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Some 3,4,5-Trisubstituted-1,2,4-triazole Synthesis, Antimicrobial Activity, and Molecular Docking Studies

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Abstract

Methyl 4-aminopicolinate 1 interacted with hydrazine hydrate and subsequently with carbon disulfide to produce a triazole thiol derivative, which then reacted with different aldehydes to produce the appropriate Schiff base products. 4a-c. The reaction of Schiff base products 4a-c with benzoyl chloride resulted in the formation of trisubstituted triazoles 5a-c. The spectroscopic studies of the produced chemicals helped to clarify their structures. The antibacterial activity of the produced compounds against various bacterial and fungal strains was tested. Molecular docking studies of newly synthesized 1,2,4-triazoles were also conducted.

Keywords: Triazole; Schiff base; Molecular Docking; Antimicrobial activity.

1. Introduction

Triazole is a five-membered ring containing three nitrogen atoms and two carbons that is used in synthetic medicines as well as numerous bioactive naturally occurring compounds. Triazoles have also been found to have antibacterial [1-3], antifungal, [4, 5] anti-tubercular action, [6] antihistamine activity, [7], TB and protein inhibitors [8,] in addition to their usage as potassium channel activators [9-11]. Because they are stable molecules that may imitate peptide linkages, heterocycles with triazole skeletons are essential pharmacophores for drug development. [12]. Also, one for the marked efficient drug deferasirox, that used as iron chelator to treat patients with high level of iron in their blood (Figure 1). Triazole in certain cases able to inhibit the formation of fog in photographic emulsions and it has various biological applications [13-17]. There are marked antifungal drugs such as Vericonazole, itraconazole and Fluconazole (Figure 1). Based on above survey, we aimed to synthesize Triazole derivatives and evaluate their activity as antibacterial agents, starting from methyl 4-aminopicolinate 1 to afford trisubstituted triazole.

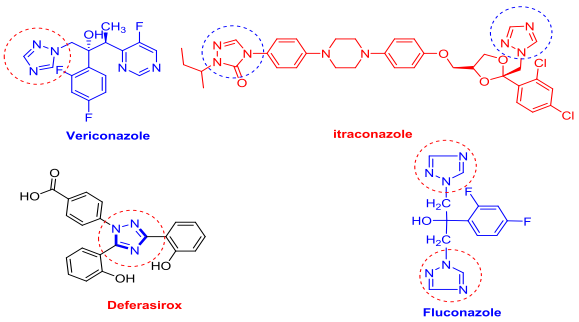

Figure 1: Some remarkable Triazole drivatives

2. Experimental

The hot stage method was used to determine melting points (FALC melting point device). Fourier-transform infrared spectroscopy (FT-IR) was performed utilizing the SHIMADZU (8300), KBr disc, ^{13}C-NMR, and Bruker instruments. The ^{1}H-NMR spectra were recorded using an Ultrasheild 400 MHz spectrophotometer with tetramethylsilane as the internal standard and DMSO as the solvent (Isfahan University of Technology (IUT), Iran). The yields are of pure isolated components obtained by column

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chromatography on Merck Kiesel gel F254 precoated plates and thin layer chromatography (TLC) on Merck Kiesel gel 60 (Merck) precoated plates (Merck, Darmstadt, Germany). TLC was used to monitor the reactions and evaluate the purity of the compounds on silica gel-precoated aluminum sheets (Type 60, F 254, Merck, Darmstadt, Germany), and the spots were identified by briefly exposing the sheets to a UV light at 254 nanometers. The chemical names assigned to the produced compounds are based on the IUPAC system. Solvents were dried/purified in accordance with published methods.

Synthesis and characterization

Synthesis of 4-aminopicolinohydrazide 2

After refluxing hydrazine hydrate 80 percent (0.31 mL, 0.0065 mol.) and methyl 4-aminopicolinate 1 (1 g., 0.0065 mol.) in 5 mL ethanol for 5 hours (TLC monitoring), the reaction mixture was evaporated under reduced pressure to produce compound 2 in excellent 82 percent yield (ethanol). [18]

Product 2 was isolated as colorless crystals, with a yield of 82 percent. m.p 202-204°C. 3458-3328 (NH_2, NH), 3041 (CH-aromatic), 1680 (C=O), IR (KBr, cm^{-1}): 3458-3328 (NH_2, NH), 3041 (CH-aromatic), 1680 (C=O). 4.01 (s, 1H, NH2 hydrazide), 5.54 (s, 1H, NH_2 pyridine ring, 6.13-7.69 (m, 3H, Ar-H), 9.64 (s, 1H, NH_2 pyridine ring, 6.13-7.69 (m, 3H, Ar-H), 9.64 (s, 1H, NH_2 pyridine ring, 6.13-7.69 (m, 3H, Ar-H) (s, 1H, NH). 103, 115, 139, 151, 155, 160 ^{13}C NMR (100 MHz, DMSO).

4-Amino-5-amino-5-amino-5-amino-5-amino-5 (4-aminopyridin-2-yl) -4H-1,2,4-triazole-3-thiol 3

0.73 g (0.131 mol) In 15 mL 100% ethanol, 2 g of 4-aminopicolinohydrazide 2 (0.0131 mol.) was mixed with potassium hydroxide. This mixture was agitated until potassium hydroxide was dissolved, then carbon disulphide (0.78 mL, 0.0131 mol.) was added with continuous stirring until hydrogen sulfide was evaluated (lead acetate paper). 5 mL ether was added and stirred for 15 minutes before being filtered, dried, and washed with ether (Twice). TLC was used to monitor the reaction, and strong hydrochloric acid was added to the mixture to achieve a white precipitate yield of 69 percent (ethanol). [19]

Product 3 was separated as colorless crystals, yield 69%. m.p 263-265°C. IR (KBr, cm^{-1}): 3375-3240 (NH_2), 3098 (CH-aromatic) 2332 (SH), 1600 (C=N triazole ring). 1H NMR (400 MHz, DMSO) δ 3.95 (s, 1H, NH_2 pyridine ring), 4.22 (s, 1H, NH_2 triazole ring), 6.60-8.12 (m, 3H, Ar-H pyridine ring), 11.89 (s, 1H, SH). ^{13}C NMR (100 MHz, DMSO) δ 105, 110, 132, 149, 153, 155, 162.

Reaction of 1,2,4-triazole-3-thiol derivative 3 with aldehyde derivatives in general

Aromatic aldehydes benzaldehyde (0.0024 mol., 0.22 ml.), 1-naphthaldehyde (0.0024 mol., 0.37 g.), and 9-anthraldehyde (0.0024 mol., 49 g.) were added to 1,2,4-triazole-3-thiol derivative 3 (0.0012 mol., 0.25 g) in 100% ethanol, the reaction mixture was monitored using

4-((Benzylidene)amino) -5-(4-((benzylidene)amino)pyridin-2-yl) -4H-1,2,4-triazole thiol-3-thiol-3-thiol-3-thiol 4a

Product 4a was isolated as red crystals, with a yield of 66%. m.p. : 183-185°C 3100 (CH-aromatic), 2257 (SH), 1655 (C=N imine) IR (KBr, cm-1) 7.0-8.87 (m, 13H, Ar-H), 8.44-9.21 (d, 2H, C=NH), 12.22 (d, 2H, C=NH) 1H NMR (400 MHz, DMSO) (s, 1H, SH). NMR ^{13}C (100 MHz, DMSO) 144, 147, 155, 159, 113-156

4-((Naphthalen-1-ylmethylene)amino) -5-(4-((naphthalen-1-ylmethylene)amino)pyridin-2-yl) triazole-3-thiol-4H-1,2,4-triazole-3-thiol-3-thiol-3-thiol-3-thiol-3 4b

Product 4b was isolated as orange crystals, with a yield of 72 percent. m.p 215-217°C. IR (KBr, cm^{-1}): 3059 (CH-aromatic), 2530 (SH), 1622 (C=N imine). ^{1}H NMR (400 MHz, DMSO) 7.31-8.55 (m, 17H, Ar-H), 8.55-9.43 (d, 2H, C=NH), 13.33 (s, 1H, SH). ^{13}C NMR (100 MHz, DMSO) 147, 148 (2C) triazole ring, 157, 1160 (2C) imine group, 114-156 (25C) benzene and pyridine ring

4-((Anthracen-9-ylmethylene)amino)-5-(4H-1,2,4-triazole-3-thiol)-4H-1,2,4-triazole-3-thiol (4c)

Product 4c was isolated as yellow crystals with a yield of 61 percent and a melting point of 271-273°C. 3044 (CH-aromatic), 2459 (SH), 1649 (C=N imine), IR (KBr, cm^{-1}): 3044 (CH-aromatic), 2459 (SH), 1649 (C=N imine). 7.54-8.44 (m, 21H, Ar-H), 8.58-9.25 (d, 2H, C=NH), 13.01 (400 MHz, DMSO) (s, 1H, SH). ^{13}C NMR (100 MHz, DMSO) triazole ring 145, 146 (2C), imine group 154, 158 (2C), benzene and pyridine ring 115-158 (33C).

5a-c General synthesis process of substituted 4H-1,2,4-triazol-3-yl benzothioate derivatives

Schiff bases (4a-c, 6 mmole) and substituted benzyl chloride were heated for 2-4 hours in anhydrous acetone and anhydrous potassium carbonate (6 mmole) (TLC monitoring). Compounds 5a-c (methanol) were obtained when the solvent was evaporated and the residue was cooled and washed with water [21].

S-(4-((benzothioate (benzylidene)amino)-5-(4-((benzylidene)amino)pyridin-2-yl)-4H-1,2,4-triazol-3-yl) 5a

Product 5a was isolated as colorless crystals with an 81 percent yield. m.p 129-131°C. 3076 (CH-aromatic), 1689 (C=O), 1650 (C=N imine), IR (KBr, cm-1): 3076 (CH-aromatic), 1689 (C=O), 1650 (C=N imine). 6.95-8.67 (m, 18H, Ar-H), 8.64-9.03 (d, 2H, C=NH) ^{1}H NMR (400 MHz, DMSO). ^{13}C NMR (100 MHz, DMSO) triazole ring 148, 148 (2C), imine group

154, 159 (2C), carbonyl 188 (1C), benzene and pyridine ring 115-161 (23C).

S-(4-((naphthalen-1-ylmethylene)amino)-5-(4-((naphthalen-1-ylmethylene)amino)pyridin-2-yl) benzothioate (-4H-1,2,4-triazol-3-yl) 5b

Product 5b was separated as colorless crystals with a yield of 76 percent and a melting point of 146-148°C. 3034 (CH-aromatic), 1698 (C=O), 1613 (C=N imine), IR (KBr, cm-1): 3034 (CH-aromatic), 1698 (C=O), 1613 (C=N imine). 7.30-8.30 (m, 22H, Ar-H), 8.55-9.54 (d, 2H, C=NH) 1H NMR (400 MHz, DMSO). 13C NMR (100 MHz, DMSO) triazole ring 147, 147 (2C), imine group 157, 160 (2C), carbonyl 188 (1C), benzene and pyridine ring 111-163 (31C).

(4-((anthracen-9-ylmethylene)amino)-5-(4-((anthracen-9-ylmethylene)amino)pyridin-2-yl) benzothioate (-4H-1,2,4-triazol-3-yl) 5c

Product 5c was separated as colorless crystals with a yield of 69 percent and a melting point of 177-179°C. 3076 (C-H-aromatic), 1680 (C=O), 1656 (C=N imine) IR (KBr, cm-1) 7.39-8.55 (m, 26H, Ar-H), 8.64-9.29 (d, 2H, C=NH) ^{1}H NMR (400 MHz, DMSO). 146, 147 (2C) triazole ring, 158, 162 (2C) imine group, 189 (1C) carbonyl, 113-166 (39C) benzene and pyridine ring ^{13}C NMR (100 MHz, DMSO).

Antimicrobial Potency

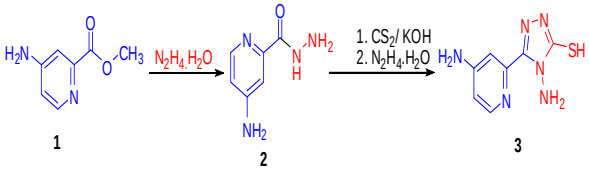
The samples were made by dissolving 10mg of the under examination items in 2ml of methanol, and 100l of solution (containing 500g of the desired product) was utilized in this test. The agar cup plate technique was used to test the antibacterial activity of various substances. Staphylococcus aureus (Gram +ve) and Pseudomonas aeruginosa (Gram -ve) were employed as test microorganisms. In the case of bacteria and yeast, nutrient agar plates were extensively seeded evenly with 0.1ml of 105-106 cells/ml. Then, in a sterile environment, a hole (1cm diameter) was created in the medium using a gel cutter (Cork borer). Then, to create a foundation layer, one drop of molten agar was put into the hole and allowed to harden. After that, 0.1 ml of the tested sample was put into the hole. Plates were then maintained at a low temperature (4°C) for 2-4 hours to allow for maximal diffusion. The plates were then incubated at 37°C for 24 hours for bacteria and 30°C for 48 hours in an upright position to allow the organisms to develop to their full potential. The test agent's antibacterial activity was evaluated by measuring the diameter of the zone of inhibition in millimeters (mm). The experiment was repeated many times, and the mean reading was recorded [22, 23].

Molecular docking

AutoDock 4.2 was used, as well as docking calculations using Gasteiger partial charges applied to ligand (designed drug) atoms. The ligand–protein pattern computations were performed. Nonpolar hydrogen atoms were linked together, and rotatable bonds were elucidated. The AutoDock tools were used to apply Kollman unified atom type charges and solvation parameters after the insertion of fundamental hydrogen atoms [24-26]. Van der Waals and electrostatic terms were calculated using AutoDock parameter set- and distance-dependent dielectric functions, respectively. Simulative docking was carried out using the Lamarckian genetic algorithm and the Solis and Wets local search method [27]. In addition, the ligand molecule's initial location, orientation, and torsions were determined. During docking, all rotatable torsions were removed. Each docking experiment was created using ten separate runs, and it was programmed to stop after a total of 250 000 energy estimations. The limit was set at 150 people. A translational step of 0.2 and quaternion and torsion steps of 5 were used throughout the investigation.

3. Results and Discussion

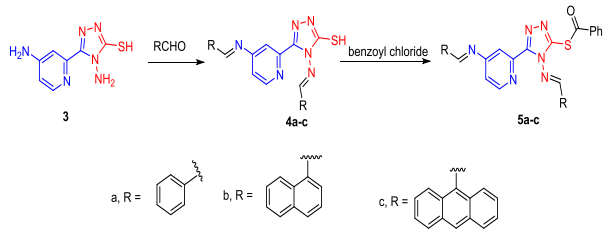
At reflux temperature, methyl 4-aminopicolinate 1 interacted with hydrazine hydrate to produce 4-aminopicolinohydrazide 2. In the presence of hydrazine hydrate, compound 2 interacted with carbon disulfide to provide 4-amino-5-nitrobenzene (4-aminopyridin-2-yl) Excellent yield of -4H-1,2,4-triazole-3-thiol (3) (Scheme 1). Compounds 2 and 3's structures were determined using IR, ^{1}H NMR, and ^{13}C NMR (cf. Experimental).



Scheme 1: Synthetic pathway of triazole derivative 3

In 100% ethanol, compound 3 was reacted with different aldehydes, including benzaldehyde, 1-naphthaldehyde, and 9-anthraldehyde, to yield the corresponding Schiff bases 4a-c (Scheme 2). IR, ^{1}H NMR, and ^{13}C NMR were used to confirm the structures of the novel Schiff bases 4a-c (cf. Experimental).

Compound 4a, for example, was isolated as red crystals. Its infrared spectra (KBr, cm-1) showed a significant absorption band at 3100 (CH-aromatic), 2257 (SH), and 1655 (C=N imine). Furthermore, its ^{1}H NMR (400 MHz, DMSO) shows aromatic protons as multiplet 7.0-8.87 ppm, imine protons as multiplet 8.44-9.21 (C=NH), and typical thiol protons as singlet 12.22.



Scheme 2: Synthetic pathway of substituted triazole 4a-c and 5a-c

Similarly, pyridin-2-yl-4H-1,2,4-triazol-3-ylbenzothioate derivatives 5a-c were produced by reacting compound 4a-c with benzoyl chloride in basic potassium carbonate medium (Scheme 2). The structures of compounds 5a-c were determined using IR, ^{1}H NMR, and ^{13}C NMR. (See also Experiment.)

Antibacterial activity

The antimicrobial activity of newly synthesized triazole derivatives was assessed against two distinct test microorganisms, namely Staphylococcus aureus (Gram +ve), Pseudomonas aeruginosa (Gram -ve), using the agar diffusion technique and amoxicillin as the reference medication.

Compounds 4a-c had significant activity against Staphylococcus aurous, whereas compounds 4a,b shown good action against Pseudomonas aeruginosa (Table 1). In compared to Amoxicillin, compounds 5a-c had lesser activity.

1st Table The novel produced chemicals have antimicrobial action against a variety of harmful bacteria.

Compound	Gram negative Pseudomonas aeruginosa	Gram Positive Staphylococcus aurous
4a	14	20
4b	10	18
4c	7	15
5a	5	9
5b	1	6
5c	0.9	4
Amoxicillin	25	25
Control	DMSO	DMSO

Molecular Docking

Auto Dock is a novel approach for displaying and proving the biological advantages of Triazole and heterocycles with five membered rings including three nitrogen atoms and two carbons, as well as giving light on the experimental results. Docking was utilized to combine ligands (guests) with a range of hosts (different protein receptors), including P. aeruginosa (5i39) and B. subtilis (5h67). The energy of the docking operation was also examined. HB plots (Figures 2-9), according to calculation, can indicate a significant interaction involving all receptors with comparable performance. Inter-hydrogen bonding was clearly seen in all proteins. The manner of interaction inside the docking molecules is depicted in two-dimensional graphs (Figures 2-9). In the bacterium B. subtilis (5h67) and P. aeruginosa, the contact between the four chemicals (2, 3,4a, and 5a) and the amino acid of proteins generally happens via hydrogen bonding (5i39).

For B. subtilis (5h67) with four compounds (2, 3, 4a and 5a) we find the effect of end compound (4a and 5a) than start one (2 and 3 compounds), also we find compound 4a more active than 5a compound, and this is compatible with the biological study as follow: amino acids interacted with ligand as follow: 3ty7-Staphylococcus Aureus with four compounds 2, 3, 4a and 5a. Start with compound 2, 3ty7-h//A/ASP`238/OD1–with H length of the band = 2.0 Å, 3ty7- h//A/ASP`238/OD2– with H-band = 2.5 Å, with binding power = −4.3 kcal mol^{-1} (Figures 2), with compound 3; 3ty7- h//A/ASP`45/OD1 – with H-band = 2.4 Å and 3ty7- h//A/GLU`212/OE1– with H-band = 3.3 Å, with binding power = −4.3 kcal mol^{-1} (Figures 4), with compound 5a, 3ty7-h//A/GLU`49/OE2 – with H-band = 3.3 Å, 3ty7 -h//A/HIS`213/HE1– with H-band = 2.2 Å, 3ty7 -h//A/HIS`213/HE1– with H-band = 3.3 Å and 3ty7-h//A/GLU`212/O – with H-band = 2.1 Å, with binding power = −5.3 kcal mol^{-1} (shapes 4), The most active compound 4a, 3ty7- A-h//A/PRO`209/O – with H-band = 2.0 Ao, 3ty7 -A-h//A/VAL`467/CG2– with H-band = 3.4 Å, 3ty7- h//A/ASP`238/OD2 – with H-band = 2.0 Å, 3ty7- h//A/GLU`212/OE1– with H-band = 2.3 Å, 3ty7 -h//A/HIS`213/HE1 – with H-band = 3.1 Å and 3ty7- h//A/GLU`212/O – with H-band = 2.3 Å, and binding power= − 5.3 kcal mol^{-1}. (Figures 5), 5i39-P. aeruginosa with four compounds 2, 3,4a and 5a. Start with compound 2, 5i39-h/A1/A/GLN`92/OE1–with H- length of band = 3.2 Å, 5i39- h/A1/A/SER`93/OG – with H-bond = 1.8 Å and 5i39- h/A1/A/PHE`395/HD1 – with H-band = 2.7 Å with binding power = −6.7 kcal mol$^{-1}$ (Figures 6), with compound 3; 5i39- h/A1/A/THR`436/O – with H-band = 2.3 Å, 5i39- h/A1/A/SER`93/OG – with H-band = 2.9 Å and 5i39- h/A1/A/SER`93/OG – with

H-band = 2.2 Å, with binding power = −7.3 kcal mol^{-1} (Figures 7), with compound 5a, 5i39-h/A1/A/GLN`92/OE1– with H-band = 3.1 Å, 5i39-h/A1/A/GLY`437/O – with H-band = 3.5 Å, 5i39-h/A1/A/SER`93/OG – with H-band = 2.8 Å, 5i39-h/A1/A/LEU`65/H – with H-band = 1.9 Å, 5i39-h/A1/A/ALA`255/O – with H-band = 3.1 Å and 5i39-h/A1/A/ALA`255/O – with H-band = 3.2 Å, with binding power = −10.2 kcal mol^{-1} (Figures 8), The most active compound 4a, 5i39- h/A1/A/VAL`316/O – with H-band = 2.8 Ao, 5i39- h/A1/A/GLN`99/O – with H-band = 3.3 Å, 5i39- h/A1/A/THR`441/OG1 – with H-band = 2.8 Å, 5i39- h/A1/A/TRP`438/O – with H-band = 3.4 Å, 5i39-h/A1/A/GLU`212/OE1– with H-band = 2.2 Å, 5i39- h/A1//A/GLU`212/OE1 – with H-band = 3.1 Å, 5i39- h/A1/A/THR`434/HG1 – with H-band = 2.1 Å, 5i39- h/A1/A/ALA`435/H – with H-band = 2.4 Å, 5i39- h/A1/A/ALA`255/O – with H-band = 3.2 Å, and 5i39- h/A1/A/ALA`255/O – with H-band = 3.4 Å, and binding power = − 7.6 kcal mol^{-1}. (Figures 9).

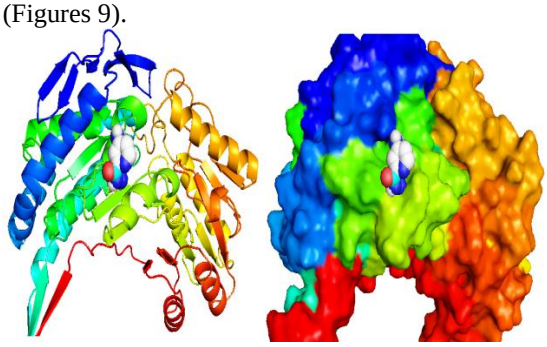


Figure 2 Interaction of compound 2 for 3ty7-Staphylococcus Three-dimensional map of the Aureus receptor

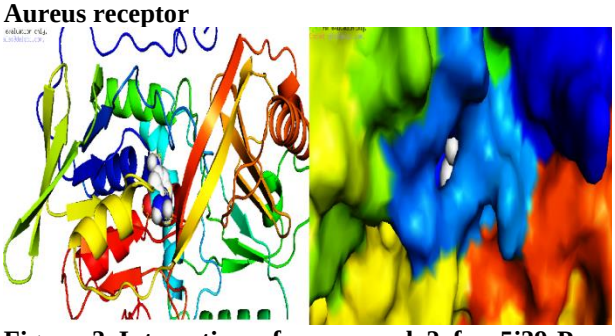


Figure 3 Interaction of compound 2 for 5i39-P. aeruginosa In a three-dimensional diagram, the receptor is shown

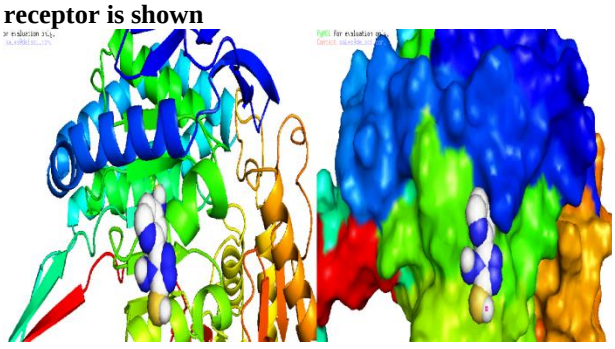


Figure 4 Interaction of compound 3 with 3ty7-Staphylococcus Aureusreceptor in three dimensional plot

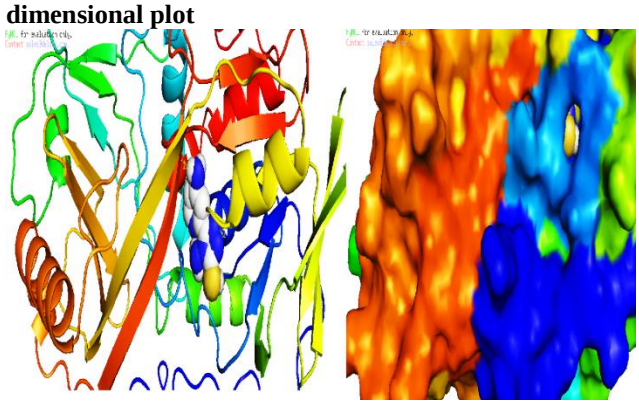


Figure 5 Interaction of compound 3 for 5i39-P. aeruginosa In a three-dimensional diagram, the receptor is shown

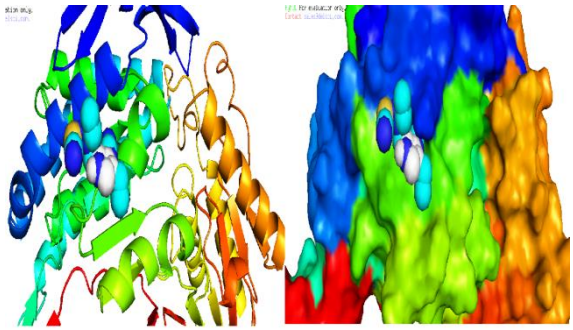


Figure 6 Interaction of compound 4a with 3ty7-Staphylococcus Aureusreceptor in three dimensional plot

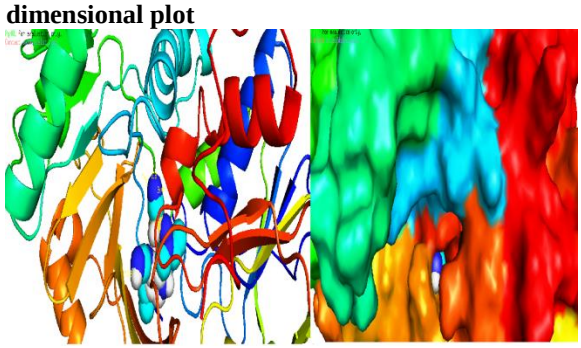


Figure 7 Interaction of compound 4a with 5i39-P. aeruginosa In a three-dimensional diagram, the receptor is shown

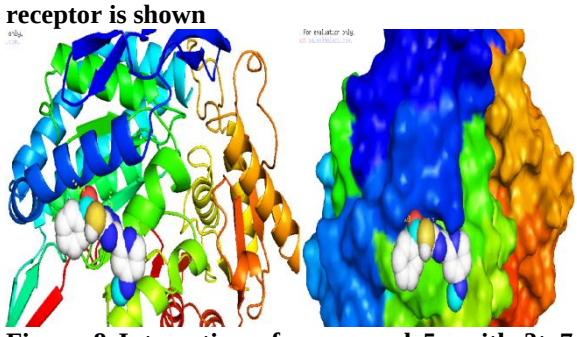


Figure 8 Interaction of compound 5a with 3ty7-Staphylococcus aureus receptor in three dimensional graph

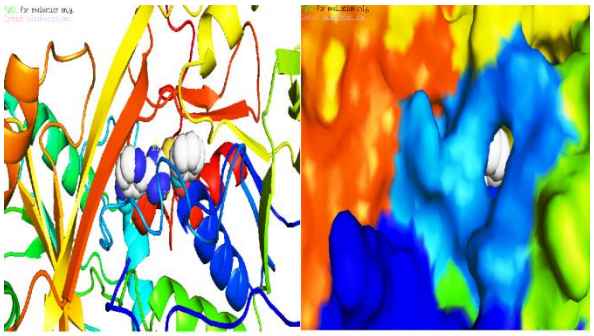


Figure 9 Interaction of compound 5a with 5i39-P. aeruginosa receptor in three dimensional plot

4. Conclusions

The structures of novel synthesized compounds were verified by spectroscopic studies of 4-aminopicolinohydrazide derivatives with a 1,2,4-triazole moiety. Furthermore, their antibacterial results indicated strong activity that was comparable to that of a conventional medication.

Acknowledgments

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