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Research Article

Novel 1, 3, 4-Oxadiazole-pyridine hybrids as potential DNA gyrase B inhibitors (5D7R): ADMET prediction and molecular docking study

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Abstract

A small molecule (ligand) is placed in the binding site of its macromolecular target (receptor) using a computational process called molecular docking, which also calculates the binding affinity of the small molecule. With the use of PyRx software, the current study tried a high-throughput in-silico screening of 16 compounds docked with the crystal structure of DNA gyrase B receptors (PDB ID: 5D7R). In the range of -8.0 and -8.1, 3 of these 16 compounds displayed very good mol dock scores. As a typical medicine, amoxicillin medications have a mol dock score of -7.1. According to the results, all of the investigated ligands occupy similar positions and directions within the putative binding site of DNA gyrase B receptors (PDB ID: 5D7R), which reveals a sizable area surrounded by a membrane binding domain that acts as a pathway for substrate entry into the active site. Additionally, any small molecule's affinity can be viewed as a special instrument in the field of drug design and provide a possibility for future study to create an antibacterial activity. Additionally, ADME evaluations must be used to confirm compounds that are candidates for oral administration. The findings demonstrated that compound 4a, 4b, 4c, 4d, 4i, 4j, and 4k absorbed from GIT and compound 4i, 4j, and 4k fulfilled the Lipinski rule.

Keywords: 1, 3, 4-Oxadiazole, ADME Evaluation, molecular docking, antimicrobial activity

INTRODUCTION:

Traditional methods for finding innovative therapeutic medicines were very expensive, time-consuming, and possibly less effective. Virtual screening, supported by the presentation of structural information, is a rational and straightforward strategy that is introduced to solve the shortcomings of existing strategies. Virtual screening techniques are frequently categorised as structure- and ligand-based drug design methodologies. While ligand-based tactics address quantitative structure activity relationship (QSAR) and pharmacophore modelling, the structure-based drug approach discusses molecular tying up [1]. The molecular docking method determines how a chemical interacts with a target molecule. By identifying the preferred orientation of the least free energy, it predicts the affinity of molecules for binding to form a stable complex with the supermolecule [2]. For the most part, Shape Complementarity and Simulation are the two fundamental techniques used in molecular docking.

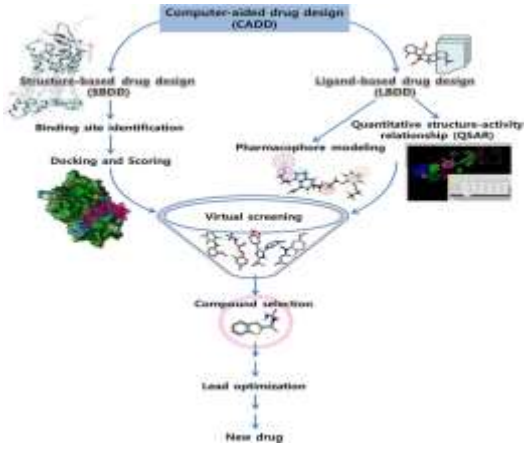

Figure 1 Computer-aided drug design

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1,3,4-Oxadiazole is a 5-membered planar aromatic group represents affluent heterocyclic group and its derivatives have played a major role in the pharmaceutical chemistry. 1,3,4-Oxadiazole derivatives are the heterocyclic that have received considerable attention during the last two decades as they possess wide range of biological properties include antibacterial[3], antituberculosis[4], anti-inflammatory[5], antifungal[6], analgesic[7], anticancer[8], immunosuppressive[9], anticonvulsant[10], and tyrosinase inhibitor.[11]

MATERIALS AND METHODS:

Software required:

The study of molecular docking was conducted on a computer equipped with the computational tools swiss dock, PyRx, and Biovia discovery studio visualizer tools (HP Pavilion AMD RyzenTM 5 Hexa Core 5500 APU @ 2.1GHz with turbo boost up to 4GHz Processor version 5500U and 16.00 GB RAM with 64-bit Windows-11 operating system).

Ligand and macromolecule preparation:

The chemical structures of the ligands utilised in this work were created and optimised using the free Chemsketch 2021 programme, and they were stored in mol format before being translated to PDB format by Open Bable 2.3.2, which was necessary for PyRx software execution. Before beginning the molecular docking procedure, the target enzyme was prepped by removing the natural ligand and water molecules that were linked to it. After that, the investigation ligand was loaded with hydrogen atoms added, their torsions and rotatable bonds were assigned, and the files were saved as ligand pdbqt.

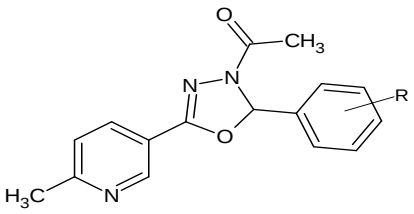


Figure. No: 2

R-			
-H	2-OCH3	3-Cl	4-NO2
2-CH3	3-OCH3	4-Cl	2-OH
3-CH3	4-OCH3	2-NO2	3-OH
4-CH3	2-Cl	3-NO2	4-OH

Ligand Identification:

The ligands were 1,3,4-oxadiazole derivatives (Table-2). Azithromycin, ciprofloxacin, and amoxicillin are some of the contemporary antibacterial medications. They were obtained from the drug bank database and used in comparison and docking investigations (Table-1). The Open Babel application was used to download the known structures in SDF format and convert them to PDB format. The next step was to conduct docking research using PyRx and the Biovia Discovery Studio visualizer tools.

In silico ADME (Absorption, Distribution, Metabolism and Excretion Studies):

ADME describes the pharmacokinetics of substances in an organism's body. It assesses the danger associated with administering a pharmaceutical substance to an individual or another creature. Pre ADMET (https://preadmet.bmdrc.kr/), Swiss ADME (http://www.swissadme.ch/), and other online tools are used to identify these pharmacokinetic features in silico. The molecules become inactive when there are two or more violations of Lipinski's rule of five. To assess whether a molecule is similar to existing drugs on the market, a complex balancing act involving several chemical properties and structural traits must be performed.

In this way, the 16 different conformers were generated (Figure-2) and blind docking was performed to know whether these molecules bind in the active site or anywhere in the target was demonstrated by the biovia discovery studio program.

Table-1 Showing Structure and Standard of known drug.

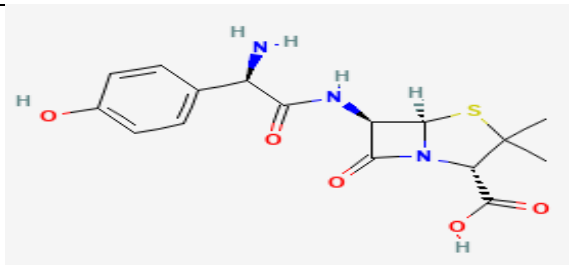
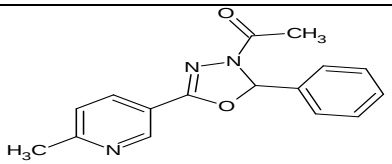
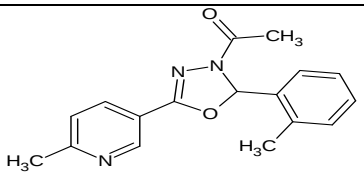
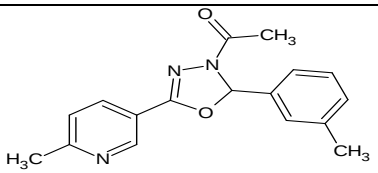
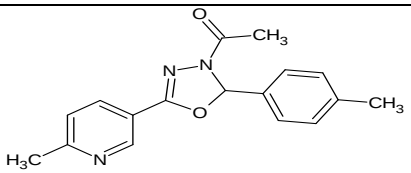
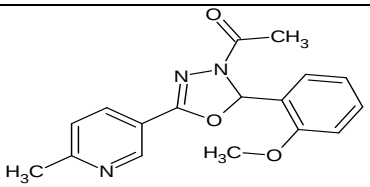
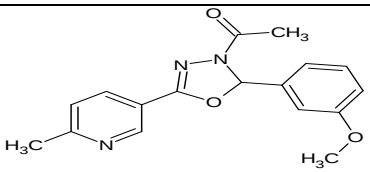
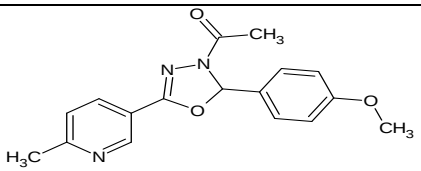
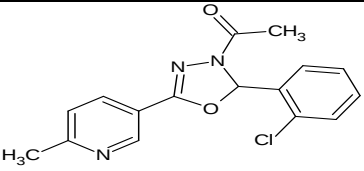
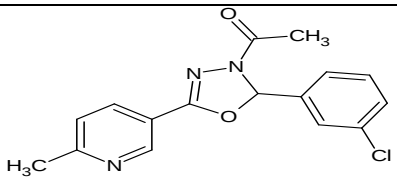
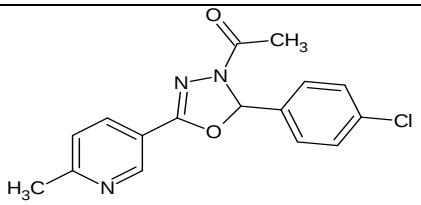
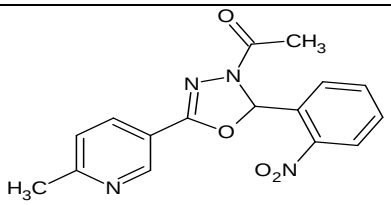
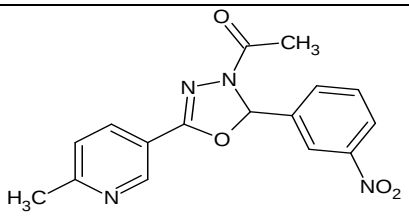
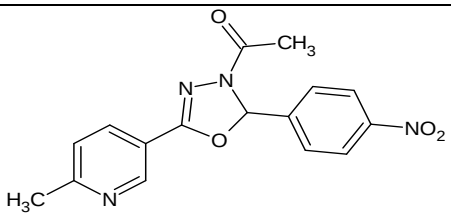
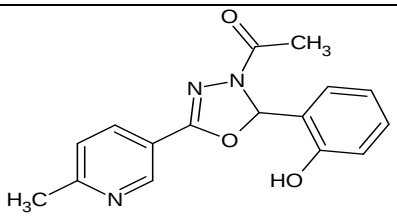
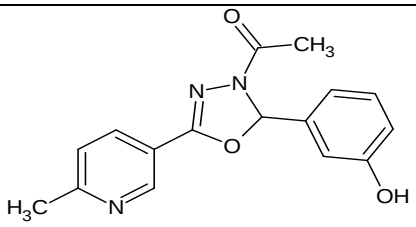
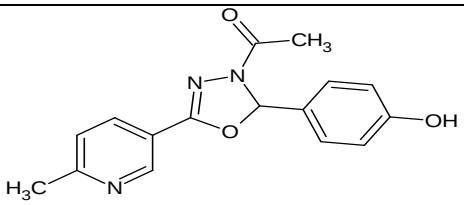
Sl.No.	Ligand	PubChem CID	Structures
1	amoxicillin	33613	

Table-2 Showing structures of 1,3,4-oxadiazole derivatives used as ligands. (4a-4p)

Ligand code	IUPAC /Ligand name	Structures
4a	1-[5-(6-methylpyridin-3-yl)-2-phenyl-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	
4b	1-[2-(2-methylphenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	
4c	1-[2-(3-methylphenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	
4d	1-[2-(4-methylphenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	
4e	1-[2-(2-methoxyphenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	
4f	1-[2-(3-methoxyphenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	
4g	1-[2-(4-methoxyphenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	
4h	1-[2-(2-chlorophenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	
4i	1-[2-(3-chlorophenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	
4j	1-[2-(4-chlorophenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	

4k	1-[5-(6-methylpyridin-3-yl)-2-(2-nitrophenyl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	
4l	1-[5-(6-methylpyridin-3-yl)-2-(3-nitrophenyl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	
4m	1-[5-(6-methylpyridin-3-yl)-2-(4-nitrophenyl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	
4n	1-[2-(2-hydroxyphenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	
4o	1-[2-(3-hydroxyphenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	
4p	1-[2-(4-hydroxyphenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one	

RESULTS AND DISCUSSION:

Absorption, distribution, metabolism and excretion (ADME results:

We can say that the molecules are orally active because all the created compounds adhere to the same rule. Tables 3 and 4 present the findings of ADME investigations. The octanol water partition coefficient (mol log P) of the proposed compounds must not be larger than 5. The compounds' good oral bioavailability is indicated (Table 3). The logarithm of molar concentration is used to represent the water solubility. The usual range for the skin permeability of designed compounds is between -5.50 to -6.07 cm/s. The suggested compounds are only moderately water-soluble because they have lipophilic functionalities intended to increase cell permeability. Using a volume of distribution, blood-brain barrier permeability, and fraction unbound, the drug's distribution in the body was estimated. A higher value for the volume of distributions denotes a better drug distribution in tissues compared to plasma, and a log volume of distributions value greater than 0.40 denotes a greater tissue distribution.

Table-3: Drug likeness analysis of designed 1,3,4-Oxadiazole derivatives (4a-4p)

Comp Code	Physicochemical Properties						Lipinski Rule	%Abs[d]	MR	N rot[f]
	R	MW[a]	TPSA[b]	milogP[c]	H_A	H_D				
4a	H	281.31	54.79	2.37	4	0	Yes	90.09	86.07	3
4b	2-CH_3	295.34	54.79	2.62	4	0	Yes	90.09	91.04	3
4c	3-CH_3	295.34	54.79	2.62	4	0	Yes	90.09	91.04	3
4d	4-CH_3	295.34	54.79	2.62	4	0	Yes	90.09	91.04	3
4e	2-OCH_3	311.34	64.02	2.07	5	0	Yes	86.91	92.56	4
4f	3-OCH_3	311.34	64.02	2.07	5	0	Yes	86.91	92.56	4
4g	4-OCH_3	311.34	64.02	2.07	5	0	Yes	86.91	92.56	4
4h	2-Cl	315.75	54.79	2.89	4	0	Yes	90.09	91.08	3
4i	3-Cl	315.75	54.79	2.89	4	0	Yes	90.09	91.08	3
4j	4-Cl	315.75	54.79	2.89	4	0	Yes	90.09	91.08	3
4k	2-NO_2	326.31	100.61	2.26	6	0	Yes	74.28	94.89	4
4l	3-NO_2	326.31	100.61	2.26	6	0	Yes	74.28	94.89	4
4m	4-NO_2	326.31	100.61	2.26	6	0	Yes	74.28	94.89	4
4n	2-OH	352.42	75.02	1.83	5	1	Yes	83.11	88.09	3
4o	3-OH	352.42	75.02	1.83	5	1	Yes	83.11	88.09	3
4p	4-OH	297.31	75.02	1.83	5	1	Yes	83.11	88.09	3

[a]**MW:** molecular weight, [b]**TPSA:** total polar surface area, [c]**miLogP:** molinspiration partition coefficient, [d]**%Abs:** %Abs = 109 − (0.345 × TPSA), [e]**nviol:** number of violations,[f]**nrotb:** number of rotatable bonds, **H_A:** number of hydrogen bond acceptors, **H_D:** number of hydrogen bond donors.

Table-4: *In silico* ADME properties of 1,3,4-Oxadiazole designed derivatives. (4a-4p)

Comp.Code	R	Intestinal absorption (%absorbed)	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log K_p (skin permeation) (cm/s)
4a	-H	High	No	Yes	Yes	No	No	-6.40
4b	2-CH_3	High	No	Yes	Yes	No	No	-6.23
4c	3-CH_3	High	No	Yes	Yes	No	No	-6.23
4d	4-CH_3	High	No	Yes	Yes	No	No	-6.23
4e	2-OCH_3	High	No	Yes	Yes	No	No	-6.61
4f	3-OCH_3	High	No	Yes	Yes	No	No	-6.61
4g	4-OCH_3	High	No	Yes	Yes	No	No	-6.61
4h	2-Cl	High	No	Yes	Yes	No	No	-6.17
4i	3-Cl	High	No	Yes	Yes	No	No	-6.17
4j	4-Cl	High	No	Yes	Yes	No	No	-6.17
4k	2-NO_2	Low	No	Yes	Yes	No	No	-6.80
4l	3-NO_2	Low	No	Yes	Yes	No	No	-6.80
4m	4-NO_2	Low	No	Yes	Yes	No	No	-6.80
4n	2-OH	High	No	No	No	No	No	-6.75
4o	3-OH	High	No	No	No	No	No	-6.75
4p	4-OH	High	No	No	No	No	No	-6.75

Molecular docking results:

The target antibacterial drug discovery In-silico docking study of 16 compounds gave us an idea about the derivatives responsible for anti-microbial activity. The obtained results indicated that all studied ligands have similar positions and orientation inside the putative binding site of crystal structure DNA gyrase B receptors or (PDB ID: 5D7R) which reveals a large space bounded by a membrane-binding domain which serves as an entry channel for substrate to the active site. In addition, the affinity of any small molecule can be considered as a unique tool in the field of drug design. There is a relationship between the affinity of organic molecules and the free energy of binding. This relationship can contribute in the prediction and interpretation of the activity of the organic compounds toward the specific target protein and may be the possible mechanism by which derivatives displayed their anti-microbial activity as on this protein constituent are most appropriately docked.

Based on the docking binding score of the 4m and 4n compounds has resulted in a good binding affinity score of -8.1kcal/mol in comparison to the other derivatives and also it exhibited that activity approx. nearly with the standard drug amoxicillin of -7.11kcal/mol. The same 5D7R protein has interacted with the 4m and 4n compounds in comparison with standard amoxicillin drugs having better therapeutic activity. The various residues of amino acids (e.g., ILE175, ILE51, GLU58, ILE86, SER55, ASP51, PRO87, ARG84, ARG144, GLY85, GLU58,) have interacted with the 4m and 4n scaffolds. The standard amoxicillin has interacted similarly with some of the amino acid residues (ARG84, SER55, GLU58, ILE86, ILE179).

Table-5: Docking score of the designed 1,3,4-Oxadiazole derivatives.

Comp. Code	R	Molecular formula	Molecular weight	Rmsd/ub	Rmsd/lb	Docking Score (kcal/mol)
4a	-H	$C_{12}H_{15}N_3O_2$	281.30	0	0	-7.3
4b	2-CH_3	$C_{17}H_{17}N_3O_2$	295.33	0	0	-7.7
4c	3-CH_3	$C_{17}H_{17}N_3O_2$	295.33	0	0	-7.7
4d	4-CH_3	$C_{17}H_{17}N_3O_2$	295.33	0	0	-7.6
4e	2-OCH_3	$C_{17}H_{17}N_3O_3$	311.33	0	0	-7.6
4f	3-OCH_3	$C_{17}H_{17}N_3O_3$	311.33	0	0	-7.5
4g	4-OCH_3	$C_{17}H_{17}N_3O_3$	311.33	0	0	-7.4
4h	2-Cl	$C_{16}H_{14}ClN_3O_2$	315.75	0	0	-7.7
4i	3-Cl	$C_{16}H_{14}ClN_3O_2$	315.75	0	0	-7.6
4j	4-Cl	$C_{16}H_{14}ClN_3O_2$	315.75	0	0	-7.5
4k	2-NO_2	$C_{16}H_{14}N_4O_4$	326.30	0	0	-7.8
4l	3-NO_2	$C_{16}H_{14}N_4O_4$	326.30	0	0	-8.0
4m	4-NO_2	$C_{16}H_{14}N_4O_4$	326.30	0	0	-8.1
4n	2-OH	$C_{16}H_{15}N_3O_3$	297.30	0	0	-8.1
4o	3-OH	$C_{16}H_{15}N_3O_3$	297.30	0	0	-7.5
4p	4-OH	$C_{16}H_{15}N_3O_3$	297.30	0	0	-7.4
amoxicillin		$C_{16}H_{19}N_3O_5S$	365.4	0	0	-7.1

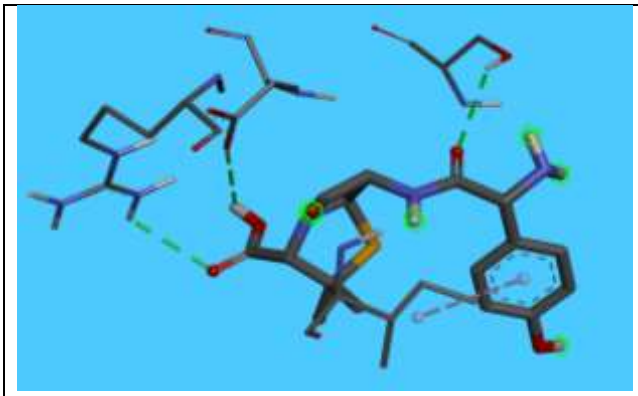


Fig.3: 3D structure of amoxicillin interacts with DNA gyrase B inhibitors (5D7R)

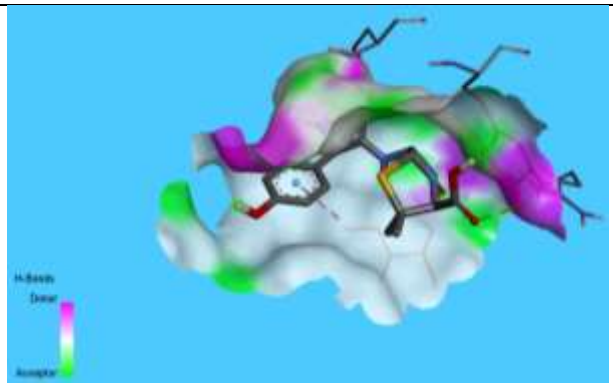


Fig.4: 3D structure of amoxicillin, hydrogen bond interaction with DNA gyrase B inhibitors (5D7R)

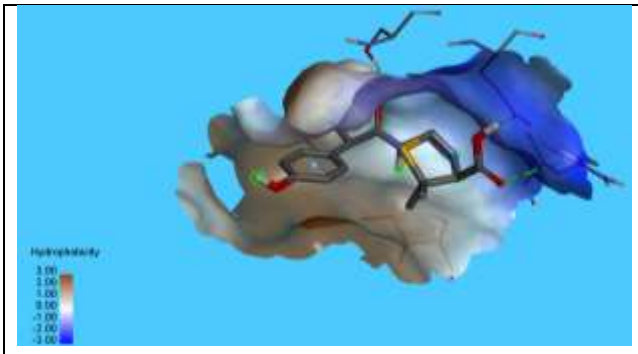


Fig.5: 3D structure of amoxicillin, hydrophobicity interaction with DNA gyrase B inhibitors (5D7R)

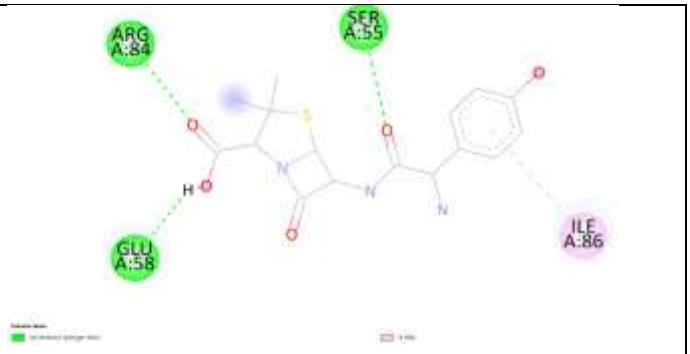


Fig.6: 2D structure of amoxicillin interaction with DNA gyrase B inhibitors (5D7R)

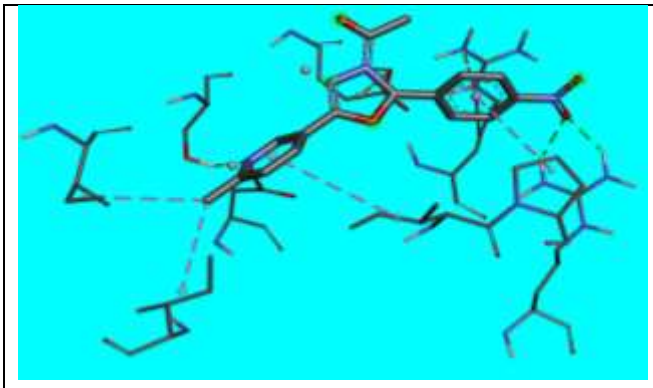


Fig.7: 3D structure of 1-[5-(6-methylpyridin-3-yl)-2-(4-nitrophenyl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one interacts with DNA gyrase B inhibitors (5D7R)

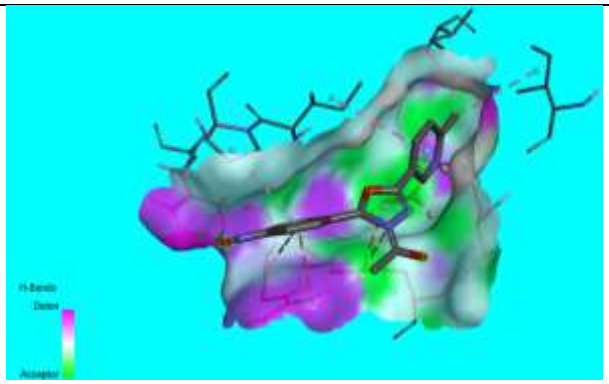


Fig.8: 3D structure of 1-[5-(6-methylpyridin-3-yl)-2-(4-nitrophenyl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one, hydrogen bond interaction with DNA gyrase B inhibitors (5D7R)

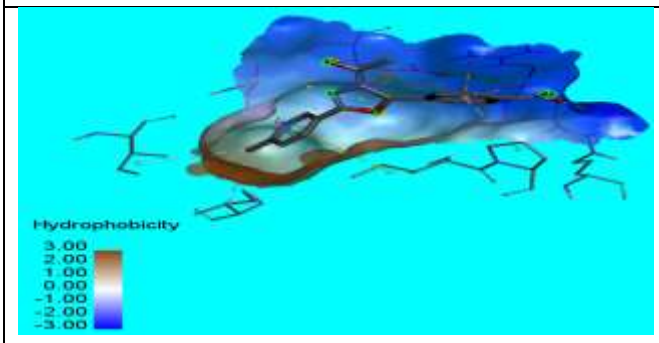


Fig.9: 3D structure of 1-[5-(6-methylpyridin-3-yl)-2-(4-nitrophenyl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one, hydrophobicity interaction with DNA gyrase B inhibitors (5D7R)

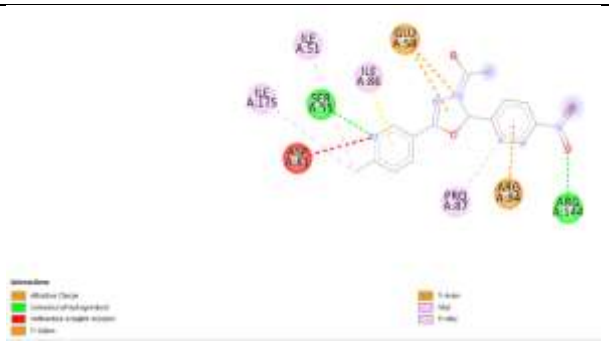


Fig.10: 2D structure of interaction 1-[5-(6-methylpyridin-3-yl)-2-(4-nitrophenyl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one with DNA gyrase B inhibitors (5D7R)

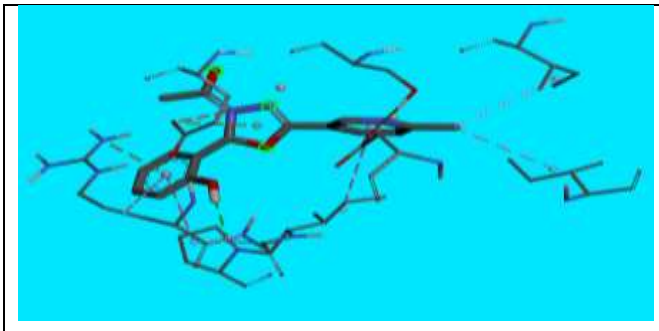


Fig.11: 3D structure of 1-[2-(2-hydroxyphenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one interacts with DNA gyrase B inhibitors (5D7R)

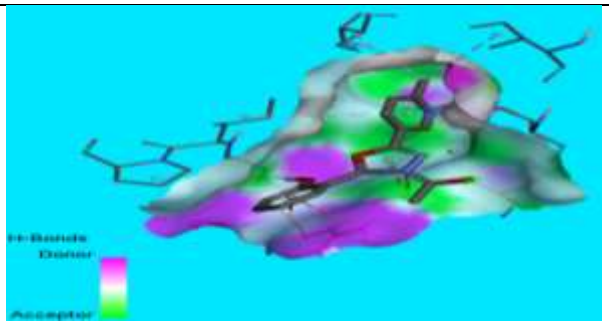


Fig.12: 3D structure of 1-[2-(2-hydroxyphenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one, hydrogen bond interaction with DNA gyrase B inhibitors (5D7R)

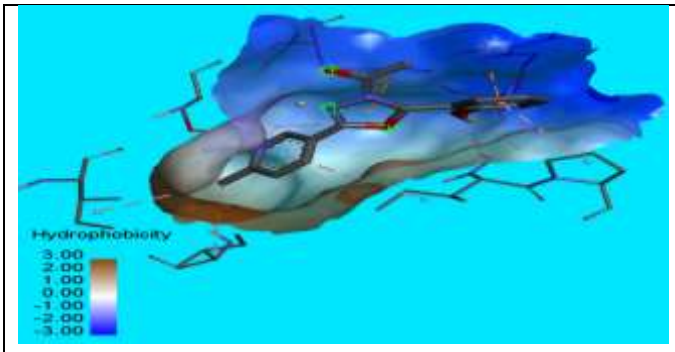


Fig.13: 3D structure of 1-[2-(2-hydroxyphenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2*H*)-yl]ethan-1-one, hydrophobicity interaction with DNA gyrase B inhibitors (5D7R)

Fig.14: 2D structure of 1-[2-(2-hydroxyphenyl)-5-(6-methylpyridin-3-yl)-1,3,4-oxadiazol-3(2H)-yl]ethan-1-one, hydrogen bond interaction with DNA gyrase B inhibitors (5D7R)

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AUTHOR CONTRIBUTION:

Nagaraj N Durgadasheemi and Shivanand N Kolageri both did a proper literature survey, collected data, design the work, and wrote a portion of paper and provided maximum effort in the correction, both did a proper design the manuscript. Shivanand N Kolageri Conceived and design the analysis. The final draft was checked by all the authors.

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