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Preparation With Studying Biological Activity For New 1,2,3-Triazole Derivatives Of Sulfamethoxazole

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Abstract

A serious 1,2,3-triazole derivatives were prepared by reaction between4-azido-N-(5-methylisoxazol-3-yl)benzene sulfonamide with different triple bond derivatives in presence CuCl and sodium ascorbate as catalyst. FTIR, and NMR have established the chemical structures of the target compounds. All end derivatives were evaluated to in vitro antifungal testing against two types of fungi (Aspergillus niger and Candida albicans) and antibacterial screening against four pathogenic strains (Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus epidermidis, Escherichia coli). The findings indicate that the compounds being tested displayed promising activity and warranted further consideration as potential anti-micro bales.

Keywords: Sulfamethoxazole, Antibacterial Activity, Antifungal, 1,2,3Triazole, Heterocyclic.

Introduction

Antimicrobial resistance has been designated by the World Health Organization (WHO) as one of the most important threats to global health today [1]. The antibiotic resistance dilemma has been blamed on overuse and misuse of antibiotics, as well as a lack of new medication research by the pharmaceutical industry due to restricted economic incentives and burdensome regulatory requirements [2–6].Over the last decade, several highly resistant bacterial diseases have developed sophisticated strategies to counteract the effects of numerous treatment medications[7]. The bacterial infection Staphylococcus aureus has become a big concern for healthcare workers all around the world.

Antibacterial resistance has been found in isolated S. aureus strains, including – macrolides[8] , fluoroquinolones[9-11], lactam antibiotics[12], oxazolidinones[13] and glycopeptides [14].Enterococci were once assumed to be innocuous commensal bacteria with little clinical significance, but they have now been identified as dangerous nosocomial infections that cause endocarditis, urinary tract infections, bloodstream infections, meninge infections, wound infections, and infections of the biliary tract [15]. Only coagulase-negative Staphylococcus and Staphylococcus aureus are more frequently isolated nosocomial pathogens (Infections in hospitals account for 12% of all infections), according to recent surveillance data [16].Antibiotic resistance, which raises the risk of infection and colonization, is directly tied to clinical importance of the Enterococcus genus. Many routinely used antibiotic drugs (penicillins, ampicillins, cephalosporins, clindamycin) are intrinsically resistant to enterococci, and they also have native resistance to clinically attainable aminoglycoside doses. Despite the fact that E. faecalis is naturally resistant to dalfopristin-quinupristin, strains of E. faecalis that lack special resistance traits find this combination to be extremely successful. Enterococci are resistant for cell-wall active compounds' (usually) bactericidal action.Tolerance means that the bacteria can be inhibited by antibiotic concentrations that are clinically available, but only killed by concentrations that are substantially higher than the inhibitory concentration [17]. Multi-resistant E. faecalis strains have emerged, making treatment more challenging, necessitates the search for and identification of new treatment techniques.Triazoles are resistant toreductive/oxidative conditions in addition to acidic/basic hydrolysis, indicating that they have a high aromatic stability. This moiety resists metabolic breakdown to a large extent. The therapeutic properties of 1,2,3-triazole and its derivatives have piqued interest during the last two decades, with reports of a wide spectrum of biological activity. [18] antifungal, [19] antitubercular, [20] antiallergic, [21] anti-HIV, [22] antibacterial, [23] a-glycosidase inhibitor, [24] antimicrobial, [25] anticoccidiostats, [26] anticonvulsant, [27] antimalarial, [28] antiviral, [29] and antimycobacterial. [30]Triazole was employed to improve the intended drug's pharmacokinetic qualities. [31] The preparation andantimicrobial properties for certain derivatives based on 1,2,3-triazole were investigated in this study. As illustrated in Figure 1, the produced compounds were 1,2,3-triazoles coupled to sulfamethoxazole. These derivatives were made from reacting 4-azido-N-(5-methylisoxazol-3-yl)benzenesulfonamide with various triple bond derivatives in the presence of CuCl and sodium ascorbate. [32]

Materials and Methods

The reagents, solvents, and starting substanceswere obtained from Sigma Aldrich Chemicals, Thomas Baker, Merck, Fluke, and a commercial supplier, among others. TLC plates, which were supplied on a Merck silica gel SG-40, were used to track the development of all reactions. On the Bruker ALPHA, University of Kufa, Faculty of Science, FTIR spectra were recorded using Fourier transformation infrared. Mashhed University validated NMR spectrum on Bruker apparatus, 400MHz for ^{1}HNMR and 100MHz for ^{13}CNMR. The elemental composition was determined using a Perkin-Elmer 204E instrument.

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

From Sulfamethoxazole (80 mmole) was dissolved in 1.7 mL of HCl and 10mL distilled water . In an ice-water bath, the mixture was chilled to (0-5 ^{o}C). After that, a solution of $NaNO_2$ (0.01mol) was dissolved in 5 mL distilled water, which was then chilled at (0-5 ^{o}C). This solution was then added to the mixture drop by drop, stirring constantly. The solution of diazonium salt was then added in portions to a solution of sodium azide (80 mmol) and kept at temperature (0-5^{o}C). For 30 minutes, the mixture was stirred . The mixture was set aside for the night. Filtration was used to isolate the product, which was then washed multiple times with distilled water then recrystallized from ethanol.

(1b): 4-azido-N-(5-methylisoxazol-3-yl)benzenesulfonamide: It was produced in yield (92%) as a white crystalline substance with the following chemical formula: $C_{10}H_9N_5O_3S$; m.p. 93-95 ^{o}C; FTIR, ν (cm^{-1}) 3236,3057, 2978, 2171,1587, 1451, 1365, 1290,1064 ; ^{1}H-NMR (400MH_Z,DMSO-d_6)δ ppm: 10.09 (s, 1H), 7.74 – 7.66 (m, 2H), 7.36 – 7.28 (m, 2H), 6.09 (s, 1H), 2.30(s, 3H). ^{13}C-NMR (100MHz, DMSO-d_6) δ 169.89, 155.86, 144.96, 136.62, 129.23, 118.96, 96.60, 12.26.

Synthesis of 1,2,3-triazole derivatives (2b,3b,4b,5b)

In DMF (20mL) , (1.1mmol) of 4-azido-N-(5-methylisoxazol-3-yl)benzenesulfonamide comp.(A) with (1.1mmol) from triple bond derivatives (propargyl bromide, propargyl chloride, propargyl alcohol, propargyl glyacine) were dissolved. CuCl (0.2 mmol) and (0.4mmol) sodium ascorbate were added to this mixture . The solution then stirred at (60-70 ^{o}C) until T.L.C. confirmed that the reaction was finished and that the azide had been consumed. Diethyl ether and water were used to dilute the mixture. The water phase was extracted twice with diethyl ether after the organic phase was separated. $MgSO_4$ was used to dry the organic phase. The solvent was removed and the hexanes-chloroform was used for recrystallization .

(2b):4-(5-(bromomethyl)-1H-1,2,3-triazol-1-yl)-N-(5-methylisoxazol-3yl) benzene sulfonamide:

It was produced in yield (76%) as a white crystalline substance with the following chemical formula: $C_{13}H_{12}BrN_5O_3S$; m.p 153-155 ºC; FT-IR, ν (cm^{-1}) 3275,3101, 2975, 2864,1599, 1461, 1301, 1290,1047; ^{1}H-NMR (400 MH_Z, DMSO-d_6)δ ppm 11.20 (s, 1H, -NH-sulfonamide), 7.51 (s, 1H, triazole ring proton), 7.98 – 7.84 (m, Ar-H), 6.21 (s, 1H, Sulfamethoxazole ring proton), 5.17 (-CH2-triazole), 2.34(s,3H,methyl protons). ^{13}C-NMR(100MHz, Chloroform-d) δ 169.75, 155.91, 143.35, 137.65, 136.03, 133.32, 128.78, 122.81, 96.39, 50.35,44.35,35.88.

(3b): 4-(5-(chloromethyl)-1H-1,2,3-triazol-1-yl)-N-(5-methylisoxazol-3yl) benzenesulfonamide: It was prepared as a white crystalline, Chemical Formula: $C_{13}H_{12}ClN_5O_3S$, 80% yield; m.p 173-175 ºC; FTIR, ν (cm^{-1}) 3286,3112, 2891, 1589, 1453, 1376, 1291,1114; ^{1}H-NMR (400 MH_Z, DMSO-d_6)δ ppm 11.12 (s, 1H, -NH-sulfonamide), 7.61 (s, 1H, triazole ring proton), 7.94 – 7.84 (m, ArH), 6.17 (s, 1H, Sulfamethoxazole ring proton), 5.23 –(-CH_2-triazole), 2.35(s,3H,methyl protons). ^{13}C-NMR(100MHz, Chloroform-d) δ 169.75, 155.84, 142.78, 137.61 (d, J = 6.5 Hz), 132.66, 128.75, 121.87, 96.31,50.84,46.54, 36.14.

(4b): 4-(5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-(5-methylisoxazol-3-yl) benzenesulfonamide: It was produced in yield (82%) as a white crystalline substance with the following chemical formula: $C_{13}H_{13}N_5O_4S$; m.p 179-181 ºC; FT-IR, ν (cm^{-1}) 3301,3132, 2971, 2912,1587, 1461, 1375, 1280,1068; ^{1}H-NMR (400 MH_Z, DMSO-d_6)δ ppm 11.21 (s,1H, -NH-sulfonamide), 7.63 (s, 1H, triazole ring proton), 7.98 – 7.84 (m, Ar-H), 6.15 (s, 1H, Sulfamethoxazole ring proton), 5.11 (s, 2H, CH_2-triazole), 4.77 (s, 1H, hydroxyl proton), 2.63(s, 3H,methyl protons). ^{13}C-NMR(100MHz, Chloroform-d) δ 169.75, 155.89, 143.40, 137.64, 135.86, 135.17, 128.75, 123.21, 96.31, 51.34 42.86, 36.24.

(5b): 2-amino-3-(1-(4-(N(5-methylisooxazol-3yl)sulfamoyl)phenyl)-1H1,2,3-triazol-5-yl)propa- noic acid: It was produced in yield (78%) as a white crystalline substance with the following chemical formula: $C_{15}H_{16}N_6O_5S$; m.p 156-158 ºC; FT-IR, ν (cm^{-1}) 3298,3125, 2971, 2934,1599, 1451, 1365, 1286,1167; ^{1}H-NMR (400 MH_Z, DMSO-d_6)δ ppm 12.31(s,1H, carboxylic protont), 11.3 (s, 1H, -NH-sulfonamide), 7.87 (s, 1H, triazole ring proton), 7.51-7.24 (m, Ar-H), 6.20 (s, 1H, Sulfamethoxazole ring proton), 4.75 (s, 2H, -NH2),5.25 (q, J= 6.7 Hz, 2H CH-NH_2),3.96 (d, J = 6.7 Hz, 2H, -CH_2-triazole), 2.31 (s, 3H, methyl protons). ^{13}C NMR (100 MHz, Chloroform-d) δ 193.21, 169.75, 155.93, 144.1, 137.65, 129.68, 128.79, 122.45, 96.42, 53.15,41.36, 35.97.

Antimicrobial activity assay

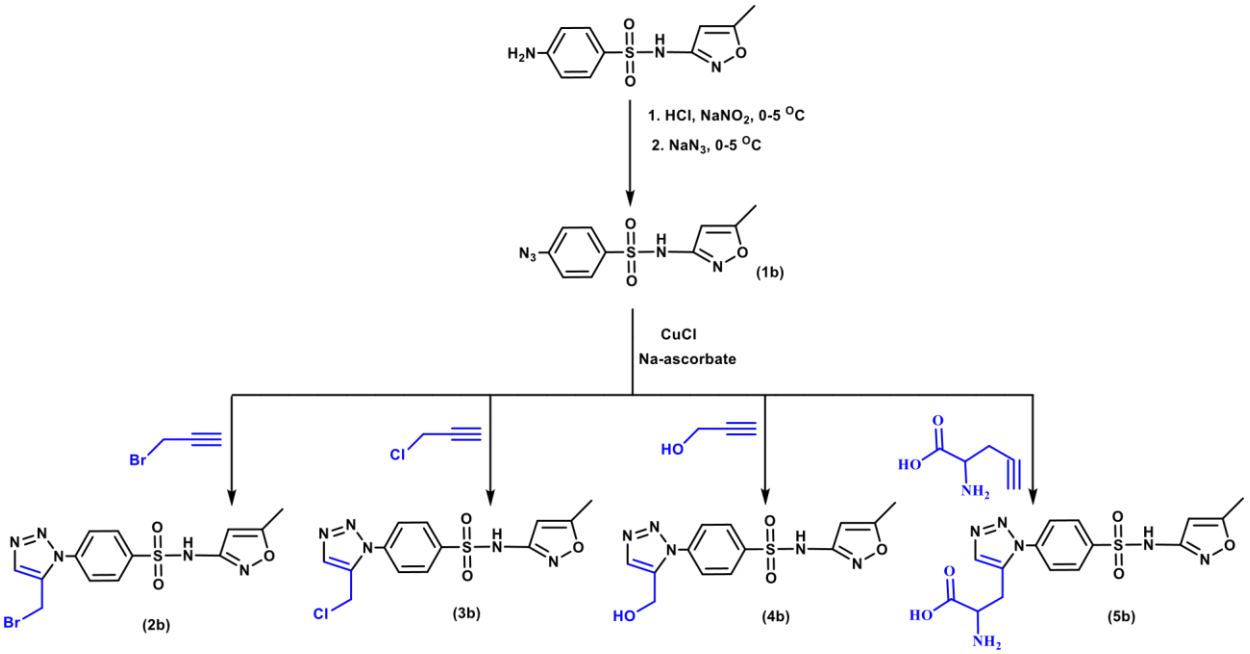
All the target compounds (2b-5b) were tested against two bacterial strains Bacteria that are Gram-positive and Gram-negative and screening against four pathogenic strains (Pseudomonas aeruginosa,

Bacillus subtilis, Staphylococcus epidermidis, Escherichia coli). for its antibacterial function. The prepared compounds' antifungal activity had been checked against (Candida albicans and Aspergillus niger).The MICs for the synthesized tetrazole derivatives assays were conducted by the susceptibility procedure of micro dilution. Ciprofloxacin and fluconazole have been used as an antibacterial and an antifungal reference agent respectively. Dissolved in dimethyl sulfoxied (DMSO) atconcentration 400 µg/mL.The research compounds ciprofloxacin and fluconazole; They were then diluted in the culture medium (potato dextrose agar for fungi and nutrient agar for bacteria) and prepared for dilution with a double-series solution (100, 50, 25, 12.5 and 6.25 µg/mL).The tubes then incubated at 36 °C for 48 hours for fungi and 24 hours for bacteria.The compounds' minimal inhibitory concentrations (MICs, µg / mL) were reported as that the lowest concentration for each chemical derivative in turbidity-free tubes of inoculated fungi / bacteria.

Results and Discussion

Chemistry

Syntheticstrategies (Scheme 1) followed in order to synthesize the end compounds (2b-5b). The starting materials that is, azido sulfamethoxazole [25, 26] and propargyl bromide, propargyl chloride, propargyl alcohol, propargyl glycine [27] were synthesizerd according to the previously studies. The target compounds (2b,3b,4b,5b) were prepared in good yields by reaction of azido sulfamethoxazole with the appropriate propargyl bromide, propargyl chloride, propargyl alcohol, propargyl glycine in presence of Cu(I) and DMF at 60-70 ºC.



Scheme 1. Synthesis 1,2,3-triazole derivatives

FTIR data

The appearance of a distinctive band at 3101,3112, 3132, 3125 cm^{-1} in the FTIR analysis of synthesized 1,2,3-triazole (2b-5b) evidenced the preparation of 1,,3-triazole compounds. The synthesized 1,2,3-triazole derivatives (2b-5b) showed two absorption peaks in the region 3275, 3286, 33018, 3298 cm^{-1} that were due to the -NH-sulfonamide stretching vibrations. On the other hand, IR spectrum of triazoles derivatives showed disappearance bands in the triple bond region due to propargyl componds were due to alkyne moiety, whereas disappearance bands at 2171 cm^{-1}forazide group in sulfamethoxazole azides .

^{1}H-NMR data

In the ^{1}H NMR analysis of triazole derivatives (2b-5b) and b1 showed signlet signal at 10.09,11.2,11.12,11.21,11.3 ppm due to -NH-sulfonamide protons. In (5b) compond a broad peak appeared at 12.31ppm, 4.74 ppm assigned carboxylic (OH) group and amine protons respecivily, whereas in compound (4b) a signlet signal at 4.77ppm due to (OH) group of propargyl moiety, which is made up of protons that can be exchanged with D2O. A new sharp peak and distinguishing signal singlet at 7.51, 7.61, 7.63, 7.88 ppm due to (-CH proton) were found to have 1,2,3-triazole rings proton. On the other hand, one sharp singlet peak of (-CH2) methylene protons (triazole-CH_2-) at 5.17, 5.23, 5.11,5.25 ppm in (2b-5b) compounds respectively, and one signlet signal at 2.34,2.35,2.36,2.31 ppm due to methyl attached sulfamethoxazole ring in (2b-5b) compounds respectively.

^{13}C NMR data

In the ^{13}C NMR analysis, new peaks and signals of 1C-5 and 1C-4 carbon atoms of the 1,2,3-triazole ring (2b-5b) appeared at 122.81,121.87,123.21,122.45 ppm and 143.35,142.78,143.40,144.01 ppm respectively. The peak appeared 193.21ppm was due to carbon atoms of the carbonyl carboxylic group in compound (5b). Whereas new peaks appeared at 12.26 ,12.88, 13.14, 12.24,12.97 ppm methyl carbon atoms were attached to sulfamethoxazole ring (b1-b5). On the other hand,^{13}C NMR spectrum showed peaks at 50.35,50.84,51.34,53.15 ppm due to carbon atoms of sulfamethoxazole ring were attached to -NH-sulfonamide moiety. Methylene carbons that bind to the Cl,Br,OH, glyacine showed peaks at 44.35, 46.54,42.68,41.36 ppm of (2b-5b) respectively.

Antimicrobial Activity

In the present study, the tatrazole deivatives were examined for the antimicrobial properties against the Gram-negative and Gram positive bacteria screening against four pathogenic strains(Pseudomonas

aeruginosa, Bacillus subtilis, Staphylococcus epidermidis and Escherichia coli). The antifungal activity of the compounds has been tested against two types of fungus (Candida albicans and Aspergillus niger)using (PDA) the medium Potato dextrose agar. (MIC) was calculated by a susceptibility system for microdilution. Ciprofloxacin and fluconazole have been used as a common antibacterial and antifungal drug respectively. The obtained results of the antimicrobial properties of control medicines and tetrazole compounds are summarized within the Table 1. All samples' MIC values were determined as the lowest concentration that totally inhibited the microorganisms' growth. (fungi and bacteria) visible growth. Antibacterial testing investigation exposed of the target compounds showed good -to-moderate inhibition in DMSO solvents at 25-100µg/mL. All of the compounds that have been prepared a good action against B is multiplied. Subtilis and S. (MIC 25µg/mL). P. aeuroginosa aureus (MIC 50 and 25 µg/mL) as well as mild activity against E. Coli. Compound (b) good job against B. Subtle,P. aeuroginosaand E. Coli, (MIC 50 µg/mL), and mild anti-S behaviors. (MIC: 100 µg / mL). The antifungal testing investigation exposed that the synthesized compounds showed a good -to-moderate inhibition in DMSO solvent at 25–50 µg / mL. The compound (a) has been found to be more active against C than compound (b). (MIC: 25 µg / mL) Albicans A. Niger: 50 µg / mL (MIC). Compound b, on the other hand, is effective against Candida Albicans (MIC 50 µg/mL) and mild anti-A behaviors. (MIC 100 µg / mL).

Table 1: Minimum inhibitory concentration (MIC, µg/mL) of the synthesized compounds 2b ,3b ,4b ,5b

Compound	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	S. aureus	*B. subtilis*	*E. coli*	*P. aeuroginosa*	*A. niger*	*C. albicans*
2b	50	25	100	50	50	25
3b	100	50	50	50	100	50
4b	75	100	75	75	25	50
5b	50	75	50	100	50	50
Ciprofloxacin	6.25	6.25	6.25	6.25		
Fluconazole					6.25	6.25

Conclusion

In conclusion, new 1,2,3-triazole compounds have been prepared & identified by some spectra analysis. The antimicrobial effect of all the prepared compounds was tested in vitro with compared to control medications, the tested compounds (2b-5b) demonstrated considerable antifungal and antibacterial activity.

References

1. Holpuch, A. UN meeting tackles the “fundamental threat” of antibiotic-resistant superbugs. Guardian 2016.

2. Viswanathan, V.K. Off-label abuse of antibiotics by bacteria. Gut Microbes 2014, 5, 3–4.

3. Read, A.F.; Woods, R.J. Antibiotic resistance management. Evol. Med. Public Health 2014, 2014, 147.

4. The antibiotic alarm. Nature 2013, 495, 151.

5. Lushniak, B.D. Antibiotic resistance: A public health crisis. Public Health Rep. 2014, 129, 314–316.

6. Michael, C.A.; Dominey-Howes, D.; Labbate, M. The antimicrobial resistance crisis: Causes, consequences, and management. Front. Public Health 2014, 2, 145.

7. Laxminarayan, R.; Duse, A.; Wattal, C.; Zaidi, A.K.; Wertheim, H.F.; Sumpradit, N.; Vlieghe, E.; Hara, G.L.; Gould, I.M.; Goossens, H.; et al. Antibiotic resistance-the need for global solutions. Lancet Infect. Dis. 2013, 13, 1057–1098.

8. Moran, G.J.; Krishnadasan, A.; Gorwitz, R.J.; Fosheim, G.E.; McDougal, L.K.; Carey, R.B.; Talan, D.A.; Group, E.I.N.S. Methicillin-resistant S. aureus infections among patients in the emergency department. N. Engl. J. Med. 2006, 355, 666–674.

9. Frazee, B.W.; Lynn, J.; Charlebois, E.D.; Lambert, L.; Lowery, D.; Perdreau-Remington, F. High prevalence of methicillin-resistant Staphylococcus aureus in emergency department skin and soft tissue infections. Ann. Emerg. Med. 2005, 45, 311–320

10. Fridkin, S.K.; Hageman, J.C.; Morrison, M.; Sanza, L.T.; Como-Sabetti, K.; Jernigan, J.A.; Harriman, K.; Harrison, L.H.; Lynfield, R.; Farley, M.M.; et al. Methicillin-resistant Staphylococcus aureus disease in three communities. N. Engl. J. Med. 2005, 352, 1436–1444.

11. Moran, G.J.; Amii, R.N.; Abrahamian, F.M.; Talan, D.A. Methicillin-resistant Staphylococcus aureus in community-acquired skin infections. Emerg. Infect. Dis. 2005, 11, 928–930.

12. Chambers, H.F. Community-associated MRSA—Resistance and virulence converge. N. Engl. J. Med. 2005, 352, 1485–1487.

13. Wilson, P.; Andrews, J.A.; Charlesworth, R.; Walesby, R.; Singer, M.; Farrell, D.J.; Robbins, M. Linezolid resistance in clinical isolates of Staphylococcus aureus. J. Antimicrob. Chemother. 2003, 51, 186–188.

14.Hiramatsu, K. Vancomycin-resistant Staphylococcus aureus: A new model of antibiotic resistance. Lancet Infect. Dis. 2001, 1, 147–155.

15. Hollenbeck, B.L.; Rice, L.B. Intrinsic and acquired resistance mechanisms in enterococcus. Virulence 2012, 3, 421–433.

16. World Health Organization (WHO). Antimicrobial Resistance: Global Report on Surveillance; WHO: Geneva, Switzerland, 2014.

17. Kristich, C.J.; Rice, L.B.; Arias, C.A. Enterococcal infection—Treatment and antibiotic resistance. In Enterococci: From Commensals to Leading Causes of Drug Resistant Infection; Gilmore, M., Clewell, D., Ike, Y., Eds.; Massachusetts Eye and Ear Infirmary: Boston, MA, USA, 2014.

18.Hueso-Falcón, I.; Amesty, Á.; Anaissi-Afonso, L.; Lorenzo-Castrillejo, I.; Machín, F.; Estévez-Braun, A. Synthesis and biological evaluation of naphthoquinone-coumarin conjugates as topoisomerase II inhibitors. Bioorg. Med. Chem. Lett. 2017, 27, 484–489.

19. R. C. Venkata, V. D. Mukund, G. T. Santosh, and K. Yadagiri, “Novel 1,2,3 triazole antifungal agents and preparation thereof” (US Patent US 9,981,923B2;

20. K. N. Venugopala, M. A. Khedr, Y. R. Girish, S. Bhandary, D. Chopra, M. A. Morsy, B. E. Aldhubiab, P. K. Deb, M. Attimarad, A. B. Nair, “Crystallography, In Silico Studies, and In Vitro Antifungal Studies of 2, 4, 5 Trisubstituted 1, 2, 3-Triazole Analogues,” Antibiotics 9 (2020): 350.

21. K. N. Venugopala, G. B. Dharma Rao, S. Bhandary, M. Pillay, D. Chopra, B. E. Aldhubiab, M. Attimarad, O. I. Alwassil, S. Harsha, and K. Mlisana, “Design, Synthesis, and Characterization of (1-(4-Aryl)-1H-1,2,3-Triazol-4-yl)Methyl, Substituted Phenyl-6-Methyl-2-Oxo-1,2,3,4-Tetrahydropyrimidine-5-

Carboxylates against Mycobacterium tuberculosis," Drug Design, Development and Therapy 10 (2016): 2681–90.

22. (a) S. G. Agalave, R. S. Maujan, and V. S. Pore, "Click Chemistry: 1,2,3-Triazoles as Pharmacophores," Chemistry - An Asian Journal 6 (2011): 2696–2718

23. M. Hussain, T. Qadri, Z. Hussain, A. Saeed, P. A. Channar, S. A. Shehzadi, M. Hassan, F. A. Larik, T. Mahmood, and A. Malik, "Synthesis, Antibacterial Activity and Molecular Docking Study of Vanillin Derived 1,4-Disubstituted 1,2,3- Triazoles as Inhibitors of Bacterial DNA Synthesis," Heliyon 5 (2019): e02812. 2

24. M. R. Senger, L. C. Gomes, S. B. Ferreira, C. R. Kaiser, V. F. Ferreira, and F. P. Silva, "Kinetics Studies on the Inhibition Mechanism of Pancreatic a-Amylase by Glycoconjugated 1H-1,2,3-Triazoles: A New Class of Inhibitors with Hypoglycemiant Activity," ChemBioChem: A European Journal of Chemical Biology 13, no.11 (2012): 1584–93.

25. T. El. Malah, H. F. Nour, A. A. E. Satti, B. A. Hemdan, and W. A. El-Sayed, "Design, Synthesis, and Antimicrobial Activities of 1,2,3-Triazole Glycoside Clickamers," Molecules 25, no. 4 (2020): 790.

26. M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. Edward Emmert, S. A. Garmon, D. R. Graber, K. C. Grega, J. B. Hester, D. K. Hutchinson, et al. "Substituent Effects on the Antibacterial Activity of Nitrogen-Carbon-Linked (Azolylphenyl)Oxazolidinones with Expanded Activity against the Fastidious Gram-Negative Organisms Haemophilus influenzae and Moraxella catarrhalis," Journal of Medicinal Chemistry 43, no. 5 (2000): 953–70.

27. R. J. Bochis, J. C. Chabala, E. Harris, L. H. Peterson, L. Barash, T. Beattie, J. E. Brown, D. W. Graham, F. S. Waksmunski, M. Tischler, et al. "Benzylated 1,2,3-Triazoles as Anticoccidiostats," Journal of Medicinal Chemistry 34, no. 9 (1991): 2843–52.

28. J. L. Kelley, C. S. Koble, R. G. Davis, E. W. Mclean, F. E. Soroko, and B. R. Cooper, "1-(Fluorobenzyl)-4-Amino-1H-1,2,3-Triazolo[4,5-c]Pyridines: Synthesis and Anticonvulsant Activity," Journal of Medicinal Chemistry 38, no. 20 (1995): 4131–4.

29. R. Raj, P. Singh, P. Singh, J. Gut, P. J. Rosenthal, and V. Kumar, "Azide-Alkyne Cycloaddition en Route to 1H-1,2,3-Triazole-Tethered 7-Chloroquinoline-Isatin Chimeras: Synthesis and Antimalarial Evaluation," European Journal of Medicinal Chemistry 62 (2013): 590–6.

30. M. H. Shaikh, D. D. Subhedar, M. Arkile, V. M. Khedkar, N. Jadhav, D. Sarkar, and B. B. Shingate, “Synthesis and Bioactivity of Novel Triazole Incorporated Benzothiazinone Derivatives as Antitubercular and Antioxidant Agent,” Bioorganic & Medicinal Chemistry Letters 26, no. 2 (2016): 561–9.

31. B. L. Wilkinson, H. Long, E. Sim, and A. J. Fairbanks, “Synthesis of Arabino Glycosyl Triazoles as Potential Inhibitors of Mycobacterial Cell Wall Biosynthesis,” Bioorganic & Medicinal Chemistry Letters 18, no. 23 (2008): 6265–7.

32. V. V. Rostovtsev, L. G. Green, V. V. Fokin, and K. B. Sharpless, “A stepwise huisgen cycloaddition process: copper(I)- catalyzed regioselective ‘Ligation’ of azides and terminal alkines,” Angewandte Chemie International Edition, vol. 41, pp. 2596–2599, 2002.