Synthesis and Biological Evaluation of Novel 1,4-Disubstituted 1,2,3-Triazoles and Bis 1,2,3-Triazoles as Anti-Bacterial Agents

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Abstract

A library of novel 1,4-disubstituted 1,2,3-triazoles 3a-3k was prepared by using Click-chemistry concept. In this 1,3-dipolar cycloaddition, the 3-methoxy-4-(prop-2-yn-1-yl)oxybenzaldehyde (1) was used as alkyne partner which was synthesized from vanillin and propargyl bromide and was reacted with differently substituted arylpropoxy azides to furnish series of mono and bis 1,4-disubstituted-1,2,3-triazoles. All the synthesized compounds were characterized spectroscopically and were evaluated for their antimicrobial activity. Preliminary results of antibacterial screening revealed that various synthesized compounds have the highest inhibitory effects then the control ciprofloxacin against the growth of a wide range of both gram positive and gram negative bacterial strains. Compounds 3g and 3b were found to be the most active against various strains of gram-positive and gram-negative bacteria.

Keywords: Click chemistry; Azide-alkyne cycloaddition 1,4-disubstituted 1,2,3-triazoles; Antibacterial agents; Antimicrobial activity

Introduction

Antimicrobial resistance (AMR) is the major threat to human health growing in the field of infectious diseases caused by bacteria, fungi, viruses and parasites. According to a survey in 2016, around 490,000 people have multidrug-resistant Tuberculosis (MDR-TB) worldwide, and the drug resistance is commencing to complicate the battle against HIV as well as malaria [1]. With the passage of time, the need for effective antimicrobial in general and anti-bacterial in particular has become essential to control the spread of ‘superbugs’; microorganisms that develop antimicrobial resistance are sometimes referred to as superbugs [2].

The triazoles have grabbed significant attention of organic and medicinal chemists since the inception of copper catalyzed azide-alkyne cycloaddition (CuAAC) [3-6]. This method has superiority over conventional thermal method [7] where reaction of an alkyne and azide would generate a mixture of both 1,4- and 1,5-disubstituted 1,2,3-triazoles. While in CuAAC exclusively 1,4-disubstituted 1,2,3-triazoles are obtained in excellent yields [8,9] which has a very promising role in pharmaceutical industry [10-12].

The importance of triazoles in medicinal chemistry is inevitable with both biological and pharmaceutical applications [13-15]. Recently 1,2,3-triazoles have emerged as active components in the agrochemical [16], pesticidal, polymer [17-19], materials chemistry fields [20-23]. 1,2,3-triazoles have also applications as optical brighteners [24], corrosion inhibitors [25,26], photo stabilizers for fibers, plastics or dyes [27] and UV-screens for the protection of human skin [28]. In addition, several compounds of the 1,2,3-triazole family have shown a broad spectrum of biological properties such as antibacterial [29], and anti-HIV activity [30], anticancer [31,32], antifungal [33,34], herbicidal [35,36], anti-inflammatory [37] and anti-tuberculosis [38,39]. 1,2,3-Triazole moiety is present in many available drugs [40,41] and there are several reports on the antibacterial activity of triazoles [42].

In the present study we report the synthesis of novel derivatives of 1,2,3-triazoles via click strategy using copper catalyzed azide-alkyne cycloaddition (CuAAC) being regioselective, efficient, easy-to-use and hazards free with broad substrate scope. Using this strategy mono and homo-dimers of 1,2,3-triazoles have been synthesized in search of new antibacterial agents.

Experimental

General remarks and instrumentation

The melting points were recorded on electrothermal series digital melting point apparatus. IR spectra were recorded on potassium bromide (KBr) disk on a. 1HNMR spectra were recorded on 300 MHz in deuterated dimethylsulfoxide (DMSO,d6). Chemical shift values are given in part per million (ppm). The mass spectra were recorded using MAT CH-5 spectrophotometer at 70 eV EI. The above triazole compounds were synthesized according to literature.

Chemistry

Synthesis of 1a and 1b: Vanillin and 4,4’-methylenebis(2-methylenepheno) were reacted with propargyl bromide in the presence of potassium carbonate as base and dimethylformamide as solvent. To a stirred solution of respective phenol (5.0 mmol) in dry DMF (15 mL), anhydrous potassium carbonate (15.0 mmol) was added and heated to 55-60°C for 30 minutes under inert atmosphere. The mixture was then cooled to room temperature and propargyl bromide (80% solution in toluene) (1.026 g, 8.62 mmol) was added dropwise through a septum.

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using syringe. The mixture was stirred for 2 hours at 60°C and poured on the ice water with stirring. Stirring was continued for 10 minutes; the solid separated was filtered and dried under vacuum to afford the desired compounds 1a and 1b. Recrystallization was performed from EtOAc: n-hexane (1:2) and by slow evaporation.

**Synthesis of alky or arylpropyl azides 2a-k:** To a stirred solution of arylpropoxy bromide, a slight excess of sodium azide was added in the presence of dimethylformamide as solvent. The reaction mixture was stirred at room temperature for 1-2 hour. Afterwards dimethylformamide was removed by large dilution with water and extraction with chloroform. The organic layers were collected, dried (K2CO3) and filtered. The filtrate was evaporated to get the solid separated was filtered and dried under vacuum to afford the compound.

According to general procedure bis(3-methyl-4-(prop-2-yn-1-yloxy)phenyl) methylene 1b (1.6 g, 5.3 mmol) 1 was reacted with 1-(3-azidopropoxy)-4-nitrobenzene 2c (2.3 g, 10.6 mmol) in the presence of copper (II) sulphate pentahydrate (0.07 g, 0.27 mmol) and 2 mol % sodium ascorbate (0.21 g, 1.06 mmol) for twelve hour in DMF. After workup and purification 3f was obtained in 78% Yield; m.p: 101-102°C; IR (KBr) ν max/cm⁻¹, 1700 (C=O), 1670, 2210 (N=O), 3380 (N-H); ¹H NMR (300 MHz, DMSO-d₆) δ: 8.80 (s, 1H, Ar-CHO), 7.9 (d, 8H, Ar-H), 6.3 (d, 2H, OCH₂), 4.7 (t, 2H, J=7.3 Hz), 4.3 (s, 2H, OCH₂), 4.0 (t, 2H, J=7.3 Hz), 3.9 (t, 2H), 3.7 (m, 2H), 3.6 (m, 2H), 3.4 (m, 2H), 3.2 (m, 2H, ArCH₂Ar), 3.5 (s, 3H, ArCCH), 2.6 (t, 2H, PhOCH₂CCH), 2.1 (d, 6H, ArCH₂Ar), 3.7 (d, 2H, ArCH₂Ar), 3.5 (s, 3H, ArCH₂Ar), 2.3 (s, 3H, ArCH₂Ar), 2.1 (d, 6H, ArCH₂Ar), 3.7 (d, 2H, ArCH₂Ar), 3.5 (s, 3H, ArCH₂Ar), 2.3 (s, 3H, ArCH₂Ar), 2.1 (d, 6H, ArCH₂Ar), 3.7 (d, 2H, ArCH₂Ar), 3.5 (s, 3H, ArCH₂Ar), 2.3 (s, 3H, ArCH₂Ar), 2.1 (d, 6H, ArCH₂Ar), 3.7 (d, 2H, ArCH₂Ar), 3.5 (s, 3H, ArCH₂Ar), 2.3 (s, 3H, ArCH₂Ar), 2.1 (d, 6H, ArCH₂Ar); MS m/z (%): 526 (M +, 100): Anal. Calculated for C₃₀H₃₀N₄O₅ (526): C, 68.17; H, 6.10; N, 10.60; Found: C, 68.2; H, 6.1; N, 10.9%.  

**3-methoxy-4-((1-(3-(4-nitrophenoxy)propyl)-1H-1,2,3-triazol-4-yl) methoxy)-3-methoxybenzaldehyde (3a):** According to general procedure 3-methoxy-4-(prop-2-yn-1-yloxy)benzaldehyde 1a (1.0 g, 5.3 mmol) was reacted with 1-(3-azidopropanoyl)-4-bromobenzene 2a (2.7 g, 10.6 mmol) in the presence of copper (II) sulphate pentahydrate (0.07 g, 0.27 mmol) and 20 mol % sodium ascorbate (0.21 g, 1.06 mmol) for twelve hour in DMF. After workup and purification 3a was obtained in 82% Yield; m.p: 101-102°C; IR (KBr) ν max/cm⁻¹, 1700 (C=O), 1670, 2285 (C=C); ¹H NMR (300 MHz, DMSO-d₆) δ: 8.98 (s, 1H, Ar-CHO), 8.3 (s, 1H, H-triazole), 7.5 (m, 2H, Ar-H), 7.4 (dd, 2H, Ar-H), 7.2 (d, 2H, Ar-H), 6.8 (d, 1H, Ar-H), 5.2 (s, 2H, OCH₂), 4.5 (t, 2H, J=7.3 Hz), 4.0 (s, 2H, OCH₂), 3.8 (t, 2H, J=7.3 Hz), 2.33-2.29 (m, 2H, ArCH₂CH₂CH₃); MS m/z (%): 445 (M⁺, 100); Anal. Calculated for C₁₅H₁₄BrN₃O₇ (445): C, 58.8; H, 5.5; N, 9.3;  

5-((2-methyl-4-((3-methyl-4-(prop-2-yn-1-yloxy)benzaldehyde (3b): According to general procedure bis(3-methyl-4-(prop-2-yn-1-yloxy) phenyl)methylene 1b (1.6 g, 5.3 mmol) 1 was reacted with 1-(3-azidopropanoyl)-3-nitrobenzene 2c (2.3 g, 10.6 mmol) in the presence of copper (II) sulphate pentahydrate (0.07 g, 0.27 mmol) and 20 mol % sodium ascorbate (0.21 g, 1.06 mmol) for twelve hour in DMF. After workup and purification 3f was obtained in 78% Yield; m.p: 129-130°C; IR (KBr) ν max/cm⁻¹, 1700 (C=O), 1677, 2189 (C=C); ¹H NMR (300 MHz, DMSO-d₆) δ: 8.23 (s, 1H, H-triazole), 7.8 (d, 1H Ar-H), 7.6 (s, 1H Ar-H), 7.50 (t, 1H, J=8.2 Hz Ar-H), 7.3 (dd, 1H, Ar-H), 7.0 (m, 6H Ar-H), 5.1 (s, 2H, ArOCH₂), 4.7 (d, 2H), 4.5 (t, 2H, ArOCH₂CH₂CH₂), 4.1 (t, 2H, ArOCH₂CH₂CH₂), 3.7 (s, 2H ArCH₂Ar), 3.5 (s, 1H ArCH₂Ar), 2.3 (s, 3H, ArCH₂Ar), 2.1 (d, 6H, ArCH₂Ar), 3.7 (d, 2H, ArCH₂Ar); MS m/z (%): 445 (M⁺, 100); Anal. Calculated for C₁₅H₁₄BrN₃O₇ (445): C, 58.8; H, 5.5; N, 9.3;  

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**Figure 1:** Antibacterial activity of compound 3g and ciprofloxacin (control) against gram-positive bacterial strains.
In a 100 mL round bottomed flask containing stirred solution of 3-methoxy-4-(prop-2-yn-1-yloxy)benzaldehyde 1a (1.0 g, 5.3 mmol) 1 was reacted with 4-(3-formyl-2-methoxyphenoxy)methyl)-1H-1,2,3-triazole 3f in the presence of copper (II) sulphate pentahydrate (0.07 g, 0.27 mmol) and 20 mol % sodium ascorbate (0.21 g, 1.06 mmol) for twelve hour in DMF. After workup and purification 3f was obtained in 69% Yield; m.p. 114-115°C; IR (KBr) νmax/cm⁻¹, 1700 (C=O), 1670, 2180 (C=C); 1H NMR (300 MHz, DMSO-d6): δ: 9.52 (s, 2H, Ar-CHO), 8.3 (s, 1H, H-triazole), 7.7 (s, 1H, Ar-H), 7.5 (d, 2H, Ar-H), 7.5 (d, 1H, Ar-H), 7.4 (d, 1H, Ar-H), 7.3 (d, 2H, Ar-H), 7.1 (d, 2H, Ar-H), 6.9 (s, 1H, Ar-H), 5.2 (s, 2H, OCH 2), 4.0 (t, 2H), 3.7 (t, 4H, ArO-CH 3); MS m/z (%): 425 (M +, 100); Anal. Calculated for C 22H23N3O6 (425.43): C, 62.11; H, 5.45; N, 9.88; %Found: C, 62.10; H, 5.46; N, 9.86.

**General experimental procedure for the synthesis of bis-triazoles 3g-k:** In a 100 ml round bottomed flask containing stirred solution of 3-methoxy-4-(prop-2-yn-1-yloxy)benzaldehyde 1a (1.0 g, 5.3 mmol) in 20 ml DMF was added appropriate bis1-(3-azidopropoxy)naphthalene 2a (2.4 g, 10.6 mmol) in the presence of copper (II) sulphate pentahydrate (0.07 g, 0.27 mmol) and 20 mol % sodium ascorbate (0.21 g, 1.06 mmol) for twelve hour in DMF. After workup and purification 3f was obtained in 69% Yield; m.p. 114-115°C; IR (KBr) νmax/cm⁻¹, 1700 (C=O), 1670, 2180 (C=C); 1H NMR (300 MHz, DMSO-d6): δ: 9.52 (s, 2H, Ar-CHO), 8.3 (s, 1H, H-triazole), 7.7 (s, 1H, Ar-H), 7.5 (d, 2H, Ar-H), 7.5 (d, 1H, Ar-H), 7.4 (d, 1H, Ar-H), 7.3 (d, 1H, Ar-H), 7.1 (d, 2H, Ar-H), 6.9 (s, 1H, Ar-H), 5.1 (s, 2H, Ar-CH 2), 4.4 (t, 2H), 4.0 (s, 3H, OCH 3), 3.8 (t, 2H), 2.2 (m, 2H, ArCH 2CH 2CH 2), 3.5 (s, 6H, ArO-CH 3); MS m/z (%): 425 (M +, 100); Anal. Calculated for C 24H23N3O4 (417): C, 69; H, 5.4; N, 10.3.

3-methoxy-4-((1-(3-naphthalen-2-yloxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy) benzaldehyde (3d): According to general procedure 3-methoxy-4-(prop-2-yn-1-yloxy)benzaldehyde 1a (1.0 g, 5.3 mmol) 1 was reacted with 2-(3-azidopropoxy)naphthalene 2f (2.4 g, 10.6 mmol) in the presence of copper (II) sulphate pentahydrate (0.07 g, 0.27 mmol) and 20 mol % sodium ascorbate (0.21 g, 1.06 mmol) for twelve hour in DMF. After workup and purification 3d was obtained in 69% Yield; m.p. 111-112°C; IR (KBr) νmax/cm⁻¹, 1700 (C=O), 1670, 2285 (C=C); 1H NMR (300 MHz, DMSO-d6) δ: 9.6 (s, 1H, Ar-CHO), 7.5 (d, 2H, Ar-H), 7.4 (dd, 1H, Ar-H), 7.3 (d, 2H, Ar-H), 7.1 (d, 2H, Ar-H), 6.9 (d, 1H, Ar-H), 5.2 (s, 2H, Ar-CH 2), 4.4 (t, 2H), 4.0 (s, 3H, OCH 3), 3.8 (t, 2H), 2.2 (m, 2H, ArCH 2CH 2CH 2), 3.5 (s, 6H, ArO-CH 3); MS m/z (%): 417 (M +, 100); Anal. Calculated for C 24H23N3O4 (417): C, 69; H, 5.4; N, 10.

**Table 1:** In vitro antibacterial screening (mm) of synthesized 1,2,3-triazoles.

<table>
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<tr>
<th>Compounds</th>
<th>E. coli</th>
<th>S. typhii</th>
<th>P. aeruginosa</th>
<th>S. paratyphi B</th>
<th>Shigella</th>
<th>S. paratyphi A</th>
<th>K. pneumonia</th>
<th>Entero-bacteriaceae</th>
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<td>15.5</td>
<td>26.5</td>
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<td>22</td>
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<td>23.5</td>
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<td>16.5</td>
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<td>19</td>
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<tr>
<td>3c</td>
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<td>24</td>
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<td>18</td>
<td>22</td>
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<td>20</td>
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<tr>
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<td>15</td>
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<td>19</td>
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<tr>
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<td>-</td>
<td>18</td>
<td>25</td>
<td>18</td>
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* (–): Inactive (no inhibition)
solvent system; EtOAc:n-Hexane). After completion of reaction the color of reaction mixture was changed from green to brown. DMF was separated by freeze drying and filtered through filter paper. Reaction mixture was dissolved in dichloromethane and solvent was evaporated under reduced pressure. The products were purified by silica gel column chromatography using ethyl acetate:n-hexane (3:7) as eluent.

**Synthesis and characterization data of bis-triazoles 3g-k:***

4,4′-(((naphthalene-2,7-diylioxy)bis(propene-3,1-diyl))bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene)bis(oxy))bis(3-methoxybenzaldehyde) (3g): According to general procedure 3-methoxy-4-(prop-2-yn-1-yl)benzaldehyde 1a (1.0 g, 5.3 mmol) was reacted with 1,3-bis(3-azidopropoxy)benzene 2g (4.6 g, 16.8 mmol) in the presence of copper (II) sulphate pentahydrate (0.07 g, 0.27 mmol) and 20 mol % sodium ascorbate (0.21 g, 1.06 mmol) for twelve hour in DMF. After workup and purification 3g was obtained in 82% Yield; m.p. 123-125°C; IR (KBr) ν max/cm⁻¹: 1700 (C=O), 1677, 1700 (C=C; C=C); ¹H NMR (300 MHz, DMSO-d⁶): δ: 9.65 (s, 2H, Ar-CHO), 7.95 (s, 2H, HCCN), 7.4 (d, 2H, Ar-H), 7.3 (d, 2H, Ar-H), 6.8 (d, 2H, Ar-H), 5.2 (s, 4H, Ar-CH₄), 4.1 (m, 4H, ArCH₂CH₃CH₂), 3.7 (s, 4H, ArOCH₃). ESI-MS (m/z) (%): 760.3 (M⁺, 100): Anal. Calculated for C₄₁H₄₀Cl₂N₆O₈ (815.70); C, 66.30; H, 5.83; Cl, 8.69; N, 10.30; O, 15.69%.

**Antimicrobial activity**

The novel compounds were tested against series of eight gram positive and eight gram-negative bacterial strains by using standard protocol of agar well diffusion method [43] on Mueller-Hinton agar (MHA). The inhibition zones were reported in millimeter (mm) and all experiments were run in triplicate.

**Results and Discussion**

**Chemistry**

Various alkyl azides 2a-k were prepared according to previously reported procedure [15]. For this purpose various bromopropoxy arylamines were refluxed with sodium azides to get 3-azidopropoxy arynes 2a-f as shown in Scheme 1. Some bis(azidopropoxy)aryl compounds were also synthesized 2g-k. The alkyne partner 1a namely 3-methoxy-4-(prop-2-yn-1-yl)benzaldehyde was synthesized starting from easily available vanillin while 1b bis(3-methyl-4-(prop-2-yn-1-yl)phenyl) methane from 4,4′-methylenebis(2-methylphenyl) by propargylation in the presence of potassium carbonate as base (Scheme 1). The synthesized azides 2a-k were then reacted with alkyne partner 1 in the presence of Cu(I) catalyst which was generated in situ by the reduction of CuSO₄·5H₂O with sodium ascorbate to deliver 3-methoxy-4-((1-(3-arylpropyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde 3a-k in good yield (Scheme 1). All the synthesized triazoles were structurally characterized by IR, NMR, Mass spectrometry and by elemental analysis.

**Spectroscopic analysis**

The ¹H NMR spectra of all the products showed a characteristic signal of the presence of potassium carbonate as base (Scheme 1). The synthesized azides 2a-k were then reacted with alkyne partner 1 in the presence of Cu(I) catalyst which was generated in situ by the reduction of CuSO₄·5H₂O with sodium ascorbate to deliver 3-methoxy-4-((1-(3-arylpropyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde 3a-k in good yield (Scheme 1). All the synthesized triazoles were structurally characterized by IR, NMR, Mass spectrometry and by elemental analysis.

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Biological activity

The synthesized series of triazoles 3a-k was subjected to antibacterial activity and were screened to determine their in vitro ability to inhibit the growth of selected pathogens by well diffusion method. The antibacterial inhibition was tested against eight Gram-positive bacterial strains such as *Bacillus subtilis*, Methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *Vancomycin-resistant Enterococcus*; and eight Gram-negative bacteria strains such as *Escherichia coli*, *S. Typhi*, *Shigella*, *Salmonella paratyphi* A, *Klebsiella pneumonia* and *Enterobacteriaceae*.

The % inhibition of all the compounds against gram positive bacteria are given in Table 1, while for gram negative bacteria are given in Table 2. The zone of inhibition is calculated in mm using standard agar well diffusion method [43]. The values are compared using a control (Ciprofloxacin) which was prepared in the same way as the plates using DMSO as a solvent and all experiments were run in a triplicate.

Antibacterial activity: The synthesized library of triazoles showed promising activity against most of the strains of bacteria. From these results a structure activity relationship (SAR) can be deduced for the tested triazoles. The antibacterial screening was explored by varying the differently substituted aromatics at propyl group at position 1 of 1,2,3-triazoles (3a-k). Different electron donating (CH) and electron withdrawing (Br, Cl and NO2) substituents on the aromatic rings of azide partners were tried to unravel the antimicrobial potency. Overall bis-1,2,3-triazoles (3g-k) were found to be more potent against gram positive bacterial strains (Table 1). Compound 3g with benzene ring as aromatic linker between both triazoles showed promising activity against *Bacillus subtilis*, Methicillin-resistant, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus* and *Vancomycin-resistant Enterococcus*. In the first two strains it inhibited the growth even more then the positive control ciprofloxacin. A comparison of inhibition potential of compound 3g with control against gram-positive bacterial strains has been shown in Figure 1. When linker was replaced with bulky naphthyl or diphenylmethyl groups, the decrease in activity against various gram-positive strains was observed (Table 1, Compounds 3h-k).

Against gram-negative strains compound 3g showed promising activity against growth of *Escherichia coli*, *S. Typhi*, *Pseudomonas aeruginosa*, *Shigella* and *Enterobacteriaceae* while in case of *Salmonella paratyphi* A and *Klebsiella pneumonia* it was moderately potent. However, it has less activity against *Salmonella paratyphi* B.

A broader pattern was observed for activity of other triazoles and bis-triazoles against gram negative bacterial strains, so a generalized SAR could not be established. Although some compounds such as 3a was quitting potent against *Salmonella typhi* and has good activity against *Salmonella paratyphi* B and *Shigella*. While compound 3g was more potent against *Salmonella paratyphi* A, *Klebsiella pneumonia* and *Enterobacteriaceae*. Overall most of the compounds showed good to moderate activity against various strains of bacteria.

Conclusion

In summary a series of new vanillin-derived 1,2,3-triazoles and bis 1,2,3-triazoles substituted with different aromatic rings were synthesized via [3+2] cycloaddition of arylpropoxy azides and terminal alkynes using Click-chemistry. Structural confirmation of compounds was performed by spectroscopic and elemental analysis. Their antimicrobial activity was evaluated against gram-positive strains *Bacillus subtilis*, Methicillin-resistant *Staphylococcus aureus*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *Vancomycin-resistant Enterococcus* as well as gram-negative strains such as *Escherichia coli*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Salmonella paratyphi*, *Shigella*, *Salmonella paratyphi* A, *Klebsiella pneumonia* and *Enterobacteriaceae* using agar well diffusion method. The preliminary anti-bacterial screening of synthesized triazoles manifested moderate to good in vitro anti-microbial potency. In case of mono 1,2,3-triazoles, compound 3a and 3b containing electron withdrawing -bromo and -nitro groups were the most active against gram positive bacteria while 3c-3f exhibited moderate activity. Compound 3g was the most active in the series for most of the gram-positive strains. It was also potent for *Escherichia coli*, *Salmonella typhi*, *Pseudomonas aeruginosa* in gram-negative bacteria. These results demonstrated that vanillin-derived 1,2,3-triazoles and bis triazoles are of biological significance and have the perspective as a new member of anti-microbial agents.

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Conflict of Interest

Authors declare that there is no conflict of interest.

References


