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Synthesis of (*E*)-1-(2,4-*Bis*((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-phenylprop-2-en-1-one Derivatives and their Antimicrobial Activity

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A new series of chalcone based *bis* 1,4-disubstituted 1,2,3-triazole heterocyclic molecules (**6a-j**) were synthesized *via* the reaction of 1-(2,4-*bis*((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)ethanone (**6a-e**) with substituted benzaldehyde. All the molecules were characterized by IR, ^{1}H and ^{13}C NMR and MS spectra spectral data. Compounds **6a-j** were evaluated for their antimicrobial effects using a broth disc diffusion method. The compounds were evaluated for their *in vitro* antimicrobial potential against Gram-positive (*Micrococcus luteus*, Methicillin-resistant *Staphylococcus aureus*, *Bacillus subtilis* and *Bacillus cereus*), Gram-negative (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli* and *Proteus vulgaris*) bacterial and fungal (*Microsporum canis*, *Microsporum gypseum* and *Epidermophyton floccosum*) strains by comparison of the reference drugs, zentamycin sulphate (antibacterial) and nystatin (antifungal). The screened compounds **6f**, **6e**, **6c** and **6i** were found to be the most active against all the tested bacterial and fungal strains.

Keywords: Chalcone, 1,2,3-Triazoles, Click chemistry approach, Antimicrobial activity.

INTRODUCTION

1,2,3-Triazoles are as excellent origin of inventiveness for medicinal researchers due to their synthetic convenience through click chemistry and also their various pharmacological properties such as antifungal [1], antibacterial [2], anticancer [3], growth factor b1 type receptor inhibitory [4], antibiotics [5] and antitubercular activities [6]. The cellulose supported copper nanoparticles catalyzed cycloaddition between terminal alkynes and organic azides is an exceptional method for the click synthesis of 1,2,3-triazoles in ecofriendly conditions in good yield [7]. The Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) concept provides a versatile synthetic protocol to 1,2,3-triazole heterocyclic analogs, which are accompanied with a wide spectrum of pharmacological properties, including antiviral [8-10], antidiabetic [11,12], anti-HIV [13-15], anti-inflammatory [16-18], antimalarial [19,20], antioxidant [21,22], antiproliferative properties [23-25].

In addition, chalcones, also known as α,β-unsaturated ketones, are not only important forerunners for synthetic manipulation but also form a major constituent of the natural products [26]. Chalcones as well-known as their synthetic derivatives appearance enormous biological activities [27-29] and widely used as frameworks in drug design. Furthermore, chalcones have also been reported by way of biologically active molecules. Agarwal *et al.* [30] reported that some novel molecules containing chalcone and 1,2,3-triazole moieties in the single frame work showed the promising activities, such as antimicrobial and cytotoxic activities, Moreover, newly synthesized 1,2,3-triazole chalcone hybrids, I, II, III and IV were showed broad spectrum of compounds anti-plasmodia activity, cytotoxicity and antibacterial activity, respectively (Fig. 1). Lal *et al.* [31] reported fluorinated chalcone-1,2,3-triazole I conjugates derivatives for antimicrobial activity (Fig. 1). Further, a series of 1,2,3-triazole clubbed chalcone showed notable antimalarial activity against *Plasmodium falciparum* strains [32], a family of 1,2,3-triazole bound β-lactam-chalcone bifunctional hybrids also exhibited moderate to be good cytotoxicity [33]. Similarly, 1,2,3-triazole derivatives of flavone showed estrogen receptor α-positive breast cancer inhibitors [34].

Due to excellent pharmacological properties of chalcone and 1,2,3-triazole, we attempt to synthesize a series of chalcone linked 1,2,3-triazole hybrids as potential antimicrobial agents.

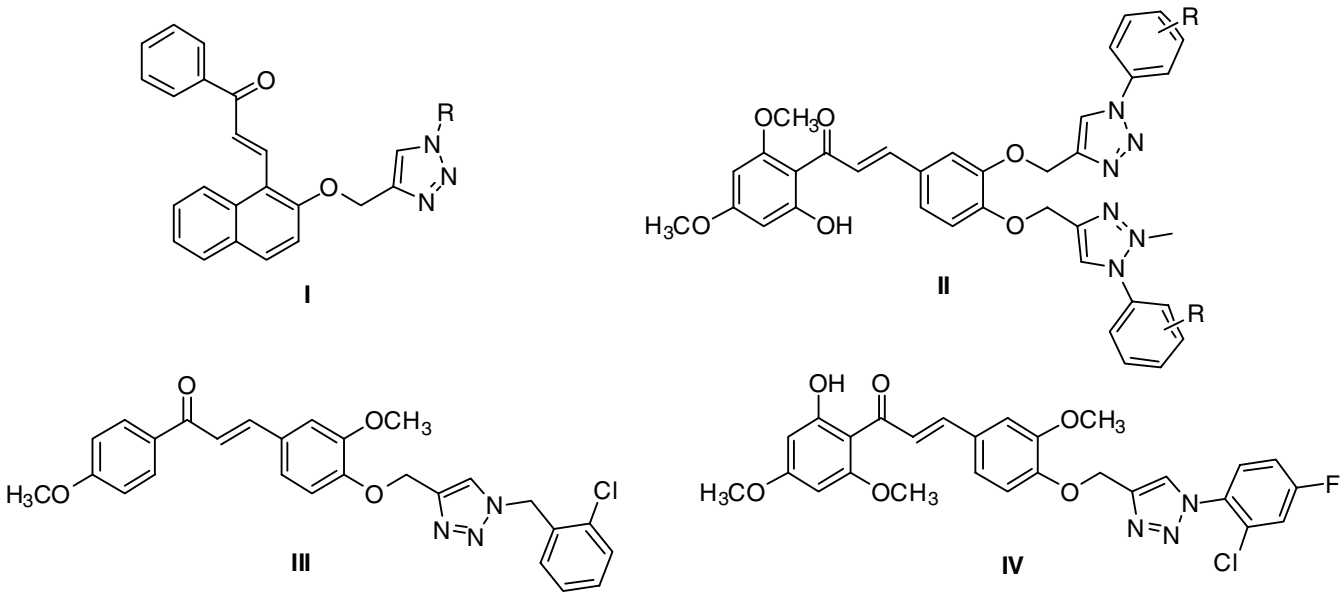


Fig. 1. Structure of newly synthesized 1,2,3-triazole chalcone hybrids

EXPERIMENTAL

All the reagents obtained from the commercial suppliers were used without further purification. Melting points were determined on an Electrothermal 9100 melting point apparatus (Weiss-Gallenkamp, Loughborough, UK) and are uncorrected. IR spectra were recorded on an IRPrestige-21 Fourier transform infrared spectrophotometer (Shimadzu, Japan). ^{1}H & ^{13}C NMR spectra were recorded on a Varian Mercury-400 FT NMR spectrometer (Agilent, Palo Alto, USA).

Synthesis of 1-(2,4-dihydroxyphenyl)ethanone (2): Acetic acid (3 g, 0.05 mol) was mixed with freshly fused zinc chloride (6.8 g, 0.05 mol) and heated at 120 ºC for 0.5 h along with the addition of resorcinol (5.5 g, 0.05 mol). Then the composition was heated for 0.5 h at 140 ºC. The TLC was used to observe the complete reaction. The reaction mixture was cooled to room temperature and added 100 mL of ice cold water followed by the addition of EtOAc (3 × 50 mL). Then 20% HCl (50 mL) was used to wash the mixed organic layers and saturated with Na_2CO_3 (25 mL) and conc. NaCl solution (2 × 25 mL). The organic layer was dried using anhydrous Na_2SO_4. Further at reduced pressure, crude product was concentrated. The column chromatography accompanied by 100-200 mesh silica was employed to purify the crude product. Then eluted in ethyl acetate (10%) to obtain pure 1-(2,4-dihydroxyphenyl)ethanone as reddish brown crystals (yield: 76%, m.p.: 142-144 ºC).

(2,4-*bis*(Prop-2-yn-1-yloxy)phenyl)ethanone (4): To a completely agitated composition of 1-(2,4-dihydroxyphenyl)-ethanone (**2**) (3g, 0.019 mol) in dry acetone, K_2CO_3 (2.72 g, 0.019 mol) and propargyl bromide of 80% prepared in toluene (0.019 mol) was added on dropwise and the composition was refluxed for 8 h. The progression of reaction was screened by TLC. Then at reduced pressure, the mixture was allowed to reach room temperature and acetone present in excess amount was allowed to evaporate. Further diluted in water (50 mL) and pulling out using EtOAc (3 × 50 mL). The brine solution (2 × 25 mL) was used wash the mixed organic layers. Then organic layer was allowed to dry on anhydrous sodium sulphate and filtered followed by concentration in vacuum. The column chromatography with 100-200 mesh silica gel was employed to purify the product. Then eluted in $CH_3COOC_2H_5$ (5%) in petroleum ether to obtain 1-(2,4-*bis*(prop-2-yn-1-yloxy)phenyl)-ethanone (**3**) as white solid. m.f.: $C_{11}H_{10}O_3$, Yield: 92%, state: white solid, m.p.: 196-198 ºC, R_f value = 0.3 (20% $CH_3COOC_2H_5$/hexane), IR (KBr, ν_{max}, cm^{-1}): 3410, 2356, 1639.5, ^{1}H NMR (300×10^6 Hz, $CDCl_3$): δ ppm 12.6 (s, 1H), 7.63 (dd, J = 7.05, 2.3 Hz, 1H), 6.46-6.43 (m, 2H), 4.71 (d, J = 2.3 Hz, 2H), 2.55 (s, 3H), 2.53 (d, J = 2.28 Hz, 1H), Mass: (ES+) m/z = 191 $[M+H]^+$.

Synthesis of 1-(2,4-*bis*((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)ethanone (5a-e): Compound 1-(2,4-*bis*-(prop-2-yn-1-yloxy)phenyl)ethanone (**4**) (0.438 mmol) was mixed with 5 mL aqueous DMF (50%) and then subsequently $CuSO_4 \cdot 5H_2O$ (5 mol %), sodium ascorbate (10 mol %) and various substituted azide (1.315×10^{-3} mol) were added. Then the composition was mixed for 1 h at room temperature. The complete process of reaction was checked through thin layer chromatography technique. Then the entire transformation of starting materials, the composition was transferred to ice pieces. The procured solid was filtered, washed with water and allowed to dry. The pure form of product was obtained from crude form by using chromatography with 100-150 mesh silica gel and EtOAc in petroleum ether. The pure product obtained was 1,4-disubstituted 1,2,3-triazole analogues (**5a-e**).

Synthesis of (*E*)-1-(2,4-*bis*((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-phenylprop-2-en-1-one (6a): To a solution of 1-(2,4-*bis*((1-phenyl-1*H*-1,2,3-triazol-4-yl)-methoxy)-phenyl)ethanone (**5a**) (0.214 mol) in EtOH was added KOH (0.321 mol). Then composition was mixed for 15 min at room temperature. To the reaction mixture benzaldehyde (0.214 mol) was mixed and agitated for 8 h at the same room temperature. The reaction progress was checked through TLC. Then ice cold

water was added to mixture followed by neutralization with 0.1-0.2 N HCl to yield the precipitate. The compound formed was filtered and washed with distilled water and methanol to obtain pure (*E*)-1-(2,4-*bis*((1-phenyl-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-3-phenylprop-2-en-1-one (**6a**) as white solid. Yield: 80%, m.f.: $C_{33}H_{26}N_6O_3$, m.p.: 170-172 ºC. IR (KBr, ν_{max}, cm^{-1}): 1648 (C=O), ^{1}H NMR (400 × 10^6 Hz, DMSO-d_6, δ ppm): 7.92-7.38 (m, 18H), 7.08 (d, *J* = 7.57 Hz, 1H), 6.83 (s, 1H), 6.67 (s, 1H), 6.64 (s, 1H), 5.30 (s, 2H), 5.24 (s, 2H). ^{13}C NMR (100 × 10^6 Hz, DMSO-d_6, δ ppm): 187.8, 166.1, 161.6, 158.1, 158.1, 142.2, 130.4, 130.0, 129.5, 129.3, 129.0, 129.0, 128.8 (2C), 128.2 (2C), 127.5 (2C), 127.4 (2C), 127.2 (2C), 126.9 (2C), 124.6, 124.4, 121.9, 118.2, 118.0, 107.9, 101.0, 62.1, 61.6, Mass: (ES+) *m/z* = 555 $[M+H]^+$.

(*E*)-1-(2,4-*bis*((1-Phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)-phenyl)-3-(4-methoxyphenyl) prop-2-en-1-one (6b): White solid, yield: 86%, m.f.: $C_{34}H_{28}N_6O_4$, m.p.: 156-158 ºC. IR (KBr, ν_{max}, cm^{-1}): 1657 (C=O), ^{1}H NMR (400 × 10^6 Hz, DMSO-d_6, δ ppm): 8.00-07.38 (m, 15H), 7.02 (d, *J* = 7.53 Hz, 1H), 7.00-6.86 (m, 2H), 6.80 (s, 1H), 6.67-6.59 (m, 2H), 5.38-5.21 (m, 4H), 3.81(s, 3H), ^{13}C NMR (100 × 10^6 Hz, DMSO-d_6, δ ppm): 189.1, 166.1, 161.5, 159.2, 158.1, 158.0, 143.2, 131.9, 130.3, 130.0, 129.7 (2C), 1294, 129.0, 127.6 (2C), 127.5 (2C), 127.1 (2C), 126.9 (2C), 124.6, 124.4, 123.2, 121.9, 118.2, 111.6 (2C), 107.9, 101.0, 62.0, 61.6, 56.1, Mass: (ES+) *m/z* = 585 $[M+H]^+$.

(*E*)-1-(2,4-*bis*((1-(*p*-Tolyl)-1*H*-1,2,3-triazol-4-yl)meth-oxy)phenyl)-3-phenyl prop-2-en-1-one (6c): White solid, yield: 80%, m.f.: $C_{35}H_{30}N_6O_3$, m.p.: 203-205 ºC. IR (KBr, ν_{max}, cm^{-1}): 1660 (C=O), ^{1}H NMR (400 × 10^6 Hz, DMSO-d_6, δ ppm): 8.00-7.22 (m, 16H), 7.04 (d, *J* = 7.32 Hz, 1H), 6.80 (s, 1H), 6.71 (s, 1H), 6.59 (s, 1H), 5.39-05.19 (m, 4H), 2.41-2.19 (m, 6H). ^{13}C NMR (100 × 10^6 Hz, DMSO-d_6, δ ppm): 187.6, 166.2, 161.7,158.2, 158.0, 142.3, 131.7, 131.6, 129.4, 129.3, 129.1 (2C), 129.0, 128.7, 128.4 (2C), 127.5 (2C), 127.5 (2C), 127.3 (2C), 127.0 (2C), 124.5, 124.2, 121.8, 118.2, 118.0, 107.9, 101.1, 62.2, 61.1, 21.5, 21.3, Mass: (ES+) *m/z* = 583 $[M+H]^+$.

(*E*)-1-(2,4-*bis*((1-(*p*-Tolyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (6d): White solid, yield: 85%, m.f.: $C_{36}H_{32}N_6O_4$, m.p.: 183-185 ºC. IR (KBr, ν_{max}, cm^{-1}): 1656 (C=O), ^{1}H NMR data (400 × 10^6 Hz, DMSO-d_6, δ ppm): 8.00-7.21 (m, 15H), 7.07-7.01 (m, 2H), 6.98 (s, 1H), 6.78 (d, *J* = 7.29 Hz, 1H), 6.77-6.62 (m, 2H), 5.39-5.20 (m, 4H), 3.82 (s, 3H), 2.41-2.20 (m, 6H). ^{13}C NMR (100 × 10^6 Hz, DMSO-d_6, δ ppm): 189.1, 166.1, 161.6, 159.2, 158.2, 158.0, 143.3, 131.8, 130.3, 130.1, 129.3 (2C), 129.1, 128.8, 128.5 (2C), 127.5 (2C), 127.4 (2C), 127.3 (2C), 127.1 (2C), 124.6, 124.3, 121.9, 118.1, 118.0, 108.0, 101.2, 62.4, 61.2, 56.1, 21.4, 21.2, Mass: (ES+) *m/z* = 613 $[M+H]^+$.

(*E*)-1-(2,4-*bis*((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-phenylprop-2-en-1-one (6e): White solid, yield: 78.5%, m.f.: $C_{33}H_{24}N_6O_3Cl_2$, m.p.: 178-181 ºC. IR (KBr, ν_{max}, cm^{-1}): 1655 (C=O), ^{1}H NMR (400 × 10^6 Hz, DMSO-d_6, δ ppm): 8.00-7.38 (m, 16H), 7.14-7.03 (m, 1H), 6.82 (s, 1H), 6.69 (s, 1H), 6.60 (s, 1H), 5.43-5.18 (m, 4H). ^{13}C NMR (100 × 10^6 Hz, DMSO-d_6, δ ppm): 187.3, 166.3, 161.6, 158.1, 158.0, 142.1, 132.4, 132.3, 129.5, 129.4, 129.2 (2C), 129.1, 129.0, 128.8 (2C), 128.7 (2C), 127.9 (2C), 127.7 (2C), 126.3 (2C), 124.4, 124.1, 121.5, 118.1, 118.0, 107.8, 101.3, 62.0, 61.3, Mass: (ES+) *m/z* = 623 $[M+H]^+$.

(*E*)-1-(2,4-*bis*((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (6f): White solid, yield: 75%, m.f.: $C_{34}H_{26}N_6O_4Cl_2$, m.p.: 156-158 ºC. IR (KBr, ν_{max}, cm^{-1}): 1656 (C=O), ^{1}H NMR (400 × 10^6 Hz, DMSO-d_6, δ ppm): 8.11-7.25 (m, 13H), 7.07-7.02 (m, 1H), 7.01-6.93 (s, 1H), 6.83 (d, *J* = 7.26 Hz, 1H), 6.78-6.59 (m, 2H), 5.38-5.21 (m, 4H), 3.81 (s, 3H). ^{13}C NMR (100 × 10^6 Hz, DMSO-d_6, δ ppm): 189.1, 166.2, 161.7, 159.3, 158.1, 158.0, 143.4, 131.9, 130.4, 130.0, 129.2 (2C), 129.0, 128.7, 128.1 (2C), 127.5 (2C), 127.3 (2C), 127.2 (2C), 127.0 (2C), 124.9, 124.3, 121.0, 118.0, 117.7, 108.3, 101.2, 62.5, 61.3, 56.3, Mass: (ES+) *m/z* = 653 $[M+H]^+$.

(*E*)-1-(2,4-*bis*((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-phenyl prop-2-en-1-one (6g): White solid, yield: 76%, m.f.: $C_{33}H_{24}N_6O_3Br_2$, m.p.: 207-209 ºC. IR (KBr, ν_{max}, cm^{-1}): 1658 (C=O), ^{1}H NMR (400 × 10^6 Hz, DMSO-d_6, δ ppm): 7.99-7.28 (m, 16H), 7.15-7.05 (m, 1H), 6.83 (s, 1H), 6.68 (s, 1H), 6.59 (s, 1H), 5.44-5.17 (m, 4H), ^{13}C NMR (100 × 10^6 Hz, DMSO-d_6, δ ppm): 187.2, 166.2, 161.7, 158.3, 158.1, 142.2, 132.7, 132.2, 129.9, 129.7, 129.6 (2C), 129.3, 129.1, 128.9 (2C), 128.6 (2C), 127.8 (2C), 127.6 (2C), 126.4 (2C), 124.0, 123.2, 121.7, 118.3, 118.1, 107.9, 101.5, 62.1, 61.6, Mass: (ES+) *m/z* = 711 $[M+H]^+$.

(*E*)-1-(2,4-*bis*((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (6h): Light yellow solid, yield: 80%, m.f.: $C_{34}H_{26}N_6O_4Br_2$, m.p.: 186-188 ºC. IR (KBr, ν_{max}, cm^{-1}): 1657 (C=O), ^{1}H NMR (400 × 10^6 Hz, DMSO-d_6, δ ppm): 8.08-7.21 (m, 13H), 7.08-7.01 (m, 1H), 6.95 (s, 1H), 6.89 (d, *J* = 7.34 Hz, 1H), 6.76-6.58 (m, 2H), 5.37-5.21 (m, 4H), 3.80 (s, 3H). ^{13}C NMR (100 × 10^6 Hz, DMSO-d_6, δ ppm): 189.4, 166.4, 161.4, 159.4, 158.2, 158.1, 142.6, 132.8, 130.4, 130.1, 129.4 (2C), 128.9, 128.4, 128.3 (2C), 127.8 (2C), 127.6 (2C), 127.4 (2C), 127.2 (2C), 124.7, 124.3, 121.3, 118.1, 117.9, 108.4, 101.0, 62.1, 61.6, 56.4, Mass: (ES+) *m/z* = 741 $[M+H]^+$.

(*E*)-1-(2,4-*bis*((1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-phenylprop-2-en-1-one (6i): Yellow solid, yield: 88%, m.f.: $C_{33}H_{24}N_8O_7$, m.p.: 302 ºC, IR (KBr, ν_{max}, cm^{-1}): 1646 (C=O), ^{1}H NMR (400 × 10^6 Hz, DMSO-d_6, δ ppm): 8.40-8.22 (m, 4H), 7.95-7.35 (m, 12H), 7.06 (d, *J* = 7.33 Hz, 1H), 6.82 (s, 1H), 6.70 (s, 1H), 6.61 (s, 1H), 5.34 (s, 2H), 5.25 (s, 2H). ^{13}C NMR (100 × 10^6 Hz, DMSO-d_6, δ ppm): 187.0, 166.4, 162.0, 158.5, 158.4, 148.2, 147.9, 133.3 (2C), 133.2 (2C), 130.1, 129.9, 129.7, 129.6 (2C), 129.3, 129.1, 127.9 (2C), 127.8 (2C), 126.6 (2C), 124.2, 123.3, 121.8, 118.2, 118.0, 108.1, 101.5, 62.0, 61.2, Mass: (ES+) *m/z* = 645 $[M+H]^+$.

(*E*)-1-(2,4-*bis*((1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(4-methoxy phenyl)prop-2-en-1-one (6j): Yellow solid, yield: 90%, m.f.: $C_{34}H_{26}N_8O_8$, m.p.: 304 ºC. IR (KBr, ν_{max}, cm^{-1}): 1649 (C=O), ^{1}H NMR (400 × 10^6 Hz, DMSO-d_6, δ ppm): 8.38-8.20 (m, 4H), 7.93-7.36 (m, 9H), 7.08-6.92 (s, 3H), 6.78 (d, *J* = 7.30 Hz, 1H), 6.72-6.59 (m, 2H), 5.32 (s, 2H), 5.24 (s, 2H), 3.81 (s, 3H), ^{13}C NMR (100 × 10^6 Hz, DMSO-d_6, δ ppm): 189.3, 166.2, 161.3, 161.1, 159.3, 158.3, 158.1, 148.2, 147.9, 143.2, 133.2 (2C), 133.0 (2C), 131.8, 129.7

(2C), 129.6 (2C), 127.9 (2C), 127.8, 124.2, 123.3, 121.8, 118.2, 118.0, 116.3 (2C), 108.1, 101.5, 62.0, 61.7, 56.2, Mass: (ES+) *m/z* = 675 [M+H].

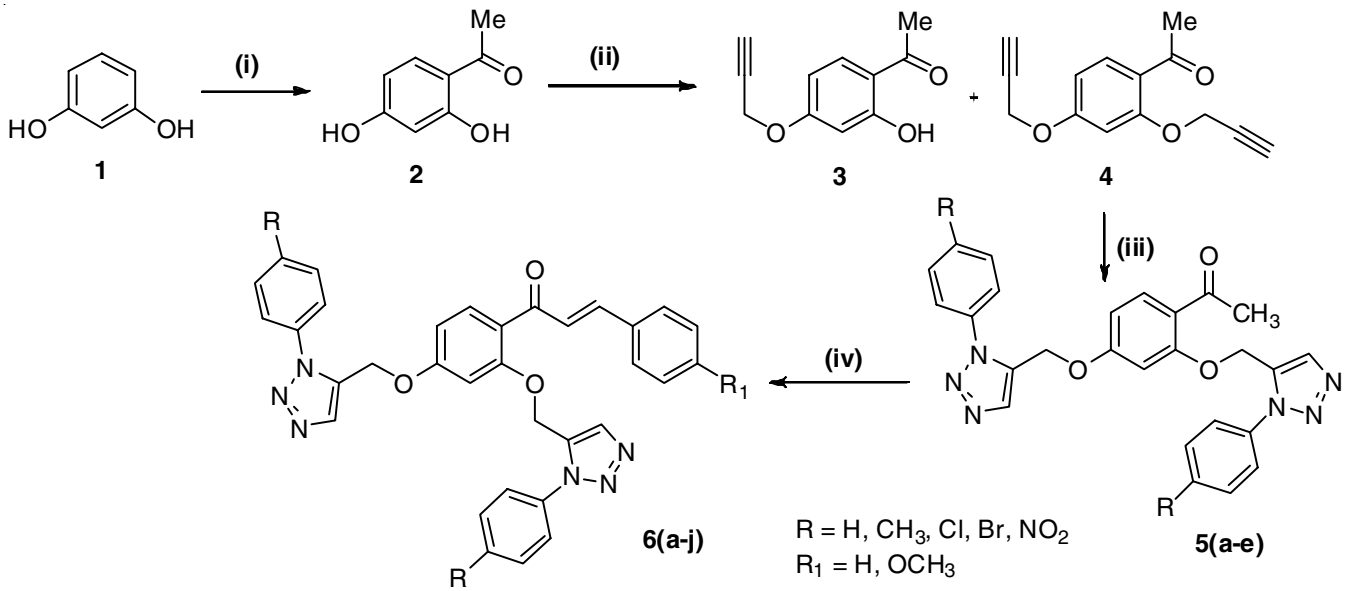
Microbiology: The antimicrobial activities of the synthesized compounds were tested using a broth disc diffusion method [35]. Tested mold strains were *Micrococcus luteus*, Methicillin-resistant *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli* and *Proteus vulgaris.* Minimum zone of inhibition concentration was defined as the lowest concentration of compounds that inhibited visible growth. Zentamycin was used as a standard antibacterial agent. The antifungal effects of the compounds on molds were tested using a broth disc diffusion method with some modifications. Tested mold strains were (*Microsporum canis*, *Microsporum gypseum*, *Epidermophyton floccosum*). Nystatin was used as an antifungal agent.

RESULTS AND DISCUSSION

As shown in **Scheme-I**, (*E*)-1-(2,4-*bis*((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-phenylprop-2-en-1-one derivatives (**6a-j**) were synthesized, initially resorcinol (**1**) undergoes condensing with acetic acid in presence of freshly fused zinc chloride to produced 1-(2,4-dihydroxyphenyl)ethanone (**2**) with 76% yield. The selective O-alkylation of compound (**2**) done through refluxing it with propargyl bromide in presence of K_2CO_3, dry acetone under atmospheric nitrogen for 8 h to obtain *para* alkylated product (**3**) with a yield of 92%. Reason for the production of the *para*-alkylated compound as major is due to steric parameters and mesmeric effect, in compound (**3**) the *ortho* –OH group possess low nucleophilicity than the *para* –OH group. The ^{1}H NMR analysis was used to confirm the structure, which exhibited specific singlet at δ 12.6, doublet at δ 4.71 and a triplet at δ 2.53 ppm peaks due to the presence of chelated phenolic hydrogen of *ortho* –OH group, O-CH_2- and ≡CH, respectively. It is evident that final major compound was 1-(2-hydroxy-4-(prop-2-yn-1-yloxy)phenyl)ethanone (**3**).

The generation of 1-(2,4-*bis*((1-phenyl-1*H*-1,2,3-triazol-5-yl)methoxy)phenyl)ethanone derivatives (**5a-j**) was readily achieved by cycloaddition reaction the 1-(2,4-*bis*(prop-2-yn-1-yloxy)phenyl)ethanone (**4**) with substituted aromatic azides using click chemistry in good yields. The all resulted triazoles were confirmed by ^{1}H NMR spectra showed singlet at δ 3.81 ppm for three protons suggesting the presence of methyl ketone group, peaks at δ 5.24 ppm for two doublet four protons suggesting the presence of two –OCH_2 groups. In ^{13}C NMR spectrum showed that the compounds **5a-e**, the carbonyl O-CH_2 appears at δ 185.4 and 56.2 ppm, respectively and disappear at δ 76.1 ppm corresponds to –C=CH, which confirmed the formation of compounds **5a-e**.

Finally, the target (*E*)-1-(2,4-*bis*((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-phenylprop-2-en-1-one derivatives (**6a-j**) were synthesized by involving of all 1-(2,4-*bis*((1-phenyl-1*H*-1,2,3-triazol-5-yl)methoxy)phenyl)ethanone derivatives (**5a-j**), then it was treated with substituted benzaldehyde to produce corresponding chalcone based 1,4-disubstituted 1,2,3-triazole (**6a-j**) in good yield. The spectroscopic analysis of representative compound, (*E*)-1-(2,4-*bis*((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-phenylprop-2-en-1-one (**6a**), the IR peak observed at 1657 cm^{-1} recommended the existence of ketone (>C=O). In ^{1}H NMR spectrum showed two peaks as singlets each for single proton at δ 8.31 and δ 8.20 ppm indicating the presence of two triazole protons which is also showing two multiplet peaks each for four protons in a region of δ 5.47-5.15 and δ 4.51-4.14 ppm indicating the presence of four oxygen attached (-OCH_2-) protons and four nitrogen attached (-NCH_2-) protons, respectively. Further confirmation of compound **6a** was done by using ^{13}C NMR spectrum showed the resonance of carbonyl carbon was observed



Reagents and conditions: (i) AcOH, $ZnCl_2$, 120-140 °C, 30 min, 76% (ii) propargyl bromide, K_2CO_3, acetone, reflux, 8 h, 92%; (iii) substituted aryl azides (iv) Ar_1CHO **7(a-b)**, ethanol, room temparature, 8 h

Scheme-I: Synthesis of the target compounds **6a-e** and **8a-j**

TABLE-1
ANTIBACTERICIDAL ACTIVITIES OF THE CHALCONE BASED 1,2,3-TRIAZOLE ANALOGUES **(6a-j)**

Compound No.	Conc. (10^{-6} g/mL)	Inhibition zone (10^{-3} M)							
		Gram-positive bacteria				Gram-negative bacteria			
		M. luteus	MRSA	*B. subtilis*	*B. cereus*	*K. pneumoniae*	*E. coli*	*P. aeruginosa*	*P. vulgaris*
6a	75	20	22	20	23	18	20	22	20
	100	23	26	24	27	21	24	26	24
6b	75	20	23	23	24	20	23	24	21
	100	24	27	26	29	25	25	29	25
6c	75	24	25	26	26	24	23	27	24
	100	27	32	29	30	27	28	30	28
6d	75	19	20	17	21	17	19	22	18
	100	21	22	19	24	19	21	26	20
6e	75	30	27	24	22	24	26	28	26
	100	34	33	28	31	28	32	30	31
6f	75	33	30	28	29	28	30	32	30
	100	30	34	35	34	33	34	36	34
6g	75	19	22	18	21	17	21	20	18
	100	22	25	23	25	22	23	26	23
6h	75	20	26	21	27	20	21	24	21
	100	23	28	25	28	22	25	27	26
6i	75	21	23	22	24	21	20	24	23
	100	26	28	26	29	22	24	29	26
6j	75	12	12	12	13	11	12	15	14
	100	17	17	16	17	18	17	18	17
Zentamycin (std.)	75	26	30	30	30	29	26	30	28
	100	32	32	32	33	33	32	34	32

at δ 188.5, where as the two oxygen attached (-OCH_2-), two nitrogen atoms attached (-NCH_2-) aliphatic carbons appeared at δ 61.9, δ 61.4, δ 49.3 ppm (for two carbons), respectively. The mass spectrum pertaining to compound **6a** showed peak at *m/z* 555 $[M+H]^+$ in the form of base peak, corresponding to the molecular weight of compound **6a**.

Antimicrobial activity: The newly syntheszed chalcone clubbed *bis*(1,4-disubstituted)-1,2,3-triazoles (**6a-j**) were examined for their antibactericidal activity. These triazoles showed significant inhibition of growth of tested Gram-positive and Gram-negative bacteria analyzed to standard drug gentamycin sulphate. Among the compounds tested, compounds **6f**, **6e**, **6c** and **6i** was proven powerful antibactericidal properties at different concentrations *viz.* 75×10^{-6} and 100×10^{-6} g/mL against *Micrococcus luteus*, Methicillin-resistant *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli* and *Proteus vulgaris* (Table-1). Compounds **6b**, **6h**, **6a** and **6g** also exhibited good antibacterial profile against tested bacterial strains. These results inferred the existence of strong electron donor group (OMe) at *ortho*- and *para*-positions of phenyl ring of chalcone may increasing the antibacterial activity than the other disubstituted and monosubstituted chalcone based triazoles.

Antifungal activity: Antifungal activity studies were also conducted for the synthesized compounds **6a-j** in two different concentrations *viz.,* 75×10^{-6} g/mL and 100×10^{-6} g/mL on three skin inhabiting fungi (*Microsporum canis*, *Microsporum gypseum* and *Epidermophyton floccosum*). Among all the screened analogues, the antifungal activity was found high in the compound **6e** & **6f** against screened strains of fungi relative to standard medicine nystatin (Table-2).

TABLE-2
ANTIFUNGAL ACTIVITIES OF NOVEL CHALCONE BASED 1,2,3-TRIAZOLE ANALOGUES **6a-j**

Compound No.	Conc. (10^{-6} g/mL)	Inhibition zone (10^{-3} m)		
		M. canis	*M. gypseum*	*E. floccosum*
6a	75	06	04	04
	100	13	09	09
6b	75	11	11	10
	100	16	14	14
6c	75	16	15	14
	100	24	19	19
6d	75	12	12	04
	100	14	14	08
6e	75	22	18	19
	100	26	21	21
6f	75	22	21	20
	100	27	24	25
6g	75	07	05	05
	100	09	07	08
6h	75	11	11	10
	100	17	16	15
6i	75	14	16	11
	100	16	18	17
6j	75	12	05	05
	100	14	10	11
Nystatin(std)	75	22	20	21
	100	26	22	24

Conclusion

In present work, a new series of (*E*)-1-(2,4-*bis*((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-phenylprop-2-en-1-one analogues **6(a-j)** were successfully synthesized in high yields using click chemistry approach and its antimicrobial

activities were also evaluated. The screened compounds **6f**, **6e**, **6c** and **6i** were found to be the best active against all the tested bacterial and fungal strains among all the demonstrated compounds of biological study.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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