Virtual screening, computational molecular docking, and ADME prediction of some reduced Schiff base containing benzoxazole derivatives as a promising antibacterial agent

Divya Nasare[1], Disha Dhabarde[1], Jagdish Baheti[1], Diksha Meshram[1], Gayatri Sonkusare[1], Prachi Choudhari[1], Trupti Kosarkar[1]

[1]Kamla Nehru College of Pharmacy, Butibori, Nagpur-441108

Corresponding email: dishamandave20@gmail.com

ABSTRACT:

Background:

Benzoxazole has grown significantly in the domain of medicine owing to the large spectrum of pharmacological actions that heterocycles exhibit.One of the greatest problems confronting public health current century is antibiotic resistance thus driving up the need for antimicrobial medication is necessary. As tetrahydrofolate oversees transferring mono-carbon residues to produce nucleotides and amino acids, the Dihydrofolate reductase receptor (DHFR) is a crucial impetus in the metabolism of DNA and amino acids.

Method:

The dihydrofolate reductase receptor (PDB ID: 3SRW and Resolution 1.70Å) was the target of molecular docking investigations for a series of reduced Schiff base derivatives containing benzoxazole.For this,softwares used arePyRx, Pymol, and Discovery studio visualizer. For the pharmacokinetics studies, BOILED Egg visuals, toxicity, and bioactivity were studiedby Swiss ADME, PreADMET, PkCSM, ADMETSAR, and Molinspiration respectively.

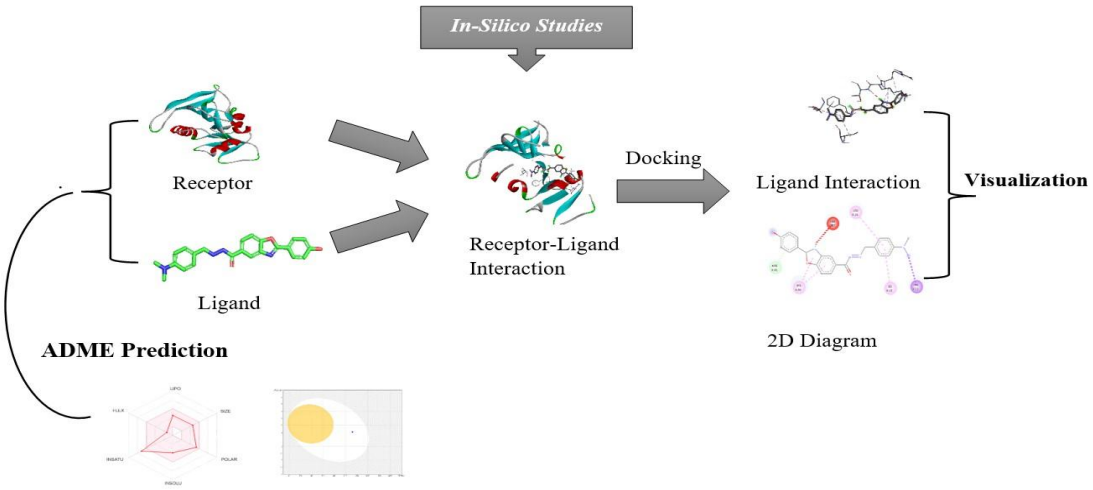
Result:

ReducedSchiff base designedderivatives showeda superior binding affinity between -9.9 to -10.9 kcal/mol whereas referenced drug ciprofloxacin based on broad-spectrum antibioticshowedtightbinding affinity of -7.5kcal/mol and Boxazomycinat -8.8 kcal/mol.THR X:47, GLY X: 95, THR X: 97, ASN X: 19, and LEU X:63 is some of the amino acids that interact at the protein site via conventional hydrogen bonding.The physicochemical parameters showed that each of the recommended compounds had good synthetic effectiveness and do not break Lipinski's rule of five.Furthermore, Boiled egg visuals demonstrated an elevated score of being absorbed by the mammalian Intestinal tract and perhaps reaching the nervous system. Whereas, all designed compound revels applicable toxicology properties and shows moderate bioactivity.

Conclusion:

Inconclusion, all the designed compounds have demonstrated outstanding pharmacokinetic characteristics and good bioavailability characteristics optimized as novel antimicrobial medications.

Graphical Abstract:



Introduction:

Multidrug-resistant microbial infections have become increasingly common over the last few decades, which has created a significant healthcare issue. One issue that is becoming more and more significant is the advent ofgram-positive bacterial infections with multidrug resistance..[1]The necessity for new types of antimicrobial medication still exists in order to avert these major medical issues.[2]Anxiety about infection cases is increased by new research revealing mortality and morbidity rates.[3]Annually, antimicrobial resistance harms around 700,000 people worldwide, and by 2050, it is predicted to be responsible for over 10 million fatalities and an estimated $100 million in economic costs.[4]

A large extended family of both natural and synthesized chemicals shares the basic structure of the benzoxazole scaffold.[2]In the arrangement of nucleic acids, the adenine, and guanine bases are analogous to the benzoxazole ring system, which is regarded as a key ring system for simple interaction, particularly in antibacterial activity.[5]An oxazole ring structure joined to benzene makes up the aromatic heterocyclic molecule known as benzoxazole, with the chemical formula C_7H_5NO. IUPAC The compound -Oxa-3-aza-1H-indene has a melting point between 27 and 30ºC, a molar mass of 119.12 g/mol, a fragrance like a pyridine, and is insoluble in water.[6]

The importance of oxazole-containing heterocyclic compounds in medicine has increased as a result of their wide variety of biological effects.[7]The antibacterial, antifungal, anticancer, antipsychotic,

HIV-1 reverse transcriptase, and novel non-nucleoside DNA polymerase inhibitor characteristics of a huge proportion of benzoxazole derivatives were comprehensively explored.[8]

Virtual screening, in silico pharmacokinetic predictions, and computer-aided structure-based drug development were employed in the current learning as time and money-saving methods for finding novel Dihydrofolate reductase inhibitors with potent antimicrobial activity. [9]This strategy was developed in response to the common usage of the structure-based drug development ininvestigationthrough molecular appreciation.[10-11]

One of the most well-known therapeutic targets is DHFR.[12-13]The methylation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), as well as cell development and replication, depend on DHFR for the proper conservation ofpools of THF and its products within cells. As the only source of THF, DHFR is a liability for cells that proliferate quickly.[14]Antibacterial DHFR inhibitors serve by preventing the production of DNA, RNA, and proteins, hence preventing expansion of cell. [12-15]

Method:

Computational drug design approach:

The custom of computational drug design techniques enabled the design of a new Dihydrofolate reductase inhibitor with improved therapeutic properties that may one day be used as a potential anti-microbialfor the creation of novel dihydrofolate reductase inhibitors, a design compound was chosen. The dihydrofolate reductase inhibitor target protein was docked with the designed ligands employing the PyRx program through AutoDock Vina 4.2 version software.The pdbqt file of the macromolecule and ligand used for interactionwas done by pymol software and exported to the molecule in the PDB file.The docking results of molecules were visualized and examined utilizing Discovery Studio Visualizer software. Physicochemical parameters including Boiled Egg additional assessments were done using SWISS ADME, PreADME. ADME SAR, PkCSM employed for toxicity prediction of the designed compound. Furthermore, the bioactivity of the compoundswas investigated by Molinspiration online web server.The 2D chemical structure of intended compounds is shown in Table 1.

The designed Compound as Dihydrofolate reductase inhibitor:

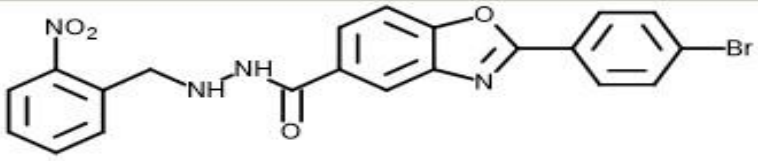
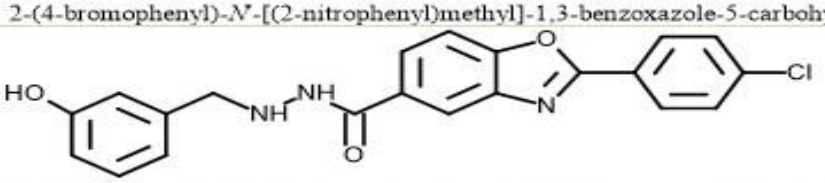
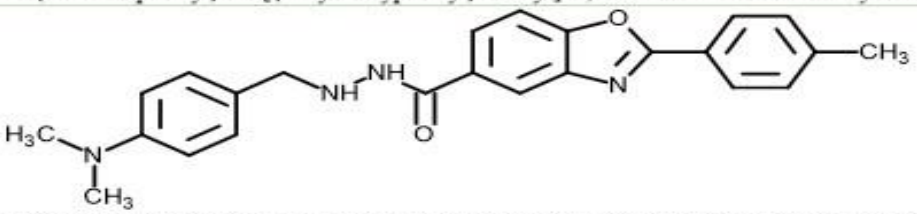
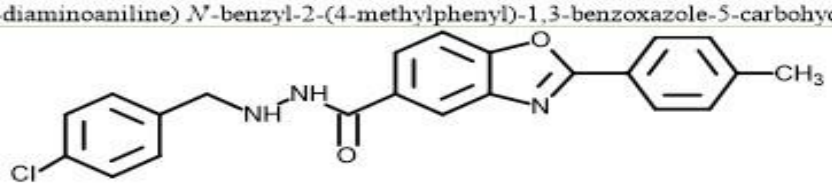
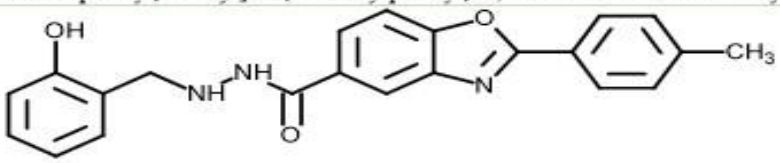
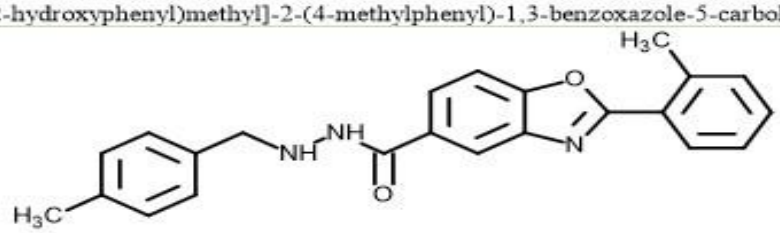
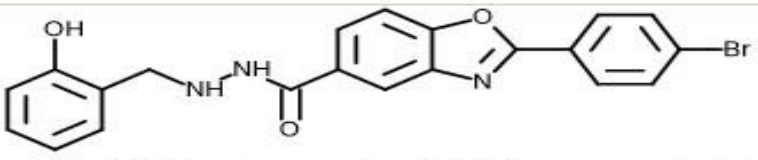
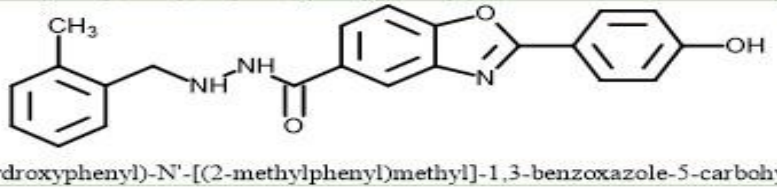
Sr. No	Designed Compound
1.	 2-(4-bromophenyl)-*N*'-[(2-nitrophenyl)methyl]-1,3-benzoxazole-5-carbohydrazide
2.	 2-(4-chlorophenyl)-*N*'-[(3-hydroxyphenyl)methyl]-1,3-benzoxazole-5-carbohydrazide
3.	 2-(4-diaminoaniline) *N*'-benzyl-2-(4-methylphenyl)-1,3-benzoxazole-5-carbohydrazide
4.	 N'-[(4-chlorophenyl)methyl]-2-(4-methylphenyl)-1,3-benzoxazole-5-carbohydrazide
5.	 N'-[(2-hydroxyphenyl)methyl]-2-(4-methylphenyl)-1,3-benzoxazole-5-carbohydrazide
6.	 2-(2-methylphenyl)-N'-[(4-methylphenyl)methyl]-1,3-benzoxazole-5-carbohydrazide
7.	 2-(4-bromophenyl)-N'-[(2-hydroxyphenyl)methyl]-1,3-benzoxazole-5-carbohydrazide
8.	 2-(4-hydroxyphenyl)-N'-[(2-methylphenyl)methyl]-1,3-benzoxazole-5-carbohydrazide

Table 1: 2D Chemical structure of the designed compound.

Preparation of target macromolecule and ligands:

The synthesis of the nitrogen compounds purines and pyrimidines, which go on to form DNA, depends on folic acid. Antimetabolites combine their effects to exhibit bacteriostaticactivity at two distinct stages of folic acid synthesis.[16-17]Examples include dapsone, p-aminosalicylic acid, and sulfonamides. Sulfonamides hinder the establishment of dihydrofolic acid by inhibiting the activity of dihydropteroate synthetase, which uses PABA as a substrate. Tetrahydrofolic acid is synthesized by the enzyme dihydrofolate reductase (DHFR), which is blocked by trimethoprim.[18]The protein's three-dimensional structure (PDB code: 3SRW), which was attained from the Protein Data Bank website (http://www.rcsb.org/pdb), was generated by eliminating heteroatoms and water molecules with the Discovery Studio Visualizer 2016 edition and then exported in the PDB file format to be utilized in molecular docking procedures.Like the proposed ligands, 2D inhibitor structures were designed using chem sketch software and saved in mol format for molecular docking.[19] The docking process's prepared protein and ligand are shown in figure 1.

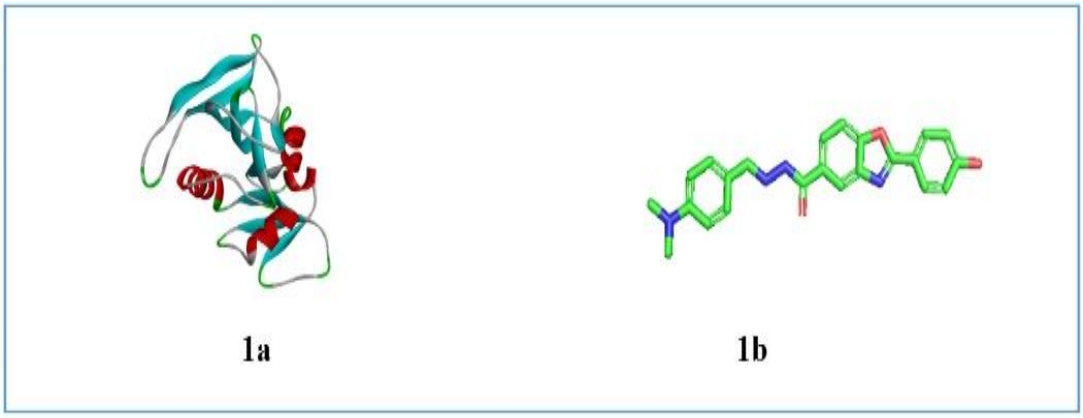


Figure 1:1a, 1b Prepared Macromolecule, and Ligand compatibly.

Molecular docking and visualization:

A molecular dockingwas run to establish the score function for the binding affinity, and theability to observe and assess macromolecule-ligand interactions to investigate the binding style and functionality of theligand. Version 4.2 of AutoDock Vina with PyRx softwarewith the 2020 edition of the software Discovery Studio Visualizer was employed to develop the scoring functions (binding affinities) and to observe the interaction of the macromolecule with the ligandconsisting of non-bonding polar and hydrophobic interactions.[20]

ADME Prediction: With the comprehensive range of recent studies on computer-aided drug expansion for years, estimations of drug candidates' profiles can be made. Several pharmacokinetic parameter values, including ADME,log P,Molecular size, hydrogen bond donor-receptor, and

TPSAa lot ofsubstances were created utilizing the Swiss ADMEmethod(http://www.swissadme.ch/)[21-23] and (https://preadmet.qsarhub.com/adme/).[24]admetSAR 2.0 admetSAR (ecust.edu.cn),[25-26]pkCSM(pkCSM (uq.edu.au)[27] was employed to investigate toxicity studies of the designed compound. Molinspiration(Calculation of molecular properties and bioactivity score (molinspiration.com)was acquired as an online web tool to figureout the bioactive scores of the designed inhibitors.[28]

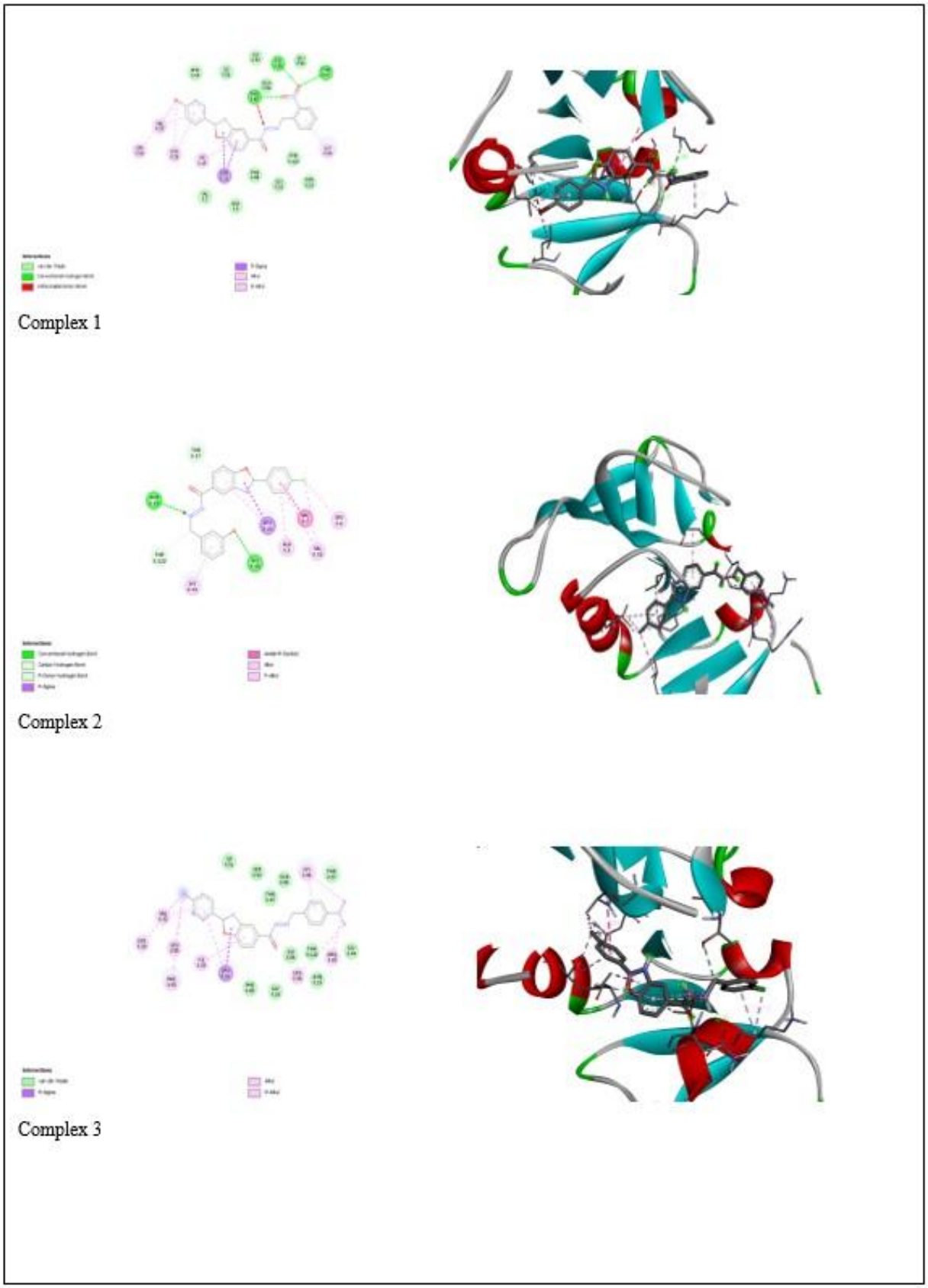
Result and Discussion:

Molecular docking:

To expand the understanding of conventional antibiotics to benzoxazole compounds with suspected antibacterial action, a docking investigation of certain proteins implicated to produce activity against bacteria. The proteins used were DHFR from Staphylococcus aureus. To identify the kinds of residuesanswerable, molecular docking analysis was conducted by using (PDB code: 3SRW)[29].All the designed compounds' estimated binding affinities vary from -9.9 to 10.9 kcal/mol, while a reference medication (ciprofloxacin) was anticipated to have a binding affinity of -7.5 kcal/mol.This indicated thatprovided functional protein structure (PDB: 3SRW) with the ligand 3D structure at the protein target's binding site. Some of the developed compounds were envisaged using the Discovery Studio Visualizer program to investigate the molecular interactions and amino acid residues in charge of the observed chemical effect at the receptor's location.Table 2 displays the conclusions of a molecular docking analysis for several designed compounds and a reference medication (ciprofloxacin).According to the observations, all the designed drugs have binding energies ranging from -10.2 to -10.9 kcal/mol, while ciprofloxacin (the reference drug) has a binding energy of -7.5 kcal/mol.A minimal hydrogen bond, van der Waals, pi-alkyl, pi-sigma, and amide-pi-stacked connections have all been identified between the compounds and this enzymatic activity.All designed compounds interlinked with amino acid residues as shorter hydrogen bond lengths of less than 3.0Å as compound 1 THR X:47: 2.37, THR X: 97: 2.55; compound 7 GLN X: 96: 2.72; compound8THR X: 122: 2.67, LEU X:63: 2.58 shows superior linkagethan referenced drug and shows a short hydrogen bond length ALA X:8: 2.25, LEU X: 6: 2.37 demonstrated in table 2 and Fig 1.

Table 2: Binding affinity, amino acid residues, and distance of hydrogen bonding of designed compound

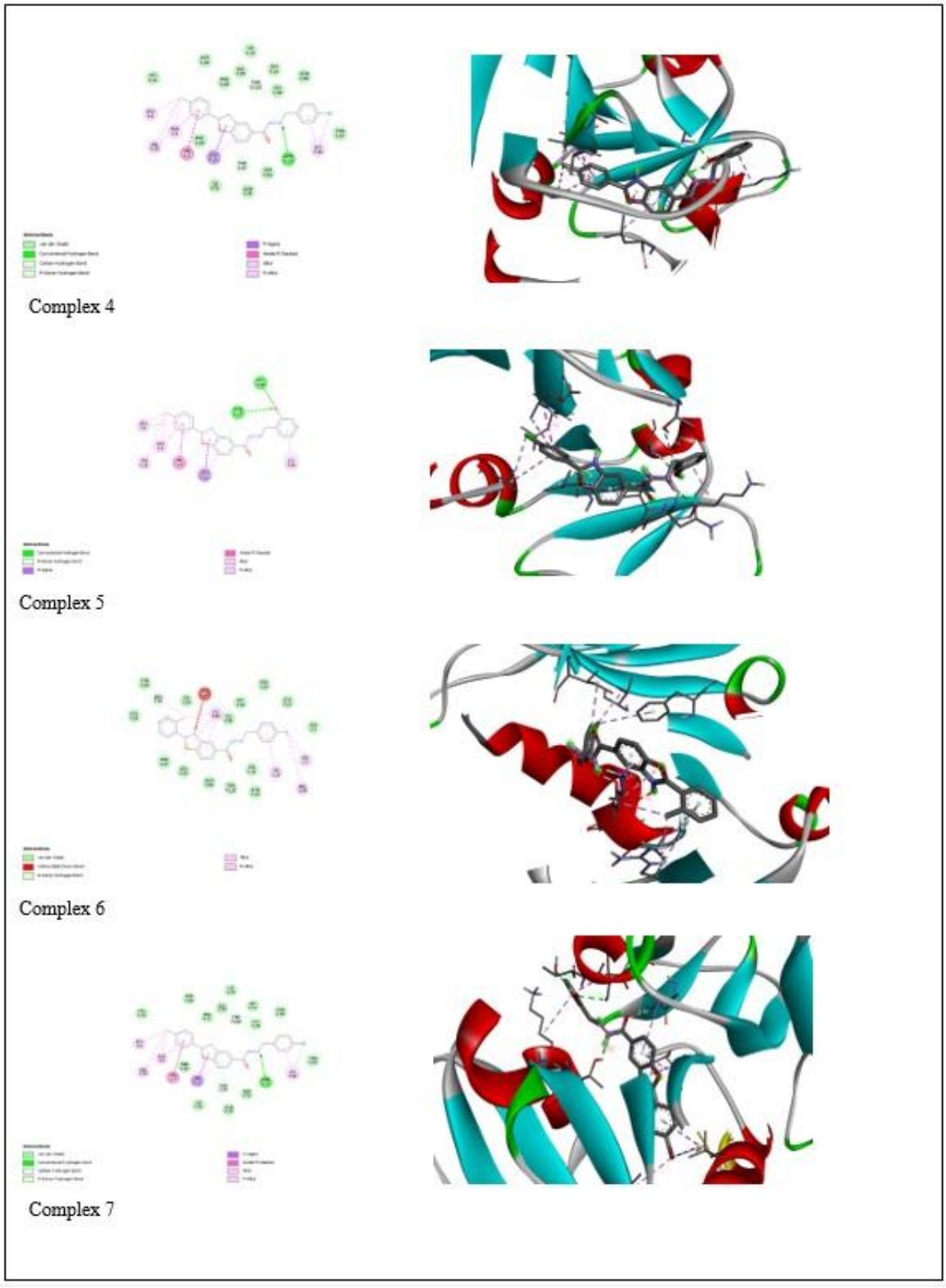
Sr No.	Binding Affinity (kcal/mol)	Amino Acid Residues	Distance Å (Hydrogen bonding)
		Designed compound	
1	-10.9	THR X:47, GLY X: 95, THR X: 97, LEU X: 21, LYS X: 46, ILE X: 15, LEU X: 29, VAL X: 32, LEU X:55	THR X:47: 2.37, GLY X: 95: 2.28, THR X: 97: 2.55
2	-10.7	ASN X: 19, GLY X: 95, LEU X: 21, VAL X: 7, ALA X: 8, VAL X: 32, LEU X :7, LYS X: 46, THR X: 122, THR X: 47	ASN X: 19: 2.17 GLY X: 95: 2.27
3	-10.5	LEU X: 21, LYS X: 46, ARG X: 45, LEU X: 98, ILE X: 15, PHE X: 93, Val X:32, LEU X: 29, LEU X: 55	-
4	-10.5	ASN X:19, LYS X:46, THR X: 122, THR X: 47, LEU X: 21, VAL X: 7, ALA X:8, VAL X: 32, LEU X: 6, HIS X: 31.	ASN X:19: 2.20
5	-10.4	THR X:47, GLY X: 95, LYS X: 46, LEU X: 21, Val X: 7, ALA X : 8, VAL X: 32, LEU X :6	THR X:47: 2.09, GLY X: 95: 2.35
6	-10.4	THR X: 47, ARG X:45, LYS X: 46, ILE X: 15, VAL X: 7, PHE X: 99	-
7	-10.3	GLN X: 96, THR X:97, THR X: 122, LYS X: 46, GLY X:16, ILE X: 15, LEU X: 21, VAL X: 32, LEU X: 55. LEU X: 29, THR X: 47	GLN X: 96: 2.72, THR X:97: 2.22
8	-10.2	THR X: 122, LEU X:63, ARG X: 45, LYS X: 46, LEU X: 21, THR X: 47, ILE X: 15, GLN X: 96	THR X: 122: 2.67, LEU X:63: 2.58
		Ciprofloxacin	
9	-7.5	ALA X:8, LEU X: 6, Val X: 7, LEU X: 21, VAL X:32, LEU X: 29, ILE X: 51	ALA X:8: 2.25, LEU X: 6: 2.37
		Boxazomycin B	
10	-8.8	LEU X: 6, PHE X:93, ALA X: 8, VAL X :32 PHE X: 99, GLY X: 94, ILE X :15	LEU X: 6: 2.34 PHE X:93: 2.72 ALA X: 8: 2.34



Complex 1

Complex 2

Complex 3



Complex 4

Complex 5

Complex 6

Complex 7

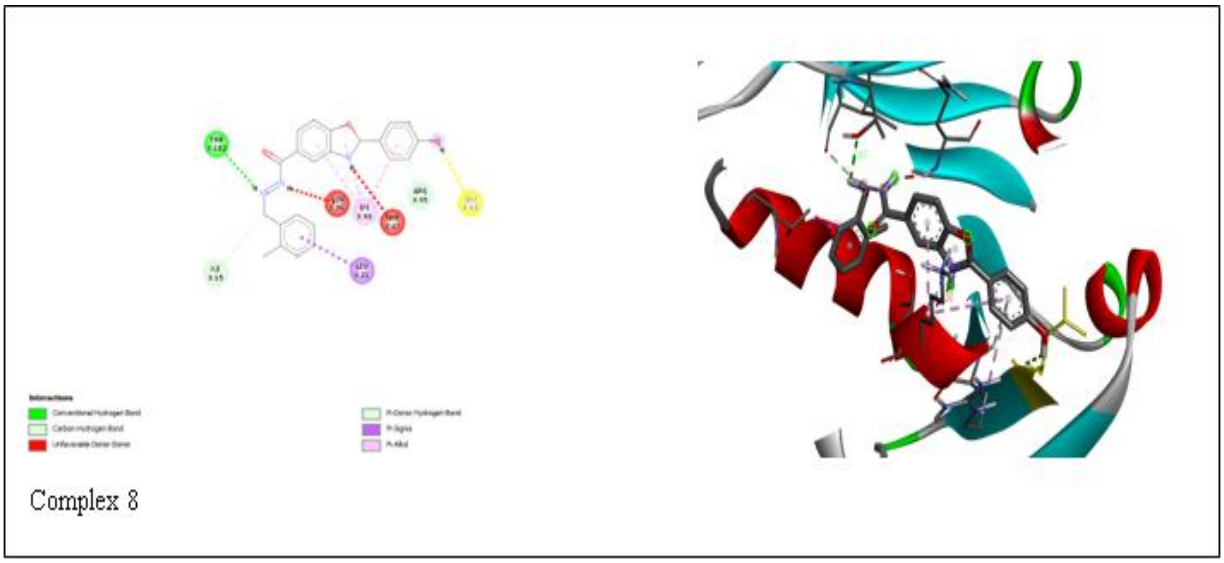


Fig 2: 2D visuals of designed receptor interacting with amino acids of dihydrofolate reductase receptor and interacting bond length between the ligand and macromolecule.

***In-Silico* prediction ADME/Pharmacokinetics properties:**

Drug success is determined by both its high productivity and a proper ADME (absorption, distribution, metabolism, and excretion) profile. Molecular weight (MW), the logarithm of the partition coefficient (miLog P), the number of hydrogen bond acceptors (n-ON), the number of hydrogen bond donors (nOHNH), the topological polar surface area (TPSA), the number of rotatable bonds (n-ROTB) of Lipinski's rule of five[23] have all been calculated using swissADMEonlineweb software and the outcomes were assessed against a reference medication (ciprofloxacin).BOILED-Egg illustration of human intestine absorption (HIA) and brain access or penetration of a pharmaceutical compound. The areas of the egg that are most likely to penetrate the brain and the areas that are most likely to be absorbed by the human digestive system correspond to the white and yellow regions, respectively.[30] According to Table 3, none of the designed compounds, including the mentioned medication ciprofloxacin, violated Lipinski's rule of five. This implies that all the designed inhibitors have favorable drug-like or pharmacological characteristics that could facilitate oral bioavailability.

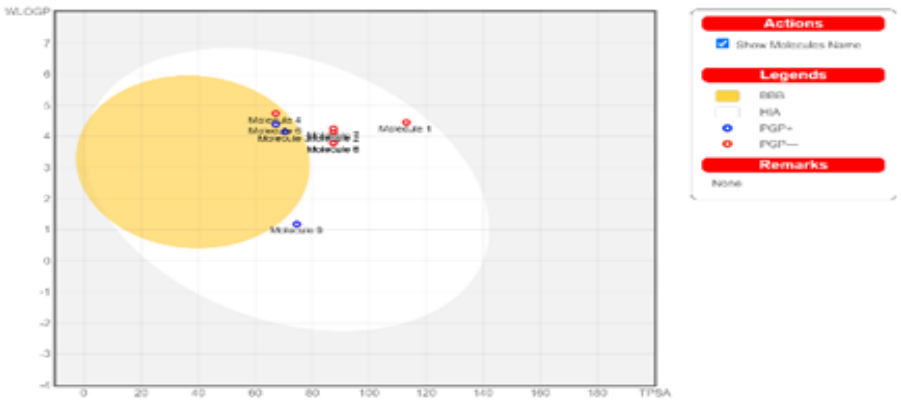


Figure 3: Boiled Egg Visuals of designed and referenced compound.

Table 3: In-Silico prediction ADME of designed inhibitors

Sr. No	Molecular Weight (≤500)	C LogP (≤5)	H-bond Acceptors (≤10)	H-bond Donors (≤5)	Rotatable Bonds (≤7)	Blood-brain barrier	GIT
Designed compound							
1	467.27 g/mol	3.33	6	2	7	No	High
2	393.82 g/mol	3.23	5	3	6	No	High
3	400.47 g/mol	3.47	4	2	7	Yes	High
4	391.85 g/mol	3.85	4	2	6	Yes	High
5	373.40 g/mol	3.25	5	3	6	No	High
6	371.43 g/mol	3.78	4	2	6	Yes	High
7	438.27 g/mol	2.21	5	3	6	No	High
8	373.40 g/mol	2.77	5	3	6	No	High
Ciprofloxacin							
9	331.34 g/mol	2.24	5	2	3	No	High
Boxazomycin B							
10	300.27 g/mol	1.76	7	3	2	No	High

Similarly, Table 4 displayed the expected ADMET properties for a few designed compounds.Basedon ADMET estimations that the parameters for the qualities of absorption

properties exposed to be under the criterion values, all the developed compounds, were confirmed to be P-glycoprotein II inhibitors. (%Human Intestinal absorption > 30%, and Skin Absorptivity log Kp > 2.5). This suggests that all the drugs designed had great pharmacological characteristics and good intestinal absorption in humans. The expected absorptivity suggested that the designed molecule (Table 4) had remarkable beneficial abilities as a dihydrofolate reductase inhibitor.

Table 4: ADME/ Pharmacokinetics prediction of designed and referenced compound

		Designed Compound								Reference Drug	
Properties	**Parameters**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Ciprofloxacin**	**Boxazomycin**
Absorption	Water solubility	0.1492	0.237	0.11	0.02	0.32	0.093	0.099	0.91	82.32	-2.847
	Intestinal absorption (% absorbed)	89.76	94.08	95.6	95.79	93.3	95.41	94.60	93.3	96.57	78.16
	Skin permeability	-3.53	-3.68	-2.80	-2.83	-3.48	-2.70	-3.57	-3.49	-4.30	-4.85
	P-glycoprotein II inhibitor	Inhibitor	Non	Non	Inhibitor	Non	Non	Non	Non	Non	Non
Distribution	Plasma protein binding	100.00	91.3	91.72	90.25	88.4	94.42	96.77	90.25	46.5	48.41
	BBB Permeability	0.73	0.55	0.56	1.49	0.620	1.18	0.64	0.501	0.014	0.165
Metabolism	CYP1A2 Inhibitor	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non
	CYP2C19 inhibitor	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non
	CYP2C9 inhibitor	Non	Inhibitor	Inhibitor	Non	Inhibitor	Non	Inhibitor	Inhibitor	Non	Non
	CYPD6 inhibitor	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non
	CYP3A4 inhibitor	Non	Non	Non	Non	Non	Non	Non	Non	Non	Yes
Excretion	Total clearance	-0.266	-0.438	0.962	-0.381	0.819	0.884	-0343	0.745	0.531	0.812
	Renal OCT2 substrate	No	No	No	No	No	No	No	No	No	No

Drug discovery is plagued by attrition because of toxicity and clinical safety issues.Toxicology is the extent to which a chemical can injure an organism or the sub-structure of the organism.[31] In order to ensure consumer safety, all the developed dihydrofolate reductase inhibitors were used to study organ toxicity, genomic toxicity, and eco-toxicity characteristics. The genomic toxicity data demonstrate that compound 1 and the ciprofloxacin reference medication displayed AMES mutagenesis, and all the developed compounds and reference drugs are non-carcinogenic apart from hepatotoxicity. The developed compounds exhibit similar results when compared to reference medications in terms of ecotoxicity as well.

Table 5: Toxicity studies of Designed inhibitor compared with reference drugs.

		Designed Compound								Reference Drugs	
Toxicities	**Parameter**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Ciprofloxacin**	**Boxazomycin**
Organ toxicity	hERG inhibition	-	-	-	-	-	-	-	-	-	-
	Hepatotoxicity	+	+	+	+	+	+	+	+	+	+
	Eye irritation	-	-	-	-	-	-	-	-	-	-
	Skin Sensitization	-	-	-	-	-	-	-	-	-	-
Genomic toxicity	AMES mutagenesis	+	-	-	-	-	-	-	-	+	-
	Carcinogenesis	-	-	-	-	-	-	-	-	-	-
Eco-toxicity	*T. Pyriformis* toxicity	0.288	0.297	0.299	0.3	0.298	0.299	0.297	0.292	0.341	0.286
	Avian toxicity	-	-	-	-	-	-	-	-	-	-

Predicting medicinal chemistry, drug-likeness, and bioactivity score properties of some designed inhibitors:

Using web-based online tools, the medicinal chemistry, drug-likeness, and bioactivity characteristics of several designed compounds were further studied. Table 4 displays anticipated bioactivity scores and medicinal chemistry features.PAINS alarms are projected.The result revealed that compounds 1,2,4,6,8 and referenced drugsdo nothave pain alerts (PAINS ALERT=0) while compound 3 has 2 pain alerts and compound 5,7 has 1 pain alert. A synthetic accessibility or complexity score of 1-4 indicates an easy, 4-7 medium, and 8-10 challenging work to synthesize.It is fascinating to note that all the designed compounds and the referenced drug had synthetic accessibility scores that started falling between the easy (i.e., 1-4) and projected values (i.e., 3.21 to 3.58) ranges.[20,33,34] This would be extremely simple to synthesize in the lab.For the designed compounds, the bioactivity scores of kinase inhibitor, enzyme inhibitor, ion channel modulator, nuclear receptor ligand, and G protein-coupled receptor ligand were evaluated.If the expected value is greater than 0.00 (> 0), the molecule is considered more bioactive; if it is moderately active (between -0.5 and 0.00), it is considered non-

active; and if it is non-active, it is considered inactive (less than -0.5).[35-36]All the designed compounds exhibited moderate bioactivity as demonstrated in table 5.

Table 6: Medicinal chemistry, drug-likeness, and bioactivity of designed compound compared with reference drugs

		Newly designed inhibitors								Reference drug	
Predicted properties	**Predicted Parameters**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Ciprofloxacin**	**Boxazomycin**
Medicinal chemistry	**PAINS alerts**	0 alert	0 alert	2 alert	0 alert	1 alert	0 alert	1 alert	0 alert	0 alert	0 alert
	Synthetic accessibility	3.44	3.13	3.58	3.32	3.30	3.46	3.21	3.27	2.51	3.06
Drug likeness	**Lipinski violations**	0	0	0	0	0	0	0	0	0	0
Bioactivity score	**GPCR ligand**	-0.3	-0.1	-0.1	-0.2	-0.2	-0.1	-0.2	-0.1	0.12	-0.02
	Ion channel modulator	-0.5	-0.4	-0.5	-0.5	-0.5	-0.5	-0.5	-0.4	-0.04	-0.16
	Kinase inhibitor	-0.3	-0.1	-0.1	-0.2	-0.2	-0.2	-0.2	-0.2	-0.07	-0.04
	Nuclear receptor ligand	-0.4	-0.1	-0.2	-0.2	-0.1	-0.2	-0.2	-0.1	-0.19	-0.08
	Enzyme inhibitor	-0.2	-0.2	-0.1	-0.1	-0.1	-0.1	-0.1	-0.07	-0.28	-0.22

Conclusion:

In the present investigation, a reduced Schiff base containing benzoxazole compounds were designed via an *in-silico* drug design approach. 38 compounds were exposed to identify the binding strategies and amino acid residues included in the physiologic interface between ligands and macromolecule of PDB code 3srw (designed inhibitors).The designed compound's potential binding affinity for the dihydrofolate reductase receptor ranges from -9.9 to -10.9 kcal/mol when analyzed with standard drug ciprofloxacin based on a broad-spectrum antibiotic, whose binding affinity is revealed to be -7.5 kcal/moland Boxazomycin on basis of a moiety, whose binding affinity is revealed to be -8.8 kcal/mol.According to the results of molecular docking, the macromolecule and the designed inhibitors had significant physiological interactions, notably hydrogen bonds and hydrophobic interactions.Predictions of ADMET and in silico pharmacokinetic characteristics were inspected in order to examine the drug-like profiles and pharmacological characteristics of the designed inhibitors. The pharmaceutical in concern, as well as all other designed inhibitors, didn't

contravene Lipinski's rule of five, according to the computed physicochemical parameters.Similar ADME properties demonstrated that the designed compound has high permeability, distribution, metabolism, and excretion characteristics.The BOILED-Egg illustrations demonstrated that all the designed inhibitors are highly likely to be absorbed by the human gastrointestinal tract, and some of the designed compounds may cross the brain quickly.Additionally, all the designed compounds are easily synthesizable (i.e.,between 1-4) based on their recommended values, which ranged from 3.13 to 3.44. As a result, compounds would be extremely simple to synthesize in a laboratory. According to the projected bioactive characteristics, each of the designed compounds would be a moderately viable therapeutic candidate.The designed compounds could be improved upon in the context of these results to serve active therapeutic as potential dihydrofolate reductase inhibitors.

Abbreviations:

DHFR: Dihydrofolate reductase; SBDD: Structure-based drug discovery; dUMP: deoxyuridine monophosphate; dTMP: deoxythymidine monophosphate; 2D: Two-dimensional structures; Pyrx: Python Prescription; PDB: Protein database bank; nOHNH: the number of hydrogen bond donors;ROTB: the number of rotatable bonds; 3D: Three-dimensional structure; ADMET: Absorption, distribution, metabolism, excretion; HIA: human intestine absorption; hERG: Human ether-a-go-go related gene; PAINS: Pan assay interference; GPCR: G protein-coupled receptor.

Acknowledgments:

We expressed gratitude to the Department of Pharmaceutical Chemistry, Kamla Nehru College Of Pharmacy Nagpur for providing the necessary facilities.

Authors' contributions

Disha M. Dhabarde and Jagdish R. Baheti conceived, analyzed, and interpreted the results. Divya P. Nasare and Diksha D. Meshram performed the computational study. All authors have read and approved the manuscript.

Funding

The authors received no funds.

Availability of data and materials

All data and materials are available from the college facilities.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

No competing interests

Author details:

Department of Chemistry, Kamla Nehru College of Pharmacy Butibori, Nagpur.

REFERENCES:

[1] Dalhoff A (1994): Quinolone resistance in Pseudomonas aeruginosa and Staphylococcus aureus. Development during therapy and clinical significance. Infection 22:111–121.

[2] TugbaErtan-Bolelli, I lkayYildiz, SeldaOzgen-Ozgacar(2016): Synthesis, molecular docking and antimicrobial evaluation of novel benzoxazole derivatives. Med Chem Res 25:553–567.

[3] Jessica M. A. Blair, Mark A. Webber, Alison J. Baylay, David O. Ogbolu, and Laura J. V. Piddock (2015): "Molecular Mechanisms of Antibiotic Resistance," Nature Reviews: Microbiology 13, no. 1: 42–51.

[4] Kathrin U. Jansen, Charles Knirsch, and Annaliesa S. Anderson (2018): "The Role of Vaccines in Preventing Bacterial Antimicrobial Resistance" Nature Medicine 24, 10–9.

[5] Leon Oehlers, Carolyn L. Mazzitelli, Jennifer S. Brodbelt, Mireya Rodriguez, and Sean Kerwin (2004) "Evaluation of Complexes of DNA Duplexes and Novel Benzoxazoles or Benzimidazoles by Electrospray Ionization Mass Spectrometry," Journal of the American Society for Mass Spectrometry 15, no. 11: 1593–603.

[6] Priyanka Lokwani, B.P. Nagori, Nikhil Batra, Anju Goyal, Stuti Gupta, and Nisha Singh (2011): Benzoxazole: The molecule of diverse biological activities, J. Chem. Pharm. Res., 3(3):302-311.

[7] R.D. Viirre, G. Evindar, R.A. Batey, (2008) J. Org. Chem., 73, 3452.

[8] Jayanna, N D (2013): Synthesis and study of plausible biological activity of benzoxazole derivatives, Journal of Chemistry 2012 Volume.

[9] Meng, X.Y.; Zhang, H.X.; Mezei, M.; Cui, M. (2011): Molecular docking: A powerful approach for structure-based drug discovery. Curr. Comput. Aided Drug Des., 7, 146–157.

[10] Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD (2015) Molecular docking and structure-based drug design strategies. Molecules. 20(7):13384– 13421.

[11] Huang, S.Y.; Zou, X (2010): Advances, and challenges in protein-ligand docking. Int. J. Mol. Sci., 11, 3016–3034.

[12] Xiaoming Li, Mark Hilgers, Mark Cunningham, Zhiyong Chen, Michael Trzoss, Junhu Zhang, Lucy Kohnen, Thanh Lam, Chris Creighton, Kedar GC, Kirk Nelson, Bryan Kwan, Mark Stidham, Vickie Brown-Driver, Karen J. Shaw, John Finn (2011): Structure-based design of new DHFR-based antibacterial agents: 7-aryl-2,4-diaminoquinazolines Bioorg. Med. Chem. Lett. 21 (2011) 5171-5176.

[13] Schnell, J.; Dyson, H. J.; Wright, P. Annu.(2004): Rev. Biophys. Biomol. Struct. 33, 119.

[14] Stephen Hawser, Sergio Lociuro, Khalid Islam (2006): Dihydrofolate reductase inhibitors as antibacterial agents. biochemical pharmacology 71 941–948.

[15] Hitchings GH, Burchall JJ. (1965): Inhibition of folate biosynthesis and function as a basis for chemotherapy. Adv EnzymolRelat Areas, 27:417–68.

[16] Murray, P.R, Rosenthal, K.S. Pfaller M.A (2006): MicrobiologiaMédica, Mosby, Elsevier: 5th ed.

[17] Huang L, Crothers, K. Atzori, C. Benfield, T. Miller, R. Rabodonirina M. Helweg-Larsen, (2004) Dihydropteroate synthase gene mutations in pneumocystis and sulfa resistance. Emerg. Infect. Dis. 10, 1721–1728.

[18] Olasupo SB, Uzairu A, Shallangwa GA, Uba S (2020) Chemoinformatic studies on some inhibitors of dopamine transporter and the receptor targeting schizophrenia for developing novel antipsychotic agents. Heliyon 6(7): e04464.

[19] T. Katsila, G.A. Spyroulias, G.P. Patrinos, M.-T. Matsoukas (2016): Computational approaches in target identification and drug discovery. Comput. Struct. Biotechnol. J. 14, 177–184.

[20] Daina A, Michielin O, Zoete V (2017) SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 7:42717.

[21] Pliska, V., Testa, B. & van de Waterbeemd, H. (1996): In Lipophilicity in Drug Action and Toxicology Wiley-VCH Verlag GmbH, 1-6.

[22] Arnott, J. A. &Planey, S. L. (2012): The influence of lipophilicity in drug discovery and design. Expert Opin. Drug Discov. 7, 863–875.

[23] Hiba Najeh Al-Saad, Ammar A. Razzak Mahmood Kubba (2020): Evaluation of New Thiosemcarbazides Derived from Captopril as Angiotensin-Converting Enzyme Inhibitors with Docking Study, and Predicted-ADMET Analysis, Research J. Pharm., and Tech. 13(6).

[24] Cheminformatics M (2018) Calculation of molecular properties and bioactivity score. Comput software] Retrieved from Calculation of molecular properties and bioactivity score (molinspiration.com).

[25] Cheng F, Li W, Zhou Y, Shen J, Wu Z, Liu G, Lee PW, Tang Y (2012): admeSAR: a comprehensive source and free tool for assessment of chemical ADMET properties. J chem Inf Model 52:3099-3105.

[26] Yang H, Lou C, Sun L, Li J, Cai Y, Wang Z (2019) admetSAR 2.0: web-service for prediction and optimization of chemical ADMET properties. Bioinformatics 35(6):1067–1069.

[27] Pires DEV, Blundell TL, Ascher DB (2015) pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. J Med Chem 58(9):4066–4072.

[28] Maria José Alves, Hugo J. C. Froufe, Ana F. T. Costa, Anabela F. Santos, Liliana G. Oliveira, Sara R. M. Osório, Rui M. V. Abreu, Manuela Pintado, and Isabel C. F. R. Ferreira (2014): Docking Studies in Target Proteins Involved in Antibacterial Action Mechanisms: Extending the Knowledge on Standard Antibiotics to Antimicrobial Mushroom Compounds, Molecules, 19, 1672-1684.

[29] Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J (2001): Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings Adv. Drug Deliv. Rev., 46, 3–26.

[30] Antoine Daina and Vincent Zoete (2016) A BOILED-Egg to Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules, ChemMedChem, 11, 1117 – 1121.

[31] Wang, Y. et al (2015): In silico ADME/T modelling for rational drug design. Q Rev Biophys 48, 488–515.

[32] Baell, J. B. & Holloway, G. A. (2010): New substructure filters for removal of pan assay interference compounds (PAINS) from screening libraries and for their exclusion in bioassays. J. Med. Chem. 53, 2719–2740.

[33] Roy S, Samant LR, Chowdhary A (2015) In silico pharmacokinetics analysis and ADMET of phytochemicals of Datura metel Linn. and Cynodondactylon Linn. J Chem Pharm Res 7:385–388.

[34] Ertl P, Schuffenhauer A (2009) Estimation of synthetic accessibility score of drug-like molecules based on molecular complexity and fragment contributions. J Cheminform 1(1):8.

[35] Tahmeena Khan & Shalini Dixit & Rumana Ahmad & Saman Raza & Iqbal Azad & Seema Joshi & Abdul Rahman Khan (2017): Molecular docking, PASS analysis, bioactivity score

prediction, synthesis, characterization, and biological activity evaluation of a functionalized 2-butanone thiosemicarbazone ligand and its complexes, J Chem Biol.

[36] Proudfoot JR (2002) Drugs, leads, and drug-likeness: an analysis of some recently launched drugs. Bioorg Med Chem Lett 12:1647– 1650.