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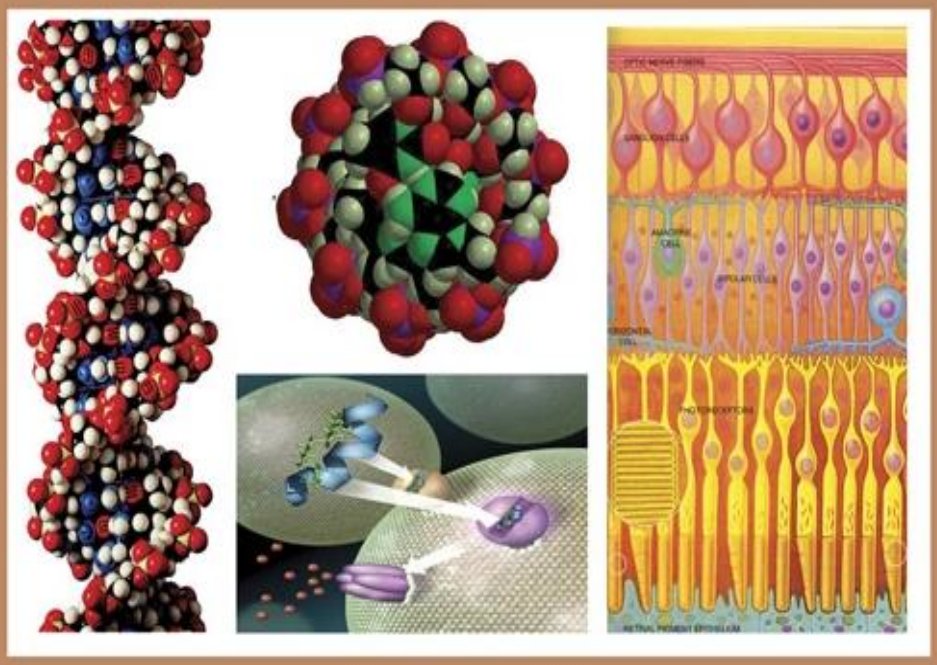

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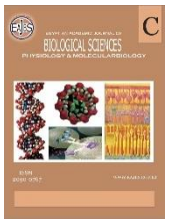

Synthesis, Characterization, and Study of Antibacterial Activity of Some New Amphiphilic Sulfamethoxazole Derivatives

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ABSTRACT

In a continuous attempt to develop novel antibacterial drugs, we have generated and evaluated fresh 1,2,3-triazole derivatives from sulfametoxazole. The synthetic approach was started by the synthesis of sulfametoxazole moiety with alkyl chain or phenyl skeleton. Subsequently, sulfametoxazole nucleus was functionalized with sodium azide to produce 4-azido-N-(5-methylisoxazol-3-yl)benzenesulfonamide. The end 1,2,3-triazoles were synthesized via a click reaction of the azide compound and triple bond derivatives that attached with alkyl chain or phenyl group in good yields. The structures of all prepared compounds were identified by using NMR and IR techniques. The synthesized compounds were screened for their in vitro antibacterial activity against one gram-positive bacteria *S. aureus* and one gram-negative bacteria E. coli. Among the synthesized compounds, compound 12 was found to be the most potent against *staphylococcus aureus* with MIC = 20 µg/mL compared with the other prepared compounds. Whereas compound 15 was found to be the most potent against *Escherichia coli* with MIC = 21 µg/mL compared with the other end compounds.

INTRODUCTION

Particularly the five-membered heterocyclic compounds (thiazoles, thiadiazoles, triazoles, 1,3,4-oxadiazoles, and benzimidazole ring) have demonstrated an extremely intriguing biological activity [A.S. Saghyan *et al.,* 2014]. Moreover, these substances demonstrated extremely encouraging antiviral efficacy against many viruses [S.S. Tawfik *et al.,* 2020]. The usefulness of triazole-based derivatives as therapeutic medications in the fields of antibacterial, antiviral, antifungal, anticancer, and antihypertensive agents has drawn the attention of researchers. Via the production of hybrids, the 1,2,3-triazole ring serves as a linker to improve biological activity [C. H Zhou *et al.*,2012]. In contrast, 1,2,3-triazole derivatives are desirable candidates in medicinal chemistry because they serve as the foundation for a variety of 1,2,3-triazole compounds with useful pharmacological properties, including antibacterial [N. Boechat et al ,2014– M. Aarjane et al ,2019- K. Sri, S. Praveena *et al.*,2021- N. Kuntala *et al.*,2015], antitumoral [O. Grytsai et al, 2020- M.A. Almehmadi et al, 2021], anticancer [C.P. Kaushik *et al.,* 2020– K.S.S. Praveena *et al.*, 2015- J. Mareddy *et al.*,2013], antiityrosinase [Z. Peng et al, 2020], and anti-inflammatory [M.J. Assarzadeh *et al.,* 2014] compounds. Several 1,2,3-triazole-based medications have also been produced, some of which include Rufinamide (anticonvulsants), Cefatrizine (antibacterial), and Tazobactam (antifungal).

Worldwide, microbial infections are becoming more of a problem and are mostly responsible for mortality in underdeveloped nations (E.A. Scott *et al.,*2020). There is a high demand for new and effective antimicrobial drugs due to the numerous negative effects and evolution of bacterial resistance to a wide range of antibacterial agents (S.E. Walsh *et al.,* 2003). In the present study, we synthesized new 1,2,3-triazole derivatives from sulfamethoxazole and evaluated them against two pathogenic bacteria. This work is a continuation of our studies on the development of new antibacterial agents (M. Aarjane *et al.,* 2021-M. Aarjane *et al.,* 2020), and it places special emphasis on the 1,2,3-triazole system's broad range of biological activity.

MATERIALS AND METHODS

Multiple supply chemicals firms such as Sigma Aldrich chemicals, Thomas Baker, Merck, Fluke, and industrial suppliers have purchased all reagents, solvents and starting materials. For the aforementioned progress of all reactions, supplied on silica gel SG-40 by Merck Company, TLC plates were used. At Bruker ALPHA, University of Kufa, Faculty of Science, Fourier transformation infrared was used to record FTIR spectra. NMR spectrum, 400MHz for 1HNMR and 100 MHz for ^{13}CNMR, Mashhed University, were confirmed on the Bruker apparatus.

Synthesis 4-azido-N-(5-methylisoxazol-3-yl)benzenesulfonamide (1)[Ehab K *et al.,*2020**]:**

In a mixture of distilled water and Hydrochloric acid in a ratio of (1:3) mL, (15mmol) of sulfamethoxazole is dissolved, and then the mixture is cooled with a salt-ice bath to a temperature of 0 °C. During this, an aqueous solution of sodium nitrite was prepared (15mmol) and it is also cooled to 0 °C, after which a nitrite solution is added to the sulfadiazine solution drop by drop where after several additions the color of the solution turned to a slightly-yellow color, after completing the addition the solution is left for stirring for 45 min during this an aqueous solution of sodium azide was prepared (2eq), after which the sodium azide solution was added in batches where bubbles were observed during the addition. After the completion of the addition, the solution is left for stirring for 2hrs. The sediment that is formed is filtered and washed several times with distilled water.

4-azido-N-(5-methylisoxazol-3-yl) benzenesulfonamide (1):

It was prepared as a white crystalline, Chemical formula: $C_{10}H_9N_5O_3S$; 88% yield; mp 93-95 ºC; FTIR, ν (cm^{-1}) 3242(N-H), 3077(C-H, aromatic), 2986, 2842(C-H, aliphatic), 2103(N_3),1686(C=C), 1344(asy SO_2 group), 1169(sy SO_2), ^{1}H NMR (300 MHz, DMSO-d6) δ 11.48 (s, 1H, N-H, sulfonamide), 7.90–7.32 (m, 4H, Ar-H), 6.16 (s, 1H, C-H-sulfamethoxazole ring), 2.32 (s, 3H, -CH_3). ^{13}CNMR (75 MHz, DMSO-d6) δ 169.15, 156.74, 146.04, 136.61, 129.75, 119.16, 96.83, 12.54.

Synthesis of 3-methoxy-4-(prop-2-yn-1-yloxy) benzaldehyde (2):

To (15mmol) from the 4-hydroxy-3-methoxybenzyldehydedissolved in acetone, 2 equivalents of anhydrous potassium carbonate K_2CO_3 were added, and cooling the reaction below 15ºC, 2.7 equivalents of the 3-bromo-1-propyne solution is added in small quantities and in batches, after which the reaction was left under reflux, the completion of the reaction was monitored using TLC. The solvent is removed under reduced pressure. The residue is dissolved in distilled water, and extraction is accomplished by adding ethyl acetate twice. Anhydrous magnesium sulfate was used to dry the organic layer. To obtain the desired product, the solvent is removed under reduced pressure, and purified by column chromatography (3:2) using a mixture of hexane and ethyl acetate as the eluent**.**

3-methoxy-4-(prop-2-yn-1-yloxy) benzaldehyde (2):

It was prepared as a white crystalline, Chemical formula: $C_{11}H_{10}O_3$; 85% yield; mp 68-70 ºC; FTIR data (cm^{-1}): 3242(≡C-H), 3078(C-H aromatic), 2978, 2929(C-H aliphatic), 2110 (C≡C group), 1686(C=O aldehyde), 1586,1508(C=C

aromatic), 1264(C-O aromatic), 1003(C-O aliphatic), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.86 (s, 1H, -CHO), 7.57-722 (m, 4H, Ar-H), 4.94 (s, 2H, O-CH_2-C≡C), 3.84 (s, 3H, O-CH_3), 3.66 (s, 1H, C≡C-H).

Synthesis of 4-((3-methoxy-4-(prop-2-yn-1-yloxy)benzylidene)amino)phenol (3):

A mixture of prepared 3-methoxy-4-(prop-2-yn-1-yloxy)benzaldehyde(2), (10mmol) and 4-amino phenol (10mmol) in EtOH (20 mL), in the presence of a few drops of glacial acetic acid as a catalyst, was heated under reflux for 5 h and then allowed to cool to room temperature. The precipitated solid was filtered off, dried, and recrystallized from methanol to afford compound (3).

(E)-4-((3-methoxy-4-(prop-2-yn-1-yloxy) benzylidene)amino)phenol (3):

It was prepared as a white crystalline, Chemical formula: $C_{11}H_{10}O_3$; 85% yield; mp 68-70 ºC; FTIR data (cm^{-1}): 3241(≡C-H), 3071(C-H aromatic), 2998, 2841(C-H aliphatic), 2118(C≡C group), 1680(C=O aldehyde), 1585,1504(C=C aromatic), 1259(C-O aromatic), 996 (C-O aliphatic), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.40 (s, 1H, OH, phenol), 8.61 (s, 1H, H-C=N-), 7.48 – 7.19 (m, 7H, Ar-H), 4.89 (s, 2H, O-CH2-C≡C), 3.84 (s, 3H, O-CH3), 3.61 (s, 1H, C≡C-H).

Synthesis ether derivatives (4-9):

To the prepared4-((3-methoxy-4-(prop-2-yn-1-yloxy)benzylidene)amino)phenol(4) (10mmol) in DMSO, 1.5 equivalents of sodium hydroxide NaOH were added, and stirred the reaction mixture, then 1.2 equivalents of alkyl halide was added in small quantities and in batches, after which the reaction was left under reflux, the completion of the reaction was monitored using TLC. The solvent is removed under reduced pressure. The residue is dissolved in distilled water, and extraction is accomplished by adding chloroform twice. Anhydrous magnesium sulfate was used to dry the organic layer. To obtain the desired product, the solvent is removed under reduced pressure, and purified by column chromatography (4:1.5) using a mixture of hexane and ethyl acetate as the eluent**.**

N-(4-(decyloxy)phenyl)-1-(3-methoxy-4-(prop-2-yn-1-yloxy)phenyl)methanimine (4):

It was prepared as a white crystalline, Chemical formula: $C_{27}H_{35}NO_3$; 85% yield; mp 68-70 ºC; FTIR data (cm^{-1}): 3277(≡C-H), 3107(C-H aldehyde), 2918, 2829 (C-H aliphatic), 2114(C≡C group), 1645(C=O aldehyde), 1590,1527(C=C aromatic), 1274(C-O aromatic), 1168(C-O aliphatic), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.38 (s, 1H, (-CH=N-), 7.44-7.18 (m, 7H, Ar-H), 4.80 (s, 2H, O-CH_2-C≡C), 4.02 (t, J = 6.1 Hz, 2H, -O-CH_2-alkyl chain), 3.85 (s, 3H, -O-CH_3), 3.63 (s, 1H, C≡C-H), 1.76 (m, 2H, -CH_2-), 1. 33–1.22 (m, 14H, -$(CH_2)_7$), 0.85 (t, J = 6.1 Hz, 3H, -CH_3), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 153.20(-C=N-), 148.73, 145.55, 144.22, 138.97, 129.58, 124.31, 122.54, 115.11, 114.74, 111.03 (10 C, Ar-C), 78.41(-C≡C-H), 76.40(-C≡C-H), 61.14(O-CH2), 58.13(O-CH_2-), 56.11(O-CH_3), 31.86(β-CH_2-), 29.68, 29.56, 29.53, 29.47, 29.33, 26.13, 22.76 (7-CH_2-), 14.12 (CH_3).

(E)-N-(4-(dodecyloxy) phenyl)-1-(3-methoxy-4-(prop-2-yn-1-yloxy) phenyl) methanimine (5):

It was prepared as a white crystalline, Chemical formula: $C_{29}H_{39}NO_3$; 85% yield; mp 68-70 ºC; FTIR data (cm^{-1}): 3271(≡C-H), 3107(C-H aldehyde), 2924, 2829 (C-H aliphatic), 2117(C≡C group), 1648(C=O aldehyde), 1591,1528(C=C aromatic), 1268(C-O aromatic), 1173(C-O aliphatic), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H, (-CH=N-), 7.51-7.22 (m, 7H, Ar-H), 4.82 (s, 2H, O-CH_2-C≡C), 4.03 (t, J = 6.2 Hz, 2H, -O-CH_2-alkyl chain), 3.84 (s, 3H, -O-CH_3), 3.62 (s, 1H, C≡C-H), 1.75 (m, 2H, -CH_2-), 1.34–1.22 (m, 18H, -$(CH_2)_9$), 0.87 (t, J = 6.1 Hz, 3H, -CH_3), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 154.54(-C=N-), 149.13, 145.12, 143.32, 139.92, 129.87, 125.11, 123.27, 116.27, 114.13, 112.14, (10 C, Ar-C), 78.51 (-C≡C-H), 76.68(-C≡C-H), 60.08(O-CH2), 58.84(O-CH_2-), 56.67(O-CH_3), 31.79(β-CH_2-)29.89, 29.82, 29.78, 29.51, 29.43, 29.19, 29.06, 26.62, 22.59(10-CH_2-), 14.32 (CH_3).

(E)-N-(4-(tetradecyloxy)phenyl) -1-(3-methoxy-4-(prop-2-yn-1-yloxy)phenyl) methanimine (6):

It was prepared as a white crystalline, Chemical formula: $C_{31}H_{43}NO_3$; 85% yield; mp 68-70 ºC; FTIR data (cm^{-1}): 3241(≡C-H), 3110 (C-H aldehyde), 2998, 2841(C-H aliphatic), 2118(C≡C group), 1680(C=O aldehyde), 1585,1504(C=C aromatic), 1259(C-O aromatic), 1123(C-O aliphatic),^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.37 (s, 1H, (-CH=N-), 7.48-7.19 (m, 7H, Ar-H), 4.83 (s, 2H, O-C$\underline{H_2}$-C≡C), 4.05 (t, J = 6.1 Hz, 2H, -O-C$\underline{H_2}$-alkyl chain), 3.82 (s, 3H, -O-C$\underline{H_3}$), 3.59 (s, 1H, C≡C-$\underline{H}$), 1.76 (m, 2H, -CH_2-), 1.35–1.23 (m, 22H, -$(CH_2)_{11}$), 0.85 (t, J = 6.1 Hz, 3H, -CH_3), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 154.54(-C=N-), 149.13, 145.12, 143.32, 139.92, 129.87, 125.11, 123.27, 116.27, 114.13, 112.14 (10 C, Ar-C), 78.51(-C≡$\underline{C}$-H), 76.68(-$\underline{C}$≡C-H), 62.08(O-CH2), 58.84(O-CH_2-), 56.57(O-CH_3), 31.81 (β-CH_2-) 29.86, 29.76, 29.57, 29.54, 29.51, 29.44, 29.42, 29.24, 29.02, 26.59, 22.59(12-CH_2-), 14.35(CH_3).

(E)-N-(4-(hexadecyloxy)phenyl) -1-(3-methoxy-4-(prop-2-yn-1-yloxy)phenyl) methanimine (7):

It was prepared as a white crystalline, Chemical formula: $C_{33}H_{47}NO_3$; 85% yield; mp 68-70 ºC; FTIR data (cm^{-1}): 3277(≡C-H), 3107(C-H aldehyde), 3006, 2918 (C-H aliphatic), 2114(C≡C group), 1645(C=O aldehyde), 1590,1527(C=C aromatic), 1274(C-O aromatic), 1168(C-O aliphatic), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.61 (s, 1H, (-CH=N-), 7.45-7.22 (m, 7H, Ar-H), 4.87 (s, 2H, O-C$\underline{H_2}$-C≡C), 4.05 (t, J = 6.4 Hz, 2H, -O-C$\underline{H_2}$-alkyl chain), 3.83 (s, 3H, -O-C$\underline{H_3}$), 3.64 (s, 1H, C≡C-$\underline{H}$), 1.80 (m, 2H, -CH_2-), 1.39–1.23 (m, 26H, -$(CH_2)_{13}$), 0.87 (t, J = 6.1 Hz, 3H, -CH_3), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 154.22(-C=N-), 149.77, 143.98, 143.07, 139.97, 129.66, 124.55,122.77, 116.11, 114.74, 111.03 (10 C, Ar-C), 79.44(-C≡$\underline{C}$-H), 78.44(-$\underline{C}$≡C-H), 62.14(O-CH2), 59.14(O-CH_2-), 58.14(O-CH_3), 31.81(β-CH_2-)29.97, 29.86, 29.76, 29.63, 29.57, 29.54, 29.51, 29.44, 29.42, 29.24, 29.02, 26.59, 22.59(14-CH_2-), 14.35 (CH_3).

(E)-N-(4-(octadecyloxy)phenyl) -1-(3-methoxy-4-(prop-2-yn-1-yloxy)phenyl) methanimine (8):

It was prepared as a white crystalline, Chemical formula: $C_{35}H_{51}NO_3$; 85% yield; mp 68-70 ºC; FTIR data (cm^{-1}): 3237(≡C-H), 3107(C-H aromatic), 3006, 2918(C-H aliphatic), 2117(C≡C group), 1645(C=O aldehyde), 1590,1527(C=C aromatic), 1274(C-O aromatic), 1168(C-O aliphatic), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.33 (s, 1H, (-CH=N-), 7.42-7.20 (m, 7H, Ar-H), 4.83 (s, 2H, O-C$\underline{H_2}$-C≡C), 4.06 (t, J = 6.1 Hz, 2H, -O-C$\underline{H_2}$-alkyl chain), 3.86 (s, 3H, -O-C$\underline{H_3}$), 3.64 (s, 1H, C≡C-$\underline{H}$), 1.76 (m, 2H, -CH_2-), 1.37–1.20 (m, 30H, -$(CH_2)_{15}$), 0.87 (t, J = 6.1 Hz, 3H, -CH_3), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 155.20(-C=N-), 146.74, 143.56, 142.23, 139.97, 128.58, 123.33, 121.55, 114.17, 113.77, 112.03 (10 C, Ar-C), 76.41(-C≡$\underline{C}$-H), 74.40(-$\underline{C}$≡C-H), 62.14 (O-CH2), 59.13(O-CH_2-), 54.11(O-CH_3), 31.79 (β-CH_2-)30.21, 29.95, 29.84, 29.72, 2953, 29.51, 29.40, 29.34, 29.21, 29.13, 29.04, 28.91, 28.54, 26.58, 22.59(16-CH_2-),14.41(CH_3).

(E)-N-(4-(benzyloxy)phenyl)-1-(3-methoxy -4-(prop-2-yn-1-yloxy) phenyl) methanimine (9):

It was prepared as a white crystalline, Chemical formula: $C_{24}H_{21}NO_3$; 85% yield; mp 68-70 ºC; FTIR data (cm^{-1}): 3277(≡C-H), 3107(C-H aromatic), 3006, 2918(C-H aliphatic), 2850, 2724(C-H aldehyde "FERMI doublet"), 2117(C≡C group),1661(C=O aldehyde), 1588,1502(C=C aromatic), 1261(C-O aromatic), 1163(C-O aliphatic),^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.36 (s, 1H, (-CH=N-), 7.47-7.12 (m, 7H, Ar-H),5.03(s, 2H, -CH_2-Ph), 4.82 (s, 2H, O-C$\underline{H_2}$-C≡C), 3.84 (s, 3H, -O-C$\underline{H_3}$), 3.62 (s, 1H, C≡C-$\underline{H}$), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 155.20(-C=N-), 148.77, 144.55, 144.24, 138.99,136.18, 129.60,128.90,128.19,127.10, 124.70, 122.69, 115.17, 114.77, 112.54 (14 C, Ar-C), 79.39(-C≡$\underline{C}$-H), 77.46(-$\underline{C}$≡C-H),72.51 (-O-C$\underline{H_2}$-Ph), 57.14(O-CH_2-$\underline{C}$≡C-H), 55.19 (O-CH_3).

Synthesis of 1,2,3-triazoles derivatives(10-15):

(1.2eq) From compounds (5-10) to (0.55mmol) from compound **(1)** dissolved in 20 mL DMF after the mixture remained on stirring for 10 minutes added (5mol%) from $CuSO_4.5H_2O$ and (10mol%) sodium ascorbate, after which the reaction is left for stirring at laboratory temperature, after the completion of the reaction (as indicated by TLC, ethylacetate:n-hexane: ethanol 3:1.5:0.5), the solvent was removed using a rotary evaporator, then the sediment was washed recrystallization using glacial acetic acid and ethanol (1:3).

4-(4-((4-(((4-(decyloxy) phenyl) imino)methyl) -2-methoxyphenoxy)methyl) -1H-1,2,3-triazol -1-yl)-N-(5-methylisoxazol -3-yl) benzenesulfonamide (10):

It was prepared as a white crystalline, Chemical formula: $C_{37}H_{44}N_6O_6S$; 85% yield; mp 68-70 ºC; FT-IR data (cm-1): 3164(C-H triazole), 3091(C-H aromatic), 1528(C=C aromatic), 1242(C-O aromatic), 1083(S=O str), 1050(C-O aliphatic), 972(S-N), 874(C-S),^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.45 (s, 1H, -NH-), 8.41 (s, 1H, (-CH=N-), 8.31 (s, 1H, triazole ring), 7.77-7.25 (m, 7H, Ar-H), 6.19 (s, 1H, C-H-methoxazole ring), 4.91 (s, 2H, O-CH_2-, triazole ring), 4.05 (t, J = 6.1 Hz, 2H, -O-CH_2-alkyl chain), 3.85 (s, 3H, -O-CH_3), 2.31 (s, 3H, methoxazole ring -CH_3), 1.74 (m, 2H, β-CH_2-), 1.34 –1.23 (m, 12H, -$(CH_2)_7$), 0.87 (t, J = 6.1 Hz, 3H, -CH_3), ^{13}C-NMR (75 MHz, DMSO-d_6) δ169.97(CH_3-C-methoxazole ring),158.47(sulfonamide-C-methoxazole ring),153.45(-C=N-), 145.47 (C4, triazole ring), 122.87 (C5, triazole ring), 147.87, 145.72, 143.28,140.61,138.78,135.49, 129.57,128.49, 124.87, 122.78, 120.68, 115.78, 114.17, 111.48 (14 C, Ar-C), 96.68(CH-methoxazole ring), 61.27 (-O-CH_2-, alkyl chain), 56.69(O-CH_3), 32.45(β-CH_2-), 29.98, 29.82, 29.55, 29.41, 29.30, 26.74, 22.41 (7-CH_2-), 14.31 (CH_3), 12.28(methoxazole ring-CH_3).

4-(4-((4-(((4-(dodecyloxy) phenyl)imino) methyl)-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide(11):

It was prepared as a white crystalline, Chemical formula: $C_{39}H_{48}N_6O_6S$; 85% yield; mp 68-70 ºC; FT-IR data (cm-1): 3190(C-H triazole), 3107(C-H aromatic), 1592(C=C aromatic), 1242(C-O aromatic), 1099(S=O str), 1050(C-O aliphatic), 964(S-N), 838(C-S), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.44 (s, 1H, -NH-), 8.34 (s, 1H, (-CH=N-),8.55 (s, 1H, triazole ring), 7.40 7.22 (m, 7H, Ar-H), 6.18 (s, 1H, C-H-methoxazole ring), 4.89 (s, 2H, O-CH_2-, triazole ring), 4.07 (t, J = 6.1 Hz, 2H, -O-CH_2-alkyl chain), 3.88 (s, 3H, -O-CH_3), 2.34 (s, 3H, methoxazole ring -CH_3), 1.77 (m, 2H, β-CH_2-), 1.33 –1.23 (m, 12H, -$(CH_2)_9$), 0.84 (t, J = 6.1 Hz, 3H, -CH_3), ^{13}C-NMR (75 MHz, DMSO-d_6) δ167.88(CH_3-C-methoxazole ring),153.77(Sulfonamide-C-methoxazole ring),152.22(-C=N-), 143.17 (C4, triazole ring), 121.12 (C5, triazole ring), 146.76, 144.54, 143.23,142.25, 137.98,134.49, 128.55,128.52, 123.33, 122.53, 121.50, 117.10, 116.77, 114.14 (14 C, Ar-C), 97.67(CH-methoxazole ring), 60.13 (-O-CH_2-, alkyl chain), 55.12(O-CH_3), 33.86(β- CH_2-),32.12, 29.77, 29.67, 29.60, 29.49, 29.47,29.35 25.16, 20.75 (9-CH_2-), 13.33 (CH_3), 13.22(methoxazole ring-CH_3).

4-(4-((4-(((4-(tetradecyloxy) phenyl) imino)methyl) -2-methoxyphenoxy) methyl)-1H-1,2,3-triazol-1-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide(12):

It was prepared as a white crystalline, Chemical formula: $C_{41}H_{52}N_6O_6S$; 85% yield; mp 68-70 ºC; FT-IR data (cm-1): 3159(C-H triazole), 3107(C-H aromatic), 1594(C=C aromatic), 1242(C-O aromatic), 1099(S=O str), 1050(C-O aliphatic), 964(S-N), 838(C-S), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.45 (s, 1H, -NH-), 8.41 (s, 1H, (-CH=N-),8.31 (s, 1H, triazole ring), 7.77-7.25 (m, 7H, Ar-H), 6.19 (s, 1H, C-H-methoxazole ring), 4.91 (s, 2H, O-CH_2-, triazole ring), 4.05 (t, J = 6.1 Hz, 2H, -O-CH_2-alkyl chain), 3.85 (s, 3H, -O-CH_3), 2.31 (s, 3H, methoxazole ring -CH_3), 1.77 (m, 2H, β-CH_2-), 1.38–1.23 (m, 22H, -$(CH_2)_{11}$), 0.84 (t, J = 6.1 Hz, 3H, -CH_3), ^{13}C-NMR (75 MHz, DMSO-d_6) δ170.88(CH_3-C-methoxazole

ring),157.75(sulfonamide-C-methoxazole ring),155.21(-C=N-), 146.12 (C4, triazole ring), 121.12 (C5, triazole ring), 149.78, 147.55, 145.22,144.23, 139.97,138.43, 129.55,128.55, 126.30, 123.54, 122.57, 114.12, 112.74, 111.14 (14 C, Ar-C), 95.55(CH-methoxazole ring), 62.12 (-O-CH_2-, alkyl chain), 54.12(O-CH_3), 33.88(β-CH_2-),31.13, 29.77, 29.59, 29.48, 29.43, 29.36,29.33,29.29 28.26,26.16, 21.75 (11-CH_2-), 15.12 (CH_3), 12.23(methoxazole ring-CH_3).

4-(4-((4-(((4-(hexadecyloxy) phenyl) imino)methyl)-2-methoxyphenoxy) methyl) -1H-1,2,3-triazol-1-yl)-N-(5-methylisoxazol-3-yl) benzenesulfonamide (13):

It was prepared as a white crystalline, Chemical formula: $C_{43}H_{56}N_6O_6S$; 85% yield; mp 68-70 ºC; FT-IR data (cm-1): 3159(C-H triazole), 3107(C-H aromatic), 1568 (C=C aromatic), 1267(C-O aromatic), 1099(S=O str), 1003(C-O aliphatic), 964(S-N), 838(C-S), ^{1}H-NMR (300 MHz, DMSO-*d_6*) δ 11.42 (s, 1H, -N<u>H</u>-), 8.39 (s, 1H, (-CH=N-),8.33 (s, 1H, triazole ring), 7.81-7.23(m, 7H, Ar-H), 6.16 (s, 1H, C-H-methoxazole ring), 4.90 (s, 2H, O-C<u>H</u>$_2$-, triazole ring), 4.03 (t, J = 6.1 Hz, 2H, -O-C<u>H</u>$_2$-alkyl chain), 3.86 (s, 3H, -O-C<u>H</u>$_3$), 2.35 (s, 3H, methoxazole ring -CH_3), 1.80 (m, 2H, β-CH_2-), 1.38–1.25 (m, 26H, -$(CH_2$-$)_{13}$), 0.82 (t, J = 6.1 Hz, 3H, -CH_3), ^{13}C-NMR (75 MHz, DMSO-*d_6*) δ169.88(CH_3-C-methoxazole ring),153.77(sulfonamide-C-methoxazole ring),151.29(-C=N-), 146.14 (C4, triazole ring), 122.51 (C5, triazole ring), 149.76, 146.58, 143.24,141.28, 139.97,137.43, 129.52,128.57, 126.33, 125.10, 124.53, 117.11, 116.74, 113.14 (14 C, Ar-C), 94.54(CH-methoxazole ring), 63.11 (-O-CH_2-, alkyl chain), 58.11(O-CH_3), 33.66(β-CH_2-), 31.15,29.87, 29.77,29.69, 29.61, 29.57, 29.50, 29.40,29.39,29.33 29.30,26.19, 21.77 (13-CH_2-), 12.12 (CH_3), 11.23(methoxazole ring-CH_3).

4-(4-((4-(((4-(octadecyloxy) phenyl) imino) methyl)-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide(14):

It was prepared as a white crystalline, Chemical formula: $C_{45}H_{60}N_6O_6S$; 85% yield; mp 68-70 ºC; FT-IR data (cm-1): 3168(C-H triazole), 3107(C-H aromatic), 1594(C=C aromatic), 1290(C-O aromatic), 1099(S=O str), 1096(C-O aliphatic), 964(S-N), 838(C-S), ^{1}H-NMR (300 MHz, DMSO-*d_6*) δ 11.44 (s, 1H, -N<u>H</u>-), 8.46 (s, 1H, (-CH=N-),8.35 (s, 1H, triazole ring), 7.80-7.27 (m, 7H, Ar-H), 6.16 (s, 1H, C-H-methoxazole ring), 4.87 (s, 2H, O-C<u>H</u>$_2$-, triazole ring), 4.05 (t, J = 6.1 Hz, 2H, -O-C<u>H</u>$_2$-alkyl chain), 3.84 (s, 3H, -O-C<u>H</u>$_3$), 2.31 (s, 3H, methoxazole ring -CH_3), 1.77 (m, 2H, β-CH_2-), 1.38–1.20 (m, 30H, -$(CH_2$-$)_{15}$), 0.83 (t, J = 6.1 Hz, 3H, -CH_3), ^{13}C-NMR (75 MHz, DMSO-*d_6*) δ167.88(CH_3-C-methoxazole ring), 155.20 (sulfonamide-C-methoxazole ring), 153.77 (-C=N-), 146.12 (C4, triazole ring), 122.54 (C5, triazole ring), 149.76, 147.56, 146.25,144.24, 139.93,137.43, 129.52,128.50, 125.12, 124.39, 122.56, 117.13, 116.74, 113.04 (14 C, Ar-C), 96.57(CH-methoxazole ring), 63.15 (-O-CH_2-, alkyl chain), 55.15(O-CH_3), 29.86(β-CH_2-) ,29.98,29.86, 29.77,29.69,29.65, 29.57, 29.54, 29.47, 29.46,29.39,29.36,29.33 29.26,26.20, 21.77 (15-CH_2-), 14.12 (CH_3), 12.23(methoxazole ring-CH_3).

4-(4-((4-(((4-(benzyloxy) phenyl) imino)methyl) -2-methoxyphenoxy) methyl)-1H-1,2,3- triazol-1-yl)-N-(5-methylisoxazol-3-yl) benzenesulfonamide (15):

It was prepared as a white crystalline, Chemical formula: $C_{34}H_{30}N_6O_6S$; 85% yield; mp 68-70 ºC; FT-IR data (cm-1): 3144(C-H triazole), 3107(C-H aromatic), 1586(C=C aromatic), 1267(C-O aromatic), 1099(S=O str), 1003 (C-O aliphatic), 964(S-N), 838(C-S), ^{1}H-NMR (300 MHz, DMSO-*d_6*) δ 11.44 (s, 1H, -N<u>H</u>-), 8.46 (s, 1H, (-CH=N-),8.36 (s, 1H, triazole ring), 7.83-7.27 (m, 12H, Ar-H), 6.15 (s, 1H, C-H-methoxazole ring), 4.90 (s, 2H, -O-C<u>H</u>$_2$-Ph), 4.85 (s, 2H, O-C<u>H</u>$_2$-triazole ring), 3.86 (s, 3H, -O-C<u>H</u>$_3$), 2.37 (s, 3H, methoxazole ring -CH_3), ^{13}C-NMR (75 MHz, DMSO-*d_6*) δ169.81(CH_3-C-methoxazole ring),153.75(Sulfonamide-C-methoxazole

ring),152.23(-C=N-), 143.16 (C4, triazole ring), 120.86, (C5, triazole ring), 149.71, 146.51,145.28, 143.20, 139.95, 137.12,136.77,133.54, 129.56, 129.50, 128.10,127.15, 123.34, 123.58, 123.12, 117.14, 116.75, 113.04 (14 C, Ar-C), 96.57(CH-methoxazole ring), 72.54 (-O-$C\underline{H}_2$-Ph), 59.16(O-CH_2-, triazole ring), 57.11(O-CH_3), 14.23 (methoxazole ring-CH_3).

Antibacterial Study:

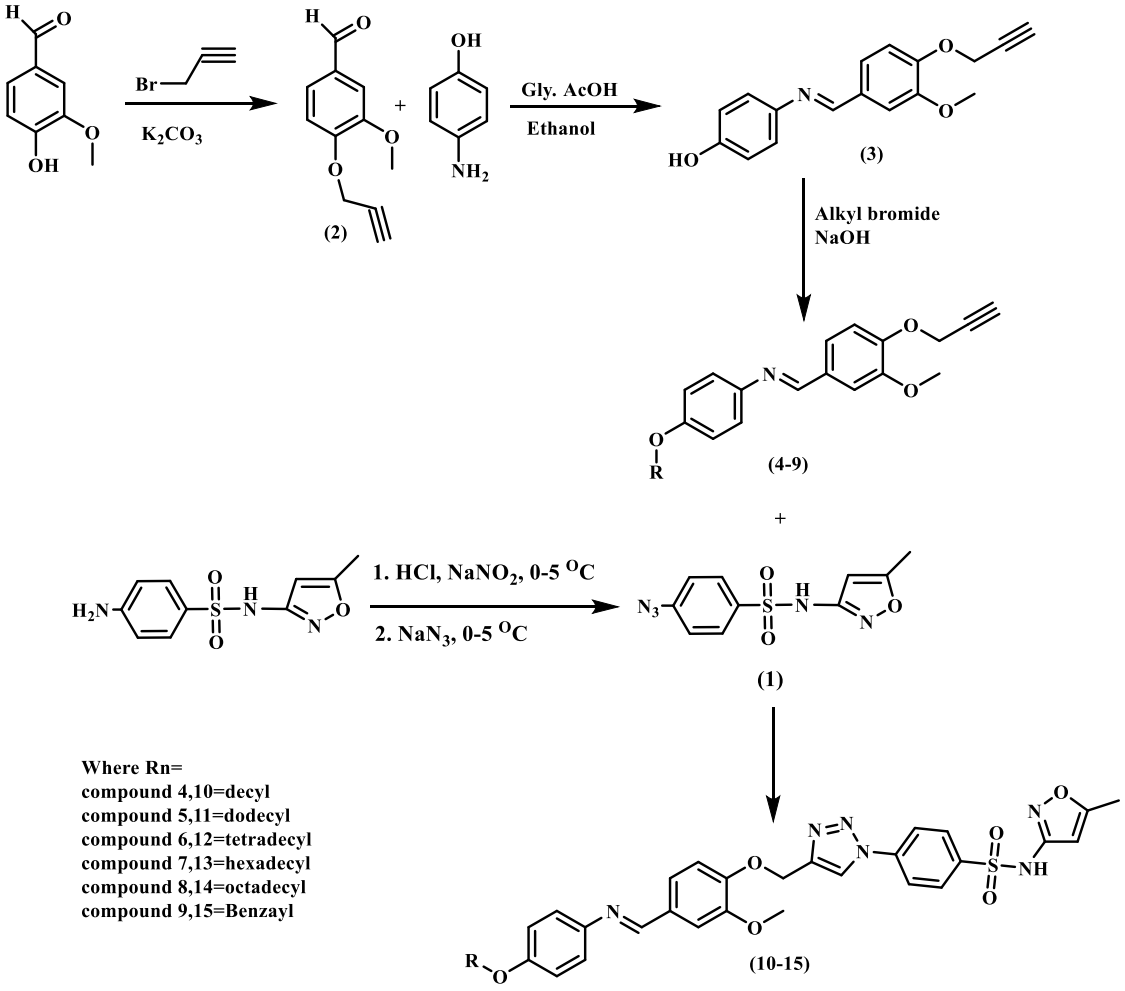
Two strains of *Staph aureus and E. coli* have been chosen. The bacterium is used for all experiments, and grown in Muller Hinton agar. All types of bacteria have been grown at 36 h and have been incubated at 37 °C. After serial optimization to reach $1.5x10^{-8}$ bacteria per ml, it is used spectrophotometry experiment to compare the OD_{600} with viable count (CFU). It is around OD_{600} 0.4 equal to $1x10^8$. Different concentrations have been prepared as follows (12.5, 25, 50 & 100) µM in (DMSO) of all prepared heterocyclic in our study, added separately to the wells on the plates that already have bacterial growth. The plates were incubated for 24 h to test the anti-bacterial effects; a ruler is used to measure the inhibition zone to the nearest millimeter (mm).

RESULTS AND DISCUSSION

Chemistry:

By the strategy briefly depicted in Scheme 1, we have synthesized 1,2,3-triazole derivatives from sulfamethoxazole via cycloaddition reaction between 4-azido-N-(5-methylisoxazol-3-yl)benzenesulfonamide.
and O-propargyl derivatives contain alkyl chain. Initially, the azide derivative of the sulfamethoxazole (1) is formed by first forming the sulfamethoxazole diazonium ion, then proceeding with the reaction via an azide attack on the diazonium ion, as suggested by Huisgen and Ugi [Huisgen, R. & Ugi, I. Zur,1956]. Because nitrogen is very stable and is lost as a gas, and the amine group (-NH_2) of the sulfadiazine is linked to the benzene ring, which contains the electron-withdrawing group (-SO_2-), this provides a strong driving force for the reaction to occur with high yield. The propargyl derivative is prepared through the Williamson reaction, in which anhydrous potassium bicarbonate (K_2CO_3) is used as a catalyst, which has a sufficient base to extract the proton of the hydroxyl group [Yina Pájaro et al,2017], as it provides a good nucleophilic (phenoxied ion) to attack the carbon atom associated with the halogen present in propagel bromide where the mechanism of this reaction is classified as SN_2 reaction, as a result, acetone one of the best solvents for this type of reactions. The Schiff base derivative (3) has been synthesized by the condensation strategy of prepared propargyl derivative (2) with 4-amino phenol, which is the most popular one, with simplicity and higher by using glacial acetic acid as catalyst and absolute ethanol as an organic solvent. The O-alkyl chain and benzyl derivatives (4-9) were obtained in high yield by O-alkylation of alkyl halide with the synthesized Schiff base (3) in the presence of a strong base (NaOH) in DMSO at 70 °C. The last step was a 1,3-dipolar cycloaddition reaction between 4-azido-N-(5-methylisoxazol-3-yl)benzenesulfonamide
and O-propargyl derivatives (4-9) in the presence of copper sulfate and sodium ascorbate in DMF, the 1,2,3-triazoles (10-15) were obtained with good yield. The structures of the synthesized compounds were fully characterized by IR, ^1H & ^{13}C NMR and mass analysis. The FTIR spectra of compounds (10-15) showed characteristic bands of 1,2,3-triazole nucleus in the range of 1500–1300 cm^{-1} corresponding to C=C & N=N bonds. The characteristic bands of (NH) of sulfonamide were detected in the range 3300–3350 cm^{-1}, whereas alkyl chain appears with high intensity in the range 2800-2900 cm^{-1}. The ^1H NMR spectra of compounds (9-15) showed characteristic signals of the protons corresponding to 1,2,3-triazole nucleus between 8.35 ppm and 8.41 ppm, in addition to aromatic protons in the region of 7.83–7.20 ppm. We also noticed the presence of a signal at 6.16 ppm corresponded to methylene groups attached to oxazole ring and a singlet signal at 8.47 ppm due to imine proton. On the other hand singlet signal at the range of 11.41-

11.46 ppm is assigned to the sulfonamide proton. In ^{13}C NMR spectra all expected carbon signals corresponding to sulfamethoxazole-1,2,3-triazole derivatives were observed, principally the signals of methyl carbons between 12 ppm and 15 ppm and signals of aromatic carbons at 125 ppm and 143 ppm corresponding to 1,2,3-triazole nucleus.



Scheme 1. Synthetic Route of heterocyclic compounds**.**

Antibacterial Activity:

The antibacterial activity of the synthesized compounds (9-15) was investigated against one gram-positive bacteria *Staphyloccocus aureus* and one gram-negative bacteria *Escherichia coli*. The antibacterial activity has been primarily tested as the observed growth inhibition zones by disk-diffusion method using Mueller Hinton Broth (MBH) medium. Then, Minimum inhibitory concentrations (MIC) were determined for the synthesized compounds. DMSO was used as a negative control for antibacterial activity. The observed minimum inhibitory concentration (MIC) antibacterial data of the synthesized compounds (9-15) are given in Figures 1 and 2. The antibacterial activity results revealed that the tested compounds exhibited various degrees of inhibition against Gram-positive and Gram-negative bacteria both tested microorganisms were observed to be the sensitive bacteria. All prepared compounds increase their effectiveness with increasing concentration.

Compounds (10,12,13,15) with alkyl or phenyl group on the sulfamethoxazole-1,2,3-triazole skeleton showed the best antibacterial activity against *Staphyloccocus aureus* with MIC values illustrated in Figure 1. except for compound

(11, 14) which did not give any activity against the selected bacteria *Staphyloccocus aureus*. Besides this, compound 12 showed the most antibacterial activity against *Staphyloccocus aureus* with a MIC value of 20 µg/mL. On the other hand, Also, compound (13) did not give any activity against the selected bacteria *Escherichia coli*. Whereas the end products (10,11,12,14,15) with alkyl or phenyl group on the sulfamethoxazole-1,2,3-triazole skeleton showed the best antibacterial activity against *Escherichia coli* with MIC values illustrated in Figure 2. Beside this, compound (15) showed most antibacterial activity against *Escherichia coli* with MIC value 21 µg/mL.

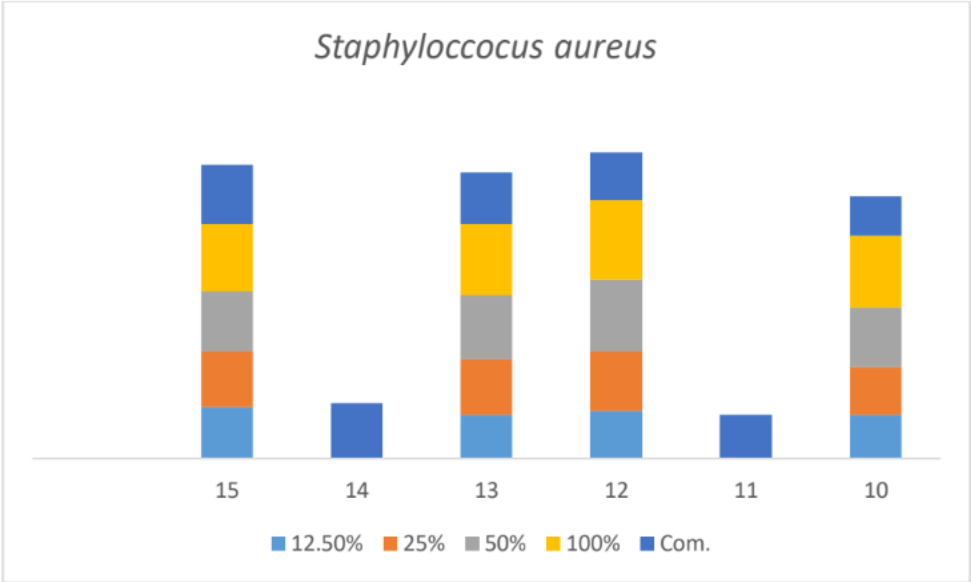


Fig. 1: The biological activity of end products (10-15) against *Staphylococcus aureusa.*

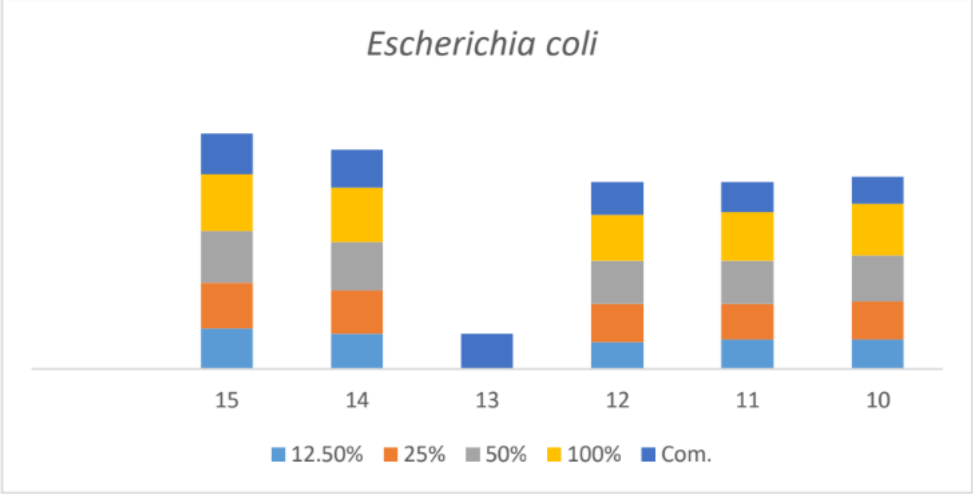


Fig. 2: The biological activity of end products (10-15) against *Escherichia coli* .

Conclusion

In summary, new 1,2,3-triazole derivatives from sulfamethoxazole were prepared, characterized and biologically evaluated. The synthesized compounds (10-15) were screened for their *in vitro* antibacterial activity against two bacteria pathogenic strains, compound 12 was found to be the most potent against *staphylococcus aureus* compared with the other prepared compounds. Whereas compound 15 was found to be the most potent against *Escherichia coli* compared with the other end compounds.

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