloroform in different ratios as mobile phase. The melting points of synthesized compounds were recorded in °C by applying an open capillary method and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 MHz at 400 MHz and 100 MHz, respectively, using DMSO as solvents. Chemical shift values are recorded on δ scale and the coupling constants (*J*) in Hertz. HRMS were obtained using a Waters Micromass Q-T of Micro (ESI) spectrophotometer and values were recorded in *m/z*. The IR spectra were recorded on Shimadzu IR affinity-I FTIR spectrophotometer using KBr powder.

General procedure for the synthesis of 1,4-disubstituted 1,2,3-triazoles: A solution of aromatic amines (**1a-1c**) (1.0

mmol) in dichloromethane was taken in round bottom flask with potassium carbonate (1.5 mmol) as base and drop-wise addition of 2-bromopropanoyl bromide (1.2 mmol) was carried out at 0-5 °C and strirred the contents for 15-20 min. After the completion of reaction, ice cold water was added to the reaction mixture, the resulting solid, 2-bromo-*N*-substituted *N*-phenyl-propanamide (**3a**-**3c**) was filtered and dried.

For the synthesis of target compounds **5a**-**5i**, the starting reactant 2-bromo-*N*-substituted propanamide (**3a**-**3c**) was stirred with aqueous sodium azide (3.0 mmol) in dimethyl formamide for 30 min at 35-50 °C in round bottom flask. In above mixture terminal hydroxyalkyne (**4a**-**4c**), aqueous $CuSO_4 \cdot 5H_2O$ (0.1 mmol) and sodium ascorbate (0.4 mmol) were added and stirring was continued for 8-10 h at same temperature. After the completion of reaction, ice cold water was added to the reaction mixture, then filtered the precipitated solid, washed with aqueous ammonia solution followed by water. The solid product was recrystallized with ethyl acetate to get pure product (**5a**-**5i**).

2-[4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]-*N*-methyl-*N*-phenylpropanamide (5a): White solid; Yield: 86 %; m.p. 94-96 °C; IR (KBr, ν_{max}, cm^{-1}): 3380 (O-H str.), 3140 (C-H str. triazole), 3058 (C-H str. aromatic ring), 2954 (C-H str., aliphatic), 1662 (C=O str. amide), 1554, 1454 (C=C str., aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (s, 1H, C-H triazole), 7.56-7.33 (m, 5H, Ar-H), 5.53 (q, 1H, *J* = 7.2 Hz), 5.22 (s, 1H), 4.55 (s, 2H, OCH_2, *J* = 8 Hz), 2.95 (s, 3H), 1.54 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.0 (C=O), 148.1 (C_4 triazole), 141.0, 130.5, 129.0, 128.9, 122.3 (C_5 triazole), 55.7, 55.5, 38.3, 18.0; HRMS (*m/z*) calculated for $C_{14}H_{16}N_4O_2$ $[M+H]^+$: 261.1273. Found: 261.1343.

***N*-Ethyl-2-[4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]-*N*-phenylpropanamide (5b):** White solid; Yield: 86 %; m.p. 76-78 °C; IR (KBr, ν_{max}, cm^{-1}): 3378 (O-H str.), 3142 (C-H str. triazole), 3058 (C-H str. aromatic ring), 2954 (C-H str., aliphatic), 1666 (C=O str. amide), 1554, 1510, 1454 (C=C str., aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (s, 1H, C-H triazole), 7.56-7.33 (m, 5H, Ar-H), 5.23-5.16 (m, 2H), 4.49 (d, 2H, OCH_2, *J* = 8 Hz), 3.70 (q, 2H, *J* = 6.4 Hz), 1.54 (d, 3H, *J* = 8 Hz), 1.02 (t, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.0 (C=O), 148.1 (C_4 triazole), 141.0, 130.5, 129.0, 128.8, 122.3 (C_5 triazole), 55.7, 55.5, 44.6, 18.3, 12.9; HRMS (*m/z*) calculated for $C_{14}H_{18}N_4O_2$ $[M+H]^+$: 275.1430. Found: 275.1503.

2-[4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]-*N*,*N*-diphenylpropanamide (5c): White solid; Yield: 93 %; m.p. 152-154 °C; IR (KBr, ν_{max}, cm^{-1}): 3383 (O-H str.), 3172 (C-H str. triazole), 3061 (C-H str. aromatic ring), 2968 (C-H str., aliphatic), 1676 (C=O str. amide), 1593, 1454 (C=C str., aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.97 (s, 1H, C-H triazole), 7.42 (brs, 10H, Ar-H), 5.48 (q, 1H, *J* = 7.2 Hz), 5.19 (t, 1H, *J* = 5.6 Hz), 4.51 (d, 2H, OCH_2, *J* = 5.6 Hz), 1.67 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.9 (C=O), 148.2 (C_4 triazole), 130.7, 129.6, 129.1, 127.3, 122.4 (C_5 triazole), 56.2, 55.5, 18.3; HRMS (*m/z*) calcu-lated for $C_{18}H_{18}N_4O_2$ $[M+H]^+$: 323.1430. Found: 323.1501.

2-[4-(2-Hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl]-*N*-methyl-*N*-phenylpropanamide (5d): White solid; Yield: 84 %; m.p. 130-134 °C; IR (KBr, ν_{max}, cm^{-1}): 3380 (O-H str.), 3148 (C-H str. triazole), 3064 (C-H str. aromatic ring), 2980 (C-H str., aliphatic), 1663 (C=O str. amide), 1542, 1463 (C=C str., aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.81 (s, 1H, C-H triazole), 7.53-7.38 (m, 5H, Ar-H), 5.47 (q, 1H, *J* = 7.2 Hz), 5.10 (s, 1H, OH), 2.95 (s, 3H), 1.54 (d, 3H, *J* = 7.2 Hz), 1.48 (s, 6H): ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.4 (C=O), 155.9 (C_4 triazole), 142.8, 130.8, 128.8, 127.8, 119.7 (C_5 triazole), 67.8, 55.3, 38.0, 31.1, 18.5; HRMS (*m/z*) calculated for $C_{16}H_{20}N_4O_2$ $[M+H]^+$: 289.1586. Found: 289.1661.

***N*-Ethyl-2-[4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl]-*N*-phenylpropanamide (5e):** White solid; Yield: 85 %; m.p. 142-144 °C; IR (KBr, ν_{max}, cm^{-1}): 3384 (O-H str.), 3140 (C-H str. triazole), 3070 (C-H str. aromatic ring), 2980 (C-H str., aliphatic), 1658 (C=O str. amide), 1543, 1463 (C=C str., aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80 (s, 1H, C-H triazole), 7.53-7.38 (m, 5H, Ar-H), 5.27 (q, 1H, *J* = 8 Hz), 5.08 (s, 1H, OH), 3.19 (q, 2H, *J* = 8 Hz), 1.54 (d, 3H, *J* = 8 Hz), 1.48 (s, 6H), 1.01 (t, 3H, *J* = 8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.4 (C=O), 155.9 (C_4 triazole), 142.8, 130.5, 128.8, 127.8, 119.9 (C_5 triazole), 67.5, 55.3, 38.0, 31.1, 18.5, 12.9; HRMS (*m/z*) calculated for $C_{16}H_{22}N_4O_2$ $[M+H]^+$: 303.1403. Found: 303.1461.

2-[4-(2-Hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl]-*N*,*N*-diphenylpropanamide (5f): White solid; Yield: 78 %; m.p. 116-118 °C; IR (KBr, ν_{max}, cm^{-1}): 3390 (O-H str.), 3163 (C-H str. triazole), 3043 (C-H str. aromatic ring), 2978 (C-H str., aliphatic), 1676 (C=O str. amide), 1593, 1452 (C=C str., aromatic ring); 1H NMR (400 MHz, DMSO-d_6): δ 7.80 (s, 1H, C-H triazole), 7.43 (brs, 10H, Ar-H), 5.47 (q, 1H, *J* = 7.2 Hz), 5.09 (s, 1H), 1.65 (d, 3H, *J* = 7.2 Hz), 1.47 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.8 (C=O), 156.0 (C_4 triazole), 128.8, 127.3, 120.1 (C_5 triazole), 67.5, 56.2, 31.3, 18.5; HRMS (*m/z*) calculated for $C_{20}H_{22}N_4O_2$[M+H]$^+$: 351.1743. Found: 351.1813.

2-[4-(2-Hydroxybutan-2-yl)-1*H*-1,2,3-triazol-1-yl]-*N*-methyl-*N*-phenylpropanamide (5g): White solid; Yield: 90 %; m.p. 66-68 °C; IR (KBr, $\nu_{m\text{-}ax}$, cm^{-1}): 3378 (O-H str.), 3140 (C-H str. triazole), 3057 (C-H str. aromatic ring), 2978 (C-H str., aliphatic), 1665 (C=O str. amide), 1593, 1454 (C=C str., aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.77 (s, 1H, C-H triazole), 7.52-7.34 (m, 5H, Ar-H), 5.47 (q, 1H, *J* = 6.8 Hz), 5.10 (s, 1H, OH), 2.95 (s, 3H), 1.71 (t, 2H, *J* = 7.6 Hz), 1.54-1.40 (m, 6H), 0.74 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.9 (C=O), 155.0 (C_4 triazole), 141.0, 130.5, 129.0, 128.8, 120.6 (C_5 triazole), 70.2, 55.6, 44.5, 37.6, 35.9, 28.6, 18.1, 8.8; HRMS (*m/z*) calculated for $C_{17}H_{22}N_4O_2$ $[M+H]^+$: 303.1743. Found: 303.1874.

***N*-Ethyl-2-[4-(2-hydroxybutan-2-yl)-1*H*-1,2,3-triazol-1-yl]-*N*-phenylpropanamide (5h):** White solid; Yield: 90 %; m.p. 68-70 °C; IR (KBr, $\nu_{m\text{-}ax}$, cm^{-1}): 3380 (O-H str.), 3140 (C-H str. triazole), 3057 (C-H str. aromatic ring), 2978 (C-H str., aliphatic), 1662 (C=O str. amide), 1593, 1454 (C=C str., aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.76 (s, 1H, C-H triazole), 7.51-7.34 (m, 5H, Ar-H), 5.19 (q, 1H, *J* = 6.8 Hz), 4.93 (s, 1H, OH), 3.67 (q, 2H, *J* = 6.4 Hz), 1.73-1.40 (m, 6H), 1.01 (t, 3H, *J* = 6.4 Hz), 0.74 (t, 3H, *J* = 8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.9 (C=O), 155.0 (C_4

triazole), 141.0, 130.5, 129.0, 128.8, 120.6 (C_5 triazole), 70.2, 55.6, 44.5, 35.9, 28.6, 18.5, 12.9, 8.8; HRMS (*m/z*) calculated for $C_{17}H_{24}N_4O_2$ $[M+H]^+$: 317.1899. Found: 317.1970.

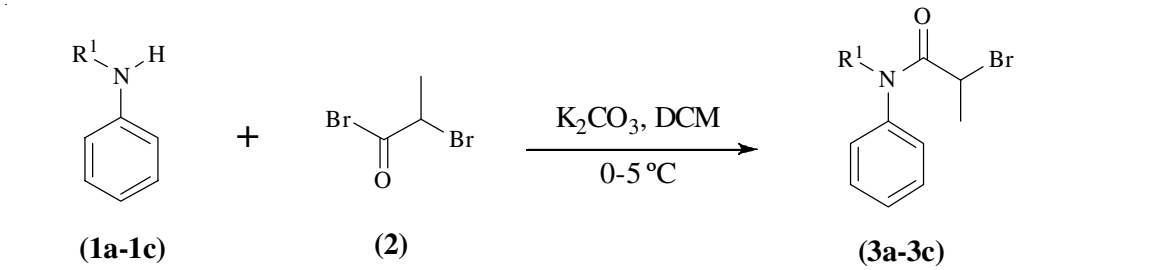
2-[4-(2-Hydroxybutan-2-yl)-1*H*-1,2,3-triazol-1-yl]-*N*,*N*-diphenylpropanamide (5i): White solid; Yield: 86 %; m.p. 76-80 °C; IR (KBr, ν_{max}, cm^{-1}): 3370 (O-H str.), 3159 (C-H str. triazole), 3061 (C-H str. aromatic ring), 2972 (C-H str., aliphatic), 1678 (C=O str. amide), 1593, 1454 (C=C str., aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79 (s, 1H, C-H triazole), 7.43 (brs, 10H, Ar-H), 5.46 (q, 1H, *J* = 4.8 Hz), 4.94 (s, 1H, OH), 1.75-1.64 (m, 5H), 1.42 (s, 3H), 0.75 (t, 3H, *J* = 8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.8 (C=O), 155.0 (C_4 triazole), 130.6, 129.6, 129.0, 127.3, 120.8 (C_5 triazole), 70.2, 56.2, 36.0, 28.7, 18.5, 8.8; HRMS (*m/z*) calculated for $C_{21}H_{24}N_4O_2[M+H]^+$: 365.1899. Found: 365.1968.

Antimicrobial activity: Compounds (**5a-5i**) were screened for *in vitro* antimicrobial activity against *Escherichia coli*, *Enterobacter aerogenes*, *Klebsiella pneumoniae, Staphylococcus aureus, Candida albicans* and *Aspergillus niger* by serial dilution method using a stock solution of 100 µg/mL concentration in five sets at different concentrations of 50, 25, 12.5, 6.25, 3.12 µg/mL. DMSO used as control solvent while, norfloxacin and fluconazole used as standard drugs, respectively for bacteria and fungus. All these dilutions were inoculated with respective bacterial and fungal strain in saline solution. Growth was assessed after incubation for 24 h at 37 °C in case of all bacteria, for 48 h at 25 °C in case of *C. albicans* and for 120 h at 25 °C for in case of *A. niger* and the minimum inhibitory concentration (MIC) value was noted. The MIC is defined as the lowest concentration of the antimicrobial agent that prevents visible growth of a microorganism under defined conditions.

RESULTS AND DISCUSSION

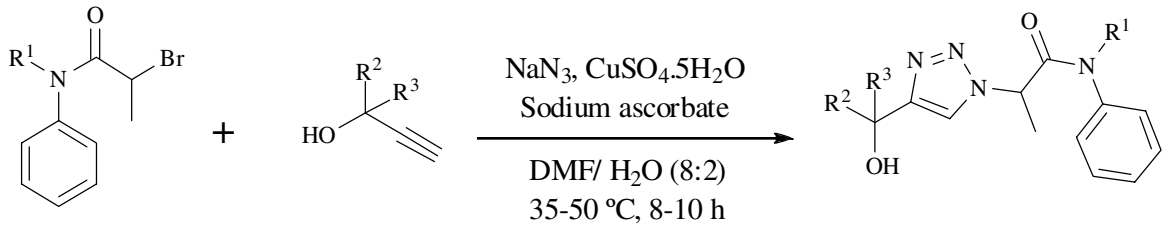
2-Bromopropanoyl bromide (**2**) was added in aromatic amines (**1a**-**1c**) in dichloromethane using potassium carbonate as a base to synthesize 2-bromo-*N*-substituted-*N*-phenylpropanamides (**3a**-**3c**). 1,4-Disubstituted 1,2,3-triazoles (**5a**-**5i**) were synthesized by reacting 2-azido-*N*-substituted-*N*-phenylpropanamides (generated *in situ* from 2-bromo-*N*-substituted *N*-phenylpropanamides and sodium azide) with hydroxyl terminal alkynes using dimethylformamide:water as solvent in the presence of copper sulphate pentahydrate and sodium ascorbate with stirring of 8-10 h at 35-50 °C (**Scheme-I**).

The characterization of synthesized compounds was carried out by the techniques FTIR, ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS. The triazole formation was confirmed by the presence of absorption bands in the region 3384-3370 (O-H str.), 3172-3140 (C-H, str., triazole ring), 1678-1662 (C=O str., amide) cm^{-1} in IR spectra. The ^{1}H NMR spectra of the



(1a-1c) **(2)** **(3a-3c)**

1a, 3a: $R_1 = CH_3$
1b, 3b: $R_1 = C_2H_5$-
1c, 3c: $R_1 = C_6H_5$-



(3a-3c) **(4a-4c)** **(5a-5i)**

4a: $R_2 = H$, $R_3 = H$
4b: $R_2 = CH_3$-, $R_3 = CH_3$-
4c: $R_2 = CH_3$-, $R_3 = C_2H_5$-

Compound	R^1	R^2	R^3	Compound	R^1	R^2	R^3
5a	CH_3	H	H	**5f**	C_6H_5	CH_3	CH_3
5b	C_2H_5	H	H	**5g**	CH_3	CH_3	C_2H_5
5c	C_6H_5	H	H	**5h**	C_2H_5	CH_3	C_2H_5
5d	CH_3	CH_3	CH_3	**5i**	C_6H_5	CH_3	C_2H_5
5e	C_2H_5	CH_3	CH_3				

Scheme-I

compounds **5a**-**5i** displayed one characteristic singlet in the region at δ 7.97-7.76 due to triazolyl proton. In the ^{13}C NMR spectra signal for C4 of the triazole moiety appeared in the region at δ 156.0-148.1, for C5 signal appeared in region δ 119.7-122.3 and signals due to carbonyl carbons of amide appeared in range of δ 168.9-167.9.

Antibacterial activity: All the synthesized compounds (**5a**-**5i**) were tested for *in vitro* antibacterial activity against Gram-negative bacteria - *Escherichia coli* (MTCC 443), *Enterobacteraerogenes* (NCDC 106), *Klebsiella pneumoniae* (NCDC 138) and Gram-positive bacteria - *Staphylococcus aureus* (MTCC 3160) by the standard serial dilution method [22]. The minimum inhibitory concentration values (MIC; corresponds to the lowest concentration that inhibits the microbial growth) of the synthesized triazoles are represented in μmol/mL and the results were compared to the control drug norfloxacin (Table-1).The screening results revealed that the compound **5f** and **5i** was found to be the broadly active against bacterial strains amongst tested compounds, while compounds **5c**, **5f**, **5h** and **5i** showed excellent activity comparable to standard against *S. aureus*.

TABLE-1
ANTIBACTERIAL ACTIVITY OF 1,4-DISUBSTITUTED 1,2,3-TRIAZOLES (**5a**-**5i**) (MIC IN μmol/mL)

Compd.	*E. coli* (MTCC 443)	*E. aerogenes* (NCDC 106)	*K. pneumoniae* (NCDC 138)	*S. aureus* (MTCC 3160)
5a	0.1914	0.0957	0.0957	0.1914
5b	0.1822	0.0911	0.0911	0.1822
5c	0.1555	0.0777	0.0777	0.0777
5d	0.1729	0.0864	0.0864	0.1729
5e	0.0826	0.0826	0.0826	0.0826
5f	0.0713	0.0713	0.0713	0.0713
5g	0.0824	0.0824	0.0824	0.1649
5h	0.0790	0.0790	0.0790	0.0790
5i	0.0685	0.0685	0.0685	0.0685
Norfloxacin	0.0391	0.0391	0.0391	0.0783

It is quite clear from antibacterial assay that in the target compounds *N*,*N*-diphenyl substituted triazole (**5g**-**5i**) derivatives possess an upper hand in activity than the *N*-ethyl-*N*-phenyl/*N*-methyl-*N*-phenyl derivatives whereas the presence of alkyl group on carbon having free hydroxyl group in the synthesized triazoles increases the antibacterial activity.

Antifungal activity: The synthesized 1,4-disubstituted 1,2,3-triazoles (**5a**-**5i**) were studied for *in vitro* antifungal activity against two fungal strains-*Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 282) using serial dilution method [22]. Fluconazole was used as the standard. The minimum inhibitory concentration (MIC) values were recorded in μmol/mL (Table-2). *In vitro* antifungal studies revealed that the compounds **5f** and **5i** displayed significant activity while the rest of the compounds showed moderate to low activity.

The structure-activity relationship study revealed that antifungal screening of synthesized compounds increases on replacement of methyl/ethyl group present on *N* of aniline by phenyl group and also the substitution of hydrogen by alkyl group on the carbon bearing hydroxy group, increases the antifungal activity in the synthesized compounds.

TABLE-2
ANTIFUNGAL ACTIVITY OF 1,4-DISUBSTITUTED 1,2,3-TRIAZOLES (**5a**-**5i**) (MIC IN μmol/mL)

Compound	*C. albicans* (MTCC 227)	*A. niger* (MTCC 282)
5a	0.0957	0.0957
5b	0.0911	0.0911
5c	0.0775	0.0775
5d	0.0864	0.0864
5e	0.0826	0.0413
5f	0.0713	0.0356
5g	0.0824	0.0824
5h	0.0790	0.0790
5i	0.0343	0.0343
Fluconazole	0.0408	0.0102

Conclusion

In the present study, regioselective synthesis of a series of 2-(4-(hydroxyalkyl)-1*H*-1,2,3-triazol-1-yl)-*N*-substituted *N*-phenylpropanamide employing click reaction has been reported. Efficient 1,3-dipolar cycloaddition between terminal hydroxyalkynes and 2-azido-*N*-substituted *N*-phenylpropanamides yielded 1,4-disubstituted 1,2,3-triazole having amide and hydroxy functionality in good yield. Some of the synthesized compound also displayed appreciable microbicidal activity.

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