QSAR, MOLECULAR DOCKING, AND ADME STUDIES OF BENZIMIDAZOLE DERIVATIVES AS ANTIBACTERIAL AGENTS

Vinod Kumar[1], Jyoti Rathi[2], Kanchan Bala[3], Anuradha Sharma[4], Suchitra Yadav[5], Mahesh Kumar[6], Balasubramanian Narasimhan[7]*

ABSTRACT

In the field of medicinal chemistry, benzimidazole is a useful pharmacophore and shows a broad range of biological activities. Modern drug development commonly use the molecular docking technique for understanding drug-receptor interaction. Various computational techniques, including 2D QSAR, molecular docking, and ADME studies of benzimidazole derivatives against ***Escherichia Coli*** and ***Staphylococcus aureus,*** were used in this research study. Molecular descriptors used in 2D QSAR studies, include topological index Balaban (J), electronic parameters like Vamp Lumo & Kier's second order alpha shape index ($k\alpha^2$) against ***Escherichia Coli*** microorganism. The antibacterial activity of benzimidazole derivatives is governed by topological parameters like third-order molecular connectivity index ($^3\chi$) against ***Staphylococcus aureus*** microorganism. According to molecular docking studies, compounds **15, 2, 4, 7** and **24** have the best docking scores against the protein **Topoisomerase II (PDB ID: 1JIJ)** and compounds **14, 27, 2, 25** and **15** have the best docking scores against the protein **DNA Gyrase (PDB ID: 1KZN)**. The Lipinski rule of five was used to determine an excellent ADME profile based on QSAR, molecular docking data, and binding interaction analysis. According to the study, these compounds may be used as lead structures for more investigation of antimicrobial resistance.

Keywords: Benzimidazole, Antimicrobial activity, QSAR, Molecular Docking, ADME, DNA Gyrase & Topoisomease II

[1]Faculty of Pharmaceutical Sciences, D.K. Pharma College of Pharmacy, Rewari , Haryana, India – 123411
[2]Faculty of Pharmaceutical Sciences, Indira Gandhi University, Meerpur, Rewari , Haryana, India – 122502
[3]Faculty of Pharmaceutical Sciences, Gurugram global College of Pharmacy, Gurgaon, Haryana, India – 122506
[4,5]Faculty of Pharmaceutical Sciences, Deen Dayal Rustagi College of Pharmacy, Gurgaon, Haryana, India – 122504
[6,7]*Faculty of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, Haryana, India – 124001

***Corresponding Author**
Prof. Balasubramanian Narasimhan
*Faculty of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, Haryana, India – 124001
Email: naru2000us@yahoo.com

DOI: 10.48047/ecb/2023.12.si5a.0471

INTRODUCTION

One of the most significant threats to public health in the twenty first century is bacterial antimicrobial resistance (AMR), which arises when changes in bacteria reduce the efficacy of the medications used to treat diseases [1]. AMR was predicted to be responsible for an estimated 4.95 million deaths in 2019, of which 1.3 million were caused only by resistant infections [2]. By 2050, if not prior to, this number is anticipated to exceed 10 million worldwide [3], mostly due to COVID-19 patients have been receiving excessive amounts of prescribed antibiotics during the previous two years [4]. Despite this urgency, conventional organic medicinal chemistry has been unable to replace the exhausted antibacterial pipeline: a 2022 analysis reported that, as of June 2021, there were just 45 "traditional" antibiotics in clinical development [5]. Therefore, the creation of the next generation of antibiotics urgently requires new methods.

A heterocyclic molecule called benzimidazole is commonly used as an element in the manufacturing process of chemical compounds. Benzimidazole is a bicyclic molecule with a benzene ring attached to a five-membered imidazole which contains two nitrogen atoms. It is also known as 1,3-benzothia zole, benzoglyoxaline, or 1H-benzimidazole [6, 7]. The condensation reaction of 1,2-phenylenedi amine with carboxaldehyde and carboxylic acids produces benzimidazoles [8]. Benzimidazole is regarded as a possible bioactive heterocyclic aromatic molecule having a variety of biological properties like antineoplastic [9], antiparasitic [10], antihypertensive [11], antimycobacterial [12], anti-inflammatory [13], antiviral [14], antimalarial [15] and anticonvulsant [16] activities and its derivatives are the most active kinds of compounds against microbes [17]. The development of anti microbial resistance to currently used medications made it necessary to find novel compounds for the treatment of bacterial infections [18, 19]. Astemizole, telmisartan, carbendazim, enviradene, candesartan, omeprazole and mebendazole are clinically authorised benzimidazole medications [20] and many more.

Type II topoisomerases are DNA gyrase and topoisomerase IV [21,22]. GyrA and GyrB are the two subunits that compose the DNA gyrase; GyrA is involved in DNA cleavage and recombination, while GyrB possesses ATPase activity and supplies the necessary energy required for these processes. Topoisomerase IV plays a role in the decatenation of DNA and the relaxation of supercoiled DNA through the actions of its two subunits, ParC and ParE [23,24]. The class of topoisomerase II enzymes in eukaryotic cells function as homodimer enzymes, compared to the prokaryotic cells where they exist [25, 26]. The interaction mechanism between bacterial topoisomerase suppressors is also less beneficial because human topo II possesses significant amounts of binding pocket blockage. The investigation carried out by AstraZeneca studied bacterial isozymes' selectivity more than three times that of human isozymes [27]. Accordingly, the identification of dual inhibitors of broad-spectrum antimicrobial activity appears to be an important strategic objective for both DNA gyrase and topoisomerase IV [28-31].

Computer aided drug designing (CADD) accelerates the discovery of a new drug process by identification of potential lead molecules from huge compound libraries [32]. It against a biological target. CADD identify and improves the pharmacokinetics of lead molecules [33]. As per the need of present time, QSAR study aim to derive more potent compounds in minimum time, based on knowledge of magnitude of sensitivity of biological response with respect to molecular substitution. QSAR is the best alternate to conquer the hitch of classical drug designing method. It facilitates designing expose detailed mechanism and limitation of drug designing to exploit and quantify the properties of promising drug candidate [34]. Hansch analysis is a 2D QSAR technique imply through lipophilicity, electronic and steric properties to predict the relationship of physiochemical parameter and structural activity [35] .

Docking study aims to achieve the most preferred orientation and conformation of the protein ligand binding and helps for screening of large databases to identify the hit molecule [36]. The time and cost of drug discovery have been decreased by the use of several computational tools for drug screening and design [37, 38].

Pharmacokinetics, also known as the absorption, distribution, metabolism, and excretion of a drug in the human body, is explained by the Lipinski rule. Due to its low cost and excellent yield, ADME modelling has generated a lot of interest from pharmaceutical researchers for drug discovery [39].

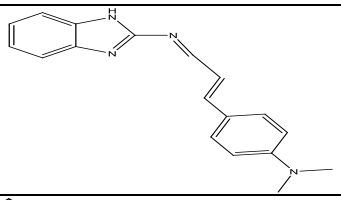
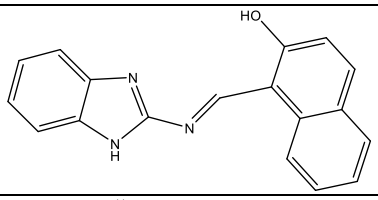
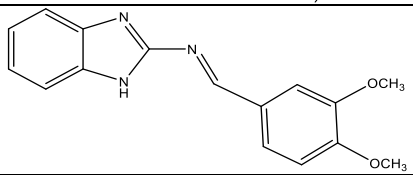
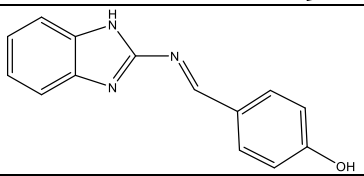
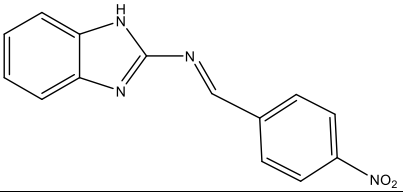
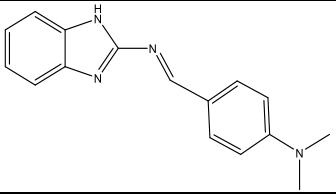
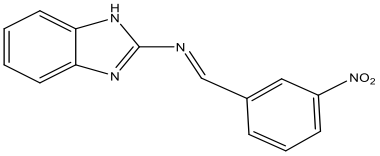
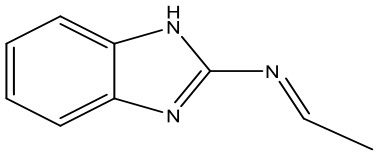
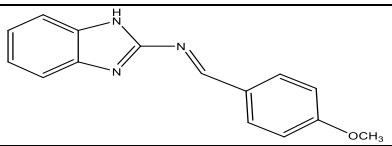
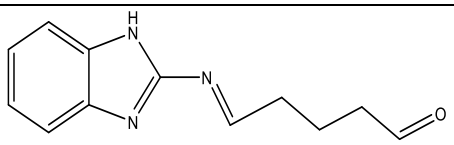
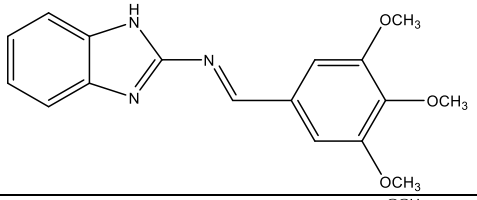
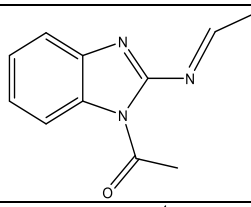
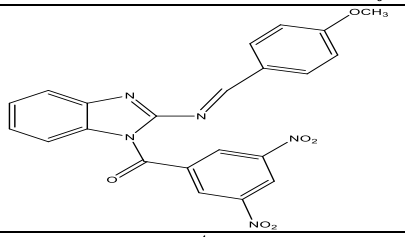
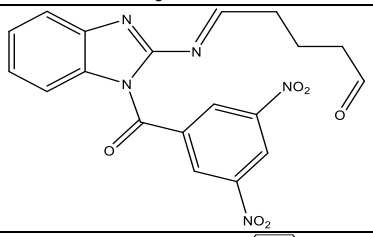
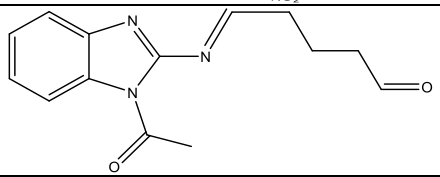
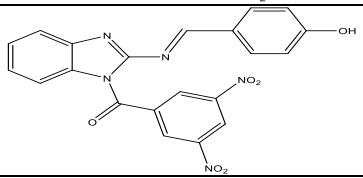
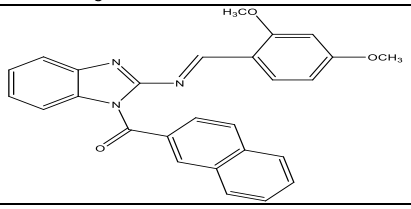
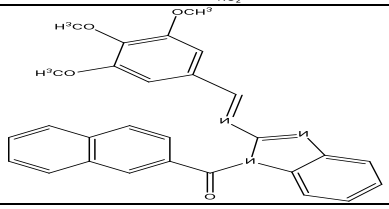
In response to the foregoing findings, and in the current study we hereby report QSAR, Molecular Docking and ADME Studies for the prediction of Benzimidazole derivatives as antibacterial agent were synthesised by Vashist *et al*., (2018) [40].

MATERIAL AND METHODS

2D QSAR Study

The derivatives of benzimidazole (1-30) **Table 1**, selected from the reported work by Vashist *et al.*, (2018), were sketched using **Chem Draw 19.0**. The biological activity was shown in MIC (μM). It was converted to pMIC values to get rid of substantial clumping and make it more reliable for the QSAR analysis, as shown in **Table 2**.

Table 1 Chemical structures of Benzimidazole derivatives used in QSAR studies

C. No.	Chemical Structure	C. No.	Chemical Structure
1		**2**	
3		**4**	
5		**6**	
7		**8**	
9		**10**	
11		**12**	
13		**14**	
15		**16**	
17		**18**	

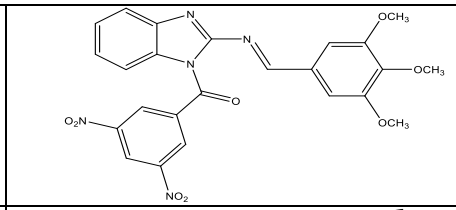
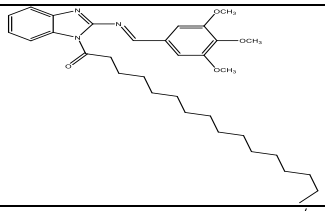
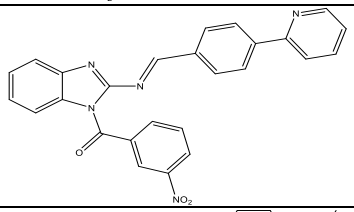
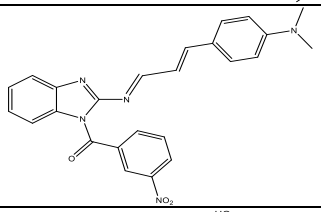
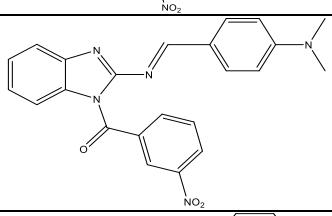
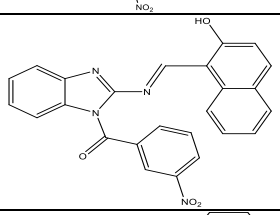
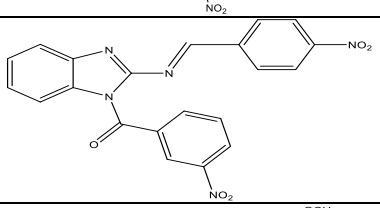
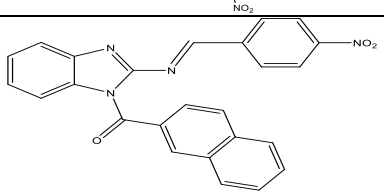
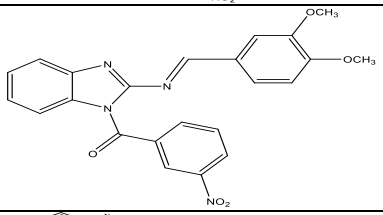
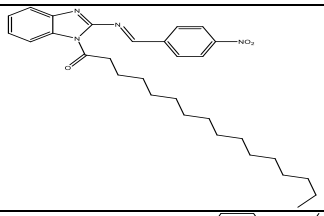
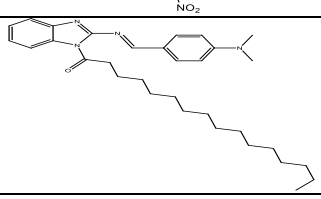
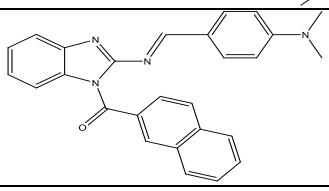
19		**20**	
21		**22**	
23		**24**	
25		**26**	
27		**28**	
29		**30**	

Table 2 Antibacterial data of Benzimidazole derivatives used in QSAR studies

C. No.	$pMIC_{EC}$	$pMIC_{SA}$	C. No.	$pMIC_{EC}$	$pMIC_{SA}$
1	0.73	1.63	**16**	1.76	1.16
2	1.64	1.64	**17**	1.46	1.16
3	1.35	1.65	**18**	1.43	1.13
4	0.82	1.72	**19**	1.69	1.09
5	1.67	1.67	**20**	1.66	1.36
6	1.67	1.67	**21**	1.45	1.15
7	1.37	1.67	**22**	1.76	1.15
8	1.59	1.89	**23**	1.78	1.18
9	1.40	1.70	**24**	1.46	1.16
10	1.16	1.76	**25**	1.78	1.18
11	1.00	1.60	**26**	1.47	1.17
12	2.40	1.19	**27**	1.76	1.16
13	1.75	1.15	**28**	1.69	1.39
14	2.30	1.39	**29**	1.67	1.37
15	2.29	1.39	**30**	1.48	1.17

Calculation of Molecular Descriptors

A number of molecular descriptors including the Molar refractivity (MR), Wiener topological index (W), log P (octanol-water partition coefficient), valence molecular connectivity indices ($^0\chi^V$, $^1\chi^V$, $^2\chi^V$, $^3\chi^V$), and Total energy (TE), Balaban topological index (J), Kier's shape indices ($k\alpha^1$, $k\alpha^2$, $k\alpha^3$), lowest unoccupied molecular orbital (LUMO)

and energies of highest occupied molecular orbital (HOMO), electronic energy and dipole moment (μ), Randic topological index (R) of benzimidazole derivatives (1-30) were calculated (**Table 3**) using **TSAR 3.3**. [41].

Table 3 Selected molecular descriptors of Benzimidazole derivatives

C. No.	μ	log P	MR	$^{1}\chi^{v}$	$^{3}\chi$	$^{3}\chi^{v}$	κ^{1}	$\kappa\alpha^{2}$	J	LUMO
1	10.95	3.80	91.72	10.72	1.24	0.58	16.84	7.00	1.16	-0.84
2	5.95	4.32	85.91	10.81	1.21	0.48	15.52	5.64	1.17	-0.99
3	5.81	3.10	80.69	10.30	1.07	0.40	15.88	6.48	1.26	-0.81
4	5.79	3.32	69.46	8.81	1.03	0.36	13.01	5.01	1.24	-0.83
5	6.22	3.56	75.09	9.72	1.24	0.39	14.92	5.61	1.24	-1.77
6	8.80	3.39	81.47	9.72	1.24	0.58	14.92	5.87	1.24	-0.64
7	4.80	3.56	75.09	9.72	1.24	0.39	14.92	5.61	1.23	-1.42
8	4.35	1.30	46.83	5.90	0.54	0.19	8.59	3.37	1.62	-0.44
9	6.84	3.35	74.23	9.35	0.95	0.35	13.96	5.64	1.23	-0.78
10	2.36	1.08	61.40	7.90	0.54	0.19	12.46	5.91	1.45	-0.55
11	3.65	2.84	87.15	11.25	1.21	0.45	17.81	7.33	1.31	-0.95
12	4.09	1.30	56.40	7.24	0.91	0.32	11.48	4.24	1.87	-0.81
13	2.94	5.17	118.62	15.87	2.35	0.75	26.07	9.56	1.30	-2.10
14	3.82	2.90	105.79	14.42	1.94	0.58	24.64	9.67	1.54	-2.01
15	1.70	1.08	70.97	9.24	0.91	0.32	15.39	6.72	1.69	-0.93
16	1.79	5.14	113.85	15.33	2.43	0.75	25.10	8.94	1.31	-2.11
17	7.73	6.01	126.88	16.17	1.81	0.74	24.68	9.36	1.15	-0.77
18	3.63	5.76	133.34	17.12	1.95	0.79	26.60	10.19	1.13	-1.10
19	3.04	4.66	131.54	17.76	2.61	0.85	29.97	11.22	1.32	-2.15
20	2.93	8.62	161.16	19.62	1.49	0.56	34.49	18.51	1.31	-1.06
21	5.54	6.24	127.44	16.60	1.98	0.71	25.64	9.80	1.07	-1.36
22	8.76	5.67	128.78	15.94	2.14	0.86	26.07	10.09	1.20	-1.19
23	8.00	5.26	118.54	14.94	2.14	0.86	24.13	8.98	1.27	-1.19
24	4.80	6.19	122.97	16.02	2.11	0.76	24.68	8.75	1.17	-1.13
25	5.01	5.42	112.15	14.94	2.14	0.68	24.13	8.73	1.27	-1.95
26	2.45	6.47	121.28	15.60	1.98	0.73	23.73	8.54	1.12	-1.78
27	5.38	4.96	117.75	15.51	1.98	0.68	25.10	9.59	1.27	-1.27
28	6.41	9.33	149.10	18.10	1.52	0.50	31.53	16.58	1.25	-1.60
29	2.75	9.17	155.48	18.10	1.52	0.69	31.53	16.90	1.25	-0.65
30	8.42	6.31	127.66	15.60	1.98	0.92	23.73	8.78	1.12	-0.88

QSAR Model Development

Using the trial version of **SPSS 28.0**, the QSAR equation was generated by linear and multiple linear regression analysis. The accuracy of the QSAR models in calculating q2 (LOO technique) and finding systemic error was determined by comparing actual and estimated values.

Molecular Docking Study

The derivatives of benzimidazole (1-30) Table 1, selected from the reported work by Vashist *et al.*, (2018) were sketched using ChemDraw 19.0. The molecular docking was done using **Schrodinger suite *v* 13.1.**

Protein Preparation

Each atom needs to possess a charge and an atom type that determines its properties to allow for docking algorithms to function. The PDB protein structure that was downloaded, though, is deficient in these features. In order to include these values along with the atomic coordinates, we have to generate the protein and ligand file. The Schrodinger suite's protein preparation wizard was used to prepare proteins. The **PDB ID: 1JIJ (for topoisomerase II)** and **PDB ID: 1KZN (for DNA Gyrase)** were downloaded in high resolution from RCSB protein data bank and preprocessed for further studies. Hydrogen atoms were added for the proper electrostatic treatment during docking. Water molecules were removed, bond order was generated [42].

PH 7.4 was used to create the protonation and tautomeric states.The Optimization of atomic charges and minimization of energy protein was done using OPLS force field to avoid steric clashes between the atoms [43].

Ligand Preparation

The mol^{2} file format is required for the preparation of 3D ligands which were needed to interact with

protein to determine their anticancer potential. A series of heterocyclic molecules selected from the literature were prepared using maestro module. Their 3D mol files were converted in the software accepted ***.maegz*** file in Ligprep. Minimization of all ligands was carried out using the OPLS force field module [44, 45]. The search algorithm and energy scoring function used in docking are used to generate and evaluate ligand poses within receptor binding sites. [46].

Grid Generation and Molecular Docking

The preprocessed protein (**1JIJ and 1KZN**) was taken and the most suitable grid was generated to around its most active site using site map tool. After the preparation of grid all the prepared ligands were added together to the grid generated receptor (active site of the protein) and using the most suitable protein ligand conformational complex, docking is done with extra precision (XP) to obtain the correct dock score values. [45] .

ADME Study

Determining ADME traits is crucial because the majority of pharmaceutical substances fail in clinical trials. The likeliness and ADME characteristics of the most active chemicals were determined using **QikProp, GLIDE,** and **Schrodinger *v* 13.1**. Using the LigPrep module of **Schrodinger *v* 13.1**, the ligand was synthesised for ADME study in Maestro format (**.maez**). Then, we went to work by navigating the QikPro dialogue box and inserting the ligand preparation file (.maez) for the synthesised derivatives in order to obtain the ADME parameters [47].

RESULTS AND DISCUSSION

2D QSAR Study

In response to the foregoing findings, and in the current study we hereby report QSAR, Molecular Docking and ADME Studies for the prediction of Benzimidazole derivatives as antibacterial agent were synthesised by Vashist *et al*., (2018) [40]. Using a variety of chemical descriptors, the structural properties of the therapeutic compounds in the current study were first quantified (**Table 3**).

After that, using multiple linear regression and linear regression, features and biological activity were quantified and associated to equations. In order to use pMIC values as the dependent variable in the QSAR investigation, biological data that was initially determined as MIC values were first converted into pMIC values (**Table 2**).

QSAR models for antibacterial potential against *Escherichia Coli* are as follows

Correlation analysis was used in the initial study. The correlation matrix for antibacterial compounds' activity against ***Escherichia coli*** is presented in **Table 4**. The colinearity ($r > 0.8$) between various variables was significant. The correlation matrix showed that the topological index **Balaban (r = 0.582, Eq. 1)** (**Table 4**) was used to define the antibacterial activity of benzimidazole derivatives.

The equation comes out as:

$$pMIC_{ec} = 1.207\ J - 0.0210 \quad (Eq.1)$$

$n= 30, r= 0.582, q^2= 0.249, F= 0.000 , SD= 0.306$

where q^2 - cross-validated, n - number of data points, F - Fischer statistics, r - correlation coefficients, r^2 - obtained by leaving one out method, SD - standard deviation

Electronic parameter Vamp Lumo was introduced to topological index Balaban to improve the r value, increasing the correlation value to 0.706 (Eq. 2).

$$pMIC_{ec} = 1.314\ J - 0.293\ VAMP\ LUMO - 0.469 \quad (Eq.\ 2)$$

$n= 30, r= 0.706, q^2= 0.396, F= 7.298, SD= 0.271$

The correlation value was increased to 0.742 (Eq. 3) by adding $K\alpha^2$ to Eq. 2 in order to further improve the r value.

$$pMIC_{ec} = 0.025\ J - 1.434\ VAMP\ LUMO - 0.253\ K\alpha^2 - 0.795 \quad (Eq.3)$$

$n= 30, r= 0.742, q^2= 0.431, F= 6.782 , SD= 0.261$

However, since the value of q^2 is not close to 0.5 or more and the value of r is not closer to 1, this shows that the model is not significant. The presence of outliers may be responsible for this. As a result, **6 outliers (compound 11, 10, 6, 4, 2, 1)** were found and eliminated, raising the value of r to 0.891 (Eq. 4). The equation has statistical significance.

$$pMIC_{ec} = 0.016\ J - 1.384\ VAMP\ LUMO - 0.160\ K\alpha^2 - 0.477 \quad (Eq.4)$$

$n= 24, r= 0.891, q^2= 0.675, F= 1.464 , SD= 0.139$

Table 4 Correlation matrix for antibacterial activity against *Escherichia Coli*

	$pMIC_{EC}$	μ	log P	MR	$^{1}\chi^{v}$	$^{3}\chi$	$^{3}\chi^{v}$	κ^{1}	$K\alpha^{2}$	J	LUMO
$pMIC_{EC}$	1.00										
μ	-0.31	1.00									
log P	-0.40	0.10	1.00								
MR	-0.23	0.02	0.92	1.00							
$^{1}\chi^{v}$	-0.21	-0.03	0.87	0.99	1.00						
$^{3}\chi$	-0.09	0.00	0.48	0.67	0.76	1.00					
$^{3}\chi^{v}$	-0.21	0.19	0.59	0.76	0.80	0.92	1.00				
κ^{1}	-0.11	-0.09	0.86	0.98	0.99	0.71	0.73	1.00			
$K\alpha^{2}$	-0.06	-0.13	0.87	0.90	0.85	0.37	0.43	0.91	1.00		
J	0.58	-0.38	-0.66	-0.60	-0.60	-0.51	-0.61	-0.49	-0.33	1.00	
LUMO	0.37	-0.49	-0.17	-0.10	0.00	0.19	-0.15	0.03	-0.06	0.24	1.00

The QSAR model is valid if the value of q2 is greater than 0.5. Plotting observed against predicted activity, however, demonstrates the validity of the QSAR model (**Figure 1; Table 4**). To determine the systemic error, the measured values were plotted against the residual values (**Figure 2**). The absence of a systemic error in the design of the QSAR model was shown by the zero residual propagation on every dimension.

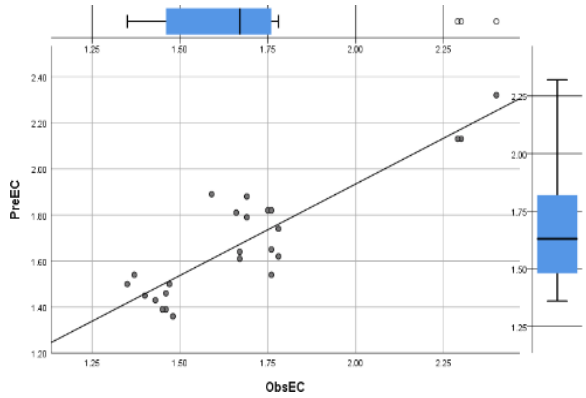


Fig. 1 Plot of Observed vs. Predicted Activity

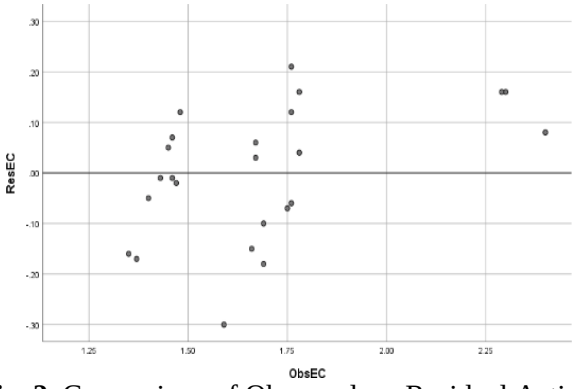


Fig. 2 Comparison of Observed vs. Residual Activity

QSAR models for antibacterial activity against *Staphylococcus aureus* are as follows

Correlation analysis was used in the initial study. The correlation matrix for antibacterial compounds' activity against ***Staphylococcus aureus*** is presented in **Table 5**. The colinearity (r > 0.8) between various variables was significant. The initial correlation of **r = 0.848** was found with the topological parameters third-order molecular connectivity index (Eq. 5) Table 5. When r is closer to 1 and q2 is identically close to or above 0.5, this suggests that the equation is statistically significant.

The equation comes out as:

$$pMIC_{sa} = -0.376\ ^{3}\chi - 1.986 \quad (\text{Eq. 5})$$

n= 30, r= 0.848, q^2= 0.674, F= 2.398, SD= 0.135

Table 5 Correlation matrix for antibacterial activity again *Staphylococcus aureus*

	$pMIC_{SA}$	μ	log P	MR	$^{1}\chi^{v}$	$^{3}\chi$	$^{3}\chi^{v}$	κ^{1}	$K\alpha^{2}$	J	LUMO
$pMIC_{SA}$	1.00										
μ	0.14	1.00									
log P	-0.52	0.07	1.00								
MR	-0.71	-0.03	0.93	1.00							
$^{1}\chi^{v}$	-0.76	-0.10	0.88	0.99	1.00						
$^{3}\chi$	-0.84	-0.03	0.57	0.74	0.81	1.00					
$^{3}\chi^{v}$	-0.82	0.19	0.65	0.79	0.82	0.92	1.00				
κ^{1}	-0.73	-0.15	0.87	0.98	0.99	0.77	0.75	1.00			
$K\alpha^{2}$	-0.48	-0.17	0.86	0.91	0.87	0.47	0.49	0.92	1.00		
J	0.16	-0.42	-0.61	-0.51	-0.49	-0.43	-0.56	-0.39	-0.27	1.00	
LUMO	-0.30	-0.60	-0.02	0.07	0.18	0.29	-0.05	0.20	0.10	0.29	1.00

The QSAR model is valid if the value of q2 is greater than 0.5. Plotting observed against predicted activity, however, demonstrates the validity of the QSAR model (**Figure 3; Table 5**). To determine the systemic error, the measured values were plotted against the residual values (**Figure 4**). The absence of a systemic error in the design of the QSAR model was shown by the zero residual propagation on every dimension.

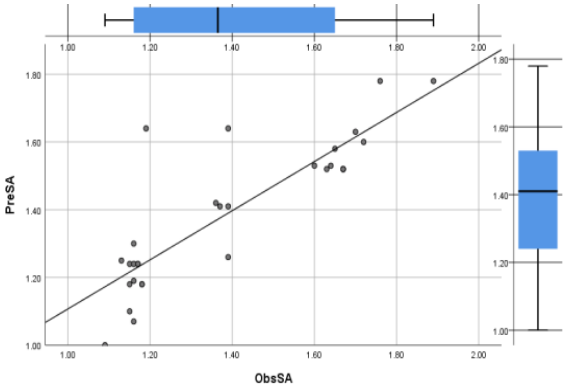


Fig. 3 Plot of Observed vs. Predicted Activity

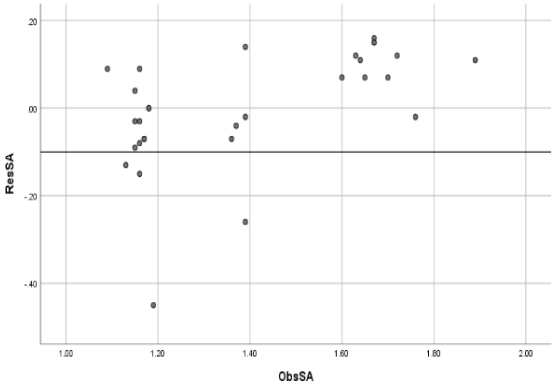


Fig. 4 Comparison of Observed vs. Residual Activity

We are able to determine from the data above that all QSAR models are authentic. In contrast, the validity of the QSAR model is demonstrated by the comparison of observed, predicted, and residual values of each of the organisms taken, shown in **Table 6**.

Table 6 Observed, predicted, and residual activity values of the benzimidazole derivatives

C. No.	*Escherichia Coli*			*Staphylococcus aureus*		
	Obs.	**Pre.**	**Res.**	**Obs.**	**Pre.**	**Res.**
1	-	-	-	1.63	1.52	0.12
2	-	-	-	1.64	1.53	0.11
3	1.35	1.50	-0.16	1.65	1.58	0.07
4	-	-	-	1.72	1.60	0.12
5	1.67	1.61	0.06	1.67	1.52	0.15
6	-	-	--	1.67	1.52	0.16
7	1.37	1.54	-0.17	1.67	1.52	0.15
8	1.59	1.89	-0.30	1.89	1.78	0.11
9	1.40	1.45	-0.05	1.70	1.63	0.07
10	-	-	-	1.76	1.78	-0.02
11	-	-	-	1.60	1.53	0.07
12	2.40	2.32	0.08	1.19	1.64	-0.45
13	1.75	1.82	-0.07	1.15	1.10	0.04
14	2.30	2.13	0.16	1.39	1.26	0.14
15	2.29	2.13	0.16	1.39	1.64	-0.26
16	1.76	1.82	-0.06	1.16	1.07	0.09
17	1.46	1.39	0.07	1.16	1.30	-0.15
18	1.43	1.43	-0.01	1.13	1.25	-0.13
19	1.69	1.88	-0.18	1.09	1.00	0.09
20	1.66	1.81	-0.15	1.36	1.42	-0.07
21	1.45	1.39	0.05	1.15	1.24	-0.09
22	1.76	1.54	0.21	1.15	1.18	-0.03
23	1.78	1.62	0.16	1.18	1.18	0.00
24	1.46	1.46	-0.01	1.16	1.19	-0.03
25	1.78	1.74	0.04	1.18	1.18	0.00
26	1.47	1.50	-0.02	1.17	1.24	-0.07
27	1.76	1.65	0.12	1.16	1.24	-0.08
28	1.69	1.79	-0.10	1.39	1.41	-0.02
29	1.67	1.64	0.03	1.37	1.41	-0.04
30	1.48	1.36	0.12	1.17	1.24	-0.07

Note: (-) used in the table refers to the outliers removed against the particular organisms.

Molecular Docking

The derivatives of benzimidazole were selected from reported work by Vashist *et al.*, (2018) (Table 2), and their antibacterial docking score and glide energy was determined by molecular docking software **Schrodinger *v* 13.1**, using **topoiso merase II (PDB ID: 1JIJ) and DNA gyrase subunit b (PDB ID: 1KZN), (Table 7) concerning a standard drug (norfloxacin).**

Table 7 Docking score and Glide energy of the Benzimidazole derivatives

C. No.	Docking Score (PDB ID: 1JIJ)	Glide Energy (PDB ID: 1JIJ)	C. No.	Docking Score (PDB ID: 1KZN)	Glide Energy (PDB ID: 1KZN)
1	-3.139	-41.909	1	-4.924	-40.380
2	-5.584	-48.221	2	-5.694	-42.415
3	-3.122	-45.254	3	-4.892	-40.512
4	-5.412	-45.331	4	-4.578	-37.147
5	-4.436	-43.791	5	-4.896	-42.936
6	-3.495	-39.866	6	-5.020	-40.062
7	-5.222	-45.730	7	-4.825	-39.607
8	-3.653	-30.336	8	-4.515	-29.675
9	-2.144	-42.239	9	-5.459	-41.327
10	-4.024	-38.416	10	-5.199	-34.512
11	-4.349	-46.785	11	-4.949	-40.178
12	-4.510	-36.767	12	-5.069	-33.517
13	-3.022	-52.130	13	-4.336	-47.189
14	-4.522	-56.001	14	-6.150	-53.381
15	-5.910	-46.479	15	-5.642	-39.551
16	-3.449	-50.369	16	-4.831	-47.563
17	-3.411	-54.375	17	-4.826	-48.829
18	-3.907	-54.466	18	-5.428	-56.119
19	-4.256	-64.657	19	-5.494	-50.874
20	-0.841	-57.486	20	-5.274	-52.425
21	-2.598	-55.694	21	-4.257	-50.302
22	-0.584	-54.494	22	-5.532	-47.710
23	-4.641	-52.333	23	-5.492	-47.725
24	-4.981	-55.172	24	-4.711	-54.153
25	-4.666	-58.485	25	-5.694	-47.722
26	-3.454	-47.272	26	-5.454	-46.947
27	-4.674	-58.501	27	-5.839	-49.059
28	-1.021	-58.073	28	-4.702	-55.049
29	-1.028	-61.297	29	-4.759	-53.418
30	-3.582	-54.091	30	-5.468	-48.057
Norfloxacin	-4.799	-36.525	Norfloxacin	-4.799	-36.525

Molecular docking was employed to investigate when the derivatives of benzimidazole interact to their specific receptors. A molecular docking analysis of benzimidazole compounds and a common drug (norfloxacin) was performed by using the active site of **Topoisomerase II (PDB ID: 1JIJ)**. According to the 2-D ligand interaction diagrammatic perspective, the oxygen atom of compound 15's amide nucleus formed hydrogen bonds with Gln190 and Gly193. Compound 2's amide nucleus' amino group formed hydrogen bonds with Gly38. The oxygen atoms of Tyr36, Val69, and Asp177 formed hydrogen bonds and the amino group also interacted with Leu57 and Gln196 in the amide nucleus of compound 4. The interaction like Gln196, Asp40, Leu40, and Gly38, the amino group of compound 7's amide nucleus formed hydrogen bonds. Compound 24's amide nucleus' oxygen atom formed hydrogen bonds with Gly38 and Asp195. The oxygen atom of the common drug Norfloxacin formed hydrogen bonds with the amino acids like Ile68, Gln190, Tyr36, and Asp177. The gliding energy and emodel values related to the docking scores were shown in negative terms. The ligand's affinity for binding to the receptor increases with decreasing docking score. **Table 8** shows the docking data for the top five compounds (**15, 2**, **4, 7 and 24**) and the reference medication. Figures **5, 6, 7, 8, 9**, and **10** illustrate the ligand interaction diagram and the binding surface of docked molecules **15, 2, 4, 7, 24**, and **norfloxacin**, respectively. According to the 2-D ligand interaction diagrammatic perspective, these compounds interact with homologous amino

acid residues to have the same homology as regular norfloxacin.

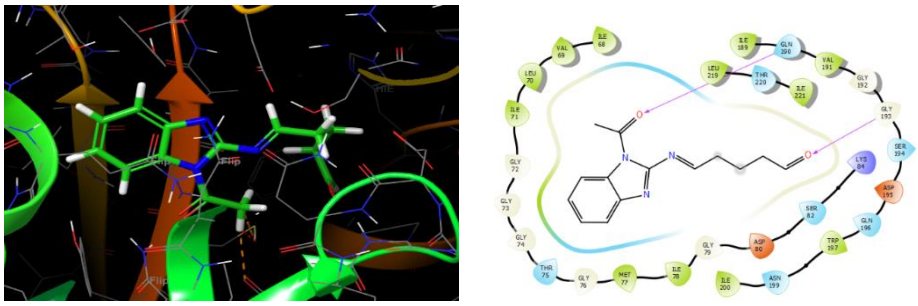


Fig 5 Binding surface and 2D interaction of molecule 15

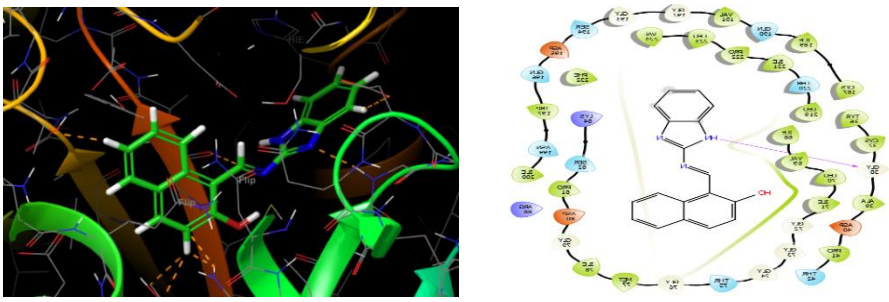


Fig 6 Binding surface and 2D interaction of molecule 2

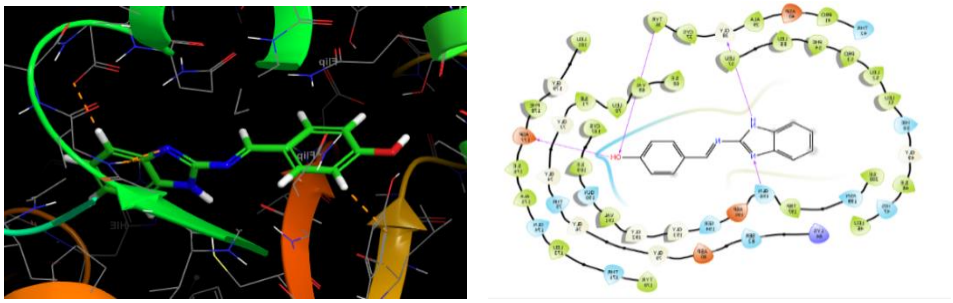


Fig 7 Binding surface and 2D interaction of molecule 4

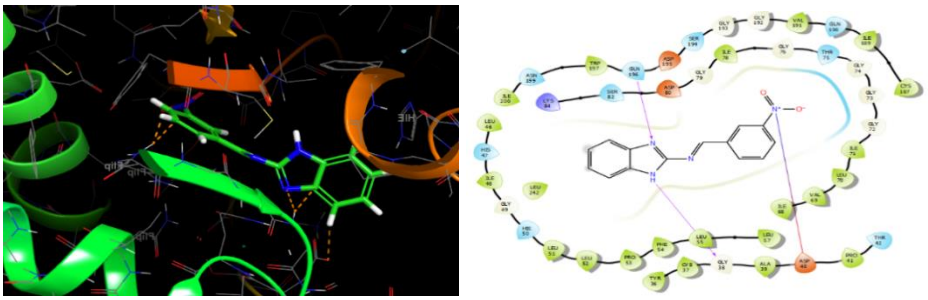


Fig 8 Binding surface and 2D interaction of molecule 7

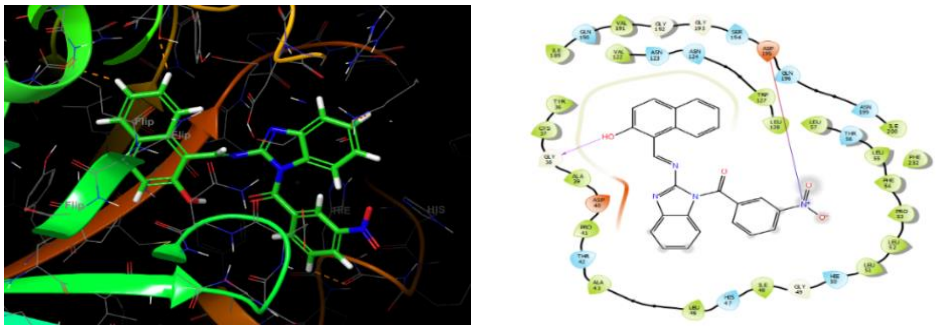


Fig 9 Binding surface and 2D interaction of molecule 24

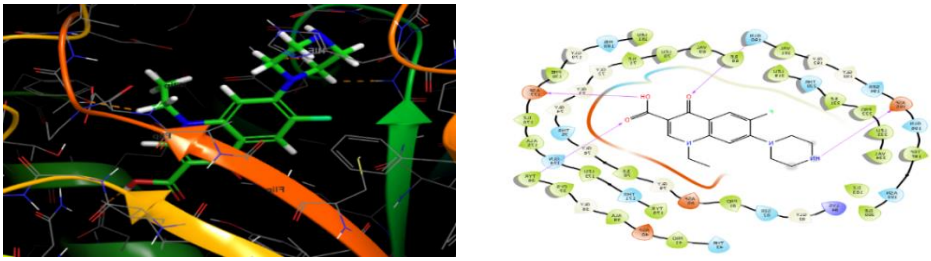


Fig 10 Binding surface and 2D interaction of Norfloxacin

Table 8 Docking score of the top five Benzimidazole derivatives using PDB ID : 1JIJ1

C. No.	Docking Score	Glide Energy	Glide Emodel	Interaxting Residues
15	-5.910	-46.479	-63.212	Gln190, Gly193
2	-5.584	-48.221	-64.768	Gly38
4	-5.412	-45.331	-61.845	Leu57, Gln196, Tyr36, Val69, Asp177
7	-5.222	-45.730	-57.683	Gln196, Asp40, Leu55, Gly38
24	-4.981	-55.172	-80.237	Gly38, Asp195
Norfloxacin	-4.799	-36.525	-42.609	Asp195, Ile68, Gln190, Tyr36, Asp177

Molecular docking was employed to investigate when the derivatives of benzimidazole interact to their specific receptors. A molecular docking analysis of benzimidazole compounds and a common drug (norfloxacin) was performed by using the active site of **DNA Gyrase (PDB ID: 1KZN)**. The 2-D ligand interaction diagrammatic perspective showed that the oxygen atom of compound 14's amide nucleus formed hydrogen interactions with the Arg76, Val120, and water amino acid residues. The oxygen atoms in the amide nucleus of compound 27 formed hydrogen bonds with the amino acid residues of gly77 and water. The oxygen atoms in the amide nucleus of compound 2 formed hydrogen bond with the amino acid residues of asp49 and water. Amino acid residues Glu50, Thr165, and water formed hydrogen bonds with the oxygen atoms of compound 25's amide nucleus. The amide nucleus of compound 15's Val120 and water amino acid residues formed hydrogen bonds with the oxygen atoms of the amide nucleus. The oxygen atom of the common drug Norfloxacin formed hydrogen bonds with the amino acid residues Asp73, Gly75, Tyr36, and water. The gliding energy and emodel values related to the docking scores were shown in negative terms. The ligand's affinity for binding to the receptor increases with decreasing docking score. **Table 9** shows the docking data for the top five compounds **14, 27**, **2, 25 and 15** and the reference medication. Figures **11, 12, 13, 14, 15**, and **16** illustrate the ligand interaction diagram and the binding surface of docked molecules **14, 27, 2, 25, 15**, and **norfloxacin**, respectively. According to the 2-D ligand interaction diagrammatic perspective, these compounds interact with homologous amino acid residues to have the same homology as regular norfloxacin.

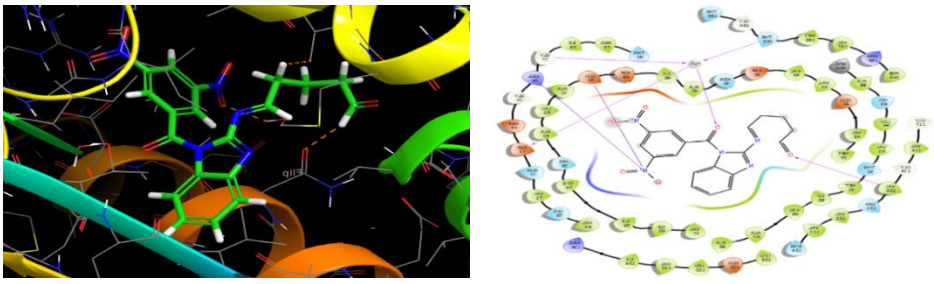


Fig 11 Binding surface and 2D interaction of molecule 14

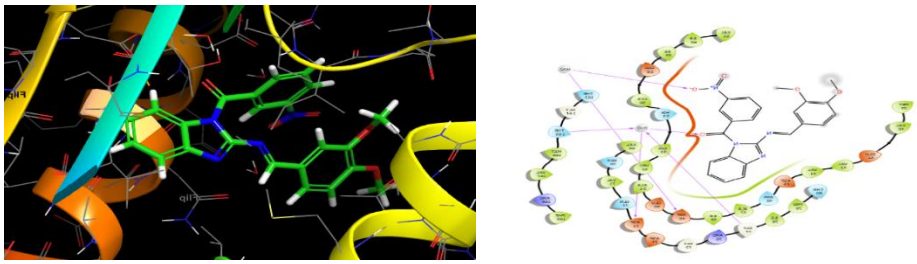


Fig 12 Binding surface and 2D interaction of molecule 27

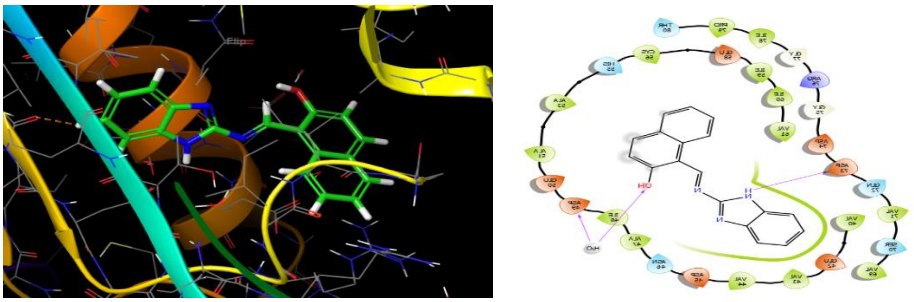


Fig 13 Binding surface and 2D interaction of molecule 2

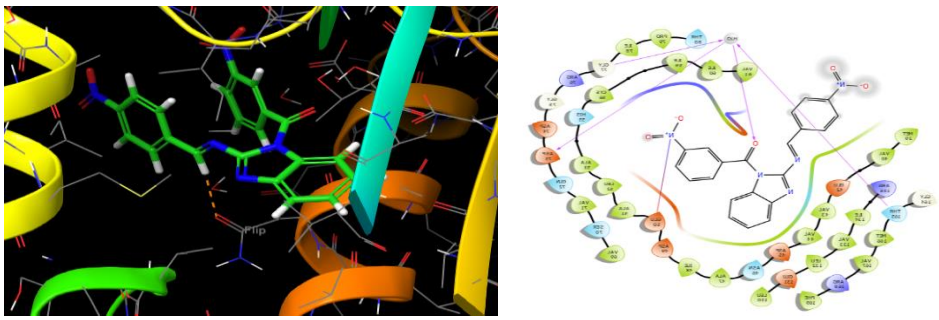


Fig 14 Binding surface and 2D interaction of molecule 25

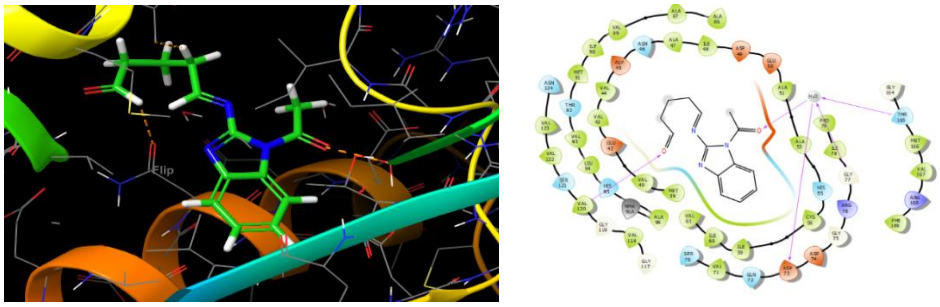


Fig 15 Binding surface and 2D interaction of molecule 15

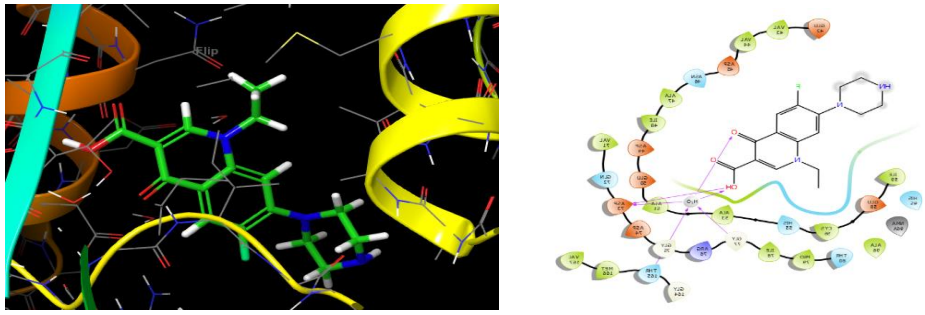


Fig 16 Binding surface and 2D interaction of Norfloxacin

Table 9 Docking score of the top five Benzimidazole derivatives using PDB ID : 1KZN

C. No.	Docking Score	Glide Energy	Glide Emodel	Interacting Residues
14	-6.150	-53.381	-63.076	Arg76, Val120, Glu50
27	-5.839	-49.059	-69.928	Gly77 and water
2	-5.694	-42.415	-53.182	Asp73, Asp49
25	-5.694	-47.722	-66.996	Glu50, Thr165
15	-5.642	-39.551	-51.897	Val120 and water
Norfloxacin	-4.799	-36.525	-42.609	Asp73, Gly75

ADME Study

The **Schrodinger *v* 13.1** QikProp module was used to determine the ADME properties of the reported benzimidazole derivatives. The most active structures, including **2, 4, 7, 14, 15, 24, 25 and 27**, possess ADMET data presented in **Table 10**. The

molecules **2, 4, 7, 14, 15, 24, 25 and 27** adhere to each component of the Lipinski rule of five. The results suggested that the compounds **2, 4, 7, 14, 15, 24, 25 and 27** follow the Lipinski's rule, recommending that these derivatives could be employed as modelling molecules in future studies.

Table 10 ADME data of most active compounds calculates using Qik Prop Simulation

C.No.	MW	QPlogPo/w	AcceptHB	QPlogBB	DonorHB	Human oral bsorption	Rule of Five
2	287.320	3.484	3.250	-0.557	2	3	0
4	237.260	2.473	3.250	-0.691	2	3	0
7	266.259	2.549	3.500	-1.121	1	3	0
14	409.357	0.678	8.500	-2.111	0	2	1
15	257.291	0.745	7.500	-1.254	0	3	0
24	436.426	3.529	7.250	-1.147	1	3	0
25	415.364	2.162	7.500	-2.097	0	3	0
27	430.419	3.077	8.000	-1.315	0	3	0

- ✓ Molecular weight, not more than 500 Da.
- ✓ Hydrogen bond donor (Accepted Limit: ≤ 5)
- ✓ Hydrogen bond acceptor (Accepted Limit: ≤ 10)
- ✓ Log P less than 5.
- ✓ Human oral absorption – 1, 2, or 3 for low, medium, or high.
- ✓ QPlogBB range from -3.0 to 1.2.

CONCLUSION

Various computational techniques, including 2D QSAR, molecular docking, and ADME studies of benzimidazole derivatives against ***S. Aureus*** and ***E. Coli***, were used in this research study. Molecular descriptors used in 2D QSAR studies, include topological index Balaban (J), electronic parameters like Vamp Lumo & Kier's second order alpha shape index ($k\alpha^2$) against ***E.Coli*** microorganisms. The antibacterial activity of benzimidazole derivatives is governed by topological parameters like third-order molecular connectivity index ($^3\chi$) against ***S. Aureus*** microorganisms. According to molecular docking studies, compounds **15, 2, 4, 7** and **24** have the best docking scores against the protein **Topoisomerase II (PDB ID: 1JIJ)** and compounds **14, 27, 2, 25** and **15** have the best docking scores against the protein **DNA Gyrase (PDB ID: 1KZN)**. The Lipinski rule of five was used to determine an excellent ADME profile based on QSAR, molecular docking data, and binding interaction analysis. According to the study, these compounds may be used as lead structures for more investigation of antimicrobial resistance.

Abbreviations

QSAR: Quantitative structure activity relationship; CADD: Computer Aided Drug Design; MIC: Minimum Inhibitory Concentration; MLR: Multiple Linear Regression; Log P: Partition Coefficient; pMIC: log of Minimum Inhibitory Concentration; µM: Micromol; SA: S.Aureus; EC: E.Coli; PDB: Protein data bank; LOO: Leave one out; ADME; Adsorption Distribution Metabolism Excretion; HOMO: Highest occupied molecular orbital; LUMO: Lowest unoccupied molecular orbital; J: Balaban topological index; W: Wiener topological index; R: Randic topological index; µ: Total dipole; MR: Molecular Refractivity

Acknowledgements

The authors thank the Head of the Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, for providing the necessary facilities to carry out this research work—special thanks to Vinod Devaraji and his team for guiding and learning Schrodinger software.

Authors' Contributions

Authors VK and BN designed the computational study; VK, JR and MK carried out the 2D QSAR study; SY and AS carried out the molecular docking study; KB carried out the ADME study of synthesised compounds; MK helped in critical revision of the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable

Conflict of interest

The authors declare no conflict of interest

Consent for publication

All authors of the research paper have approved the manuscript for submission.

Author details
[1]Faculty of Pharmaceutical Sciences, D.K. Pharma College of Pharmacy, Rewari , Haryana, India - 123411.[2]Faculty of Pharmaceutical Sciences, Indira Gandhi University, Meerpur, Rewari , Haryana, India -122502.[3]Faculty of Pharmaceutical Sciences, Gurugram global College of Pharmacy, Gurgaon, Haryana, India-122506.[4,5]Faculty of Pharmaceutical Sciences, Deen Dayal Rustagi College of Pharmacy, Gurgaon, Haryana, India - 122504. [6,7]*Faculty of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, Haryana, India – 12400.

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