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RAPID COMMUNICATION

Microwave-assisted synthesis of some new 1,2,3-triazole derivatives and their antimicrobial activity

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Abstract. A series of new 1,2,3-triazole derivatives were designed and synthesised through Cu(I) catalysed 1,3-dipolar cycloaddition of alkynes and organic azides namely click reaction, under both conventional and microwave irradiation methods. Higher yields were achieved in lesser time under microwave irradiation method by using CuI as the catalyst. Herein, the two triazole moieties are linked through the O-alkoxy oxime linkage. All the synthesised molecular structures are elucidated by ^{1}H-NMR, ^{13}C-NMR, IR and mass spectral analysis and screened for their *in vitro* antimicrobial activity.

Keywords. 1,2,3-Triazole; 1,3-dipolar cycloaddition; click chemistry; microwave irradiation; antimicrobial activity.

1. Introduction

Infectious diseases spread and caused by microorganisms every day results in tremendous economic loss and threat to human health.[1,2] The treatment for bacterial and fungal infections is unsatisfactory, because of the bacterial resistance to antibiotics and side effects to human health. With the increase of awareness about human health and microorganisms, there is a necessity to develop a new generation of antibiotics and antimicrobial agents.[3] Many of the heterocyclic rings *viz.*, indole, triazole, pyrazole, benzimidazole and their fused compounds are widely studied because of their significant biological activities.

Heterocyclic compounds especially 1,2,3-triazole display a broad spectrum of pharmacological properties and became potential targets in drug discovery over a few decades. The synthetic moieties containing these molecular structures found a large application in the discovery of drugs due to its less occurrence in nature.[4] Meanwhile, based on the literature surveys 1,2,3- triazole and their derivatives have gained enormous interest due to their pharmaceutical and therapeutic applications such as anti-cancer,[5] anti-viral,[6] antimicrobial,[7–9] anti-acetylcholinesterase,[10] anti-inflammatory,[11] antioxidant[12] and anti-diabetic.[13] Furthermore, some of the drugs which contain 1,2,3-triazole scaffolds such as TSAO[14] (anti-HIV agent), Cefatrizine[15] (antibiotic agent), CAI[16] (anti-cancer agent) and Tazobactum[17] (anti-bacterial agent) are used currently (Figure 1). The favourable properties for the enhanced biological activities of triazole ring are like rigidity, high chemical stability (generally inert for oxidising and reducing agents), dipole moment, hydrogen bonding capability under *in vivo* conditions.[18]

The synthesis of 1,2,3-triazole was widely studied.[19–21] But, the conventional route to synthesize the 1,2,3-triazole core moiety is the 1,3-dipolar cycloaddition of alkynes with azides known as Huisggen cycloaddition reaction. Nevertheless, due to the high activation energy, these reactions require high temperature, long reaction time and formation of mixture of 1,4- and 1,5-regioisomers.[22] Sharpless group and

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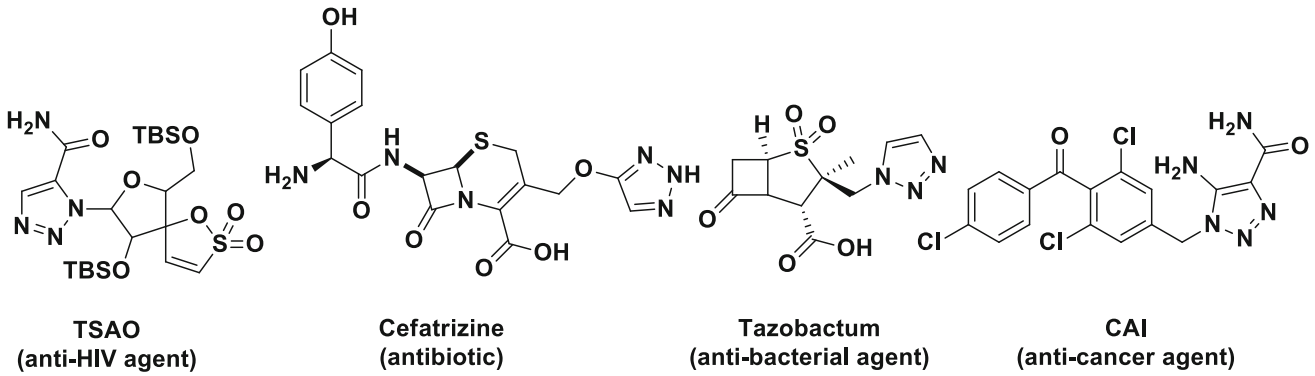


Figure 1. Some of the drugs available in the market containing 1,2,3-triazole ring.

Meldal independently developed Cu-catalysed azide-alkyne cycloaddition reaction (CuAAC) popularly known as Click-reaction, which proceeds under mild reaction conditions, hazard-free, leads to 100% regioselectivity (only 1,4-disubstituted regioisomer is formed) and excellent yielding.[23–25]

The microwave-assisted technique had become a landmark and significant contribution to preserve the environment by reducing the waste as well, as it offers an efficient internal heat transfer which reduces the reaction time as well as increasing the rate of reaction and yield. The cycloaddition of alkynes and azides through the click chemistry are also been studied under microwave irradiation method.[26–28]

Based on the biological significance of triazoles and their derivatives along with the advantages of microwave irradiation technology, we designed and synthesised a new series of 1,2,3-triazole molecules under both conventional and microwave irradiation techniques.

2. Experimental

2.1 *Materials*

All the required chemicals and solvents were purchased from Sigma Aldrich and other commercial suppliers. The progress of the reaction was monitored by thin-layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light. Column chromatography was performed on silica gel (60–120 mesh) using distilled hexane, ethyl acetate. ^{1}H NMR and ^{13}C NMR spectra were determined on Bruker AVANCE-400 spectrometer using $CDCl_3$ and DMSO solvents at 400 and 100 MHz, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiple). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a Shimadzu FT-IR-8400s spectrometer. Melting points were determined using Stuart SMP3 melting point apparatus and are uncorrected. All the microwave irradiation experiments were performed in a CEM Discover microwave system and reaction temperatures were monitored by an equipped IR sensor.

2.2 *Synthesis*

2.2a *General procedure for synthesis of 1-(5-methyl-1-aryl-1H-1,2,3-triazol-4-yl)ethanone oxime 2(a-d)*: A mixture of ketone **1a** (0.1 g, 0.43 mmol), $NH_2OH{\cdot}HCl$ (0.04 g, 0.58 mmol) and ethanol (5 mL) in glacial acetic acid (2 drops) was exposed under microwave irradiation at 180 W in 30 s intervals for 5 min and the progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into crushed ice. The solid obtained was filtered and washed with water, dried and purified by recrystallisation in ethanol to afford the desired compound.

2.2b *General procedure for synthesis of 1-(5-methyl-1-aryl-1H-1,2,3-triazol-4-yl)ethanone O-prop-2-yn-1-yl oxime 3(a-d)*: The compound **2a** mentioned above (0.1 g, 0.40 mmol) and K_2CO_3 (0.08 g, 0.58 mmol) were dissolved in DMF (10 mL). Propargyl bromide 80% in toluene (0.06 g, 0.5 mmol) was added to the mixture and stirred for 4 h at room temperature. The progress of the reaction was monitored by TLC and after completion of the reaction, the mixture was poured into crushed ice. The solid obtained was filtered and washed with an excess of water and dried. Crude was purified by column chromatography using hexane and ethyl acetate (9:1) as eluent to afford the desired compound.

2.2c *General procedure for synthesis of 1-(5-methyl-1-aryl-1H-1,2,3-triazol-4-yl)ethanone O-((1-aryl-1H-1,2,3-triazol-4-yl)methyl) oxime 5(a-p)*: (1) Conventional method

To a mixture of **3a** (0.1 g, 0.35 mmol) and azide **4a** (0.05 g, 0.35 mmol) in DMF:H_2O (1:3) (20 mL), CuI (0.003 g,

0.017 mmol) was added and heated at 80 °C for 8 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into crushed ice. The solid obtained was filtered and washed with water and dried. The crude was purified by column chromatography using hexane and ethyl acetate (3:1) as eluent to afford the desired compound.

(2) Microwave irradiation method

To a mixture of **3a** (0.1 g, 0.35 mmol) and azide **4a** (0.05 g, 0.35 mmol), in DMF:H_2O (1:3) (4 mL), CuI (0.003 g, 0.017 mmol) was added. The resulting mixture was capped in a closed vessel and exposed to microwave irradiation at 180 W for 12 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into crushed ice. The solid obtained was filtered and washed with water and dried. The crude was purified by column chromatography using hexane and ethyl acetate (3:1) as eluent to afford the desired compound.

1-(1-(4-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone oxime (2a) White solid; yield: 0.09 g, 85%; M.p.: 170–172 °C; IR (KBr, cm^{-1}): 3302, 3122, 1641, 1560, 831; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H, –OH), 7.54 (d, J = 8.8 Hz, 2H, Ar–H), 7.42 (d, J = 8.8 Hz, 2H, Ar–H), 2.49 (s, 3H, $–CH_3$), 2.48 (s, 3H, $–CH_3$); ^{13}C NMR (100 MHz, DMSO): δ 152.08, 141.58, 135.81, 134.45, 131.87, 129.83, 126.51, 12.16, 10.81; MS (ESI): 251 $[M+H]^+$.

1-(1-(4-Methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone oxime (2b) White solid; yield: 0.087 g, 82%; M.p.: 188–190 °C; IR (KBr, cm^{-1}): 3219, 3070, 1620, 1516, 829; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (s, 1H, –OH), 7.36 (d, J = 9.0 Hz, 2H, Ar–H), 7.05 (d, J = 9.0 Hz, 2H, Ar–H), 3.89 (s, 3H, $–OCH_3$), 2.49 (s, 3H, $–CH_3$), 2.44 (s, 3H, $–CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.42, 152.50, 141.08, 132.11, 128.89, 126.73, 114.64, 55.66, 12.03, 10.74; MS (ESI): 247 $[M+H]^+$.

1-(5-Methyl-1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)ethanone oxime (2c) White solid; yield: 0.086 g, 80%; M.p.: 186–188 °C; IR (KBr, cm^{-1}): 3255, 3041, 1627, 1514, 808; ^{1}H NMR (400 MHz, DMSO): δ 11.25 (s, 1H, –OH), 7.49 (d, J = 8.0 Hz, 2H, Ar–H), 7.43 (d, J = 8.0 Hz, 2H, Ar–H), 2.42 (s, 3H, $–CH_3$), 2.30 (s, 3H, $–CH_3$); ^{13}C NMR (100 MHz, DMSO): δ149.11, 141.06, 139.41, 133.22, 131.40, 129.97, 125.04, 20.68, 11.90, 10.36; MS (ESI): 231 $[M+H]^+$.

1-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone oxime (2d) White solid; yield: 0.084 g, 78%; M.p.: 172–174 °C; IR (KBr, cm^{-1}): 3265, 3072, 1593, 1479; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H, –OH), 7.57–7.54 (m, 3H, Ar–H), 7.53–7.45 (m, 2H, Ar–H), 2.50 (s, 3H, $–CH_3$), 2.48 (s, 3H, $–CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.08, 141.15, 135.66, 131.47, 129.67, 129.60, 125.26, 11.93, 10.41; MS (ESI): 217 $[M+H]^+$.

1-(1-(4-Chlorophenyl)-5methyl-1*H*-1,2,3-triazol-4yl)ethanone *O*-prop-2yn-1-yl oxime (3a) White solid; yield: 0.099 g, 86%; M.p.: 128–130 °C; IR (KBr, cm^{-1}): 3290, 3095, 1608, 1560, 1263, 867; ^{1}H NMR (400 MHz, DMSO): δ 7.72 (d, J = 9.0 Hz, 2H, Ar–H), 7.69 (d, J = 9.0 Hz, 2H, Ar–H), 4.80 (d, J = 2.3 Hz, 2H $–CH_2$), 3.51 (t, 1H, –CH), 2.47 (s, 3H, $–CH_3$), 2.34 (s, 3H, $–CH_3$); ^{13}C NMR (100 MHz, DMSO): δ 152.06, 141.18, 135.74, 134.49, 132.37, 129.82, 126.50, 79.90, 74.26, 61.679, 12.80, 10.93; MS (ESI): 289 $[M+H]^+$.

1-(1-(4-Methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone *O*-prop-2yn-1-yl oxime (3b) White solid; yield: 0.096 g, 83%; M.p.: 80–82 °C; IR (KBr, cm^{-1}): 3271, 3007, 1608, 1512, 1253, 866; ^{1}H NMR (400 MHz, DMSO): δ 7.54 (d, J = 8.8 Hz, 2H, Ar–H), 7.16 (d, J = 8.8 Hz, 2H, Ar–H), 4.79 (d, J = 2.3 Hz, 2H, $–CH_2$), 3.85 (s, 3H, $–CH_3$), 3.50 (t, 1H, –CH), 2.43 (s, 3H, $–CH_3$), 2.34 (s, 3H, $–CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.42, 152.32, 140.75, 132.57, 128.91, 126.71, 114.64, 79.97, 74.16, 61.63, 55.66, 12.80, 10.84; MS (ESI): 285 $[M+H]^+$.

1-(5-Methyl-1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)ethanone *O*-prop-2-yn-1-yl oxime (3c) White solid; yield: 0.094 g, 81%; M.p.: 68–70 °C; IR (KBr, cm^{-1}): 3200, 3041, 1610, 1516, 1267, 860; ^{1}H NMR (400 MHz, DMSO): δ 7.50 (d, J = 8.3 Hz, 2H, Ar–H), 7.43 (d, J = 8.3 Hz, 2H, Ar–H), 4.79 (d, J = 2.0 Hz, 2H, $–CH_2$), 3.51 (s, 1H, –CH), 2.45 (s, 3H, $–CH_3$), 2.42 (s, 3H, $–CH_3$), 2.34 (s, 3H, –CH3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.28, 140.85, 139.87, 133.54, 132.41, 130.09, 125.12, 79.97, 74.18, 61.63, 21.26, 12.80, 10.89; MS (ESI): 269 $[M+H]^+$.

1-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone *O*-prop-2-yn-1yl oxime (3d) White solid; yield: 0.09 g, 77%; M.p.: 60–62 °C; IR (KBr, cm^{-1}): 3248, 3066, 1595, 1498, 1253; ^{1}H NMR (400 MHz, DMSO): δ 7.67–7.61 (m, 5H, Ar–H), 4.80 (d, J = 2.3 Hz, 2H, $–CH_2$), 3.51 (t, 1H, –CH), 2.47 (s, 3H, $–CH_3$), 2.35 (s, 3H, $–CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.14, 139.86, 135.54, 132.53, 129.80, 129.63, 125.31, 80.28, 77.29, 61.35, 12.62, 10.31; MS (ESI): 255 $[M+H]^+$.

1-(1-(4-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone *O*-((1-(4-chlorophenyl)- 1*H*-1,2,3-triazol-4-yl)methyl) oxime (5a) White solid; M.p.: 198–200 °C; IR (KBr, cm^{-1}): 3143, 1737, 1595, 1222, 825; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H, Ar–H), 7.70 (d, J = 9.0 Hz, 2H, Ar–H), 7.54 (d, J = 8.8 Hz, 2H, Ar–H), 7.50 (d, J = 8.8 Hz, 2H, Ar–H), 7.40 (d, J = 9.0 Hz, 2H, Ar–H), 5.41 (s, 2H, $–CH_2$), 2.48 (s, 3H, $–CH_3$), 2.46 (s, 3H, $–CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.82, 145.97, 141.25, 135.82, 134.64, 134.44, 132.18, 130.89, 129.98, 129.85, 126.49, 121.73, 120.83, 67.55, 12.89, 10.99; MS (ESI): 442 $[M+H]^+$.

1-(1-(4-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone *O*-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl) oxime (5b) White solid; M.p.: 206–208 °C; IR (KBr,

cm^{-1}): 3014, 1737, 1595, 1227, 823; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H, Ar–H), 7.70 (d, J = 8.8 Hz, 2H, Ar–H), 7.54 (d, J = 8.8 Hz, 2H, Ar–H), 7.50 (d, J = 8.8 Hz, 2H, Ar–H), 7.40 (d, J = 8.8 Hz, 2H, Ar–H), 5.41 (s, 2H, –CH_2), 2.48 (s, 3H, CH_3), 2.46 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.81, 145.96, 141.24, 135.80, 135.50, 134.62, 134.44, 132.17, 129.97, 129.84, 126.48, 121.72, 120.83, 67.55, 12.88, 10.98; MS (ESI): 486 $[M+H]^+$.

1-(1-(4-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone *O*-((1-(4-methoxyphenyl) -1*H*-1,2,3-triazol-4-yl)methyl) oxime (5c) White solid; M.p.: 170–172 °C; IR (KBr, cm^{-1}): 3007, 1737, 1600, 1222, 821; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H, Ar–H), 7.63 (d, J = 9.0 Hz, 2H, Ar–H), 7.54 (d, J = 8.8 Hz, 2H, Ar–H), 7.40 (d, J = 8.8 Hz, 2H, Ar–H), 7.02 (d, J = 9.0 Hz, 2H, Ar–H), 5.40 (s, 2H, –CH_2), 3.87 (s, 3H, –OCH_3), 2.48 (s, 3H, CH_3), 2.46 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.86, 151.64, 145.42, 141.31, 135.76, 134.48, 132.16, 130.48, 129.82, 126.49, 122.23, 121.16, 114.78, 67.67, 55.64, 12.86, 10.98; MS (ESI): 438 $[M+H]^+$.

1-(-1(4-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone O-((1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl) oxime (5d) White solid; M.p.: 156–158 °C; IR (KBr, cm^{-1}): 3147, 1737, 1597, 1220, 817; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97(s, 1H, Ar–H), 7.61 (d, J = 8.3 Hz, 2H, Ar–H), 7.54 (d, J = 8.8 Hz, 2H, Ar–H), 7.40 (d, J = 8.8 Hz, 2H, Ar–H), 7.31 (d, J = 8.3 Hz, 2H, Ar–H), 5.40 (s, 2H, –CH_2), 2.48 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.42 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.66, 145.50, 141.31, 138.97, 135.77, 134.75, 134.48, 132.17, 130.27, 129.82, 126.50, 120.99, 120.51, 67.66, 21.12, 12.86, 10.99; MS (ESI): 422 $[M+H]^+$.

1-(1-(4-Methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone *O*-((1-(4-chlorophenyl) -1*H*-1,2,3-triazol-4-yl)methyl) oxime (5e) White solid; M.p.: 168–170 °C; IR (KBr, cm^{-1}): 3145, 1604, 1510, 1246, 825; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H, Ar–H), 7.70 (d, J = 8.5 Hz, 2H, Ar–H), 7.50 (d, J = 8.8 Hz, 2H, Ar–H), 7.35 (d, J = 8.8 Hz, 2H, Ar–H), 7.04 (d, J = 8.5 Hz, 2H, Ar–H), 5.40 (s, 2H, –CH_2), 3.88 (s, 3H, –OCH_3), 2.47 (s, 3H, –CH_3), 2.44 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.44, 152.07, 146.05, 140.79, 135.52, 134.56, 132.36, 129.94, 128.85, 126.68, 121.72, 120.85, 114.65, 67.51, 55.65, 12.86, 10.88; MS (ESI): 438 $[M+H]^+$.

1-(1-(4-Methoxyphenyl)-5-1*H*-1,2,3-triazol-4-yl)ethanone *O*-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl) oxime (5f) White solid; M.p.: 152–154 °C; IR (KBr, cm^{-1}): 3008, 1739, 1608, 1222, 825; ^1H NMR (400 MHz, DMSO): δ 8.92 (s, 1H, Ar–H), 7.90 (d, J = 8.8 Hz, 2H, Ar–H), 7.81 (d, J = 8.8 Hz, 2H, Ar–H), 7.51 (d, J = 8.8 Hz, 2H, Ar–H), 7.15 (d, J = 8.8 Hz, 2H, Ar–H), 5.32 (s, 2H, –CH_2), 3.85 (s, 3H, –OCH_3), 2.39 (s, 3H, –CH_3), 2.35 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO): δ 159.98, 150.91, 144.88, 139.72, 135.74, 132.76, 132.55, 128.34, 126.83, 122.71, 121.98, 121.30, 114.65, 66.71, 55.56, 12.64, 10.31; MS (ESI): 482 $[M+H]^+$.

1-(1-(4-Methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone *O*-((1-(4-methoxy phenyl)-1*H*-1,2,3-triazol-4-yl)methyl) oxime (5g) White solid; M.p.: 156–158 °C; IR (KBr, cm^{-1}): 3145, 1604, 1512, 1247, 825; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H, Ar–H), 7.63 (d, J = 9.0 Hz, 2H, Ar–H), 7.35 (d, J = 9.0 Hz, 2H, Ar–H), 7.03 (m, 4H, Ar–H), 5.40 (s, 2H, –CH_2), 3.88 (s, 3H, –OCH_3), 3.87 (s, 3H, –OCH_3), 2.46 (s, 3H, –CH_3), 2.44 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.42, 159.85, 151.89, 145.53, 140.87, 132.36, 130.50, 128.88, 126.70, 122.26, 121.16, 114.77, 114.64, 67.64, 55.65, 12.86, 10.90; MS (ESI): 434 $[M+H]^+$.

1-(1-(4-Methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone *O*-((1-(p-tolyl)-1*H*-1,2, 3-triazol-4yl)methyl) oxime (5h) White solid; M.p.: 148–150 °C; IR (KBr, cm^{-1}): 2997, 1739, 1608, 1222, 813; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H, Ar–H), 7.61 (d, J = 8.5 Hz, 2H, Ar–H), 7.35 (d, J = 8.8 Hz, 2H, Ar–H), 7.31 (d, J = 8.5 Hz, 2H, Ar–H), 7.04 (d, J = 8.78 Hz, 2H, Ar–H), 5.40 (s, 2H, –CH_2), 3.88 (s, 3H, –OCH_3), 2.47 (s, 3H, –CH_3), 2.44 (s, 3H, –CH_3), 2.42 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.42, 151.91, 145.60, 140.87, 138.93, 134.77, 132.37, 130.25, 128.88, 126.71, 120.97, 120.51, 114.64, 67.63, 55.66, 21.12, 12.86, 10.90; MS (ESI): 418 $[M+H]^+$.

1-(1-(4-Methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone *O*-((1-(4-butylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl) oxime (5i) White solid; M.p.:144–146 °C; IR (KBr, cm^{-1}): 3007, 1739, 1604, 1222, 837; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H, Ar–H), 7.62 (d, J = 8.5 Hz, 2H, Ar–H), 7.35 (d, J = 8.8 Hz, 2H, Ar–H), 7.32 (d, J = 8.5 Hz, 2H, Ar–H), 7.04 (d, J = 8.8 Hz, 2H, Ar–H), 5.40 (s, 2H, –CH_2), 3.88 (s, 3H, –OCH_3), 2.67–2.65 (t, 2H, –CH_2), 2.47 (s, 3H, –CH_3), 2.44 (s, 3H, –CH_3), 1.66–1.59 (m, 2H, –CH_2), 1.41–1.32 (m, 2H, –CH_2), 0.94 (t, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.42, 151.89, 145.59, 143.95, 140.86, 134.88, 132.36, 129.63, 128.88, 126.70, 121.00, 120.56, 114.64, 67.63, 55.65, 35.18, 33.46, 22.25, 13.92, 12.85, 10.90; MS (ESI): 460 $[M+H]^+$.

1-(5-Methyl-1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)ethanone *O*-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl) oxime (5j) White solid; M.p.:176–178 °C; IR (KBr, cm^{-1}): 3016, 1739, 1595, 1222, 812; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H, Ar–H), 7.70 (d, J = 8.8 Hz, 2H, Ar–H), 7.50 (d, J = 8.8 Hz, 2H, Ar–H), 7.35 (d, J = 8.5 Hz, 2H, Ar–H), 7.31 (d, J = 8.5 Hz, 2H, Ar–H), 5.41 (s, 2H, –CH_2), 2.47 (s, 3H, –CH_3), 2.46 (s, 3H, –CH_3), 2.45 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.02, 146.05, 140.91, 139.92, 134.56, 133.48, 132.22, 130.09, 129.94, 125.10, 121.72, 120.87, 118.52, 67.51, 21.26, 12.88, 10.95; MS (ESI): 422 $[M+H]^+$.

1-(5-Methyl-1-(*p*-tolyl)-1*H*-1,2,3-truazol-4-yl)ethanone *O*-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl) oxime

(5k) White solid; M.p.:192–194 °C; IR (KBr, cm^{-1}): 3016, 1739, 1564, 1220, 812; ^{1}H NMR (400 MHz, DMSO): δ 8.92 (s, 1H, Ar–H), 7.90 (d, J = 8.8 Hz, 2H, Ar–H), 7.81 (d, J = 8.8 Hz, 2H, Ar–H), 7.48 (d, J = 8.3 Hz, 2H, Ar–H), 7.43 (d, J = 8.3 Hz, 2H, Ar–H), 5.32 (s, 2H, –CH_2), 2.42 (s, 3H, –CH_3), 2.41 (s, 3H, –CH_3), 2.35 (S, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.44, 152.07, 146.12, 140.80, 136.00, 132.94, 132.36, 128.85, 126.70, 122.45, 121.96, 120.75, 114.65, 67.53, 55.66, 12.88, 10.90; MS (ESI): 466 $[M+H]^+$.

1-(5-Methyl-1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)ethanone *O*-((1-(4-methoxyphenyl)-1*H*-1,2, 3-triazol-4-yl)methyl) oxime (5l) White solid; M.p.:146–148 °C; IR (KBr, cm^{-1}): 3016, 1737, 1608, 1220, 827; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H, Ar–H), 7.63 (d, J = 9.0 Hz, 2H, Ar–H), 7.34 (d, J = 8.8 Hz, 2H, Ar–H), 7.31 (d, J = 8.8 Hz, 2H, Ar–H), 7.01 (d, J = 9.0 Hz, 2H, Ar–H), 5.40 (s, 2H, –CH_2), 3.86 (s, 3H, –OCH_3), 2.47 (s, 3H, –CH_3), 2.46 (s, 3H, –CH_3), 2.45 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.85, 151.87, 145.52, 140.98, 139.89, 133.52, 132.20, 130.51, 130.08, 125.12, 122.25, 121.17, 114.77, 67.64, 55.64, 21.25, 12.86, 10.95; MS (ESI): 418 $[M+H]^+$.

1-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone *O*-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl) oxime (5m) White solid; M.p.:178–180 °C; IR (KBr, cm^{-1}): 3061, 1737, 1595, 1220, 804; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H, Ar–H), 7.63 (d, J = 8.8 Hz, 2H, Ar–H), 7.49–7.45 (m, 3H, Ar–H), 7.43 (d, J = 8.8 Hz, 2H, Ar–H), 7.37 (dd, J = 8.0, 2.0 Hz, 2H, Ar–H), 5.34 (s, 2H, –CH_2), 2.41 (s, 3H, –CH_3), 2.40 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.95, 145.01, 140.02, 134.95, 134.48, 133.56, 131.17, 128.93, 128.68, 128.53, 124.27, 120.69, 119.80, 66.51, 11.87, 9.96; MS (ESI): 408 $[M+H]^+$.

1-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone *O*-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl) oxime (5n) White solid; M.p.: 188–190 °C; IR (KBr, cm^{-1}): 3062, 1739, 1595, 1220, 812; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H, Ar–H), 7.66 (d, J = 8.5 Hz, 2H, Ar–H), 7.64 (d, J = 8.5 Hz, 2H, Ar–H), 7.56–7.53 (m, 3H, Ar–H), 7.45 (dd, J = 8.3, 2.3 Hz, 2H, Ar–H), 5.41 (s, 2H, –CH_2), 2.48 (s, 3H, –CH_3), 2.47 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.00, 146.08, 141.05, 135.99, 132.94, 132.21, 129.71, 129.57, 125.30, 122.46, 121.96, 120.77, 67.53, 12.91, 11.00; MS (ESI): 452 $[M+H]^+$.

1-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone *O*-((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)oxime (5o) White solid; M.p.:130–132 °C; IR (KBr, cm^{-1}): 3082, 1737, 1597, 1232, 802; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H, Ar–H), 7.55 (d, J = 9.0 Hz, 2H, Ar–H), 7.48–7.45 (m, 3H, Ar–H), 7.37 (dd, J = 8.3, 2.0 Hz, 2H, Ar–H), 6.93 (d, J = 9.0 Hz, 2H, Ar–H), 5.32 (s, 2H, –CH_2), 3.78 (s, 3H, –OCH_3), 2.41 (s, 3H, –CH_3), 2.39 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.80, 150.75, 144.42, 140.07, 134.95, 131.16, 129.43, 128.64, 128.52, 124.25, 121.19, 120.18, 113.73, 66.59, 54.60, 11.84, 9.95; MS (ESI): 404 $[M+H]^+$.

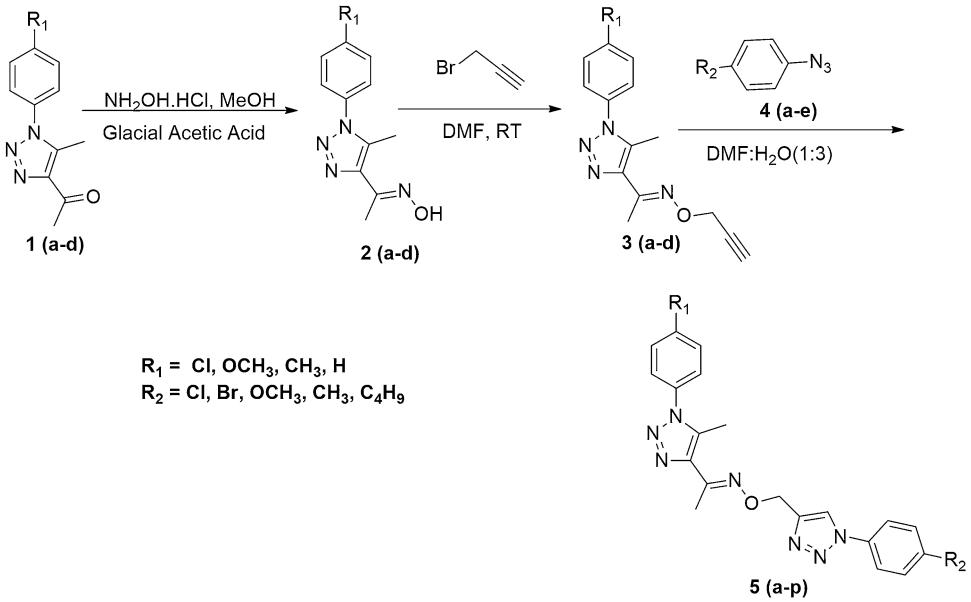
1-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone *O*-((1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl) oxime (5p) White solid; M.p.:110–112 °C; IR (KBr, cm^{-1}): 3020, 1741, 1598, 1220, 806; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H, Ar–H), 7.61 (d, J = 8.5 Hz, 2H, Ar–H), 7.56–7.53 (m, 3H, Ar–H), 7.45 (dd, J = 8.0, 2.0 Hz, 2H, Ar–H), 7.31 (d, J = 8.5 Hz, 2H, Ar–H), 5.41 (s, 2H, –CH_2), 2.48 (s, 3H, –CH_3), 2.47 (s, 3H, –CH_3), 2.42 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.80, 145.54, 141.10, 138.92, 135.99, 134.75, 132.20, 130.25, 129.68, 129.55, 125.29, 121.03, 120.48, 67.62, 21.10, 12.88, 10.99; MS (ESI): 388 $[M+H]^+$.

3. Results and Discussion

3.1 *Chemistry*

The synthetic route for the construction of the target molecules is illustrated in Scheme 1. Initially the compounds **1(a–d)** were synthesised according to literature.[29,30] The oximes **2(a–d)** were obtained by the reaction of the compounds **1(a–d)** with hydroxylamine hydrochloride in methanol using glacial acetic acid in catalytic amount, which were on treatment with propargyl bromide and K_2CO_3 in DMF gave compounds **3(a–d)**. These compounds on coupling with different azido benzenes **4(a–e)** by alkyne-azide cycloaddition reaction gave the titled compounds **5(a–p)**.

A preliminary study was carried out by the synthesis of compound **5a** in presence of different solvents and catalysts, to develop a high synthetic protocol for the synthesis of titled compounds, under both conventional and microwave irradiation methods. In this investigation, we used different solvents with water as co-solvent (THF:H_2O, EtOH:H_2O, DMF:H_2O), in different proportions (1:2 and 1:3) and two catalysts ($CuSO_4{\cdot}5H_2O$/Sodium ascorbate and CuI) as shown in Table 1. Based on the optimisation conditions, the solvent mixture DMF:H_2O (1:3) under both conventional and microwave irradiation method using CuI as a catalyst gave a better yield. Thus, utilising these optimisation conditions we synthesised the titled compounds **5(a–p)** under both conventional and microwave irradiation method through the 1,3-dipolar cycloaddition of alkynes and azides using CuI as a catalyst in DMF:H_2O mixture and summered the results in Table 2. In addition to this, there is an increment in the yield and reduction in time under microwave irradiation method in comparison with the conventional method.



Scheme 1. Synthetic route for the preparation of titled compounds.

Table 1. Optimisation of solvent and catalyst of compound **5a**

Sl. no.	Solvent	Catalyst	Conventional method		Microwave method	
			Time (h)	Yield (%)	Time (min)	Yield (%)
1	THF:H_2O (1:2)	$CuSO_4$•$5H_2O$, Sodium ascorbate	36	14	20	18
2	THF:H_2O (1:3)	$CuSO_4$•$5H_2O$, Sodium ascorbate	36	16	20	24
3	EtOH:H_2O (1:2)	$CuSO_4$•$5H_2O$, Sodium ascorbate	20	28	15	42
4	EtOH:H_2O (1:3)	$CuSO_4$•$5H_2O$, Sodium ascorbate	20	30	15	56
5	DMF:H_2O (1:2)	$CuSO_4$•$5H_2O$, Sodium ascorbate	12	38	15	58
6	DMF:H_2O (1:3)	$CuSO_4$•$5H_2O$, Sodium ascorbate	12	40	15	60
7	THF:H_2O (1:2)	CuI	36	20	20	26
8	THF:H_2O (1:3)	CuI	36	25	20	38
9	EtOH:H_2O (1:2)	CuI	20	33	15	46
10	EtOH:H_2O (1:3)	CuI	20	38	15	54
11	DMF:H_2O (1:2)	CuI	8	52	12	85
12	DMF:H_2O (1:3)	CuI	8	56	12	92

3.2 *Antibacterial and anti-fungal activity*

The synthesised scaffolds **5(a–p)** were evaluated for their *in vitro* antibacterial activity by using Agar-well diffusion method. We tested the compounds **5(a–p)** against two-Gram positive bacterial strains *viz., Staphylococcus* aureus and *Bacillus subtills* and two-Grams negative bacterial strains *viz., Escherichia coli* and *Pseudomonas* by using streptomycin as a standard drug at two different concentrations 10 μg/mL and 20 μg/mL. The zone of inhibition was measured in mm and the results were depicted in Table 3. Furthermore, the compounds **5(a–p)** were also screened for their *in vitro* antifungal activity by using Agar-well diffusion method. We tested the compounds against two fungi *viz., Aspergillus Niger* and *Aspergillus flavus* at 50 μg/mL concentration, by using Nystatin as a standard drug. The results obtained were as shown in Table 3.

From Table 3 it is clear that most of the scaffolds exhibit moderate to good activity. Among all the compounds **5(a–p)** compound **5g**, **5i**, **5l** and **5h** have a higher zone of inhibition and compound **5f**, **5o**, **5c** and **5e** shown comparable zone of inhibition with the standard drug against the tested bacterial strains. Furthermore, compound **5g** and **5i** displayed a higher zone of inhibition and compound **5l**, **5h**, **5f** and **5o** displayed comparable zone of inhibition with the standard drug against the tested fungal strains. The compounds containing OCH_3 substituents showed good activity compared to other compounds.

Table 2. Comparison of yields and reaction times under both conventional and microwave irradiation methods

			Conventional method			Microwave method		
Entity	R_1	R_2	Time (h)	Yield (%)	Yield (g)	Time (min)	Yield (%)	Yield (g)
5a	Cl	Cl	8	56	0.086	12	92	0.141
5b	Cl	Br	8	56	0.094	12	89	0.150
5c	Cl	OCH_3	8	47	0.071	12	87	0.132
5d	Cl	CH_3	8	51	0.074	12	89	0.130
5e	OCH_3	Cl	8	52	0.080	12	90	0.139
5f	OCH_3	Br	8	52	0.088	12	83	0.141
5g	OCH_3	OCH_3	8	42	0.064	12	77	0.118
5h	OCH_3	CH_3	8	49	0.072	12	83	0.122
5i	OCH_3	C_4H_9	8	49	0.079	12	83	0.134
5j	CH_3	Cl	8	55	0.087	12	82	0.129
5k	CH_3	Br	8	55	0.096	12	88	0.153
5l	CH_3	OCH_3	8	45	0.070	12	86	0.133
5m	H	Cl	8	53	0.085	12	84	0.134
5n	H	Br	8	53	0.094	12	80	0.142
5o	H	OCH_3	8	45	0.071	12	78	0.123
5p	H	CH_3	8	51	0.078	12	80	0.122

Table 3. Anti-bacterial and anti-fungal activities of compounds **5(a–p)**.

	Gram-positive bacteria				Gram-negative bacteria				Fungal strains	
	S aureus		*B subtills*		*E. coli*		*Pseudomonas*		*A. niger*	*A. flavus*
Compound	10 μg/mL	20 μg/mL	10 μg/mL	20 μg/mL	10 μg/mL	20 μg/mL	10 μg/mL	20 μg/mL	50 μg/mL	50 μg/mL
Zone of inhibition (mm) after 24 h										
5a	6	8	5	11	5	9	5	10	6	7
5b	5	9	6	12	6	10	5.5	11	9	6
5c	8	13	9.5	16.5	8	16	8.5	15	14.5	11
5d	6.5	11	7	15	7	13	7	14	12	10
5e	8	13.5	9	16	8	15.5	8.5	15	14	11.5
5f	9	15.5	10.5	17	10	17	9.5	16.5	17	13.5
5g	11	17	12.5	20	13	21	12	22	20	19
5h	9.5	16	11	18.5	11	19.5	11.5	20	17	14.5
5i	11	16.5	12	19.5	12.5	20	11.5	20	18.5	19
5j	6	11	7	15	7	14	7.5	13	12.5	10.5
5k	6.5	11.5	8.5	16	7.5	15	8	14.5	13	11
5l	10	15.5	11.5	19	12	19.5	11	21	16.5	15
5m	5.5	10	6.5	14	6	12	6	11	11	10
5n	5.5	10.5	6	13	6	11	6	12	10	9
5o	8.5	14	10	16.5	9	16.5	9	16	16	13
5p	7	12	8.5	16	7.5	15	8	14	13	10
Streptomycin	9	15	11	18	10	18	10	17	–	–
Nystatin	–	–	–	–	–	–	–	–	18	16

4. Conclusions

In summary, we reported a series of new 1-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)ethanone *O*-((1-aryl-1*H*-1,2,3-triazol-4-yl)methyl) oxime **5(a–p)** derivatives through Cu(I) mediated 1,3-dipolar cycloaddition reaction under both conventional and microwave irradiation methods. Furthermore, compounds **5g**, **5i**, **5l** and **5h** exhibited good antibacterial activity and compounds **5g** and **5i** exhibited good anti-fungal activity against the tested microorganisms. The higher yields, reduction in time, minimal purification,

simplicity in procedure, low cost, and easy availability of catalyst are the advantages of the reported method.

Supplementary Information (SI)

Figures S1–S48 are available at www.ias.ac.in/chemsci.

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