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Synthesis, antibacterial, and molecular docking study of some novel 1,2,3-triazole derivatives

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Abstract

In the present study, a novel series of (1-aryl-1*H*-1, 2, 3-triazol-4-yl) methyl esters of valine and phenyl alanine were synthesised and characterised by IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectral and elemental analysis. The compounds were screened for *in vitro* antibacterial against gram positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*, and gram negative bacteria *Escherichia coli, and Proteus vulgaris*. Agar well diffusion method was employed for determination of antibacterial activity. These novel 1,4-disubtituted 1,2,3-triazoles exhibited highly potent activity against bacterial organisms and molecular docking studies revealed the close proximity between the protein receptor and the newly synthesized ligands.

Keywords: L - aminoacides; 1,2,3-Triazoles; Anti bacterial ; Molecular docking

Introduction

Bacterial infections have increased at an alarming rate causing deadly diseases. The treatment of infectious diseases remains as an important issue because of increasing number of multi-drug resistant microbial pathogens. Majority of pathogenic microorganisms have acquired resistance toward chemotherapeutics of available marketed drugs. Therefore, there is a need for new class of chemotherapeutic drugs in treating the pathogenic microorganisms. 1,2,3-Triazoles are an imperative class of heterocycles due to their wide-ranging applications [1-3]. They were reported as anti-HIV [4,5], anti microbial [6], anti-cancer [7,8], β3-selective adrenergic receptor agonists [9], kinase-3 inhibitors [10, 11] and other enzyme inhibitors [12-14]. To date, triazolyl esters of glutamic acid were synthesized [15] and they reported as excellent antimicrobial agents. In previous work we reported the antibacterial activity of some novel 1, 2, 3-triazoles [16] . In continuation of that, we were synthesized novel 1, 2, 3-triazolyl esters of valine and phenyl alanine to evaluate their antibacterial activity and to know the interactions with receptors through molecular docking studies.

Materials and methods

All reactions were carried at room temperature. Copper (I) iodide (≥ 99.5%), K_2CO_3 (≥99.0%)n and Propargyl bromide (80 wt. % in toluene) were purchased from Aldrich Chemical Company, Boc- Amino Acids, DMF and THF were purchased from S.D. Fine Chemicals Limited. DMF and THF solvents were purified by drying and followed by distillation. Thin-layer chromatography (TLC) was performed by using Merck silica gel 60 F254 precoated plates (0.25 mm) and and column chromatography was performed by using Silica gel (particle size 60-120 mesh). ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively by using TMS as internal standard and $CDCl_3$ as solvent. Melting points were determined using a Cintex apparatus; FTIR spectra were recorded on a Bruker spectrometer; Mass spectra (ESI-MS spectrum) were recorded. The compounds were screened for their antibacterial activity by employing Agar well diffusion method coupled with pour plate technique was followed for the detection of zone of growth inhibition. All the culture used in this present study was obtained by ARS-USDA (Agriculture Research Service- United States Department of Agriculture) on request and their help in this regard is duly acknowledged.

To perform molecular docking studies, the Lamarckian genetic algorithm (LGA), inculcated in the docking program AutoDock 4.2, was employed. The native crystal structure of tyrosyl tRNA(PDB entry: 1J1J) was obtained from Protein Data Bank http://www.rcsb.org/pdb.To carry out docking studies, the 2D structures of various ligands 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 by using Maestro elements tutorial 1.8.

Typical experimental procedure for the synthesis of 1,4-disubstituted 1,2,3-triazoles

To a solution of Boc-amino acid (2.5 mmol) in THF, copper (I) iodide (0.05 mmol) and arylazide (3. mmol) were added. The reaction mixture was then stirred at room temperature for 8 hours. Progress of the reaction was monitored by TLC. After the completion of starting materials, water (20 ml) was added and extracted with ethyl acetate (20 mL) three times. The combined ethyl acetate fractions were dried over Na_2SO_4 and evaporated under reduced pressure to give crude product. Then the crude product was further purified by column chromatography

[1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methyl2-[(tert-butoxycarbonyl)amino]-3-methylbutanoate: (Compound 3a)*:* Light yellow solid**,** mp 68-70^{o}C, R_f 0.60 (50% ethyl acetate : hexanes); IR(KBr): 3351, 3134, 1745, 1693, 1593, 1524, 1399, 1333 cm^{-1}; ^{1}HNMR (400MHz, $CDCl_3$)δ 7.981 (s,1H,triazole-H);7.63-7.61 (m, 2H);7.03-7.01 (m, 2H); 5.364 (s, 2H);5.00 (s, 1H); 4.2(m, 1H); 3.869 (s, 3H); 2.15 (m, 1H);1.426 (s, 9H); 0.950-0.933 (d, *J*=6.8 Hz, 3H); 0.869-0.852 (d, *J*=6.8 Hz, 3H); ^{13}CNMR (100MHz,$CDCl_3$) δ 170, 155, 142, 130, 133, 125, 117, 116, 80, 58, 57, 31, 28, 19, 17;ESI-MSm/z: 405[M+H].Calculated for :C (58.45) H (6.71) N (14.35), found: C (58.49) H (6.72) N (14.33)

[1-(naphthalen-1-yl)-1H-1,2,3-triazol-4-yl]methyl2-[(tert-butoxycarbonyl)amino]-3-methylbutanoate: (Compound 3b)*:* Light yellow solid**,** mp 80-82^{o}C, R_f 0.75 (50% ethyl acetate : hexanes);IR(KBr):3353, 3151, 1744, 1681, 1593, 1534, 1399cm^{-1}; ^{1}HNMR (400MHz, $CDCl_3$) δ 8.05-7.96 (m, 2H); 8.01 (s, 1H, triazole-H);7.55-7.61 (m, 5H);5.46 (s, 2H); 5.00-5.02 (d, *J*=8 Hz,1H); 4.29 (m, 1H); 2.29 (m, 1H) ; 1.42 (s, 9H); 0.97-0.95 (d, *J*=8 Hz, 3H); 0.88-0.89 (d, *J*=4 Hz, 3H); ^{13}CNMR(100 MHz, $CDCl_3$) δ 172,155,142,134,133,127,122, 79, 58, 58, 31,28,19,17; ESI-MSm/z: 425[M+H].Calculated for: C (64.37) H (6.38) N (13.65), found: C (64.39) H (6.41) N (13.66).

[1-(2-fluorophenyl)-1H-1,2,3-triazol-4-yl]methyl2-[(tert-butoxycarbonyl)amino]-3-methylbutanoate : (Compound3c)*:* White solid**,** mp 66-68^{o}C, R_f 0.60 (50% ethyl acetate : hexanes); IR(KBr): 3393, 3139, 1754, 1689, 1593, 1509, 1399cm^{-1}; ^{1}HNMR (400MHz,$CDCl_3$) δ 8.05 (s,1H, triazole-H);7.95 (m, 1H); 7.28-7.48 (m, 3H); 5.42 (s, 2H); 5.0 (d, *J*=12 Hz, 2H); 4.2 (m,1H); 2.17 (m, 1H); 1.42(s, 9H);0.94-0.92 (d, *J*=8 Hz, 3H); 0.86-0.84 (d, *J*=8 Hz, 3H); ^{13}CNMR (100 MHz,$CDCl_3$) δ 170,155, 154, 152, 142, 130, 125, 117, 116, 80, 58, 31, 28, 19, 17; ESI-MSm/z: 393[M+H].Calculated for: C (57.13) H (6.13) F (5.02) N (14.81), found: C (57.11) H (6.15) F (5.08) N (14.79).

[1-(2-methylphenyl)-1H-1,2,3-triazol-4-yl]methyl2-[(tert-butoxycarbonyl)amino]-3-methylbutanoate: (Compound 3d)*:* White solid**,** mp 47-49^{o}C, R_f 0.625 (50% ethyl acetate : hexanes); IR (KBr):3350, 3144, 1738, 1692, 1593, 1514, 1399 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.844 (s, 1H, triazole-H);7.30-7.42 (m, 4H); 5.433 (s, 2H); 5.00 (s, 1H); 4.24 (m, 1H); 2.22 (m, 1H); 2.29 (s, 3H); 1.421(s, 9H); 0.84-0.85(d, *J*=4 Hz, 3H); 0.94-0.92 (d, *J*= 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172, 155, 142, 134, 133, 127, 122, 79, 58, 31, 28, 19, 17, 15; ESI-MS m/z: 389 [M+H].Calculated for: C (60.95) H (7.00) N (14.96), found: C (60.92) H (7.04) N (15.01).

{1-[5-fluoro-2-(hydroxymethyl)phenyl]-1H-1,2,3-triazol-4-yl}methyl2-[(tert-butoxycarbonyl)amino]-3-methylbutanoate:(Compound 3e)*:* Yellow solid**,** mp 51-53^{o}C, R_f 0.49 (50% ethyl acetate : hexanes); IR (KBr): 3353, 3142, 1755, 1714, 1593, 1534, 1399 cm^{-1} ; ^{1}H NMR (400 MHz, CDCl3)δ 8.10 (s, 1H, triazole-H); 7.60(m, 1H); 7.2 (m, 2H); 5.4 (s, 2H); 5.01 (s, 1H); 4.4 (s, 2H); 4.19 (m, 1H); 3.49 (brs,1H); 2.22 (m,1H);1.421 (s, 9H); 0.85-0.86 (d, *J*= 4Hz, 3H); 0.95-0.97(d,

J= 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ172, 155, 142, 134, 133, 127,122, 79, 59, 58, 58, 31, 28, 19, 17; ESI-MS m/z: 423 [M+H].Calculated for: C (55.87) H (6.17) F (4.65) N (13.72), found: C (55.89) H (6.16) F (4.60) N (13.75)

[1-(2,6-difluoro-3,5-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl]methyl2-[(tert-butoxycarbonyl)amino]-3-methylbutanoate:(Compound 3f)*:* White solid**,** mp 58-60^{o}C, R_f 0.42 (50% ethyl acetate : hexanes); IR (KBr): 3355, 3350, 3142, 1750, 1713, 1594, 1534, 1400 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H, triazole-H); 6.97 (s, 1H, Ar); 5.4 (s, 2H); 5.07 (s, 1H); 3.787 (m, 7H); 2.24 (m, 1H); 1.412 (s, 9H); 0.84-0.86 (d, *J*= 8 Hz, 3H); 0.96-0.97 (d, *J*= 4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ172, 155,142,134, 133, 127, 122, 79, 59, 58, 58, 31, 28, 19, 17; ESI-MS m/z: 493 [M+Na].Calculated for: C (52.63) H (5.74) F (8.32) N (12.27), found: C (52.66) H (5.71) F (8.35) N (12.31).

[1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methyl2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoate: (Compound 4a)*:* Brown solid**,** mp 61-63^{o}C, R_f 0.66 (50% ethyl acetate : hexanes); IR (KBr): 3354, 3134, 1745, 1693, 1593, 1524, 1399cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.828 (s, 1H, triazole-H); 7.60-7.62 (d, *J= 8.8 Hz*, 2H); 7.14-7.1(m, 3H); 7.01-7.05(m, 4H); 5.34 (s, 2H); 5.00 (s,1H); 4.66 (m, 1H); 3.879 (s, 3H); 3.00 (s, 2H); 1.407 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ171, 159, 155, 142, 135, 130, 129, 128, 122, 117, 80, 58, 55, 54, 38, 28; ESI-MS m/z: 475 [M+Na]. Calculated for: C (63.00) H (5.98) N (12.78) , found: C (63.06) H (5.95) N (12.82)

1-(naphthalen-1-yl)-1H-1,2,3-triazol-4-yl]methyl2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoate: (Compound 4b)*:* Brown solid**,** mp 64-66^{o}C, R_f 0.70 (50% ethyl acetate : hexanes); IR (KBr): 3353, 3142, 1755, 1714, 1593, 1534, 1399 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H, triazole-H); 8.05-7.97 (dd, *J*= 8 Hz, 8 Hz, 2H); 7.6 (m, 5H); 7.1-7.2 (m, 5H); 5.43 (s,2H); 4.99 (s,1H); 4.64 (m, 1H);3.11 (s,2H);1.39 (s,9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172, 155, 142, 135, 130, 129, 128, 122, 114, 79, 55, 54, 38, 28; ESI-MS m/z: 495 [M+Na]. Calculated for: C (68.11) H (5.72) N (12.22), found: C (68.09) H (5.77) N (12.28).

[1-(2-fluorophenyl)-1H-1,2,3-triazol-4-yl]methyl2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoate (Compound 4c): White solid**,** mp 62-64^{o}C, R_f 0.62 (50% ethyl acetate : hexanes); IR (KBr): 3393, 3139, 1754, 1689, 1593, 1502, 1399 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H, triazole-H); 7.964-7.05 (m, 9H, Ar); 5.2 (s, 2H); 5.00 (s, 1H); 4.6-4.5 (m, 1H); 3.01 (m, 2H); 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171, 159, 155, 142, 135, 130, 129, 128, 122, 114, 80, 55, 54, 38, 28; ESI-MS m/z: 441 [M+H]. Calculated for: C (61.96) H (5.44) F (4.46) N (13.14), found: C (61.93) H (5.48) F (4.48) N (13.16).

[1-(2-methylphenyl)-1H-1,2,3-triazol-4-yl]methyl2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoate: (Compound 4d)*:* White solid**,** mp 63-65^{o}C, R_f 0.66 (50% ethyl acetate : hexanes); IR (KBr): 3353, 3140, 1738, 1692, 1593, 1512, 1399 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H, triazole-H);7.964-7.0 (m, 9H, Ar); 5.20 (s, 2H); 4.99(s, 1H); 4.3(m, 1H); 3.02 (m, 1H); 2.25 (s, 3H); 1.4 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171, 159, 155, 142, 135, 130, 129, 128, 122, 114, 80, 58, 55, 54, 38, 28, 16; ESI-MS m/z: 459 [M+Na].Calculated for: C (65.39) H (6.20) N (13.26), found: C (65.42) H (6.22) N (13.18)

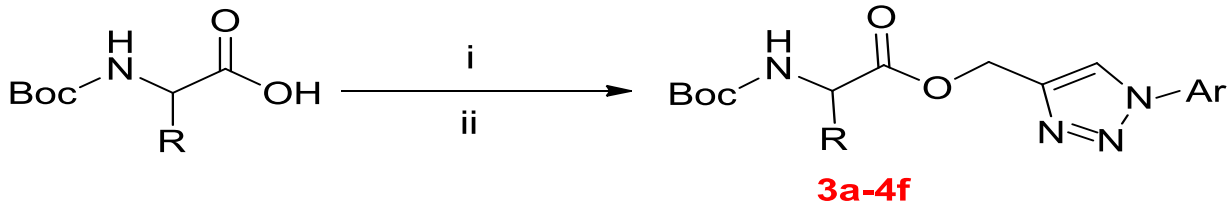
{1-[5-fluoro-2-(hydroxylmethyl)phenyl]-1H-1,2,3-triazol-4-yl}methyl2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoate: (Compound 4e)*:* Light yellow solid**,** mp58-60^{o}C, R_f 0.60 (50% ethyl acetate : hexanes); IR (KBr): 3355, 3130, 1725, 1690, 1594, 1508, 1400 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3)δ 8.05 (s, 1H, triazole-H); 7.60 (m, 3H, Ar); 7.2 (m, 5H); 5.4 (s, 2H); 5.20(s, 2H); 5.02 (s, 1H); 4.19 (m, 1H); 3.49 (brs, 1H); 3.01 (m, 1H); 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172, 155, 152, 141, 135, 128, 126, 122, 116, 79, 58, 56, 52, 38, 28; ESI-MS m/z: 471 [M+H].Calculated for: C (60.52) H (5.52) F (4.16) N (12.27) O (17.53), found: C (60.52) H (5.52) F (4.16) N (12.27) O (17.53)

[1-(2,6-difluoro-3,5-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl]methyl2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoate: (Compound 4f)*:* White solid**,** mp 60-62^{o}C, R_f 0.58 (50% ethyl acetate : hexanes); IR (KBr): 3353, 3142,1755,1714, 1593,1534 ,1399cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$)δ7.86(s,1H,triazole-H); 7.2-7.5(m,5H);6.97(s,1H,Ar); 5.4 (s, 2H); 5.27 (s, 2H); 4.4(m, 1H); 3.87 (m, 6H); 3.05 (m, 2H); 1.421(s, 9H);^{13}C NMR (100 MHz, $CDCl_3$) δ 172, 156, 155

,142,135,130,129,128,122,114,80, 58,55, 38,28; ESI-MS m/z: 519 [M+H].Calculated for: C (57.14) H (5.19) F (7.53) N (11.11), found: C (57.20) H (5.21) F (7.50) N (11.08)

Results and discussion

The *N*-Boc protected amino acids were converted to corresponding propargylic esters using propargyl bromide and K_2CO_3 in DMF at room temperature [17] and they were treated with different aryl azides [18] in presence of catalytic amount of copper (I) iodide to synthesize1,2,3-triazoles by employing click chemistry protocol[19]. 1, 4- disubstituted 1,2,3-triazoles were formed selectively in excellent yields and the results were summarized in **Scheme 1**. We synthesized 1,4-disubstituted 1,2,3-triazoles using two L-aminoacids [valine, Phenyl alanine] and aryl azides.



R= (3) $CH(CH_3)_2$; (4) $PhCH_2$

Ar = (**a**) 4-Methoxy phenyl ; (**b**) 1-napthyl ; (**c**) 2-fluro phenyl ; (**d**) 2-methyl phenyl; (**e**) 2-Hydroxymethyl-5-fluoro-phenyl; (**f**) 2,6-difluoro- 3,5-dimethoxy-phenyl

Scheme 1: Synthetic route for (1-aryl-1*H*-1, 2, 3-triazol-4-yl)methyl aminoacid esters;(i) Propargyl Bromide, K2CO3, THF (ii) ArN_3, CuI, RT, 10-12 h

Anti-bacterial Activity.

The newly synthesized compounds(**3a-4f**) were screened for antibacterial activity against gram positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*, and gram negative bacteria *Escherichia coli, and Proteus vulgaris*. Agar well diffusion method [20] was employed for determination of antibacterial activity. 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). 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. The nutrient agar medium (10 mL) was poured into each sterilized Petri plate and plates were swabbed with 100 µL inocula of the test micro organisms.The poured material was allowed to set for 30 min and there after the wells (10 to 12 mm diameter) were made by punching into the agar surface with a sterile cork borer he punched part of agar. The test solution (0.1 mL) at concentration 100µg/mL was added into the wells. The plates were incubated at 37 ^{0}C and the results were recorded after 24 h.The test solution prepared by using dimethylsulphoxide (DMSO) as solvent. DMSO was used as a negative control whereas Streptomycine was used as positive control. Each experiment was carried in triplicate and the results were recorded as the average diameter of inhibition zones in cm. The results for antibacterial studies depicted in revealed that the tested compounds displayed variable inhibitory effects on the growth of the bacterial pathogens. Most of the compounds exhibited moderate to excellent activity. The excellent activities than reference standard were observed for ***3a*** and ***4e*** against E.coli, ***3d***, ***4e*** and ***4f*** against S.aureus, ***3e*** against B.subtilis and, ***3c*** and ***3e*** against P.vulgaris (**table 1**).

Molecular modeling study

In order to gain insight into the plausible mechanism of action of compounds docking simulations were performed. Compounds were docked into active sites of S. aureustyrosyl tRNA synthetase [21] (pdb: 1JIJ) has been reported as the target receptors for docking studies in finding the suitable drug candidates against the bacteria. The docking of receptor tRNA synthetase with twelve newly synthesized ligands exhibited the good number of H-bonds in the closest distance of 2 A^0 with one or more amino acids in the receptor active pocket (**Fig. 2 & 3**). Docking studies revealed these molecules having strong affinity with the receptor and exhibited good binding energies from - 7.97 and - 6.90 kcal mol^{-1}. The information from the docking studies and antibacterial activity proved the newly synthesized compounds as more potent towards the bacterial pathogens.

Table 1: Anti-bacterial activity of synthesized (1-aryl-1*H*-1, 2, 3-triazol-4-yl)methyl aminoacid esters[a]

Entry	Compound	*E. Coli* [b]	*S. Aureus* [b]	*B. Subtilis* [b]	*P. Vulgaris* [b]
1	3a	1.8	1.1	0.8	1.2
2	3b	1.1	1.0	0.7	1.1
3	3c	1.4	0.6	0.2	1.3
4	3d	1.7	1.3	1.3	1.2
5	3e	1.6	1.1	1.6	1.6
6	3f	1.7	0.8	1.0	1.3
7	4a	1.3	1.2	0.9	1.2
8	4b	1.1	1.4	0.7	1.0
9	4c	1.5	0.8	1.0	1.2
10	4d	1.4	1.2	1.0	1.0
11	4e	1.9	1.4	0.6	1.2
12	4f	1.6	1.5	1.0	1.8
13	**S**	**1.8**	**1.3**	**1.5**	**1.7**

S = Streptomycine sulphate; [a] All the values are the mean of triplicates; [b] Zone of inhibition in (cm)

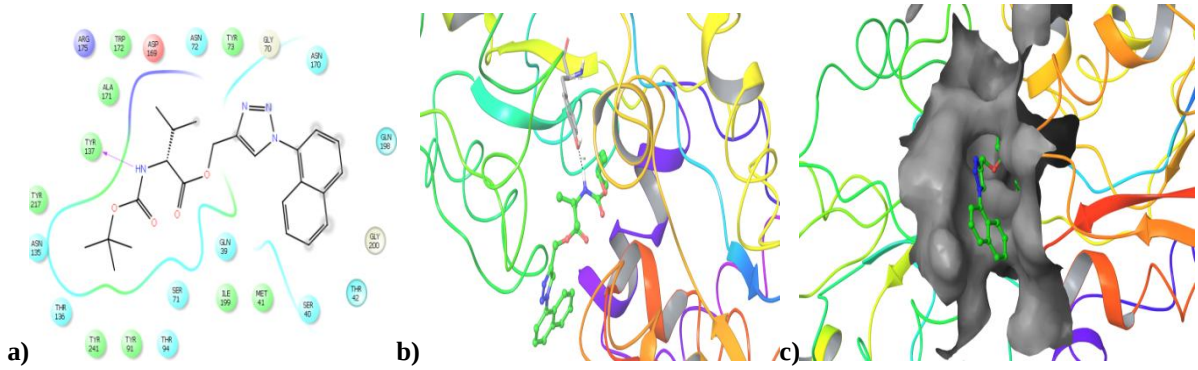


Figure 1. ABC transporter–substrate binding domain interactions with **3b** compound. a) represents 2D interactions of **3b** compound, b) represents 3D H-bond interaction formed by the **3b** compound with THR137 residue, whereas c) represents Surface area interactions of **3b** compound.

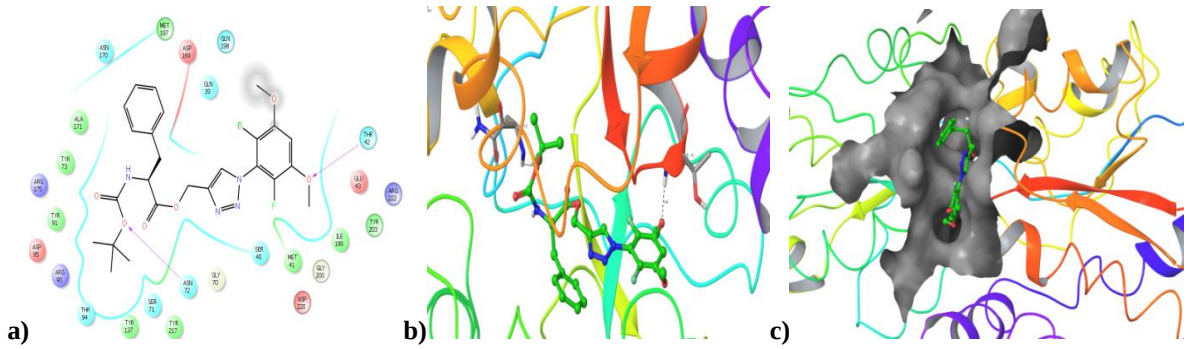


Figure 2. ABC transporter–substrate binding domain interactions with **4f** compound. a) represents 2D interactions of **4f** compound, b) represents 3D H-bond interaction formed by the **4f** compound withTHR42 and ASN72 residue, whereas c) represents Surface area interactions of **4f** compound.

CONCLUSION

In conclusion, one pot synthesis of 1,2,3-triazolyl methyl esters of selected natural aminoacids were synthesized and evaluate their anti bacterial activity. They exhibited potent activity towards both gram positive and gram negative bacteria. Some of them were found to more active than standard reference drug. Further modification of 1, 4-disubstituted 1, 2, 3-triazoles with various other substitutions to develop highly potent antibacterial agents are under progress.

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