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Original Research Paper

SYNTHESIS, BIOLOGICAL EVALUATION AND DOCKING STUDIES OF D-GLUCOSE DERIVED ARYL 1, 2, 3-TRIAZOLES

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ABSTRACT

Synthesis, characterization, antimicrobial activity and docking studies of 1, 2, 3-triazoles comprising a glucose and aryl moieties were reported. Majority of the compounds found to be active and few of them exhibited strong *in vitro* antimicrobial activity against *S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa*, *B. proteus*, *C. albicans* and *A. fumigatus.* All the compounds were subjected to docking studies against *S. aureus* tyrosyl tRNA synthetase and Lanosterol-14α-demethylase (CYP51). The docking study results demonstrated that, all are having considerable binding energies and have good affinity toward the active sites of the protein, thus, they may be considered as good inhibitors of tyrosyl tRNA synthetase and CYP51.

Keywords: O-Propargyl Glucoside, Arylazide, Click chemistry, Glucotriazoles, Antimicrobial activity, Molecular docking.

INTRODUCTION

Molecular docking studies have been occupied prominent place in drug discovery, which would describe the protein-ligand binding interactions and "best-fit" orientation of a ligand that binds to a particular protein. Molecular docking studies provide valuable information to predict the binding modes and the affinity between small molecule drug candidates and the binding sites of protein present in pathogens.[1] The discovery of novel antimicrobial molecules with broad spectrum of activity is the very active research area because there is a critical need for the development of more potent antimicrobial agents to face the challenges of substantial infectious-diseases and the global crisis in antibiotic resistance. It requires an efficient approach to design new agents with novel mechanism of action and structural modification to improve their activity. From the last decade the research on biomaterials such as heterocyclic mimic sugar molecules has gained much interest due to their broad range of applications in medicinal chemistry.[2] The appreciable understanding of the relationship existing between sugars and bioactive entities has focused their biological significance.[3] The pharmacological potential of glycosylated products was demonstrated and they have been using in many existing drugs.[4-6] Among the heterocyclic mimic sugar moieties glycosyl 1,2,3-triazole derivatives have gained increasing attention due to their biological applications.[7-9] 1,2,3-triazole ring is itself recognized as active pharmacophore[10-12] and it has proven to be an important structural scaffold in biomaterials[13-18] for drug discovery and gained interest by the medicinal chemists. 1,2,3-triazoles show a broad range of biological activities such as antiprotozoal[19], anticonvulsant[20], antimicrobial[21-26], antiallergic[27], anticancer[28], antiinflammatory[29], and antitubercular[30]. 1,2,3-

triazole as an attractive bridge group, which could connect with two pharmacophores to give a novel bi-functional active molecule, has become progressively more useful and important in constructing bioactive molecules and functional molecules.[27,28,31-33] Introduction of Cu(I) catalyzed alkyne and azide 1,3-dipolar cycloaddition (CuAAC) by Sharpless[34] made easy the preparation of bi-functional molecules. The CuAAC reaction has emerged as premier example of click chemistry because of its high efficiency, easy to purify, versatility, regioselectivity, and excellent functional group compatibility. After 2002, the carbohydrate research turned to develop the new derivatives by click chemistry reactions by incorporating alkyne and azide on carbohydrate scaffold[31,35-41]. The incorporation of triazole on carbohydrate leads to new dimension of structural diversity.[5,10,17,25,35,36,42]

In addition, many investigations established that antimicrobial activity of triazole derivatives was significantly enhanced by the introduction of variable aromatic substituent's and the aromatic rings represented a valuable strategy and were extensively employed in drug discovery.[43,26]

We reported the synthesis and the antimicrobial activity along with docking studies of the 1,2,3-triazole derivatives containing morpholine nucleus.[44] In continuation of that, we were synthesized novel 1,2,3-triazole derivatives containing glucose nucleus, their biological activities were evaluated and performed the molecular docking studies for better understanding of the drug-receptor interactions.

MATERIALS AND METHODS

Chemistry

All the compounds were purified by Column chromatography on silica gel (60-120 mesh). Melting points were determined using a Cintex apparatus. IR spectra were recorded of solids or neat films on a Perkin-Elmer Spectrum. The ^{13}C-NMR and ^{1}H-NMR spectra were recorded at 75 MHz and 300 MHz respectively. The NMR chemical shifts were recorded in ppm, by using tetramethylsilane as the internal reference and $CDCl_3$ as solvent. Mass spectra were recorded by the ESI–MS. Elemental analyses were performed on a Perkin-Elmer 240 CHN analyzer.

General Procedures for Synthesis

Synthesis of (4R)-4-[(3aR,5R,6S,6aR)-2,2-dimethyl-6-(prop-2-yn-1-yloxy)-tetrahydro-2H-furo[2,3-d] [1,3] dioxol-5-yl]-2,2-dimethyl-1,3-dioxolane (3): Hexane washed sodium hydride (60%, 6.55g, 0.17 mol) was suspended in dry THF (150 mL) placed in an ice bath. A solution of alcohol 1, 2:5,6-Di-O-isopropylidene-□-D-glucofuranose[45] **2** (15g, 57 mmol) in 80 mL THF was added drop wise using dropping funnel. After addition, the mixture was stirred for 1 h at room temperature then propargyl bromide (10.03 mL, 85 mmol) was added slowly at 0°C. The mixture was stirred for 8 h at room temperature then saturated NH_4Cl was added slowly at 0°C. The solution was extracted with $CHCl_3$, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated to give yellow liquid. The crude syrup was purified by column chromatography to propargyl ether as yellow syrup (12.90g, 76 %). ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.25 [s, 3H, Ip(CH_3)], 1.35 [s, 3H, Ip(CH_3)], 1.48 [s, 3H, Ip(CH_3)], 1.55 [s, 3H, Ip(CH_3)], 2.62 (s, 1H, yl-H), 3.75 (dd, J = 4.9, 8.7 Hz, 1H, H-3), 3.95 (m, 2H, H-6,6'), 4.21-4.30 (m, 2H, H-4,5), 4.54 (d, J = 4.2 Hz, 1H, H-2), 4.62 (s, 2H, O-CH_2), 5.83 (d, J = 2.9 Hz, 1H, H-1); MS (ESI) *m/z* 299 $[M+H]^+$.

Synthesis of 1,4-disubstituted 1,2,3-triazole derivatives of propargylated 1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose 4(a-n)

Common Procedure for 4(a-n)

To the solution of alkyne (1 mmol, 1eq) and Aryl azide (1.2 eq) in 30 mL of THF, CuI (5 mol %) was added. The reaction mixture was stirred at room temperature and monitored by TLC. After completion of the reaction, the solvent was removed and the residue dissolved in CH_2Cl_2, washed with water (3×20 mL), dried over Na_2SO_4, and evaporated in vacuum. Purification with column chromatography (SiO_2, 20% EtOAc-Hexane) to get the pure 1,4-disubstituted 1,2,3-triazoles and characterized by means of IR, ^{1}H-NMR, ^{13}C-NMR, and Mass spectra.

Spectral Data

4-({[(3aR,5R,6S,6aR)-5-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydro-2H-furo[2,3-d][1,3]dioxol-6-yl]oxy}methyl)-1-(4-methoxyphenyl)-1H-1,2,3-triazole (4a)

m.p 155–156 °C; IR (KBr ; ῡ in cm^{-1}): 3136, 3038, 2595, 1595, 1514, 1451, 1089; ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.31 [s, 3H, Ip(CH_3)], 1.35 [s, 3H, Ip(CH_3)], 1.41 [s, 3H, Ip(CH_3)], 1.50 [s, 3H, Ip(CH_3)], 3.86 (s, 3H, CH_3), 4.03 (m, 1H, H-3), 4.12 (m, 2H, H-6,6′), 4.38 (m, 2H, H-4,5), 4.65 (d, *J*=4.2 Hz, 1H, H-2), 4.89 (s, 2H, O-CH_2), 5.90 (d, *J*=2.8 Hz, 1H, H-1), 7.02 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.62 (d, *J*=8.2 Hz, 2H, Ar-H), 8.03 (s, 1H, Triazole-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 26.3 (2 CH_3) , 26.6 (2 CH_3), 55.9 (O-*C*H_3), 65.3 (C-6), 67.0 (O-*C*H_2-C), 73.2 (C-5), 76.2 (C-4), 79.6 (C-3), 82.3 (C-2), 104.2 (C-1), 107.3 (*C*(CH_3)$_2$ at 1,2), 113.5 (*C*(CH_3)$_2$ at 5,6), 114.3 (Ar-C-3,C-5), 116.6 (N-*C*H=C), 120.3 (Ar-C-1), 130.9 (Ar-C-2, C-6), 144.5 (N-CH=*C*), 160.5 (Ar-C-4); MS (ESI) *m/z* 470 [M+Na]$^+$. Elemental analysis (%) calcd for $C_{22}H_{29}N_3O_7$: C 59.05, H 6.53, N 9.39; found C 59.11, H 6.49, N 9.41.

4-({[(3aR,5R,6S,6aR)-5-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydro-2H-furo[2,3-d][1,3]dioxol-6-yl]oxy}methyl)-1-(naphthalene-1-yl)-1H-1,2,3-triazole (4b)

m.p 160–161 °C; IR (KBr ; ῡ in cm^{-1}) =3130, 3040, 2957, 2880, 1594, 1469, 1089; ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.31 [s, 3H, Ip(CH_3)], 1.34 [s, 3H, Ip(CH_3)], 1.42 [s, 3H, Ip(CH_3)], 1.51 [s, 3H, Ip(CH_3)], 3.91 (m, 1H, H-3), 4.03 (m, 2H, H-6,6′), 4.38 (m, 2H, H-4,5), 4.70 (d, *J*=4.1 Hz, 1H, H-2), 4.90 (s, 2H, O-CH_2), 5.85 (d, *J*=3.0 Hz, 1H, H-1), 7.50 (m, 5H, Ar-H), 7.95 (m, 2H Ar-H), 8.01 (s, 1H, Triazole-H); MS (ESI) *m/z* 490 [M+Na]$^+$. Elemental analysis (%) calcd for $C_{25}H_{29}N_3O_6$: C 64.23, H 6.25, N 8.99; found C 64.31, H 6.20, N 9.08.

4-({[(3aR,5R,6S,6aR)-5-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydro-2H-furo[2,3-d][1,3]dioxol-6-yl]oxy}methyl)-1-(4-methylphenyl)-1H-1,2,3-triazole (4c)

m.p 157–158 °C; IR (KBr ; ῡ in cm^{-1}) =3139, 3039, 2957, 2880, 1593, 1479, 1085; ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.32 [s, 3H, Ip(CH_3)], 1.33 [s, 3H, Ip(CH_3)], 1.41 [s, 3H, Ip(CH_3)], 1.51 [s, 3H, Ip(CH_3)], 2.35 (s, 3H), 3.93 (m, 1H, H-3), 4.02 (m, 2H, H-6,6′), 4.38 (m, 2H, H-4,5), 4.70 (d, *J*=4.3 Hz, 1H, H-2), 4.90 (s, 2H O-CH_2), 5.85 (d, *J*=3.1 Hz, 1H, H-1), 7.10 (m, 4H, Ar-H), 8.03 (s, 1H, Triazole-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 24.3 (2 CH_3), 26.1 (2 CH_3), 26.6 (Ph-CH_3), 65.6 (C-6), 67.3 (O-*C*H_2-C), 73.4 (C-5), 77.8 (C-4), 78.7 (C-3), 82.6 (C-2), 105.9 (C-1), 107.3 (*C*(CH_3)$_2$ at 1,2), 113.5 (*C*(CH_3)$_2$ at 5,6), 116.8 (N-*C*H=C), 125.3 (Ar-C-1), 129.3 (Ar-C-2, C-6), 129.8 (Ar-C-3, C-5), 138.4 (Ar-C-4), 144.5 (N-CH=*C*); MS (ESI) *m/z* 454 [M+Na]$^+$. Elemental analysis (%) calcd for $C_{22}H_{29}N_3O_6$: C 61.24, H 6.77, N 9.74; found C 61.13, H 6.71, N 9.81.

4-({[(3aR,5R,6S,6aR)-5-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydro-2H-furo[2,3-d][1,3]dioxol-6-yl]oxy}methyl)-1-(2-methylphenyl)-1H-1,2,3-triazole (4d)

m.p 159–160 °C; IR (KBr ; ῡ in cm^{-1}) =3140, 3037, 2940, 2862, 1594, 1475, 1058; ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.32 [s, 3H, Ip(CH_3)], 1.33 [s, 3H, Ip(CH_3)], 1.40 [s, 3H, Ip(CH_3)], 1.50 [s, 3H, Ip(CH_3)], 2.31 (s, 3H), 3.91 (m, 1H, H-3), 4.03 (m, 2H, H-6,6′), 4.38 (m, 2H, H-4,5), 4.68 (dd, *J*=2.8, 6.5 1H, H-2), 4.82 (s, 2H, O-CH_2), 5.75 (d, *J*=3.0 Hz, 1H, H-1), 7.10 (m, 4H, Ar-H), 8.01 (s, 1H, Triazole-H); MS (ESI) *m/z* 432 [M+H]$^+$. Elemental analysis (%) calcd for $C_{22}H_{29}N_3O_6$: C 61.24, H 6.77, N 9.74; found C 61.18, H 6.81, N 9.84.

4-({[(3aR,5R,6S,6aR)-5-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydro-2H-furo[2,3-d][1,3]dioxol-6-yl]oxy}methyl)-1-(4-bromophenyl)-1H-1,2,3-triazole (4e)

m.p 163–165 °C; IR (KBr ; ῡ in cm^{-1}) =3123, 3037, 2954, 2878, 1594, 1476, 1058; ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.34 [s, 3H, Ip(CH_3)], 1.35 [s, 3H, Ip(CH_3)], 1.41 [s, 3H, Ip(CH_3)], 1.50 [s, 3H, Ip(CH_3)], 4.01 (m, 1H, H-3), 4.12 (m, 2H, H-6,6′), 4.38 (m, 2H, H-4,5), 4.55 (d, *J*=4.1 Hz, 1H, H-2), 4.75 (s, 2H, O-CH_2), 5.73 (d, *J*=3.1 Hz, 1H, H-1), 7.20 (d, *J*=8.1, 2H, Ar-H), 7.49 (d, *J*=7.8, 2H, Ar-H), 7.93 (s, 1H,

Triazole-H); MS (ESI) *m/z* 497 $[M+H]^+$. Elemental analysis (%) calcd for $C_{21}H_{26}BrN_3O_6$: C 50.82, H 5.28, N 8.47; found C 50.96, H 5.12, N 8.51.

4-({[(3aR,5R,6S,6aR)-5-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydro-2H-furo[2,3-d][1,3]dioxol-6-yl]oxy}methyl)-1-(2,6-dibromo-4-fluorophenyl)-1H-1,2,3-triazole (4f)

m.p 145–148 °C IR (KBr ; ῡ in cm^{-1})=3120, 3037, 2954, 2880, 1594, 1459, 1051; ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.31 [s, 3H, Ip(CH_3)], 1.32 [s, 3H, Ip(CH_3)], 1.41 [s, 3H, Ip(CH_3)], 1.46 [s, 3H, Ip(CH_3)], 3.93 (m, 1H, H-3), 4.12 (m, 2H, H-6,6′), 4.35 (m, 2H, H-4,5), 4.52 (d, *J*=4.0 Hz, 1H, H-2), 4.60 (s, 2H, O-CH_2), 5.72 (d, *J*=2.8 Hz, 1H, H-1), 7.52 (m, 2H, Ar-H) 8.02 (s, 1H, Triazole-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 26.3 (2 CH_3), 26.5 (2 CH_3), 65.9 (C-6), 67.0 (O-*C*H_2-C), 73.4 (C-5), 77.8 (C-4), 78.7 (C-3), 82.6 (C-2), 105.9 (C-1), 107.3 (*C*$(CH_3)_2$ at 1,2), 113.5 (*C*$(CH_3)_2$ at 5,6), 116.9 (N-*C*H=C), 119.7 (Ar-C-3, C-5), 124.6 (Ar-C-2, C-6), 131.1 (Ar-C-1), 144.5 (N-CH=*C*), 167.3 (Ar-C-4); MS (ESI) *m/z* 594 $[M+H]^+$. Elemental analysis (%) calcd for $C_{21}H_{24}Br_2FN_3O_6$: C 42.52, H 4.08, N 7.08; found C 42.41, H 4.21, N 7.11.

{2-[4-({[(3aR,5R,6S,6aR)-5-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydro-2H-furo[2,3-d][1,3]dioxol-6-yl]oxy}methyl)-1H-1,2,3-triazol-1-yl]-4-fluorophenyl}methanol (4g):

m.p 136–139 °C; IR (KBr ; ῡ in cm^{-1}) =3258, 3128, 3037, 2965, 2878, 1593, 1471, 1054; ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.25 [s, 3H, Ip(CH_3)], 1.32 [s, 3H, Ip(CH_3)], 1.43 [s, 3H, Ip(CH_3)], 1.50 [s, 3H, Ip(CH_3)], 2.39 (s, 1H, OH), 3.98 (m, 1H, H-3), 4.10 (m, 2H, H-6,6′), 4.38 (m, 2H, H-4,5), 4.52 (d, *J*=4.3 Hz, 1H), 4.60 (s, 2H, *CH*$_2$OH), 4.79 (s, 2H, CH-O-*CH*$_2$), 5.75 (d, *J*=3.0 Hz, 1H), 7.20 (m, 2H, Ar-H), 7.6 (m, 1H, Ar-H) 8.05 (s, 1H, Triazole-H); MS (ESI) *m/z* 488 $[M+Na]^+$. Elemental analysis (%) calcd for $C_{22}H_{28}FN_3O_7$: C 56.77, H 6.06, N 9.03; found C 56.69, H 6.15, N 9.19.

4-({[(3aR,5R,6S,6aR)-5-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydro-2H-furo[2,3-d][1,3]dioxol-6-yl]oxy}methyl)-1-(4-chlorophenyl)-1H-1,2,3-triazole (4h)

m.p 136–140 °C; IR (KBr ; ῡ in cm^{-1}) =3127, 3036, 2965, 2878, 1593, 1427, 1057; ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.20 [s, 3H, Ip(CH_3)], 1.28 [s, 3H, Ip(CH_3)], 1.42 [s, 3H, Ip(CH_3)], 1.49 [s, 3H, Ip(CH_3)], 3.90 (m, 1H, H-3), 4.10 (m, 2H, H-6,6′), 4.38 (m, 2H, H-4,5), 4.56 (d, *J* = 4.3 Hz, 1H, H-2), 4.65 (s, 2H, O-CH_2), 5.80 (d, *J*=2.8 Hz, 1H, H-1), 7.11 (d, *J*=8.0, 2H, Ar-H), 7.51 (d, *J*=7.8, 2H, Ar-H) 8.00 (s, 1H, Triazole-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 26.3 (2 CH_3), 26.5 (2 CH_3), 65.9 (C-6), 67.0 (O-*C*H_2-C), 73.3 (C-5), 77.7 (C-4), 78.4 (C-3), 82.5 (C-2), 105.8 (C-1), 107.2(*C*$(CH_3)_2$ at 1,2), 113.4 (*C*$(CH_3)_2$ at 5,6), 118.1 (N-*C*H=C), 126.2 (Ar-C-1), 128.9 (Ar-C-3, C-5), 131.6 (Ar-C-2, C-6), 134.1 (Ar-C-4), 144.5 (N-CH=*C*),; MS (ESI) *m/z* 474 $[M+Na]^+$. Elemental analysis (%) calcd for $C_{21}H_{26}ClN_3O_6$: C 55.81, H 5.80, N 9.30; found C 55.69, H 5.91, N 9.22.

4-({[(3aR,5R,6S,6aR)-5-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydro-2H-furo[2,3-d][1,3]dioxol-6-yl]oxy}methyl)-1-(3-chlorophenyl)-1H-1,2,3-triazole (4i)

m.p 132–135 °C; IR (KBr ; ῡ in cm^{-1}) =3125, 3036, 2966, 2880, 1594, 1454, 1053; ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.25 [s, 3H, Ip(CH_3)], 1.35 [s, 3H, Ip(CH_3)], 1.42 [s, 3H, Ip(CH_3)], 1.50 [s, 3H, Ip(CH_3)], 3.92 (m, 1H, H-3), 4.09 (m, 2H, H-6,6′), 4.39 (m, 2H, H-4,5), 4.55 (d, *J*=4 Hz, 1H, H-2), 4.61 (s, 2H, O-CH_2), 5.81 (d, *J*=2.8 Hz, 1H, H-1), 7.55 (m, 4H, Ar-H), 8.02 (s, 1H, Triazole-H); MS (ESI) *m/z* 474 $[M+Na]^+$. Elemental analysis (%) calcd for $C_{21}H_{26}ClN_3O_6$: C 55.81, H 5.80, N 9.30; found C 55.71, H 5.89, N 9.41.

4-({[(3aR,5R,6S,6aR)-5-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydro-2H-furo[2,3-d][1,3]dioxol-6-yl]oxy}methyl)-1-(3,5-dichlorophenyl)-1H-1,2,3-triazole (4j)

m.p 143–145 °C; IR (KBr ; ῡ in cm^{-1}) =3128, 3040, 2955, 2882, 1593, 1469, 1089; ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.31 [s, 3H, Ip(CH_3)], 1.33 [s, 3H, Ip(CH_3)], 1.40 [s, 3H, Ip(CH_3)], 1.50 [s, 3H, Ip(CH_3)], 3.93 (m, 1H, H-

3), 4.03 (m, 2H, H-6,6′), 4.38 (m, 2H, H-4,5), 4.55 (d, *J*=4.3, 1H, H-2), 4.67 (s, 2H, O-CH_2), 5.81 (d, *J*=2.9 Hz, 1H, H-1), 7.35 (m, 2H, Ar-H), 7.52 (m, 1H, Ar-H), 7.91 (s, 1H, Triazole-H); MS (ESI) *m/z* 487 $[M+H]^+$. Elemental analysis (%) calcd for $C_{21}H_{25}Cl_2N_3O_6$: C 51.86, H 5.18, N 8.64; found C 51.92, H 5.24, N 8.71.

4-({[(3aR,5R,6S,6aR)-5-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydro-2H-furo[2,3-d][1,3]dioxol-6-yl]oxy}methyl)-1-(2-chloro-5-nitrophenyl)-1H-1,2,3-triazole (4k)

m.p 156–158 °C; IR (KBr ; ῡ in cm^{-1}) =3130, 3040, 2961, 2882, 1594, 1472, 1082; ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.20 [s, 3H, Ip(CH_3)], 1.30 [s, 3H, Ip(CH_3)], 1.42 [s, 3H, Ip(CH_3)], 1.49 [s, 3H, Ip(CH_3)], 3.93 (m, 1H, H-3), 4.10 (m, 2H, H-6,6′), 4.35 (m, 2H, H-4,5), 4.53 (dd, *J*=2.8, 6.5 1H, H-2), 4.65 (s, 2H, O-CH_2), 5.80 (d, *J* = 3.0 Hz, 1H, H-1), 7.78 (m, 2H, Ar-H), 7.93 (m, 1H, Ar-H), 8.11 (s, 1H, Triazole-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 26.3 (2 CH_3), 26.5 (2 CH_3), 65.9 (C-6), 67.0 (O-*C*H_2-C), 73.3 (C-5), 77.7 (C-4), 78.4 (C-3), 82.5 (C-2), 105.8 (C-1), 107.2 (*C*$(CH_3)_2$ at 1,2), 113.4 (*C*$(CH_3)_2$ at 5,6), 116.8 (N-*C*H=C), 122.5 (Ar-C-4), 125.3 (Ar-C-2) 130.1 (Ar-C-5), 133.3 (Ar-C-1), 144.5 (N-CH=*C*) 147.3 (Ar-C-3) 150.3 (Ar-C-6); MS (ESI) *m/z* 497 $[M+H]^+$. Elemental analysis (%) calcd for $C_{21}H_{25}ClN_4O_8$: C 50.76, H 5.07, N 11.28; found C 50.81, H 5.13, N 11.33.

4-({[(3aR,5R,6S,6aR)-5-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydro-2H-furo[2,3-d][1,3]dioxol-6-yl]oxy}methyl)-1-(4-nitrophenyl)-1H-1,2,3-triazole (4l)

m.p 140–143 °C; IR (KBr ; ῡ in cm^{-1}) =3132, 3038, 2971, 2883, 1593, 1488, 1086; ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.28 [s, 3H, Ip(CH_3)], 1.35 [s, 3H, Ip(CH_3)], 1.45 [s, 3H, Ip(CH_3)], 1.55 [s, 3H, Ip(CH_3)], 3.95 (m, 1H, H-3), 4.10 (m, 2H, H-6,6′), 4.33 (m, 2H, H-4,5), 4.55 (d, *J* = 4.2 Hz, 1H, H-2), 4.68 (s, 2H, O-CH_2), 5.81 (d, *J* = 2.9 Hz, 1H, H-1), 7.52 (d, *J*=7.8, 2H), 8.21 (s, Triazole-H, 1H) 8.55 (d, *J*=7.8, 2H); MS (ESI) *m/z* 485 $[M+Na]^+$. Elemental analysis (%) calcd for $C_{21}H_{26}N_4O_8$: C 50.76, H 5.07, N 11.28; found C 50.81, H 5.11, N 11.31.

4-({[(3aR,5R,6S,6aR)-5-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydro-2H-furo[2,3-d][1,3]dioxol-6-yl]oxy}methyl)-1-(3-nitrophenyl)-1H-1,2,3-triazole (4m)

m.p 157–159 °C; IR (KBr ; ῡ in cm^{-1}) =3126, 3041, 2969, 2884, 1594, 1478, 1083; ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): = 1.23 [s, 3H, Ip(CH_3)], 1.32 [s, 3H, Ip(CH_3)], 1.40 [s, 3H, Ip(CH_3)], 1.48 [s, 3H, Ip(CH_3)], 3.91 (m, 1H, H-3), 4.11 (m, 2H, H-6,6′), 4.41 (m, 2H, H-4,5), 4.55 (d, *J* = 4.2 Hz, 1H, H-2), 4.65 (s, 2H, O-CH_2), 5.81 (d, *J* = 2.9 Hz, 1H, H-1), 7.41 (m, 3H, Ar-H), 7.80 (m, 1H, Ar-H) 7.90 (s, 1H, Triazole-H); MS (ESI) *m/z* 485 $[M+Na]^+$. Elemental analysis (%) calcd for $C_{21}H_{26}N_4O_8$: C 50.76, H 5.07, N 11.28; found C 50.82, H 5.16, N 11.20.

4-({[(3aR,5R,6S,6aR)-5-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydro-2H-furo[2,3-d][1,3]dioxol-6-yl]oxy}methyl)-1-phenyl-1H-1,2,3-triazole (4n)

m.p 135–138 °C; IR (KBr ; ῡ in cm^{-1}) =3125, 3039, 2972, 2874, 1593, 1476, 1086; ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.21 [s, 3H, Ip(CH_3)], 1.29 [s, 3H, Ip(CH_3)], 1.39 [s, 3H, Ip(CH_3)], 1.51 [s, 3H, Ip(CH_3)], 3.85 (m, 1H, H-3), 4.05 (m, 2H, H-6,6′), 4.31 (m, 2H, H-4,5), 4.53 (d, *J* = 4 Hz, 1H, H-2), 4.53 (s, 2H, O-CH_2), 5.82 (d, *J* = 4 Hz, 1H, H-1), 7.45 (m, 5H, Ar-H), 8.21 (s, Triazole-H, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 26.4 (2 CH_3), 26.6 (2 CH_3), 65.9 (C-6), 67.3 (O-*C*H_2-C), 73.3(C-5), 77.6 (C-4), 78.8 (C-3), 82.5 (C-2), 105.6 (C-1), 107.3 (*C*$(CH_3)_2$ at 5,6), 113.4 (*C*$(CH_3)_2$ at 1,2), 116.5 (N-*C*H=C), 128.5 (5C's Ar), 129.6 (Ar-C-1), 144.5 (N-CH=*C*); MS (ESI) *m/z* 440 $[M+Na]^+$. Elemental analysis (%) calcd for $C_{21}H_{27}N_3O_6$: C 60.42, H 6.52, N 10.07; found C 60.31, H 6.69, N 10.15.

Evaluation of Antimicrobial Activity

The synthesized compounds were tested by the agar well diffusion method for antibacterial activity (Table 2). All the bacterial cultures were adjusted to 0.5 McFarland standards, which is visually comparable to a bacterial suspension of

around 1.5×108 CFU/ml. 10 mL of nutrient agar medium was poured into each Petri plate and plates were swabbed with 100 µL inoculum of the test microorganisms and kept for 15 to 30 min for adsorption. Using sterile cork borer of 10 to 12 mm diameter, wells were bored into the seeded agar plates and these were loaded with a 100 µL volume with concentration of 2.0 mg mL^{-1} of each compounds reconstituted in the dimethylsulphoxide (DMSO). All the plates were incubated at 37 ºC for 24 h. Antibacterial activity of each complex was evaluated by measuring the zone of growth inhibition against the test organisms with zone reader (Hi Antibiotic zone scale).

Molecular Docking

To perform molecular docking studies, the Lamarckian genetic algorithm (LGA)[46], inculcated in the docking program AutoDock 4.2, was employed. The native crystal structures of tyrosyl tRNA (PDB entry: 1J1J) synthetase and Lanosterol-14α-demethylase (PDB entry: 1EA1) were obtained from Protein Data Bank http://www.rcsb.org/pdb. To carry out docking studies, the 2D structures of compounds 4a-4n were drawn and these were converted to 3D and their energy was minimized [Chem 3D ultra 8.0 software, Molecular Modeling and Analysis; Cambridge Soft Corporation, USA (2010)]. The binding site identification was carried out using CastP (serversts-fw.bioengr.uic.edu/castp/ calculation.php). Then, finally docking results were viewed using Discovery Studio Visualizer 4.0; Maestro elements tutorial 1.8.

RESULTS AND DISCUSSIONS

Chemistry

Compounds 4a-4n (Table 1) were synthesized by cycloaddition of O-proparglyglucoside **3** with aryl azides using catalytic amount of copper iodide at room temperature.[47] Accordingly, the intermediate aryl azides were prepared from commercially available Aryl amines. Aryl amines treated with $NaNO_2$ and NaN_3 in conc. HCl at 0-5°C could give Aryl azides almost quantitatively.[48] O-proparglyglucoside **3** was synthesized in 76% yield by the reaction of glucosediacetonide **2** with propargyl bromide in the presence of NaH in anhydrous THF.[49] The reaction pathway has been summarized in scheme (Figure 1). Newly synthesized compounds were purified by column chromatography and characterized by IR, NMR, MASS spectral and C H N elemental analyses. IR spectra of triazole **4a** showed absorption at ῡ 1595 cm^{-1} due to C=N and band at ῡ 3136 cm^{-1} due to C-H bond of triazole. ^{1}H-NMR spectrum of Triazole **4a** showed a singlet at δ 8.03 is due to triazole ring C-H proton. A singlet at δ 4.89 is due to protons of CH_2 present between Oxygen and Triazole ring. ^{13}C-NMR spectrum of **4a** C5 carbon of triazole ring (C-H carbon) showed at δ 116.5. The mass spectrum of the Triazole **4a** showed molecular ion peak *m/z* 470 (M+Na), which is in agreement with the molecular formula of compound **4a**. All these data confirms the structure. The spectral values for all the compounds and C H N analyses are given in the experimental part.

Biological Activity

The newly synthesized compounds (4a-4n) were evaluated for their *in vitro* antimicrobial activity against *S. aureus*, *B. subtilis* as Gram-positive, *E. coli*, *P. aeruginosa*, *B. proteus* as Gram-negative bacteria and, *C. albicans* and *A. fumigatus* as fungi by agar well diffusion assay method. The zone of inhibition values were determined and compared with Ampicillin and Amphotericin as standard drugs. The investigation of antifungal anti bacterial screening data revealed that some of the newly synthesized compounds showed potent activity *in vitro*. 4j and 4i exhibited excellent activity against *C. albicans, S. aureus* and *B. subtilis*. The zone of inhibition values were given in Table-2. The biological activity is varied due to difference in aryl moiety. The presence of halogen substituents in aryl ring is responsible for higher activity.

Docking Studies

In order to gain insight into the plausible mechanism of action of compounds (4a-4n) docking simulations were performed. Compounds 4a-4n were docked into active sites of *S. aureus* tyrosyl tRNA synthetase (pdb: 1JIJ) and

Lanosterol-14α-demethylase (pdb: 1EA1). The *S. aureus* tyrosyl tRNA synthetase[50] and Lanosterol-14α-demethylase[51] has been reported as the target receptors for docking studies in finding the suitable drug candidates against these bacteria and fungi. The docking of receptor tRNA synthetase with newly synthesized ligands exhibited well established H-bonds with the closest range of 1.8 A^{o} with one or more amino acids in the receptor active pocket (Figure 2-7). The Binding Energies and Inhibition Constants of all the compounds were tabulated in Table-3 and Table-4. Docking studies revealed all the synthesized molecules exhibited excellent binding energy toward the receptor protein ranging from -10.22 to -8.20 kcal mol^{-1}.

CONCLUSION

In summary, a series of novel glucosyl 1,2,3-triazoles have been synthesized in excellent yields *via* Cu(I)-catalyzed 1,3-dipolar cycloaddition. Antimicrobial activity and molecular docking studies suggested that the present series of 1,2,3-triazoles exhibited promising activities against microbial pathogens.

ACKNOWLEDGEMENT

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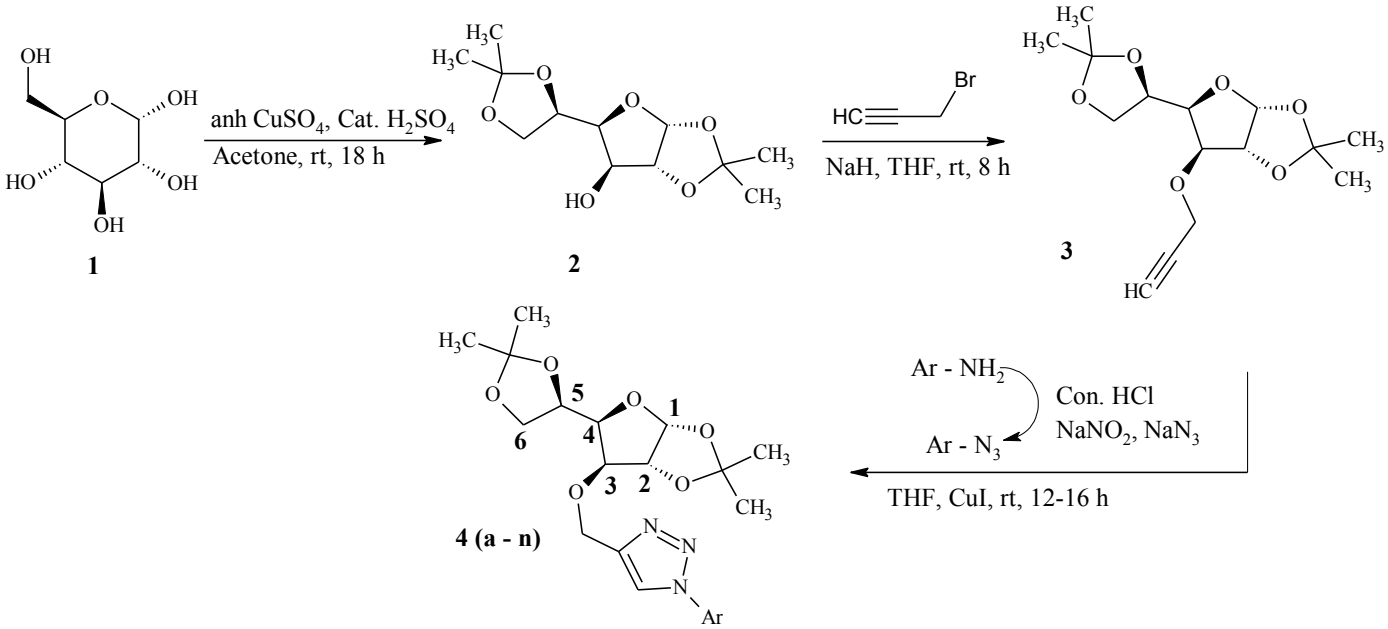


Figure 1: Synthetic Route for triazole derivatives

Table 1: Synthesized analogs of 1,4-disubstituted 1,2,3-Triazoles

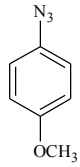
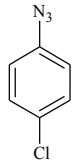
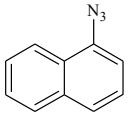
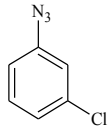
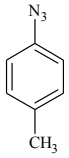
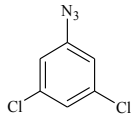
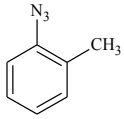
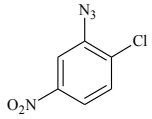
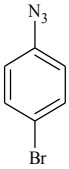
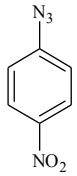
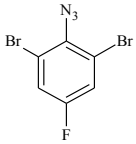
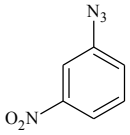
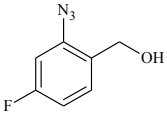
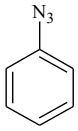
Entry	Azide	Time (hr)	Product /molecular formula	Yield (%)	Entry	Azide	Time (hr)	Product /molecular formula	Yield (%)
1		10	4a / $C_{22}H_{29}N_3O_7$	87	8		12	4h / $C_{21}H_{26}ClN_3O_6$	86
2		9	4b / $C_{25}H_{29}N_3O_6$	92	9		14	4i / $C_{21}H_{26}ClN_3O_6$	90
3		9	4c / $C_{22}H_{29}N_3O_6$	95	10		12	4j / $C_{21}H_{25}Cl_2N_3O_6$	85
4		10	4d / $C_{22}H_{29}N_3O_6$	78	11		16	4k / $C_{21}H_{25}ClN_4O_8$	92
5		10	4e / $C_{21}H_{26}BrN_3O_6$	85	12		14	4l / $C_{21}H_{26}N_4O_8$	95
6		8.5	4f/$C_{21}H_{24}Br_2FN_3O_6$	88	13		15	4m / $C_{21}H_{26}N_4O_8$	84
7		10	4g / $C_{22}H_{28}FN_3O_7$	85	14		8	4n / $C_{21}H_{27}N_3O_6$	86

Table 2: In vitro antimicrobial activity of compounds 3-4[a,b,c]

Compd	Zone of Inhibition in mm						
	C. albicans	*A. fumigatus*	*S. aureus*	*B. subtilis*	*B. proteus*	*P. aeruginosa*	*E. coli*
4a	13	14	20	12	16	16	12
4b	14	12	30	20	18	20	14
4c	-[d]	-	18	14	-	13	-
4d	-	12	18	14	-	13	-
4e	16	18	20	16	17	17	11
4f	17	17	23	17	14	18	15
4g	-	13	28	20	15	11	13
4h	14	-	28	18	18	19	13
4i	23	16	33	22	20	20	18
4j	24	18	37	24	23	22	18
4k	14	12	31	20	18	16	12
4l	18	10	24	18		-	-
4m	18	-	25	-	10	-	-
4n	-	-	18	-	-		-
A	28	28					
B			38	28	26	26	20

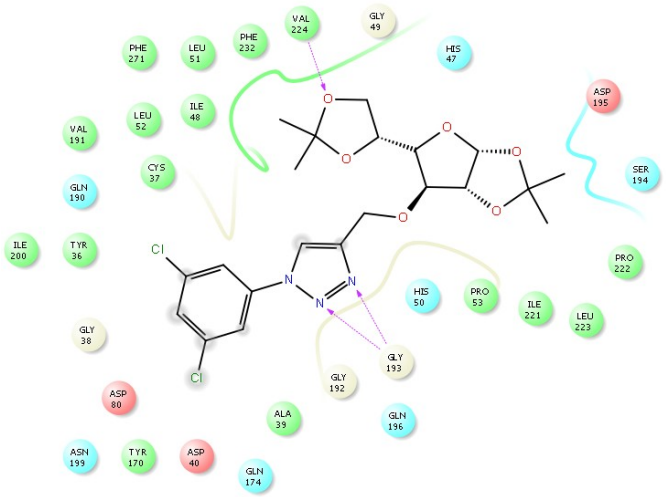
[a]zone of inhibition determined by agar well diffusion method. [b]**A** = Amphotericin, **B** = Ampicillin. [c]*C. albicans* ATCC76615, Candida albicans ATCC76615; *A. fumigatus*, Aspergillus fumigatus; *S. aureus* ATCC 29213, Staphylococcus aureus ATCC 29213; *P. aeruginosa*, Pseudomonas aeruginosa; *B. proteus*, Bacillus proteus; *B. subtilis*, Bacillus subtilis; *E. coli* ATCC 25922, Escherichia coli ATCC 25922. [d] indicates no sensitivity or mean inhibition zone diameter less than 7 mm.

Table 3: Binding energy, no. of hydrogen bonds, and residues involved in hydrogen-bonding interaction of top scorer for *S. aureus* (pdb:1JIJ)

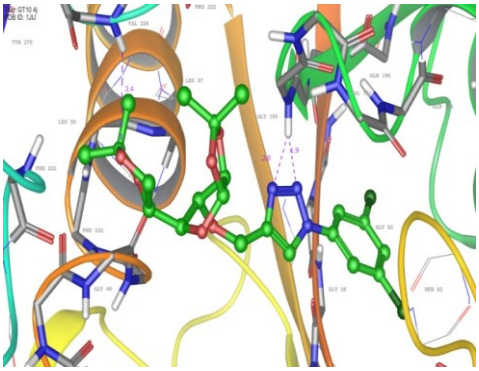
S. No.	Compound Entry	Binding energy (Kcal/mol)	Inhibition Constant Ki (nM)	No. of hydrogen bonds	Residues involved in hydrogen-bonding interactions
1.	4a	–8.91	295.92	4	GLY193, GLY193, GLY193, VAL224
2.	4b	–9.61	86.79	4	GLY193, GLY193, GLY193, VAL224
3.	4c	–8.36	739.63	3	GLY193, GLY193, GLY193,
4.	4d	–8.23	923.00	6	GLY193(3), GLN196(2), VAL224
5.	4e	–8.53	558.68	3	GLY193, GLY193, GLY193,
6.	4f	–8.71	411.78	4	GLY193, GLY193, GLY193, VAL224
7.	4g	–8.51	578.71	4	GLY38, GLY38, GLY193, GLY193
8.	4h	–8.33	788.48	4	GLY193, GLY193, GLN196, VAL 224
9.	4i	–9.22	173.15	4	GLY193, GLY193, LEU52, LEU51
10.	4j	–10.22	45.12	3	GLY193, GLY193, VAL224
11.	4k	–9.05	234.34	5	GLY193(3), VAL224(2)
12.	4l	–8.49	593.68	5	GLY193(4), VAL224
13.	4m	–8.47	618.99	3	GLY193, GLY193, VAL224
14.	4n	–8.20	974.56	2	GLY193, GLY38

Table 4: Binding energy, no. of hydrogen bonds, and residues involved in hydrogen-bonding interaction of top scorer *C. albicans* (pdb:1EA1)

S. No.	Compound Entry	Binding energy (Kcal/mol)	Inhibition Constant Ki (nM)	No. of hydrogen bonds	Residues involved in hydrogen-bonding interactions
1.	4a	–8.84	332.05	4	THR260, THR260, SER261, CYS394
2.	4b	–9.23	171.63	2	THR260,THR264
3.	4c	–9.16	191.87	3	THR260, SER261, CYS394
4.	4d	–8.69	428.27	3	THR260, THR260, SER261
5.	4e	–9.26	164.14	1	CYS394
6.	4f	–8.92	289.40	3	THR260, CYS394, CYS394
7.	4g	–8.29	842.01	2	THR260, THR264
8.	4h	–9.38	132.34	1	THR260
9.	4i	–9.37	134.71	2	THR260, THR264
10.	4j	–9.91	54.64	2	THR260, THR264
11.	4k	–8.99	258.72	3	THR260, ARG326, CYS394
12.	4l	–8.99	258.69	5	GLN72, ARG96, ARG96, THR260, THR264
13.	4m	–9.78	68.36	3	GLN72, ARG96, THR264
14.	4n	–8.90	298.25	1	THR260



(a)



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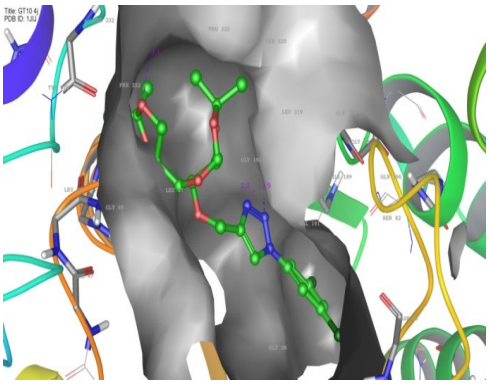
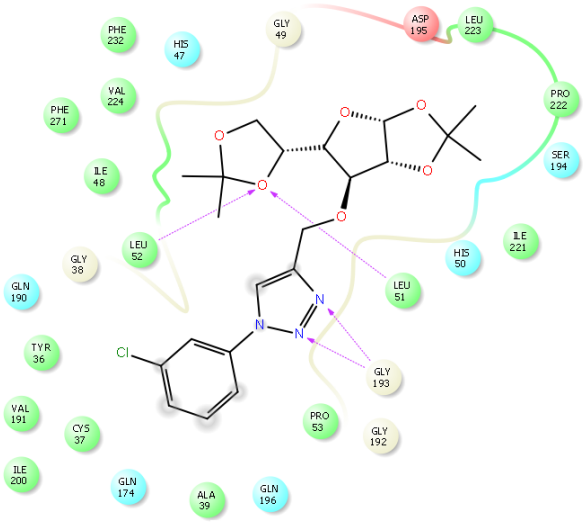
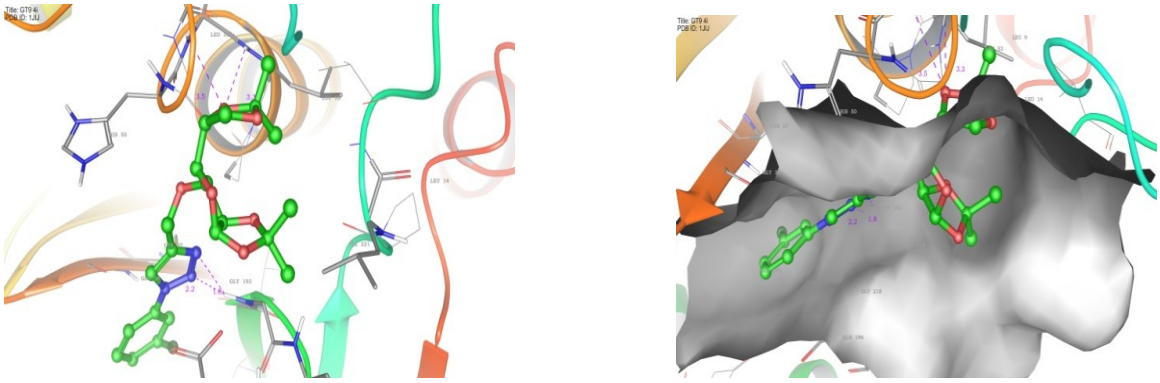


(c)

Figure 2: Interactions between compound 4j and *S. aureus* tyrosyl tRNA synthetase (pdb ID: 1JIJ) (a) represents 2D diagram (b) 3D diagram showing H-bond interaction (c) represents surface area

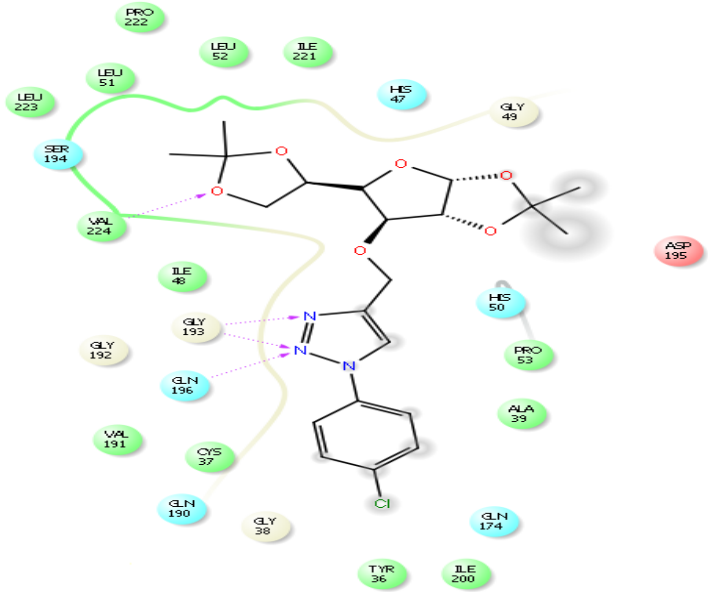


(a)

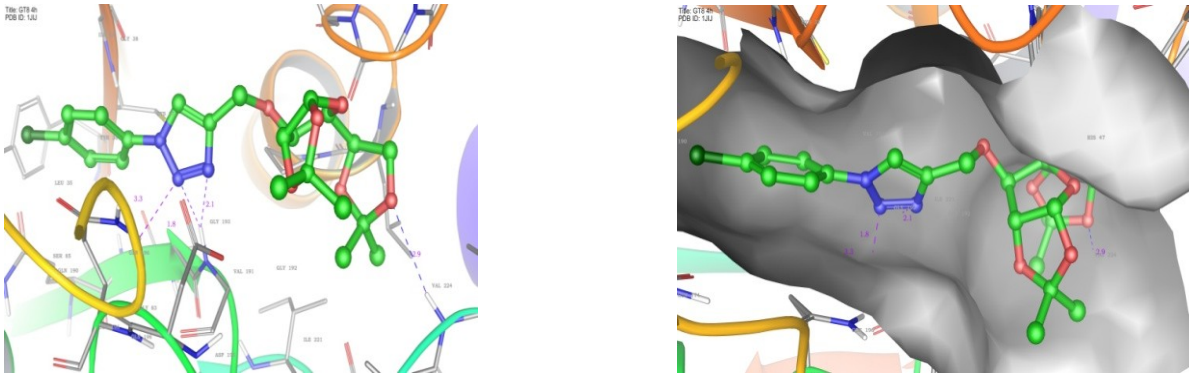


(b) **(c)**

Figure 3: Interactions between compound 4i and *S. aureus* tyrosyl tRNA synthetase (a) represents 2D diagram (b) 3D diagram showing H-bond interaction (c) represents surface area

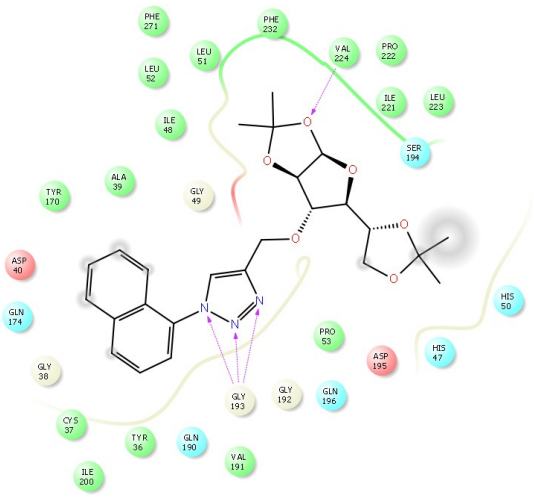


(a)

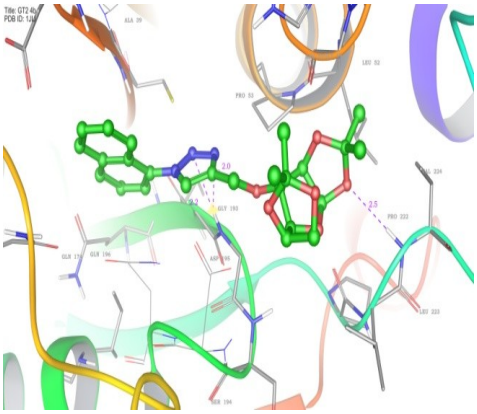


(b) **(c)**

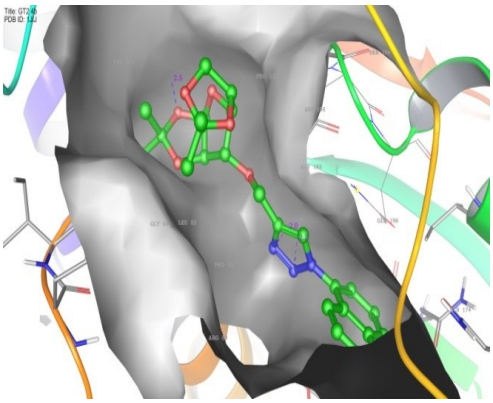
Figure 4: Interactions between compound 4h and *S. aureus* tyrosyl tRNA synthetase (a) represents 2D diagram (b) 3D diagram showing H-bond interaction (c) represents surface area



(a)

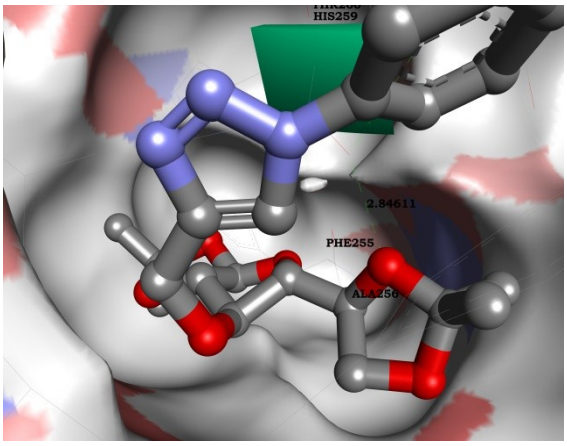


(b)

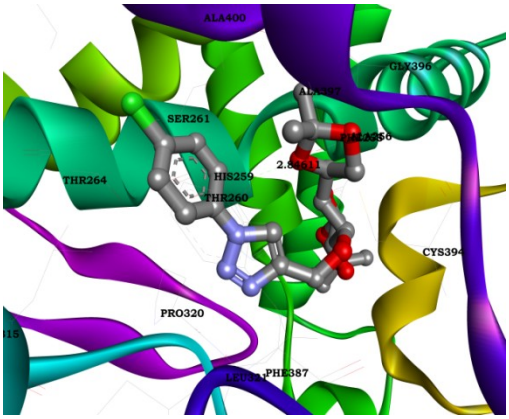


(c)

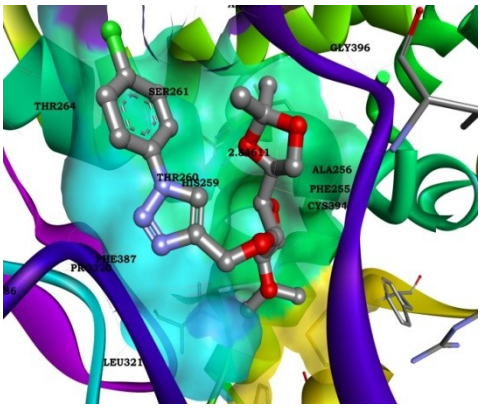
Figure 5: Interactions between compound 4b and *S. aureus* tyrosyl tRNA synthetase (a) represents 2D diagram (b) 3D diagram showing H-bond interaction (c) represents surface area



(a)

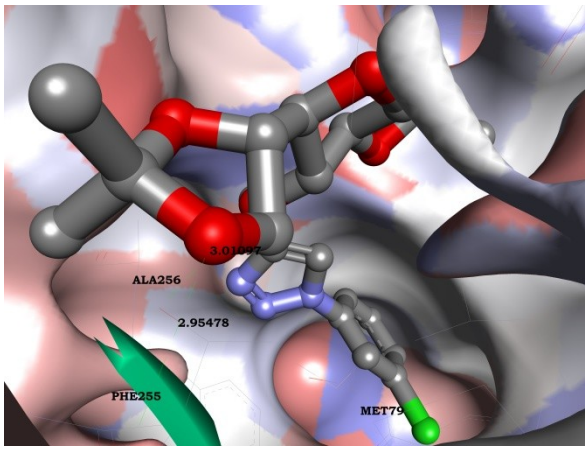


(b)

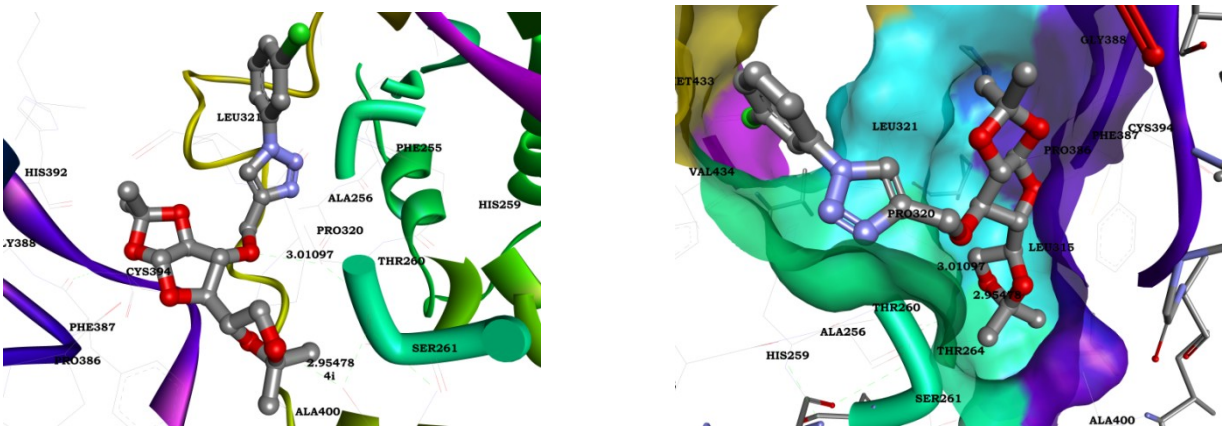


(c)

Figure 6: Interactions between compound 4h and CYP-51 (pdb ID: 1EA1) (a) represents docking pose (b) 3D diagram showing H-bond interaction (c) represents surface area



(a)



(b) **(c)**

Figure 7: Interactions between compound 4i and CYP-51 (pdb ID: 1EA1) (a) represents docking pose (b) 3D diagram showing H-bond interaction (c) represents surface area

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