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Synthesis, Characterization, Molecular Docking Study And Biological Activity Of Serotonin Derivatives Containing Tetrazole Moiety

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Abstract:

Heterocyclic compounds in which Nitrogen atomes are present have a great importance among pharmaceutical compounds due to their higher activity in medicine. The new tetrazole heterocyclic serotonin derivatives were designed and synthesized through reaction of serotonin Schiff base compounds with sodium azide to form tetrazol compounds II(a-c). whole the end products were identified by physical properties, FT-IR spectroscopy,^{1}H- NMR spectroscopy. The antibacterial activity for each end product was studied by using the manner of well diffusion and the examined products showed effect against two gram-positive (Staphylococcus aureus and Streptococcus pyogenes) and two gram-negative (Klebsiella and Escherichia coli) bacteria which compared to DMSO as control, and good activity compared to trimethoprim as astandard. For knowing that the resulted compounds interacted well with the receptors of bacteria the molecular docking was used.

Key words: Serotonin, Heterocycles, Tetrazol, Boronic acid, Molecular docking

Introduction

As known among the important things take into account when preparing or synthesizing drugs are their harmless and curative value for the human use. Serotonin (5-hydroxytryptamine or 5-HT) is an indole amine that appears naturally and acts as a neurotransmitter which transfer signals from one neuron to another in our bodies [(1)] . The chemistry of indoles was progressively studied due to the interesting effects that they have [(2, 3)]. It was found that indoles compounds have a variety of clinical uses which include anti-inflammatory. [(4)], antibacterial. [(5)], antiviral [(6, 7)], anti- TB. [(8)] and antitumor effects [(9)]. Certainly most of Compounds in which heterocycles are their main structure have great and very important uses in medicinal chemistry. Tetrazoles are heterocyclic compounds composed of five-member Nitrogen-rich structures in which one atom of carbon is linked to four atoms of nitrogen and all are organize as a planate ring [(10, 11)]. The conjugated nitrogen rich structure of tetrazoles gives them both acceptor and donor electronic properties [12]. Because of their interesting structures and good pharmacokinetics compounds of tetrazole and correspondent compounds regarded as crucial pharmacophores in medicinal chemistry. The main pharmacological uses include anti-allergic, antihypertensive, anti-ulcer, anti-analgesic, anticancer, antimicrobial and anti leishmanial activity [13,14,15,16,17)]. They also have synthetic uses which include a precursor for the synthesis of active explosives, propellants and pharmaceuticals [18, 19]. In general it is found that the derivatives of tetrazole are used as carboxylic surrogates, bioisosteres of carboxylic acids [20, 21] and lipophilic spacers in pharmaceuticals.The derivatives of tetrazole which have antimicrobial effect also found to have anti nociceptive effect [22]. Boronic acids are one of the most studied boron compounds in the organic chemistry [23].In general boronic acids have alkyl groups are less acidity than boronic acids have aryl groups [24, 25, 26]. The main biological uses of boronic acids are building blocks and as a sensor for many organic materials [27, 28] It also used in electrophoresis techniques ([29] In medicinal chemistry boronic acids have anticancer -activity [30], anti-bacterial activity [31] and anti-viral activity [32]. Molecular docking is a manner of drug design that depends on the structure of drug. It promotes the molecular interaction and forecast the mode of binding and affinity between ligands and receptors. [33]. There are different types of operations of molecular docking,the differentiation are resulted from the ligand and target molecules which are either flexible or rigid , these types include flexible ligand docking in which the molecules of the target are rigid, rigid body docking in which molecules of target and ligand are rigid and flexible docking that deal with flexible molecules of the ligand and target [34, 35]. The main uses of molecular docking include Lead optimization [36] Hit identifications [37] and drug-DNA interaction.[34]. In this our current research, we designed, synthesized, and evaluated in vitro the antimicrobial activity of new Serotonin Derivatives containing tetrazole Moiety

Materials and Methods:

Chemicals and Instrumentation

Serotonin HCL and boronic acid aldehydes were gained from Zhejiang Medicine Co.Ltd., Xinchang pharmaceutical Factory (China),other chemicals were gained from Merck(Germany),Fluka (Germany) ,Alfa (Germany), BDH (UK) chemicals companies. The main instruments used for characterizing the synthesized products were Stuart (SMP30) apparatus for recording the melting point , 6100 Type A Simadzu spectrometer in KBr discs for recording the FT-IR spectrum, Bruker (Varian) 500 MHz instrument in DMSO-D6 as a solvent and TMS as internal standard for characterizing ^{1}H-NMR spectrum.

Methods:

The public method for the synthesis of derivatives of schiff base I (a-c):

The synthesis of Schiff base derivatives was started by adding a solution of serotonin hydrochloride (1.0634gm, 0.005mol) in (30ml) of absolute ethanol little by little to a solution of aldehyde derivatives (4-dimethylamino benzaldehyde, 4-chlorobenzaldehyde, and 2-formyl-4- methoxyphenyl boronic acid) in (20ml) of absolute ethanol. As a catalyst (7) drops of glacial acetic acid was added and the mixture then refluxed for (20hrs) at (80℃), cooled and synthesized precipitate was collected by filtration, washed with the cold water and finally recrystallized from ethanol.

3-(2-((4-(dimethylamino) benzylidene) amino) ethyl)-1H-indol-5-ol (Ia):

(Orange)(70%yield);mp200-204℃;IR(KBr) ν (cm^{-1}):3221.23(OH stretching of indole), 3259.81 (NH stretching of indole),1651.12(C=N stretching of Schiff base),2829.67(C-H stretching of CH_3);^{1}H-NMR (DMSO-d_6,500 MHz):δ 8.67(S,1H,H-C=N of Schiff base),δ 10.58(S,1H,O-H of indole),δ 10.65(S,1H,N-H of indole),δ 3.02(S,6H,CH_3 of $N(CH_3)_2$ group,δ 7.05-7.67 (complex, 7H,C-H of aromatic ring).

3-(2-((4-chlorobenzylidene) amino) ethyl)-1H-indol-5-ol (Ib):

(Off white)(75%);mp 254℃;IR(KBr) ν(cm^{-1}):3217.37(OH stretching of indole);3435.34(NH stretching of indole);1626.05(C=N stretching of Schiff base);^{1}H-NMR(DMSO-d_6,500MHz):δ8.82(S,1H,H-C=N of Schiff base),δ9.70(S,1H,O-H of indole),δ10.54(S,1H,N-H of indole),δ6.64-7.55(complex,7H,C-H of aromatic ring).

(2-(((2-(5-hydroxy-1H-indol-3-yl) ethyl)imino)methyl)-4-methoxyphenyl)boronic acid (Ic):

(Dark green)(80%);mp 220-223℃;IR(KBr) ν (cm^{-1}):3369.75(OH stretching of indole); 1365.65 (B-O stretching of boronic acid);3429.55(NH stretching of indole);1606.76(C=N stretching of Schiff base);^{1}H-NMR(DMSO-d_6,500MHz):δ8.35(S,1H,H-C=N of Schiff base),δ7.94(S,2H,O-H of boronic acid),δ10.26(S,1H,O-H of indole),δ6.64-7.40(complex,6H,C-H of aromatic ring), δ3.83(S,3H,CH_3 OF (OCH_3) group).

5-Substituted-1H-tetrazoles as carboxylic acid isosteres: medicinal chemistry and synthetic methods II (a-c):

Tetrazol compounds were synthesized by adding (0.002) M (0.13004)g of sodium azide dissolved in (10ml) of absolute ethanol to (0.002)M of synthesized Schiff base I(a-c) dissolved in (10ml) of absolute ethanol. The mixture was then refluxed for (30) hours at 80 ℃ after that the solvent was removed and resulting product washed with cold distilled water and re-crystallized with ethanol.

3-(2-(5-(4-(dimethylamino) phenyl)-2,5-dihydro-1H-tetrazol-1-yl)ethyl)-1H-indol-5-ol (IIa):

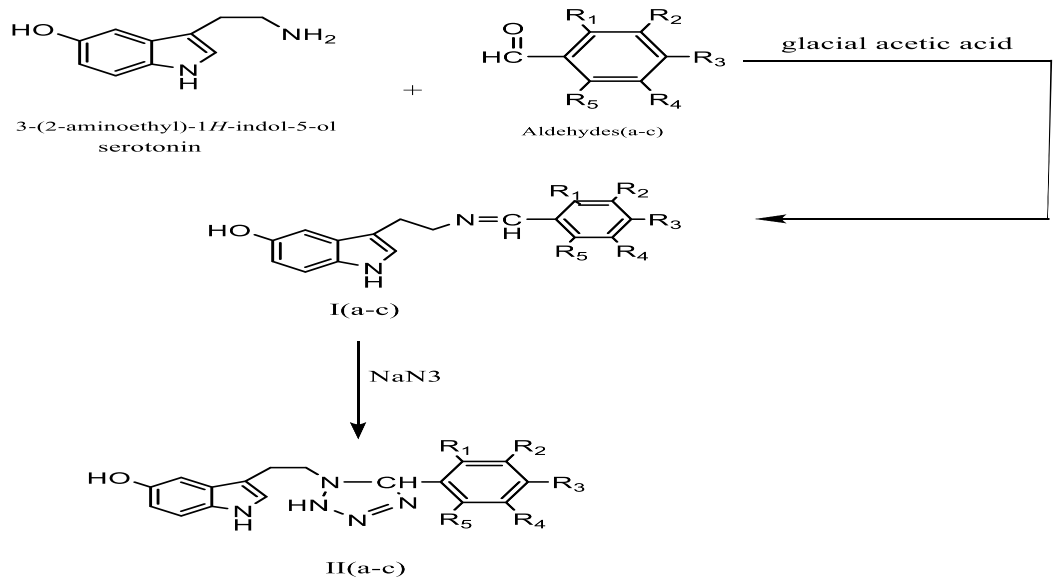
(Yellowish green)(76%);mp 211℃;IR(KBr) ν (cm^{-1}):3209.66(OH stretching of indole);3263.66 (NH stretching of tetrazol and indole rings);1068.6(N-N stretching of tetrazol);1464.02(N=N stretching of tetrazol);2949.26(C-H stretching of CH_3);3136.36(C-H stretching of aromatic);^{1}H-NMR (DMSO-d_6,500 MHZ):δ 6.60(S,1H,N-H of tetrazol ring),δ 8.31(S,1H,C-H of tetrazol ring),δ 3.07(S,6H,CH_3 of $N(CH_3)_2$ group,δ 6.61-7.88(complex,7H,C-H of aromatic ring),δ10.60(S,1H,O-H of indole ring),δ 10.66(S,1H,N-H of indole ring).

3-(2-(5-(4-chlorophenyl)-2,5-dihydro-1H-tetrazol-1-yl)ethyl)-1H-indol-5-ol (IIb):

(Light brown)(73%);mp 254℃;IR(KBr) ν (cm^{-1}):3259.81(OH stretching of indole ring);3394.83(N-H stretching of tetrazol and indole rings);1089.82(N-N stretching of tetrazol ring);1456.3(N=N stretching of tetrazol ring);3057.27(C-H stretching of aromatic ring);^{1}HNMR(DMSO-d_6,500 MHZ):δ 6.55(S,1H,N-H of tetrazol ring),δ 7.78(S,1H,C-H of tetrazol ring),δ 6.57-7.57(complex,7H,C-H of aromatic ring),δ 10.18(S,1H,O-H of indole ring),δ 10.23(S,1H,N-H of indole ring).

(2-(1-(2-(5-hydroxy-1H-indol-3-yl) ethyl)-2,5-dihydro-1H-tetrazol-5-yl)-4-methoxyphenyl)boronic acid (IIc):

(Dark brown)(70%);mp 270℃;IR(KBr) ν (cm^{-1}):3336.96(OH stretching of indole ring);3379.4(N-H stretching of tetrazol and indole rings);1037.74(N-N stretching of tetrazol ring);1458.23(N=N stretching of tetrazol ring);3082.35(C-H stretching of aromatic);1361.79(B-O stretching of boronic acid);^{1}H-NMR(DMSO-d_6,500 MHz):δ 6.65(S,1H,N-H of tetrazol ring),δ 8.12(S,1H,C-H of tetrazol ring),δ 6.77-7.72(complex,6H,C-H of aromatic ring),δ 9.83(S,1H,O-H of indole ring),δ 9.92(S,1H,N-H of indole ring),δ 8.10(S,2H,O-H of boronic acid),δ 3.73(S,3H,CH_3 of OCH_3 group).



a:R_1=H R$_2$=H R_3=N(CH3)2 R_4=H R_5=H

b:R_1=H R_2=H R_3=Cl R_4=H R_5=H

c:R_1=$B(OH)_2$ R_2=H R_3=H R_4=O-CH_3 R_5=H

Scheme (1): Synthesis of Tetrazole derivatives

Preliminary Antibacterial Studying of the synthesized compounds II(a-c):

The biological activities of synthesized compounds II(a-c) were accomplished in the Department of Clinical Laboratory Science, College of Pharmacy/mustansiriyah University by using well diffusion method. The compounds that we synthesized were investigated in vitro on nutrient agar medium on (Staphylococcus aureus and Streptococcus pyogenes) as gram positive bacteria and (Klebsiella and Escherichia coli) as gram negative bacteria.For antibacterial effect we used Trimethoprim as astandard drug.

Procedures of ADME:

We drew whole of ligands II (a-c) by using Chem draw Sketch (v. 19) ,then these ligands were transformed by software Swiss ADME tool to SMILE name to predict physical,chemical and pharmacokinetic properties. By using BOILED EGG we could determine lipophilicity and polarity of the small molecules.

Molecular docking studies:

The molecular docking was studied by using Glide™, (version 5.7, Schrödinger, LLC, New York, NY,2011.The compounds which have most activity were docked on the active sites of Staphylococcus aureus, Streptococcus pyogenes, Klebsiella and Escherichia coli bacteria that emanate from crystal structure of the enzymes convoluted with anti-bacterial drugs, Trimethoprim in which PDB ID were 3G7E,4HL2,2W9S,2XCT and 4RKX.The molecules of water and the hetero atoms were removed from enzymes behind 5Å radius of reference ligand (Trimethoprim) aftetr that the resulted structures of proteines were refined and minimized by Protein Preparation Wizard™ using the OPLS-2005 force field.We used the program of Receptor Grid Generation to contrive the grid of Staphylococcus aureus, Streptococcus pyogenes, Klebsiella and Escherichia coli also the ligands were optimized by LigPrep™ using the OPLS-2005 force field to produce the state with the lowest energy of the respective ligands. On bioactive compounds the stimulations of docking were achieved on compounds that were biologically active to produce 5 poses for each ligand and the pose that had the highest score was showed for each compound.

RESULTS AND DISCUSSION

Results of antibacterial studying:

For antibacterial studying of the synthesized compounds II (a-c) we used Trimethoprim as a reference drug and DMSO in pure state as a control. The antibacterial activities of these synthesized compounds were investigated on (Staphylococcus aureus and Streptococcus pyogenes) as gram positive bacteria and on (Klebsiella and Escherichia coli) as gram negative bacteria at four concentrations (62.5,125, 250 and 500 µg/mL).The tested compounds inhibition zone for each concentration were listed in the table(1).As shown in this table, the strongest activity was against Streptococcus pyogenes bacteria and the weakest activity appeared against Escherichia coli bacteria with interesting activity on Staphylococcus aureus and Klebsiella bacteria. The resulting activities of the synthesized compound against bacteria are considered acceptable in comparison with Trimethoprim drug.

Table (1): Antibacterial activity of compounds II(a-c) and Trimethoprim against tested bacteria

compounds	**Concentration (µg/ml)**	**Inhibition zone(mm)**			
		Gram positive		**Gram negative**	
		Staphylococcus Aureus	**Streptococcus Pyougenes**	**Klebsiella Pneumoniae**	**E.coli**
Trimethopr	5	25	25	20	13

im					
DMSO	Pure	0	0	0	0
IIa	500	10	12	10	12
	250	10	12	14	10
	125	8	15	12	10
	62.5	8	10	10	0
IIb	500	15	20	14	0
	250	10	18	10	10
	125	0	14	10	0
	62.5	8	16	15	0
IIc	500	12	18	15	8
	250	10	18	14	8
	125	8	16	12	8
	62.5	0	10	15	0

Interpretation of ADME results:

All the final compounds II(a-c) were calculated for their drug-like properties following the Lipinski's rule of five[38],which also called Pfizer's rule of five (RO5) .This rule was used broadly as a crude filter for compounds that will be more used as a lead for programs of drug design. In general Lipinski's Rule of Five states determined that the drug to be orally active must has the following:

*Hydrogen bond donors must be equal to or not more than 5 (NH and OH groups)

* Hydrogen bond acceptors must be equal to or not more than 10 (notably N and O)

* A molecular weight must be equal to or under 500 g/ mol

* A partition coefficient (log P) must be equal to or less than 5

Also the topological polar surface area (TPSA) was calculated which is considered a very important property related to the molecules' bioavailability. The absorbed compounds with a TPSA value more than 140 A° are thought to have low bioavailability[39].In the table(2) which include the main data obtained from the ADME tool we noted that all the ligands of the final compounds II(a-c) were within the accepted values range. The compounds II (a-c) have TPSA values (79.25,76.01,125.70) respectively below 140 A° and bioavailability 0.55 which mean all of them can reach the systemic circulation, also they have no violation from the Lipinski's rule of five (RO5) and fulfilled the topological descriptors and fingerprints of molecular drug-likeness structure keys as Log P and Log S. GI absorption score can be defined as the volume of the extent of absorption of the compounds from the intestine after they taken orally. When the results are high the absorption takes place. All the final products have high absorption according to the table (2) therefor they expecting to have a satisfying Intestinal absorption.

Table (2): The resulted data from ADME tool for the final compounds

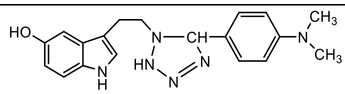
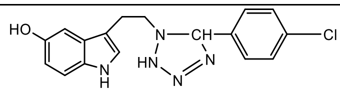
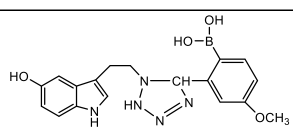
Compounds	H-bond acceptor	H-bond donor	Molar refractivity	TPSA (A°)	GI absorption	BBB permeant	Bioavailability	Lipinski violation
IIa	4	3	116.52	79.25	High	NO	0.55	0 violation
IIb	4	3	107.32	76.01	High	Yes	0.55	0 violation
IIc	7	5	118.63	125.70	High	NO	0.55	0 violation

Interpretation of docking results:

On active site of each receptor of (Staphylococcus aureus and Streptococcus pyougenes) as gram positive bacteria and (Klebsiella and Escherichia coli) as gram negative bacteria the resulted compounds was docked. Their binding affinity and orientation with amino acid residues were explored in virtual screening. The results of virtual screening and scores of binding affinity of all compounds were within the range of (-7.274to-8.27) kcal/mol on Staphylococcus aureus,(-5.154 to -6.892) kcal/mol on Streptococcus pyougenes,(-4.845to-6.753)kcal/mol on Klebsiella and(-5.148to-7.054)kcal/mol on Escherichia coli.From the table(3) and table(4) which includes the docking scores ,orientations and interactions between synthesized compounds and amino acids residues of the four types of bacteria, the main interactions that seen in these tables are H-bond ,Pi-Pi stacking ,Pi-cation and hydrophobic interactions, these interactions support and gives the compounds good activity against bacteria. The highest binding affinities were (-8.27) kcal/mol on Staphylococcus aureus that was seen with compound (IIc),(-6.892) kcal/mol on Streptococcus pyougenes with compound(IIc),(-6.753) kcal/mol on Klebsiella and (-7.054) kcal/mol on Escherichia coli. These molecular docking results were in acceptable with the experimental results.

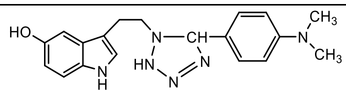
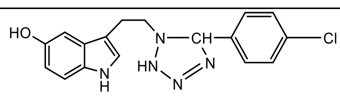
Table (3): The binding scores and main interactions between synthesized compounds and gram positive bacteria

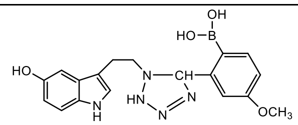
Compounds	Chemical structure	Docking score on Staphylococcus aureus	Type of interaction of ligands of compounds with Staphylococcus aureus	Docking score on Streptococcus	Type of interaction of ligands of compounds with Streptococcus pyougenes

				pyougenes	
IIa		-7.274	H-bond interaction between ASP27 and OH group of indole ring and H-bond interaction between PHE92 and NH group of indole ring as well as hydrophobic interactions which include ALA7,VAL6,ILE5,LEU28, LYS29,ILE31,LYS32,ARG57 LEU54,LEU20,TYR98,THR46 TYR98 and ILE50	-5.154	H-bond interactions between ALA283,SER286,TYR389,SER391and OH group via water(H_2O) molecule as well as hydrophobic interactions which include SER279, SER280, GLY281 SER282,GLY284,GLN304,GLY339,HIE340,ALA341,GLN332,GLY333,VAL334,CYS192 and VAL193
IIb		-7.265	H-bond interactions between LEU28ARG57 and OH group of indole ring Halogen bond between Cl and water(H_2O) molecule as well as hydrophobic interactions which include ASP27, ILE31 ,LYS32,TYR98,PHE92,THR46,LEU20,ILE50,LYS52, LEU54,PRO55,ILE5,VAL6 and ALA7	-5.335	H-bond interactions between SER280,CYS192 and OH group of indole ring as well as hydrophobic interactions which include VAL334,GLY333,GLN332,GLN162,SER279,GLY281,SER282, ALA283,GLY284,GLY339,HIE340,ALA341GLY191 and VAL193
IIc		-8.27	H-bond between SER49 and OH group of indole ring also H-bond between ARG57 and two OH groups of boronic acid as well as hydrophobic interactions which include ILE50,THR46,PHE92,LEU54,LYS32,ILE31,LEU28,HIS23,LEU20 and GLN19	-6.892	H-bond between TYR389 and OH group of indole ring via water(H_2O) molecule and H-bond between SER282 and one of OH groups of boronic acid also H-bond between GLY339 and the other OH groups of boronic acid as well as hydrophobic interactions which include TYR330,GLN332,GLY333,VAL334,ALA283,GLY281,SER280,

					CYS192,VAL193,HIE340,ALA341

Table (4): The binding scores and main interactions between synthesized compounds and gram negative bacteria

Compounds	Chemical structure	Docking score on Klebsiella	Type of interaction of ligands of compounds with Klebsiella	Docking score on Escherichia coli	Type of interaction of ligands of compounds with Escherichia coli
IIa		-5.229	Pi-Pi stacking interaction between HIE122 and benzene ring also Pi-Pi stacking interaction between HIS250 and tetrazol ring and Pi-cation interaction between LYS211 and benzene ring as well as hydrophobic interactions which include VAL73,ILE35,SER251,LEU218 SER217,LYS216,ALA215,ASP212 CYS208,TRP93 and HIS189	-5.336	H-bond interaction between ASP73 and one of N=N group via water(H2O) molecule and H-bond interactions between ARG76,PHE104 and OH group of indole ring also Pi-cation interaction between ARG76 and tetrazol ring as well as hydrophobic interactions which include VAL120,VAL44,ASN46,ARG136,VAL71,VAL111,ASP105,LYS103,GLY102,ILE94VAL167 and THR165
IIb		-4.845	Pi-Pi stacking interaction between TRP93 and pyrrole ring as well as hydrophobic interactions which include HIS250,CYS208,LYS211,HIS189 HIE122,LEU65,MET67,P	-5.148	H-bond interaction between ASP73 and one of N=N group via water(H2O) molecule as well as hydrophobic interactions which include LEU132,VAL120,VAL167,THR165, ARG76,ILE94,ASP105,PHE104, LYS103,GLY102,HIS116 and

			HE70 VAL73 and ILE35		ASN46
IIc		-6.753	Pi-Pi stacking interaction between TRP93 and benzene ring as well as hydrophobic interactions which include SER217,LYS211, CYS208,LYS125,HIE122, HIS120,HIS250,ILE35,LE U65 MET67,VAL73,HIS189	-7.054	H-bond interaction between ASN46 and one of OH groups of boronic acid and H-bond interaction between ASP73 and another OH group of boronic acid via water (H_2O) molecule also H-bond interaction between PHE104 and NH group of pyrol ring and Pi-cation interaction between ARG76 and pyrol ring as well as hydrophobic interactions which include ILE94,ALA47,THR165,ARG136 ,ASP105,LYS103,GLY102,GLY1 01,LEU52,HIS116 and VAL111

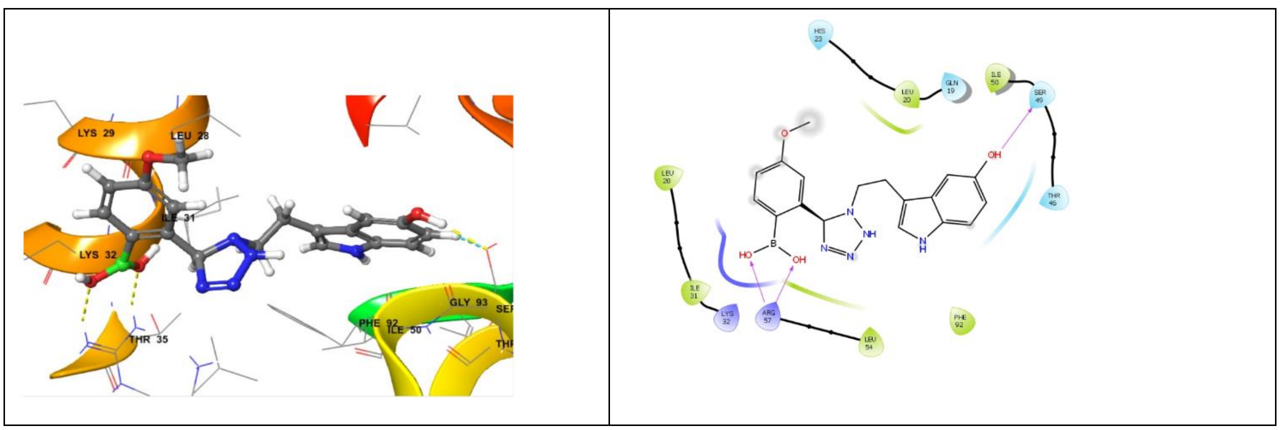


Figure (3): Compound IIc inside Staphylococcus aureus active site

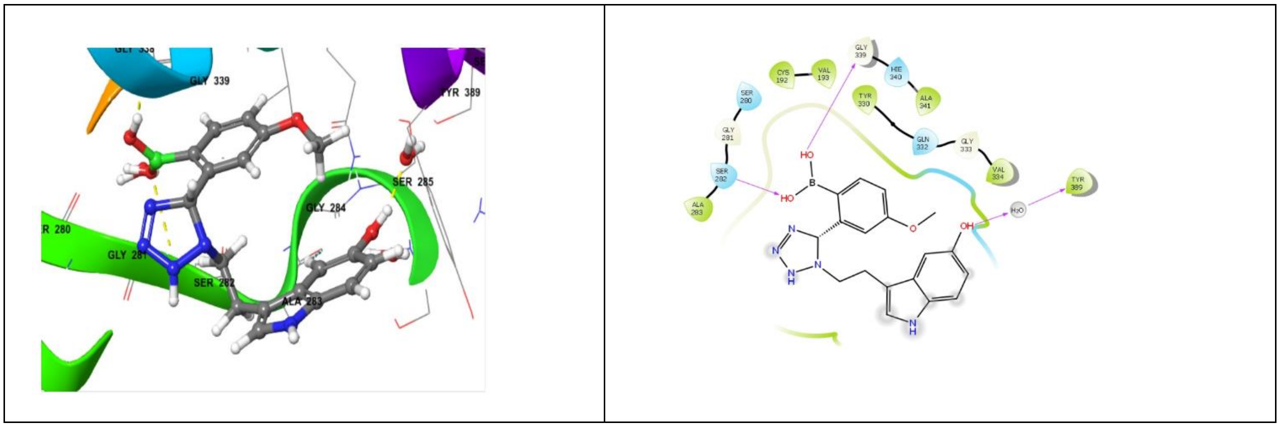


Figure (4): Compound IIc inside StreptococcusPyougenes active sites

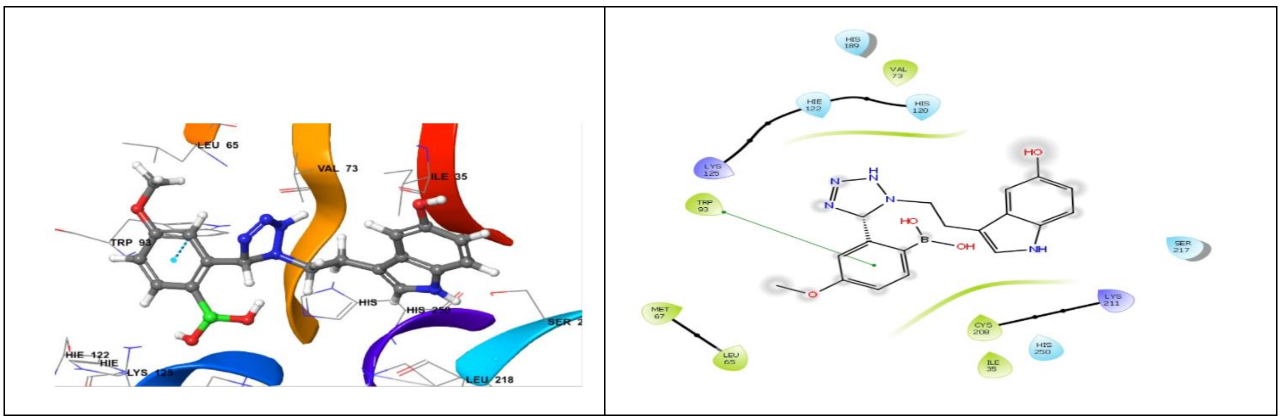


Figure (5): Compound IIc inside Klebsiella active sites

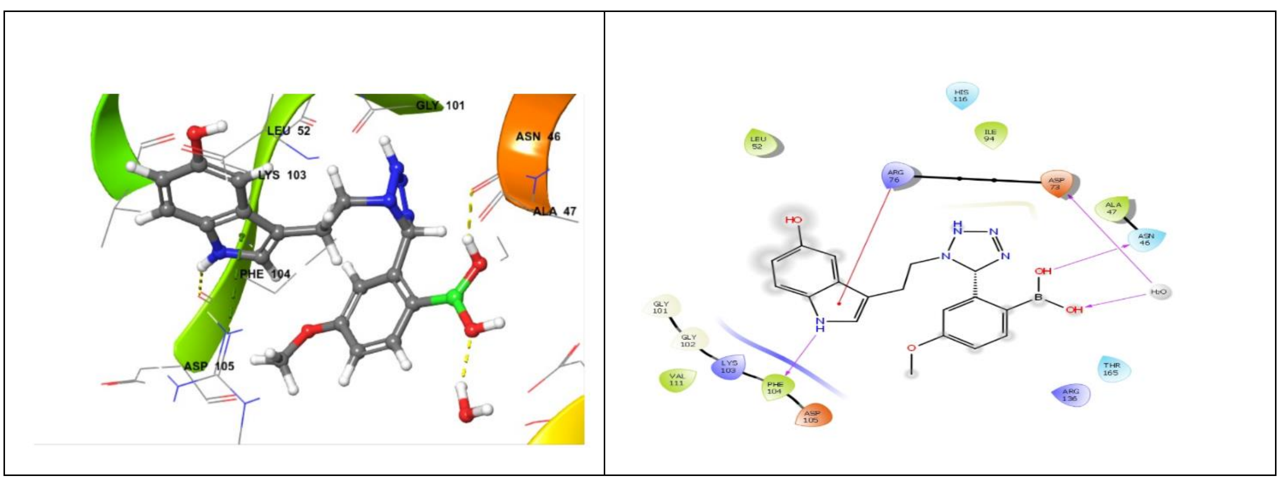


Figure (6): Compound IIc inside Escherichia coli active sites

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