Triazoles with long chain alkyl groups as a potential biological compounds

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Abstract
New series of four compounds was synthesized from multi hydroxyl group compounds such as methyl glycoside by coupling with long-chain alkyl propargyl ester ($C_{10}$, $C_{12}$, $C_{14}$ and unsaturated $C_{18}$) via click chemistry after activation the hydroxyl at C6 position by chlorination with N-chlorosuccinimide NCS and functionalized with sodium azide NaN$_3$. The chemical structures and the purity of the resulting triazoles derivatives was confirmed by elemental analysis (CHN) and spectroscopic analysis ($^1$H NMR & $^{13}$C NMR). The biological activity for the target compounds was investigated, and they show good antibacterial and antifungal properties against some selected gram-posative and fungi, which make them suitable for medical applications.

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INTRODUCTION
Heterocyclic or heterocycle is class organic compounds class that contains a ring or more in its structure with one or more different atom other than carbon such as oxygen, nitrogen, or sulfur. Triazole or pyrrodiazole an example of the 5-membered heterocyclic compound composed of three nitrogen atoms and two carbon atoms at non-adjacent positions (Kharb et al., 2011). The presence of the nitrogen atoms is responsible for the physical and chemical properties that are often quite distinct from those of their all-carbon-ring analogs. Triazole functional groups exhibit relative stability, and its linkages may modify to a variety of applications (Aflak et al., 2019). The triazol are more than just passive linker. They readily associate with biological targets through chemical interaction, such as hydrogen bonding and ion dipole (Sandip et al., 2011). Triazoles and their derivatives show good biological activity and many triazoles used as antifungal, antimicrobials, and inhibitors for some enzymes. Those properties and applications put the chemist and researchers in the race to enhance this application by finding new derivatives via synthesis. Nazariy 2013 and co-workers. Reported the Kamal and co-workers synthesis of new antitumor compounds by the coupling 1,2,3-triazole and quinoline rings (Nazary et al., 2013). Kamal and et al. reported synthetic rout for the possible synthesis of new classes of bi- and bis-triazole systems based on the connection between the two triazoles rings as bioactive compounds (Kamal et al., 2018). Ionuu and co-worker. Introduced the pyridine to the 1,2,4-triazole ring to produce new triazoles with antibacterial activity against Staphylococcus aureus (ATCC 25923) (Ledeui et al., 2015). N-alkylated analogs for 1,2,4-triazol-3 were synthesized for antimicrobial purposes by the coupling triazoles 1,2,4-triazol-3 ring with the desired alkyl halide in the basic medium (Neslihan et al., 2008). Laddi and co-worker reported the synthesis of some Anti-inflammatory from 1,2,4 triazole with alkyl (Laddi et al., 1998). The triazole-containing pyranosides with alkyl chain $C_8$, $C_{10}$, $C_{12}$ caused toxicity via apop-
tosis (Oldham et al., 2013). 1,2,3-triazole derivatives were prepared by coupling with a small molar mass alkyl group. The synthesized compounds exhibit antimycobacterial activity against multiple-drug-resistant strains of Mycobacterium tuberculosis H37Rv (Gallardo et al., 2007). Israr and co-worker reported the first use of the alkyl azide precursors in the form of alkyl diacyl peroxides in the direct of alkylation 1,2,3-triazoles (Israr et al., 2018). It’s quite clear from what mentioned above, the importance of triazole ring and its derivatives in the therapy and health sector. To overcome the resistance of bacteria and fungi to the biological activity of the currently known compounds. This present paper synthesis of a new series of alkylated triazole derivatives via click chemistry using biodegradable material such as methyl glycoside and fatty acids and investigates the biological activity.

**MATERIALS AND METHODS**

**Materials**

All chemical material and solvents used were bought from multi companies such as Fisher Scientific, Fluka, Merck and Aldrich suppliers. Triphenylphosphine. N-chlorosuccinimide, N, N-dimethylformamide, sodium azide, sodium hydrogen carbonate, magnesium sulfate ethyl, copper chloride, fatty acids (C<sub>10</sub>-C<sub>15</sub>) sodium ascorbate propargyl alcohol, p-toluene sulfinic acid, toluene acetate and hexane. They were used as received without any further purification.

**Instruments**

The melting points of the target derivatives were measured by an open capillary melting point apparatus with no further corrections. The IR spectroscopy was done on a Perkin-Elmer Spectrum 400 ATR-FT-IR spectrometer. 1H and 13C NMR spectroscopy were done on AVN Bruker 400 and 600MHz FT NMR spectrometer and JEOL Lambda 400 MHz FT-NMR spectrometer. Tetramethylsilane was used as an internal standard. Deuterated 1, 4-dioxane-d8 CD<sub>2</sub>C<sub>2</sub> were used as solvents. Elemental analysis was performed using Perkin Elmer CHNS/O 2400 series II elemental analyzer.

**Chlorination**

Compound [1] (1.0 eq.) triphenylphosphine (2.0 eq) and N-chlorosuccinimide NCS (2.0 eq.) in dry (20 mL) DMF was heated up to 65 °C with contentious stirring for a period of 2 hours. When the TLC (ethyl acetate: hexane 4:1) indicated the end of the reaction, the solution was cooled, and the remaining NCE was destroyed by 10 ml. DMF was removed, and TPP was removed by water and extraction with DCM. The solvent was evaporated to the produced white crystal of compound [2], which subjected to azidation reaction with no further purification (Khalilfah et al., 2018; Guana et al., 2018; Su et al., 2019).

**Azidation**

Suspension of compound [2] (1.0 eq.) and NaN<sub>3</sub> (6.0 eq) in (20 ml) DMF was warming up to 85 °C for a day. The solution was left aside for reach to 25°C and then extracted with DCM. The organic layer was washed with water, neutralized sodium hydrogen carbonate, dried over MgSO<sub>4</sub> and concentrated under reducing pressure. Ethanoic anhydride (2.0 eq.) in pyridine (20 ml) was added for acetylation. Recrystallization with ethanol was done to produce NMR pure white crystal of compound [3] in very good yield (Carlson and Topczewski, 2019; Kantaria et al., 2018; Hajipour and Ghorbani, 1920; Costa et al., 2017).

**The general reaction of esterification**

Corresponding fatty acid (1.0 eq.) and corresponding propargyl alcohol (1.2 eq.) with a catalytic amount of p-toluene sulfonic acid in toluene was refluxed at about 110 °C for a period 7h. The mixture was left to reach room temperature and extracted with DCM three times with saturated sodium hydrogen carbonate. The solvent was removed to get NMR pure fatty acid ester in very good yield for compounds [5-8] (Salimon, 2011; Pesyan, 2017).

**The general reaction of click chemistry**

Compound [3] (1 equiv) was stirred contentiously with (1.1 equiv) of corresponding propargyl alcohol [5-8] and (0.01equiv) copper chloride and sodium ascorbate (0.1 equiv) in methanol when TLC indicates there are no traces of the azide. The reaction mixture filtrate through ciliate and the solvent removed under reducing pressure, the residue was purified through column chromatography using 9:1 chloroform: methanol as eluent to produce the target derivatives (Yáñez-Sedeño et al., 2019; Tireli et al., 2017; Ostrovskis et al., 2013).

**Synthesis of 1-((2R,3S,4S,5R)-3,4,5-trihydroxy-6-methoxytetrahydro-2H-pyran-2-yl)methyl)-1H-1,2,3-triazol-4-yl decanoate [9]**

Compound [3] (0.22 g, 0.01 mmol) was treated with 2-propynyl decanoate [5] according the general procedures of click chemistry reaction to produced of compound [9] (0.3g83%) as pure white crystals. mp (103-105) °C. Elemental Analysis C<sub>19</sub>H<sub>33</sub>N<sub>2</sub>O<sub>2</sub>: calculated: C, 54.93; H, 8.01; N, 10.11, found :C,54.96; H, 8.06; N, 10.14. <sup>1</sup>H NMR (400 MHz,CD<sub>3</sub>OD), 8.0 (s. 1H, CH=C triazol), 5.19 (s, 1H, CH<sub>2</sub>-O), 4.51
Figure 1: Synthesis scheme of triazol derivatives

Table 1: The biological and fungal activity for the synthesized compounds

| Sample | Gram-positive bacteria inhibition zone (mm) | Gram-negative bacteria inhibition zone (mm) | Fungal strains inhibition zone (mm) |
|--------|--------------------------------------------|--------------------------------------------|---------------------------------|
|        | Enterococcus faecalis | Staphylococcus aureus | Streptococcus pyogenes | Citrobacter freundii | Salmonella typhi | Acinetobacter species | Candida albicans | Candida krusei | Aspergillus niger |
| Standard DMSO | 00 | 00 | 00 | 00 | 00 | 00 | 00 | 00 | 00 |
| Control Amoxicillin | 25 | 35 | 30 | 25 | 24 | 13 | - | - | 13 |
| Nystatin Samples 9 | - | - | - | - | - | - | 14 | 14 | 13 |
| 10 | 15 | 20 | 22 | - | - | - | 10 | 8 | 8 |
| 11 | 14 | 18 | 16 | - | - | - | 8 | - | - |
| 12 | 20 | 17 | 15 | - | - | - | 10 | 12 | 10 |

Synthesis of 1-(((2R,3S,4S,5R)-3,4,5-trihydroxy-6-methoxytetrahydro-2H-pyran-2-yl)methyl)-1H-1,2,3-triazol-4-yl dodecanoate [10]

Compound [3] (0.22 g, 0.01 mmol) was reacted with 2-propynyl dodecanoate [6] according the general procedures of click chemistry reaction to produced (0.36g, 81%) of compound [10] as pure white crystals. mp (109-112-111) °C. Elemental Analysis: C_{21}H_{37}N_{3}O_{7} calculated C, 56.87; H, 8.41; N, 9.47; found C, 56.90; H, 8.46; N, 9.452. 1H NMR (400 MHz,CD_{3}OD), 8.0 (s. 1H, CH=C triazol), 5.20 (s, 1H,
Figure 2: Relation between stereo chemistry and activity of compound

Figure 3: Relation between stereo chemistry and activity of compound

Figure 4: $^1$H NMR for compound [10]

Figure 5.

Synthesis of 1-((2R,3S,4S,5R)-3,4,5-trihydroxy-6-methoxytetrahydro-2H-pyran-2-yl)methyl)-1H-1,2,3-triazol-4-yl tetradecanoate [11]

Compound [3] (0.22 g, 0.01 mmol) was reacted with 2-propynyl tetradecanoate [7] according the general procedures of click chemistry reaction to produced (0.35g, 80%) of compound [11] as pure white crystals. mp (109-116-115) °C. Elemental Analysis: C$_{23}$H$_{41}$N$_{3}$O$_{7}$ calculated C, 58.58; H, 8.76; N, 8.91; O,
23.75: found C, 58.61; H, 8.82; N, 8.91; O, 23.80. $^1$H NMR (400 MHz, CD$_3$OD), 8.02 (s, 1H, CH=C triazol), 5.21 (s, 1H, CH$_2$-O), 4.66 (d, 1H, H-1), 4.54 (dd, 1H, H-6b), 3.87 (ddd, H-5), 3.65 (d-d, H-3), 3.34 (s, 3H, Me), 3.32-3.33 (ddd, d-t, H-6b), 3.13-3.17 (m, 2H, H-4 and H-2), 2.30 (t, 2H, CH$_2$), 1.63 (mc, 2H, $\beta$-CH$_2$), 1.31 (mc, 20H, bulk-CH$_2$), 0.90 (t, 3H, CH$_3$; $^3$J$_{1,2}$=3.0, $^3$J$_{2,3}$=9.0, $^3$J$_{3,4}$=9.5, $^3$J$_{4,5}$=10.0, $^3$J$_{5,6a}$=1.5, $^3$J$_{5,6b}$=8.0, $^3$J$_{6}=13.5$). $^{13}$C NMR (100 MHz, CD$_3$OD) 173.65 (C=O), 142.69 (C=quat. triazol), 125.89 (N-C=C triazol), 100.03 (C-1), 73.59 (C-2), 72.05 (C-3), 71.64 (C-5), 70.41 (C-4), 56.73 (CH$_3$), 54.20 (C-6), 51.16 (C-0), 33.53 (CH$_2$), 31.77 ($\omega$ -2), 29.95-28.84 (bulk-CH$_2$), 24.65 ($\beta$-CH$_2$), 22.41 ($\omega$ -1), 13.1 ($\omega$).

Synthesis of (1-(((2R,3S,4S,5R)-3,4,5-trihydroxy-6-methoxytetrahydro-2H-pyran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl oleate [12]

Compound [3] (0.22 g, 0.01 mmol) was reacted with ethynyl oleate [8] according the general procedures of click chemistry reaction to produced (0.42g, 87%) of compound [12] as pure white crystals. mp (125-127) $^\circ$C. Elemental Analysis C$_{28}$H$_{49}$N$_3$O$_7$: C, 62.31; H, 9.15; N, 7.79: found, 62.36; H, 9.122; N, 7.85. $^1$H NMR (400 MHz, CD$_3$OD), 8.02 (s, 1H, CH=C triazol), 5.20 (s, 1H, CH$_2$-O), 4.85 (mc, 2H, CH=CH). 4.62
the later was functionalized by the reaction with to treat the trace of the chlorination reagent, and was activated form compound [2]. Methanol was added in the present of triphenylphosphine to get the activated form compound [2]. Methanol was added to treat the trace of the chlorination reagent, and the later was functionalized by the reaction with sodium azide in the same solvent of the chlorination to yield the functionalized form compound [3], which is consider as the precursor of the target compounds. On other hands, four natural fatty acids C10, C12, C14 and unsaturated C18 were functionalized easily by simple treatment of the later with propargyl alcohol under acidic conditions to furnish 2-propynyl decanoate [5], 2-propynyl dodecanoate [6], 2-propynyl teradecanoate [7] and ethynyl oleate [8] respectively.

The coupling by click chemistry using copper acetate Cu(OAc)2 and sodium ascorbate in methanol of each mentioned compound with the precursor [3] over compounds [9], [10], [11] and [12] as white crystals of the final products in very good yields. The chemical structures and the purity of target compounds were confirmed by elemental analysis and spectroscopic methods 1H NMR and 13C NMR. Elemental analysis exhibit acceptable values for both carbon and nitrogen, while the hydrogen shows little deviation, which indicates that the final derivatives are hygroscopic. Both 1H and 13C NMR confirm the presence of all the atoms and the groups in the final triazole derivatives. 1H NMR spectrums (Figure 2) show the protons signal of the triazol rings at δ (8.0-8.04), signal of (CH2-O) at δ (5.19-5.21), the carbon-1 signal (H-1) appears at δ (4.51-4.64), while the triol ring signals (H-2 to H-5) are listed from δ (3.1) to (3.13) for H-2 and δ (3.82-3.87) for H-5. The CH2 out of the ring (H-6a/b) appears from δ (4.50) to (4.55) for 6a and δ (3.32-3.37) for 6b and the methyl group in δ 3.24. The signals of the R group located from δ 2.32 (α-CH2) to δ 0.88 (terminal CH3). (See supplementary file for 1H NMR spectrums). The 13C NMR spectrums for the last products show the carbon signal of (C=O) δ (173.55-173.90), (C-N) at about δ 142.69-143.32,(C=C) of the triazol ring at about δ (125.69-125.89), the carbon of (C-O) at δ (50.80-51.15), the anomeric carbon at around δ (99.62-100.0) Other triols ring appear from δ (69.99) to δ (74.55). The primary carbon (C-6) is located at around from δ (54.20) to (55.61), while the methyl group is listed at δ (50.80-51.16). The R group carbons appear from δ (33.48) to (34.80) (α-CH2) and δ (13.12-14.0) (CH3). 1H NMR and 13C NMR for saturated triazole derivatives[9-11] show approximately the same chemical shift of unsaturated [12] which extra signal of (CH=CH) at δ 4.85 and the signal of (CH2=CH) at δ (1.98), (See supplementary file for 13C NMR spectrums).

Biological activity
The biological activity of the synthesized compound was screened via disc scan diffusion methods using some bacteria and fungi spices. Six types of bacteria were chosen for the scanning...
purposes three gram-positive (Enterococcus faecalis, Staphylococcus aureus, Streptococcus pyogenes) and three gram-negative (Citrobacter freundii, Salmonella typhi, Acinetobacter species) in addition to another three fungal species including (Candida albicans, Candida krusei, Aspergillus niger). Those bacterial and fungal was chosen based on the sources availability and a literature survey knowledge for the bacterial type, which may show antibacterial and antifungal activity with similar to the target triazole synthesized compound. The result of the investigation is shown in (Table 1), which indicates a good interaction with the gram-positive bacteria and fungi, while the interaction with gram-negative bacteria is very poor.

The biological and fungal activity is decreased with increasing the number of carbon atoms of the saturated alkyl side chain (C₁₀–C₁₄), the reason may belong to the increasing of the hydrophobic interaction (C₁₀ < C₁₄) between the long-chain alkyl groups, which allow a good alignment of the compounds molecule then cannot reach to killing point inside the bacteria and fungi easily (Figure 2). The best biological and fungal activity result shown by the compound 11 [12] with very long unsaturated alkyl group (C₁₈), the reason may belong to the stereo chemistry of this compound which the usually found in cis configuration that allows bad alignment for this molecule within the solution. For that, they have little restriction then saturated one and can easily free in solution and reach to a killing point inside the bacteria and fungi (Figure 3).

The biological activity of the screened compounds is in a good agreement with previously reported for the triazole derivatives (Ali et al., 2016; Celik et al., 2018; Singh et al., 2018).

**CONCLUSIONS**

New triazole derivative can be accessible from multi hydroxyl group’s compounds such as methyl glycoside via click chemistry, a series of new compound show good biological activity, which can be for treatment purposes.

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**Conflict of Interest**

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

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