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Evalution of Potential Histamine H2 Receptor Antagonist: A Computational Approach

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ABSTRACT
Type 2histamine receptor (H2) is responsible for secretion of gastric acid. Ligand based computational studies were carried out to identify new lead compounds as H2 receptor. Known H2 receptor inhibitors were subjected to pharmacophore modelling using PharmaGist web server. Thousand plus hits were identified using ZINCPharmer webserver, and were filtered using Data Warrior tool. The compounds filtered were docked with H2 receptor using Autodock vina. Based on the binding energy and amino acid interaction top six ligands are subsequently evaluated for ADMET properties using pKcsm webserver. ZINC47304988, and ZINC86481136 showed good binding energies in comparison with the standard drug cimetidine. These results highlight the identification of new class of H2 receptor inhibitor that have potential to be more efficacious than cimetidine to treat H2 receptor
KEYWORDS: *Cimetidine, Famotidine, H_2, Lafutidine, Nizatidine, Ranitidine*

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INTRODUCTION

A mucosal rupture that extends deeper than 3-5 mm into the duodenum or stomach is frequently referred to as having peptic ulcer disease. Peptic ulcer disease-related mortality in our nation reached 68,108, or 0.80% of all deaths, according to the most recent information from the World Health Organization. India ranks #42 in the world with a 6.24 per 100,000 people age-adjusted death rate[1].Because of this, unlike dyspepsia, it requires endoscopic diagnosis. Clinically, dyspepsia and peptic ulcer disease can be difficult to differentiate from one another because they both appear with similar gastrointestinal symptoms. Due to the high risk of mortality, it may result in potentially fatal consequences such bleeding or perforation [2].

The imbalance between the digestive activity of acid and pepsin and the protective systems used to resist mucosal digestion is a fundamental scenario for ulcer development**.** Three etiologic categories can be used to categorize peptic ulcers: those caused by nonsteroidal anti-inflammatory drugs (NSAIDs), and ulcers caused by Helicobacter pylori infection. The Zollinger-Ellison syndrome caused by massive acid peptic hypersecretion [3].Acute mucosal ulceration of the duodenum or stomach that develops following physiologically stressful situations such burns, shock, severe sepsis, and multiple organ traumas is referred to as a stress ulcer. Shock frequently precedes stress ulcer, which results in decreased blood flow to the stomach's mucosa and duodenal reflux into the stomach. Additionally, a significant amount of pepsin is secreted. Ischemia, acid, and pepsin work together to foster the perfect environment for ulceration [4-8].There are two main ways to treat peptic ulcers; the first is to kill the *H. pylori* bacteria if it is present, eliminate or minimize the cause of NSAIDs, and the second is to reduce acid production so that lesions can heal. The main drug classes utilized are:

- Antibiotics to kill *H. pylori*
- Proton pump inhibitors
- Histamine 2 receptor blockers
- Antacids and some cytoprotective agents

The drugs commonly having side effects like diarrhea, constipation, fatigue, drowsiness, headache and muscle ache and all the drugs are hepatotoxic in nature. These facts highlight the need to adopt more effective treatment strategies for peptic ulcer treatment [9].
Hence the present work focuses to identify novel molecules to inhibit the Histamine H2 receptor for the treatment of Ulcers disease through the application of computational tools.

MATERIAL AND METHODS

Target Identification: Histamine H_2 receptor (PDB ID:7UL3) Complex with internal ligand histamine was selected as the target and the selected receptor is biologically active and stable, available structure is pre-processed [10].
Ligand Identification: The drugs chosen for the pharmacophore modeling, molecular docking and ADMET studies are mainly Cimetidine (CHEMBL2756), Ranitidine (CHEMBL3001055), Famotidine (CHEMBL5702160), Nizatidine (CHEMBL3033637), Lafutidine (CHEMBL5282136) are histamine type 2 receptor antagonist drugs currently used to treat the peptic ulcer.
Pharmacophore modeling: A pharmacophore is a three-dimensional framework formed by mapping the chemical compounds that are biologically potent and required for the ligand to bind to the correct target protein and interact with it. Molecules are submitted for pharmacophore modelling by uploading them in Sybyl Mol 2 format with a validmail ID to the free online service PharmaGist. The server considers numerous methods to mix the supplied compounds to create the pharmacophore in Jmol format [11,12].
Collecting data from zinc database: The Jmol format cluster produced by PharmaGist contains several aligned molecules, such as 7 aligned molecules stacked one on top of the other. The most aligned molecule out of these, or the 6 molecules with the highest scoring, are chosen and downloaded, and these molecules are then uploaded to ZINC pharma, a free online tool for pharmacophore modelling. This, when submitted as a query, searches the zinc database for compounds with similar pharmacophoric characteristics. A total of 950 tiny molecules are obtained after further obtained hits are filtered after queries over the zinc database provide approximately more than a lakh hit of molecules [13].
These compounds are uploaded to the data warrior, a freeware tool for pharmacophore modelling, where they are screened based on the typical drug physicochemical characteristics such molecular weight, log P, H donor, H acceptor, polar surface area, rotatable bond, and steric center. These compounds were all available as an SDF download that was utilized for molecular docking research.
Molecular Docking studies: These compounds are then subjected to molecular docking experiments after being acquired from Data Warrior, with the goal of identifying the drug's optimal fit and protein-target binding affinity. Proteins are first prepared for docking experiments by being chosen and downloaded in pdb format from the Protein Data Bank with PDB ID 7ul3. Human Monoamine Oxidase A in Complex with Clorgyline, Crystal Form A, as determined by X-ray crystallography, has a resolution of 3 angstroms.
Using the "Swiss pdb viewer," hetero groups, water molecules, and undesirable ligands were removed from the protein during protein production. AutoDock vina was used for docking, and all of the ligands were created, reduced, and optimised using this programme. PyMol version 2.4, a molecular visualization programme by Discovery Studio, was used to validate the docking methodology in subsequent testing. Because the grid generation process determines where the ligands will attach to the protein, it is essential to the docking procedure. By using the protein structure from the Protein Data Base, the co-crystallized ligand that is present with the protein is used to define the grid. The top ten structures with the best docking scores were found by screening the output of all the ligands' docked calculations [14,15].
ADMET studies: An important factor in determining a molecule's fate inside the body is its ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties. A good absorption rate is sought in molecules that are given orally. The ratio of hydrophilic and lipophilic groups in a structure will determine how a molecule is absorbed and distributed throughout the system. Effectiveness and toxicity are significant from the perspective of therapy. Using PKSCM online software, the ADME-T studies are conducted [16].

RESULTS AND DISCUSSION

Ligand-based pharmacophore modelling: Using the PharmaGist website, the pharmacophore was created using histamine 2 receptor antagonist in commercially available medications. The molecule obtained from PharmaGist has three hydrogen bond acceptors at a predetermined distance, five structure with pyridine rings, and one structure with benzimidazole ring. The ZINCPharmer screens and recovers the compounds with the same pharmacophoric characteristics from the ZINC database using the PharmaGist results that have been uploaded. The derived pharmacophore model aids in determining the structural prerequisite for blocking the histamine 2 receptor. Screened molecules were uploaded to

DataWarrior, and the molecules were further filtered based on their physicochemical characteristics, such as their molecular weight, log p value, hydrogen donor, hydrogen acceptor, and polar surface area, which are common characteristics of histamine 2 receptor inhibitors. The SDF files for all of these compounds were collected and utilized for molecular docking experiments.

Molecular docking studies: Histamine 2 blockers were molecularly docked with commercially available drugs. The target protein's active pocket with PDB ID: 7ul3 was the area where the main binding interactions that would be bioactive conformations were to be found. The relationships between molecules in the ZINC database were identified thanks in large part to this action. Molecular docking studies were performed using AutoDock Vina. Cimetidine (CHEMBL2756), Ranitidine (CHEMBL3001055), Famotidine (CHEMBL5702160), Nizatidine (CHEMBL3033637), Lafutidine (CHEMBL5282136) are the drugs currently used drugs to treat peptic ulcer through inhibiting the histamine 2 receptor. The docking score and binding interaction are given in table 1. Among the inhibitors, Lafutidine was found with the docking score of -6.7kcal/mol and as conventional hydrogen bonding with ARG142, alkyl and Pi alkyl with TYR173 and

TABLE1: MOLECULAR DOCKING SCORE AND TYPE OF INTERACTION OF MARKETED DRUGS

DRUG NAME	DOCKING SCORE (Kcal/mol)	INTERACTING RESIDUES	TYPE OF INTERACTION
Cimetidine	-5.3	LYS103, GLN166, VAL104, PRO40, LYS39	Conventional hydrogen bond, Carbon hydrogen bond, Unfavorable positive-positive, Unfavorable donor-donor, Alkyl
Ranitidine	-5	GLN166, TYR173, VAL104, LYS39, LYS103	Conventional hydrogen bond, Carbon hydrogen bond, Pi alkyl
Nizatidine	-4.6	PRO40, LYS103, THR85, GLN39, TYR87, GLN166	Conventional hydrogen bond, Carbon hydrogen bond, Pi alkyl
Lafutidine	-6.7	TYR173, AGR142, LYS103	Conventional hydrogen bond, Alkyl, Pi alkyl
Famotidine	-5.7	LYS103, PRO40, ALA84, ARG142, LYS39, GLN166, GLU107, TYR173, LYS43	Attractive charge, Pi sulfur, Pi stacked, Conventional hydrogen bond, Alkyl, Pi alkyl

TABLE2: MOLECULAR DOCKING SCORE OF MOLECULES OBTAINED FROM ZINC DATABASE

COMPOUND	DOCKING SCORE (Kcal/mol)	INTERACTING RESIDUES	TYPE OF INTERACTION
ZINC47304988	-8.4	ALA42, LEU54, PRO89, TYR49, GLU90	Conventional hydrogen bond,Pi Donor hydrogen bond,Pi Alkyl
ZINC78424587	-5.5	LYS45, ALA42, LEU54, TYR49, THR92, SER53, PRO89, SER52 GLU90	Conventional hydrogen bond,Carbon hydrogen bond,alkyl
ZINC86304697	-6.2	PRO43, GLY44, PRO89, TYR55, LEU54, TYR49	Conventional hydrogen bond,Carbon hydrogen bond,Alkyl and Pi alkyl
ZINC86481136	-6.6	PRO40, GLN38, LYS39, ARG142, LYS103, ILE106, PHE83	Conventional hydrogen bond,Unfavorable Donor-Donor bond,Alkyl and Pi alkyl
ZINC86556486	-4.9	ALA42, LYS45, GLU90, PRO89, LEU54, VAL121	Conventional hydrogen bond,Alkyl
ZINC86556487	-5.7	ILE232, ARG231, TYR126, ARG48, ARG116, ALA119, LEU229	Conventional hydrogen bond,Unfavorable positive-positive bonding, Alkyl and Pi alkyl

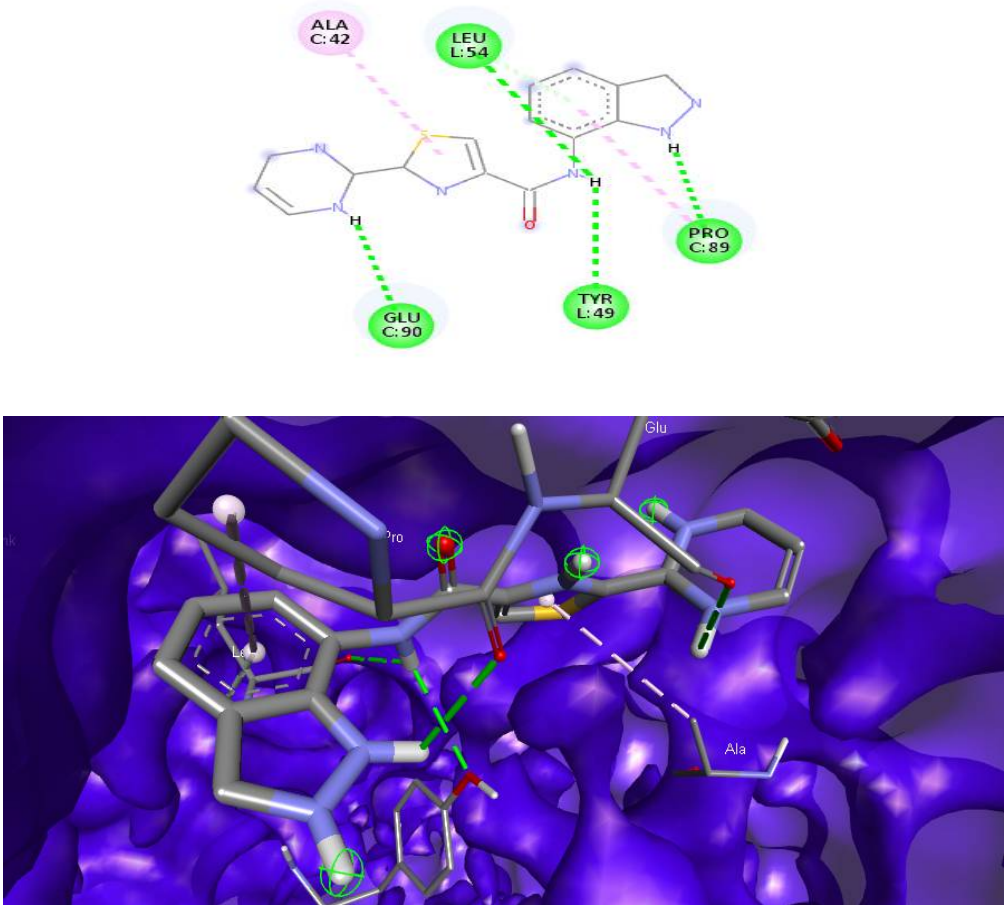
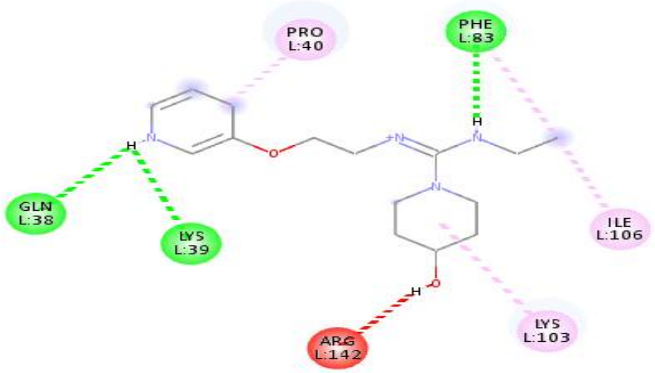


Fig 1: 2D and 3D interactionof ZINC47304988 with 7UL3



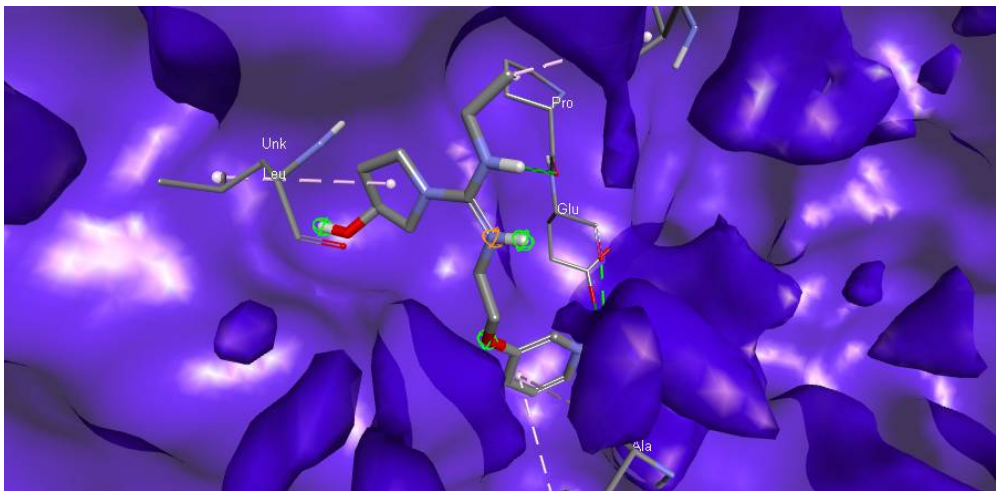


Fig 2: 2D and 3D interaction of ZINC86481136 with 7UL3

ADMET PROPERTIES: The ADMET properties with the ZINC database compound like ZINC47304988, ZINC78424587, ZINC86304697, ZINC86481136, ZINC86556486, ZINC86556487has shown good water solubility, $caco_2$ permeability, and all the compounds obey the drug likeness by Lipinski's, Veber, Egan, Muegge rules.

TABLE 3:DRUG ABILITY STUDIES OF THE LIGANDS BY LIPINISKI'S RULE OF 5

COMPOUND	MOLECULAR WEIGHT	LOG P	ROTATABLE BONDS	H-BOND ACCEPTOR	H-BOND DONOR	SURFACE AREA	LIPINSKI'S RULE
ZINC47304988	322.34	1.15	4	5	2	124.69	0
ZINC78424587	294.37	2.58	10	3	3	80.46	0
ZINC86304697	293.38	2.59	6	3	3	71.59	0
ZINC86481136	279.36	2.34	7	3	3	71.59	0
ZINC86556486	262.33	1.99	8	3	3	83.94	0

CONCLUSION

By comparing the ADMET properties of standard drug with the zinc data base drugs ZINC47304988 has a good property like water solubility, CaCo2 permeability, but it's a hepatotoxic drug. The zincdatabase molecule will obey the Lipinski rule of five, by this the molecule can observer well by orally and its showing good GI absorption. The drug development process is speed up by the drug-likeness filters based on physicochemical characteristics. The drug-likeness rules/filters based on physicochemical features, however, have drawbacks, as demonstrated by a number of researches.The molecules which are under marketed as a histamine 2 inhibitor include cimetidine, ranitidine, famotidine, nizatidine, lafutidine, used to get ligand-based pharmacophore model. The model gives molecules with similar pharmacophoric feature which is obtained from Zinc Database and DataWarrior, these molecules were subjected to docking by using AutoDock Vina and based on docking score and binding interaction, 4 molecules are obtained. Next further ADMET studies were done by using PKCSM and Swiss ADME online software. Which predicts the drug-likeness feature and oral rat chronic toxicity and hepatotoxicity. Based on the result molecule ZINC47304988 were predicted as the histamine 2 inhibitor. Further dynamic study is done to obtain stability, safety and efficacy of the drug and additional properties with potential Histamine 2 receptor inhibitor activity.

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CONFLICT OF INTEREST

The authors declare that no conflict of interest.

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