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Research Article

DESIGN AND MOLECULAR DOCKING STUDIES OF PIPERIDIN-4-ONE DERIVATIVE AS ACTIVE AGENT AGAINST *HELICOBACTER PYLORI* INFECTION

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ABSTRACT

Helicobacter pylori is one of the most common bacterial pathogens in the world and is an important global public health concern. Half of the world populations are seriously infected by *Helicobacter pylori*. In India, approximately 80% of the population is infected with the bacterium *Helicobacter pylori* by the age of 20. Among those, hundreds of millions of people are affected by peptic ulcer disease during their lifetime and tens of millions might develop to gastric cancer. *Helicobacter pylori* infections are very difficult to cure. This present work is aimed to find the solutions to overcome this problem. Black pepper is used to cure ulcer since it has piperine which has piperidin moiety. Piperidin-4-one is one of the most biological active moieties, used as drug. In the present work, more than thirty eight thousand, 2,6-diphenyl piperidone derivatives are theoretically designed and docked with 2B7N protein of *Helicobacter pylori*. PyRx virtual screening is used to dock protein with ligand to find lead molecules. The best docking piperidones are selected and their drug likeness properties are predicted computationally. Finally best lead molecule is identified.

Keywords: Molecular docking, Virtual screening, 2B7N, Piperidone, PyRx.

1. INTRODUCTION

Helicobacter pylori is a spiral shaped bacterium which lives in the stomach and duodenum. It is an important human pathogen responsible for most peptic ulcer disease, gastric malignancies and gastritis. It is also linked to the duodenal ulcer and it is the only bacterium strongly associated with gastric cancer. It penetrates mucoid lining of the stomach and it is adapted to the harsh environment of the stomach [1, 2]. Generally white and black peppers are used to cure ulcer. They contain natural piperine which cures ulcer. It has piperidine moiety. Piperidin-4-one is a very important pharmacophore present in wide range of natural alkaloids and has increasing pharmacological activities including antibacterial, anticancer and anti oxidant activities [3]. The present study seeks to prove that, the addition of some functional group into the piperidin-4-one pharmacophore with different modifications would result in compounds of potent anti *Helicobacter pylori* activity.

2. MATERIAL AND METHODS

2.1. Preparation of protein

The X-ray crystal structure of the 2B7N protein *phosphoribosyl transferase* in complex with quinolinic acid of *Helicobacter pylori* having resolution 2.30 Å was retrieved from protein data bank (http://www.rcsb.org/pdb/explore/explore.do?StructureId=2B7N) [4]. 2B7N has three identical chains. Chain A is retained and chain B & C were removed. Chain A from the enzyme is involved in the docking studies because 96% of residues are located in favoured region in Ramachandran plot**.** This procedure reduces the computation time very much.

Before docking, the structure of protein was prepared by using Discovery Studio 4.1 Visualizer [5]. It is involved in the removal of water molecule. All the hetero-atoms were removed from the 2B7N. pdb, to make complex receptor free of any ligand before docking. Polar hydrogen atoms are added to the protein, which is an important and necessary step for

the computation of partial atomic charges. The force field applied was CHARMm and the partial charge applied was Momany-Rone. The protein was then energy minimized. The Graphical user interface program PyRx [6] was used to prepare and run the docking simulations and the results were analyzed by PyMOL [7].

2.2. Ramachandran plot

The quality and structural assessment of model was analyzed by PROCHEK server. The 2B7N of *Helicobacter pylori* has been validated with Ramachandran plot [8] and depicted in Fig. 1.

From the Fig.1, the red region in the graph indicates the most favoured regions. 90.1% of residues are located at most favoured regions. 9.1% of residues are located at additional allowed region indicated as brown colour. 0.8% of the residues fall in the generously allowed regions indicated by yellow colour. In disallowed region no residue is present. The most favoured region score greater than 50% are acceptable for a reasonable protein model [9]. In the overall 2B7N Ramachandran plot, 90.1% of amino acid residues fall under the most favoured region. It confirms the good quality of the model.

2.3. ERRAT analysis

The non bonded interaction between the atoms were also computed with the ERRAT program (http://services. mbi.ucla.edu/ERRAT/), which shows the overall quality factor is 97.727 and shown in Fig. 2.

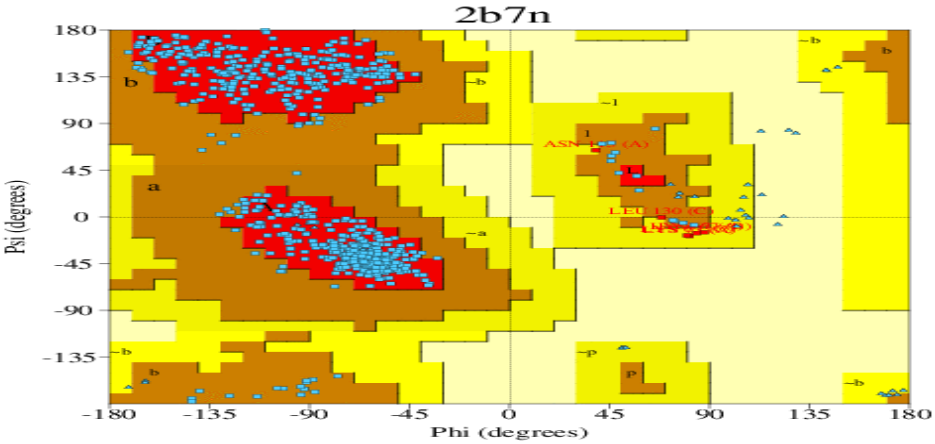


Fig. 1: Ramachandran plot analysis of 2B7N protein

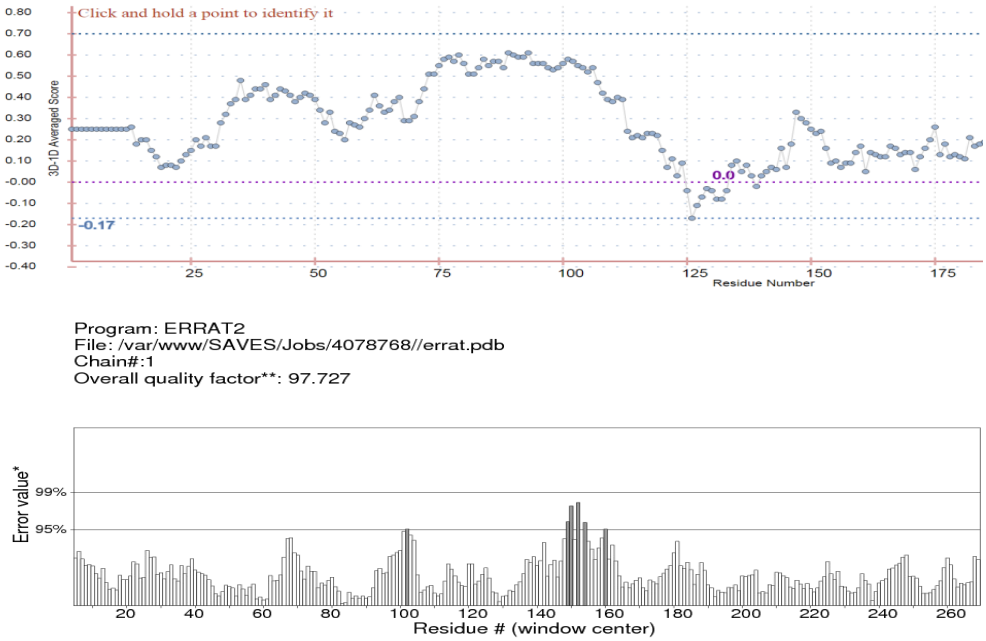
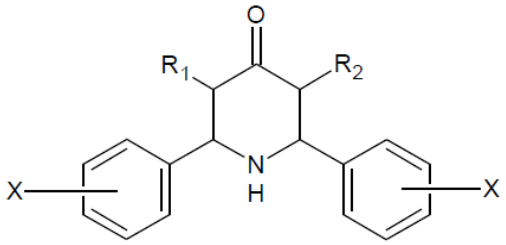


Fig. 2: ERRAT Analysis of protein 2B7N

2.4. Designing and preparation of ligands

Various 2,6-diphenyl piperidones were designed based on literature [10]. The parent structure of piperidin-4-one is shown in table 1. First a list of various aromatic mono/multi nucleus aldehydes is collected from ASPIN CO (http://www.apin.co.uk/?op=groups & group=Aromatic+Aldehydes+%26+Derivatives+(substituted)) The structures of the aromatic aldehydes are obtained from open molecules website (http://www. Open-molecules.org/name2structure.html). The names and structures of ketones are collected from various pharmaceutical websites.

Table 1: The various substituents in parent structure of piperidin-4-one



R1	R2	X
CH_3	H	X may be generally OH, Cl, Br, I, OCH_3, NO_2, CN, NH_2 etc at appropriate positions
CH_2CH_3	H	
$CH(CH_3)_2$	H	
$C(CH_3)_3$	H	
CH_3	CH_3	
CH_3	Cl	
CH_2CH_3	CH_2CH_3	
CH_2CH_3	$CH=CH_2$	
$CH_2CH_2CH_3$	H	
$CH_2CH_2C(CH_3)_2$	H	
CH_3	CH_2CH_3	
$CH_2CH_2CH_3$	OCH_3	
$CH(CH_3)_2$	OCH_3	
OCH_2CH_3	H	
CH_2CH_2OH	H	
$COOCH_3$	H	
$OCOCH_3$	H	
$CH_2COOCH_2CH_3$	H	
CH_3	Br	
Br	H	
$CH_2CH_2CH_2Br$	H	
OCH_2CH_3	CH_3	
CH_2	H	
$CH(CH_3)_2$	$CH(CH_3)_2$	
CH_2COCH_3	H	
$CH_2CH_2CH_3$	H	
CH_3	$CH_2CH_2CH_2CH_2CH_3$	
$CH_2CH_2CH_2CH_2CH_2CH_3$	H	
CH_2CH_3	$CH_2CH_2CH_3$	
$CH_2CH_2CH_2CH_2CH_3$	H	
CH_3	CH_2	
$COCH_3$	H	
CH_2Ph	H	
CH_3	Ph	
OPh	H	

OPh	CH_3
OPh	CH_2CH_3
CH_3CHPh	H
CH_2CH_2Ph	H
$OCH_2CH_2CH_3$	H
$CH_2CH_2CH_2CH_3$	$CH_2CH_2CH_2CH_3$

Based on these aldehyde and ketone structures, more than thirty eight thousands of 2,6-diphenyl piperidin-4-one analogues were designed by Chemsketch software (http://www.acdlabs.com/resources/freeware/chemsketch/) and saved as .mol file. Then the 2D structures were converted to 3D structures and energy was minimized by Avogadro tool (https://avogadro.cc/) and saved as. pdb files, since optimization leads to a stable conformation of coordinates with minimum energy. The force field applied was MMFF 94. The algorithm used was Steepest Descend algorithm.

2.5. Molecular docking

Virtual screening methods have been showing success in predicting new leads with good hit rates reported [11, 12]. Docking was performed with PyRx virtual screening with AutoDock tools. PyRx is a powerful visualization tool need for rational drug design. The AutoDock is a automated docking software designed to predict the protein ligand binding site in 3D structure [13]. Docking coordinates are x= -1.3638, y = 183.643 and z = 5.4024 with dimensions x = 78.7275, y = 43.5106 and z = 60.9476 respectively. The docking simulation was then run with an exhaustiveness of 8. Using PyMOL, the docking site was viewed and analyzed.

3. RESULTS AND DISCUSSION

This work aimed to identify new *H. pylori* inhibitors using virtual screening. In this present study, all the designed 38,361 compounds were docked with 2B7N protein using PyRx virtual screening tool. All the designed ligands are docked with the biggest pocket of the enzyme target located on chain A. The designed compounds were docked with the target protein 2B7N and the binding affinities were noted. The binding affinity value, more than -8.0 Kcal/mol was chosen at the cut off for further step. The top ranked 4872 compounds were selected for further investigations.

Oral bioavailability predictions were made using Lipinski's rule of five [14]. The drug likeness score also found using Molsoft software (http://www.molsoft.com/). Compounds with more than five hydrogen bond donors and ten hydrogen bond acceptors are excluded. The negative drug likeness score also excluded. Compounds which obey the Lipinski rule were selected. Finally 68 leads are selected for further investigations. The top most selected ten good binding affinities and drug like compounds are listed in Table 2 and Table 3.

From the Table 3, code 54291 shows good drug likeness and decided to continue for further investigations.

The binding affinity ranges of all the 38,361 compounds are listed in Table 4 and shown in Fig.3. From the Fig.3 and Table 4, anyone can find that, majority of the binding affinity of various ligands fall under 6.0-6.9 Kcal/mol range.

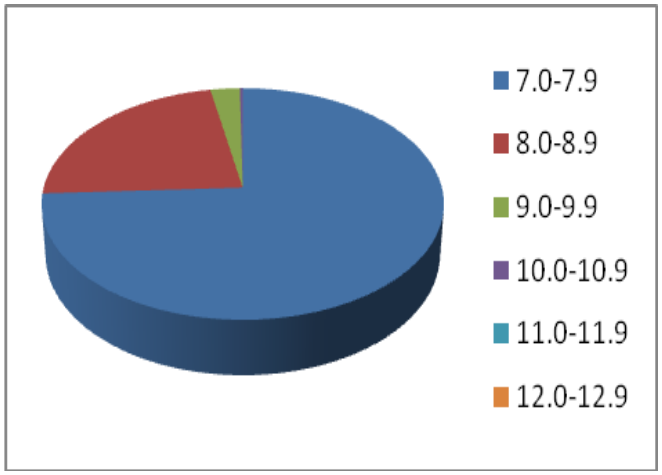


Fig.3: Pie chart of binding affinity ranges

3.1. MOPAC calculation of 54291

The target molecule (code 54291) is subjected to MOPAC [15] calculation to find out some physical parameters. The calculated physical parameters are listed in Table 5. According to the theoretical findings, the point group of the molecule is found to be C1. The heat of formation, total energy, electronic energy and core-core repulsion energy are found to be-132.378541 Kcal/mol, -5037.55496 eV, -45487.85941 eV and 40450.30444 eV respectively. The zero point energy (lowest energy of ground state) is found to be 264.041 Kcal/mol.

The rotational constant values are also predicted and shown in the Table 5. From the Table 5 it is clear that,

this molecule is having asymmetric top since A≠B≠C. Since the value of B<A, confirms that the molecule is of oblate top type. So that anyone can learn that, the rotational axis has a greater inertia than the degenerated axes of the molecule. The pKa value for all the hydroxyl groups is almost same and they are shown in the Table5.

Table 2: Docking scores of selected piperidone analogue with 2B7N protein

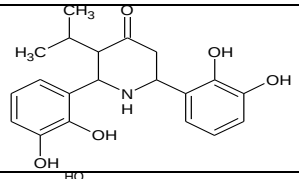
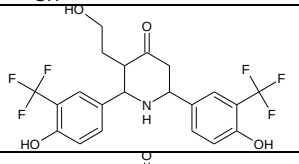
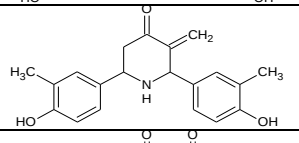
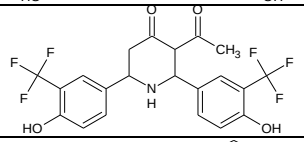
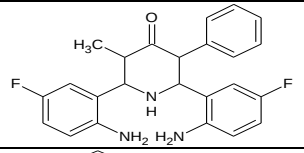
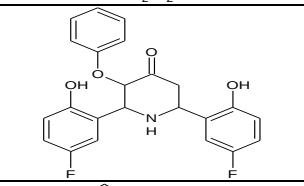
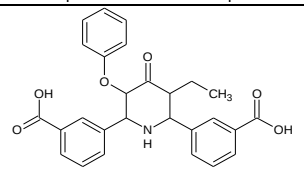
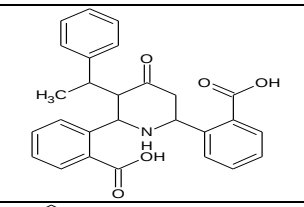
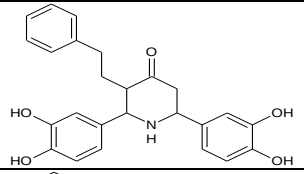
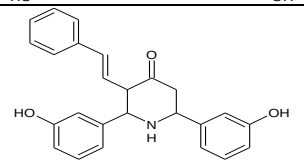
S. No	Ligand code	Structure	Binding affinity (Kcal/mol)
1	15287		-8.1
2	27518		-8.1
3	35489		-8.2
4	47518		-8.2
5	48020		-8.4
6	49395		-8.1
7	52151		-8.2
8	53438		-8.4
9	54291		-8.0
10	55468		-8.7

Table 3: Drug likeness results of selected piperidone analogues

S.No	Ligand code	Lipinski's Rule				Drug likeness score
		MW	HBD	HBA	logP	
1	15287	457	1	6	4.603598	0.20
2	27518	463	4	5	4.478801	0.52
3	35489	323	3	4	3.615638	0.18
4	47518	461	3	5	4.685401	0.36
5	48020	407	5	4	4.503799	0.02
6	49395	411	3	5	4.168398	0.17
7	52151	459	3	7	4.511500	0.10
8	53438	443	3	6	4.847700	0.26
9	54291	419	5	6	4.102798	1.17
10	55468	385	3	4	4.772200	0.05

Table 4: Binding affinity values of various ligands

Binding affinity ranges	No. of ligands
1.0-1.9	1
2.0-2.9	1
3.0-3.9	0
4.0-4.9	131
5.0-5.9	2,815
6.0-6.9	16, 532
7.0-7.9	14,009
8.0-8.9	4,310
9.0-9.9	511
10.0-10.9	48
11.0-11.9	3
12.0-12.9	0

Table 5: Physical parameters calculated by MOPAC tool for 54291

Physical parameter		Values
Molecular point group		C1
Heat of formation		-132.378541 Kcal/mol
Total energy		-5037.55496 eV
Electronic energy		-45487.85941 eV
Core-core repulsion		40450.30444 eV
Cosmo area		394.99 Square Angstroms
Cosmo volume		500.36 Cubic Angstroms
Gradient norm		0.98719 = 0.13192 per atom
Molecular weight		419.4762
No. of filled levels		80
Zero point energy		264.041 Kcal/mol
Rotational constants in cm^{-1}	A	0.00736674
	B	0.00314161
	C	0.00269491
pKa values of four hydroxyl groups		
53		10.164
54		9.772
55		9.546
56		9.678

4. CONCLUSION

In this study, docking of ligands with 2B7N was performed with PyRx virtual screening and is strongly supported the computer based drug discovery research. The final selected compounds are treated as best potent anti *Helicobacter pylori* agents. In future, from the obtained results, elongating the current studies, along with experimental and DFT studies, we can provide useful insights into drug design against *Helicobacter pylori* infection.

5. ACKNOWLEDGEMENT

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