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In silico Pharmacokinetic, Bioactivity and Toxicity Evaluation of Some Selected Anti-Ulcer Agents

Neeraj Kumar[1*], Shashank Shekhar Mishra[2], Chandra Shekhar Sharma[2], Hamendra Pratap Singh[2], Harshda Pandiya[2]

[1]*Department of Pharmaceutical Chemistry, Geetanjali Institute of Pharmacy, Geetanjali University, Udaipur-313001, Rajasthan, India*
[2]*Bhupal Nobles' College of Pharmacy, Udaipur-313001, Rajasthan, India*

ABSTRACT
Peptic ulcer is a major health burden that recognized as a group of upper gastro-intestinal tract disorders. The aim of the therapy is to provide relieve from pain and prevent ulcer complications. Therefore, it is essential to evaluate the drug-likeness and toxicity profile of existing drugs for developing new potent anti-ulcer agents. In this research work, we study the pharmacokinetic, toxicity and bioactivity profile of few selected anti-ulcer agents by *In silico* method. These research investigations provide the lead for the development of new anti-ulcer agents with lesser toxicity and more effectiveness.

Keywords: GI tract (Gastro-intestinal tract), TPSA, GPCR ligand, Toxicity, Bioactivity.

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INTRODUCTION

Peptic ulcer is a collectively term for group of upper GI tract disorders characterized by mucosal erosions equal to or greater than 0.5 cm that result from the erosive action of acid and pepsin. [1] Although peptic ulcer diseases may occur in the esophagus and small intestine, duodenal and gastric ulcer are the most common forms. Factors involved in the pathogenesis and recurrence of peptic ulcer disease include hypersecretion of gastric acid, pepsin and gastrointestinal infection by *H. pylori*, a gram-negative spiral bacterium. *H. pylori* have been found in virtually all patients with duodenal ulcers and approximately 75% of patients with gastric ulcers. Chronic use of ulcerogenic drugs (NSAIDs), cigarette smoking, alcohol consumption, emotional stress and family history are the some risk factors for recurrence of peptic ulcer diseases. [2] The aims of the anti-ulcer therapy are to promote healing, relieve pain, and prevent ulcer complications and recurrences. The development of new effective medication and the cause of the condition reduce the chances of peptic ulcer diseases that had tremendous effect on morbidity and mortality. This research investigation consists of evaluation of pharmacokinetic descriptors including Lipinski's rule of five, bioactivity score calculation and various toxicities through computational methods.

***Corresponding author: Dr. Neeraj Kumar,**
Department of Pharmaceutical Chemistry, Geetanjali Institute of Pharmacy, Geetanjali University, Udaipur-313001, Rajasthan, India; **Tel.:** +91-9414084507;
E-mail: neerajkumarkamra@gmail.com
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MATERIALS AND METHODS

In silico ADME analysis

There are various physicochemical features and pharmacokinetic descriptors were calculated for some selected anti-ulcer agents through the online tool Molinspiration Cheminformatics server (http://www.molinspiration.com). Molinspiration Cheminformatics offers broad range of tools supporting molecule manipulation and processing, including SMILES and SDfile conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in quantitative structure activity relationship (QSAR) study, molecular modeling and drug design, high quality molecule depiction, molecular database tools supporting substructure and similarity searches. This software also provides fragment-based virtual screening, bioactivity prediction and data visualization. Molinspiration tools are written in Java, therefore can be used practically on any computer platform. [3] Drug-likeness is qualitative concept used for drug like property that described as a complex balance of various molecular properties and structural features which determine whether particular molecule is similar to the known drugs. These molecular properties are mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and of course presence of various pharmacophoric features that influence the behaviour of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others. Drug-likeness evaluated by the Lipinski rule of five that deals four simple physicochemical parameter ranges (MWT ≤ 500, log P ≤ 5, Hbond donors ≤ 5, H-bond acceptors ≤ 10) associated with 90% of orally active drugs that have passed phase II clinical status. [4] Other calculation methods such as ligand efficiency and lipophilic efficiency can also be used to express drug-likeness as parameters of potency. These physicochemical parameters having acceptable range associated with aqueous solubility and intestinal permeability. Physicochemical parameters take small part of the whole chemical information about the real molecule and became popular as variables in molecular modelling studies.

In silico Bioactivity analysis

The bioactivity score of selected agents were also evaluated using the tool Molinspiration Cheminformatics server (http://www.molinspiration.com). In this computational chemistry technique large chemical databases are analyzed in order to identify possible new drug candidates. Virtual screening techniques range from simple ones, based on the presence or absence of specific substructures, or match in calculated molecular properties, up to sophisticated virtual docking methods aimed at fitting putative ligand molecules into the target receptor site. Molinspiration bioactivity tool offers very good balance between screening speed, requirements on information needed to start a new virtual screening project and screening performance.

In the Molinspiration tool, the miscreen engine first analyze a training set of active structures (in extreme case even single active molecule is sufficient to built a usable model) and compares it with inactive molecules by using sophisticated Bayesian statistics. Only SMILES or SDfile structures of active molecules are sufficient for the training, no information about the active site or binding mode is necessary. This is particularly useful in projects where structure-based approach cannot be applied because information about 3D receptor structure is not available, for example in screens aiming to find ligands modulating G-protein coupled receptors. Based on this analysis a fragment-based model is developed, where for each substructure fragment a bioactivity contribution is calculated. Once a model is build the bioactivity of screened molecules may be then calculated as a sum of activity contributions of fragments in these molecules. This provides a molecule activity score (a number, typically between -3 and 3). Molecules with the highest activity score have the highest probability to be active. Such *in silico* screening is very fast, large collections of molecules (more than 100'000 molecules) may be screened in an hour.

Based on the protocol described above, screening models developed for four important drug classes, namely GPCR ligands, ion channel blockers, kinase inhibitors, and nuclear receptor ligands. A virtual screening model for any target may be developed easily by using the miscreen built-in functionality. Another advantage of virtual screening protocol based on Bayesian statistics is, that it is able to generalize, i.e. to learn general structure requirements which are necessary for bioactivity. The identified new bioactive molecules are therefore not limited to molecules similar to the training set, but the protocol is able also to identify new active structure classes (scaffold hopping).

In silico Toxicity analysis

The toxicity of the selected anti-ulcer agents was evaluated by computational method using Pallas version 3.1 ADMETox prediction software pentium IV processor. This software tool was started by double click on the icon. The molecule to be predicted was drawn by double click on new option, and then molecule was subjected for evaluation of toxicity by selecting ToxAlert options. Various types of toxicities including oncogenicity, neurotoxicity, teratogenicity, immunotoxicity, etc. were generated and toxicity profile of molecule noted.

RESULTS AND DISCUSSION

There were eight anti-ulcer agents selected and analyzed to pharmacokinetic parameters and drug likeness (Lipinski's rule of five) which are given in Table 1.

Table 1: ADME Properties of Anti-ulcer agents

Name	Molecular formula	Molecular weight	LogP	TPSA	nON	nOHNH	nrotb	volume	*In silico* % absorption
Cimetidine	$C_{10}H_{16}N_6S$	252.35	0.14	88.89	6	3	7	231.45	78.33
Ranitidine	$C_{13}H_{22}N_4O_3S$	314.41	0.33	86.26	7	2	10	288.97	79.24
Famotidine	$C_8H_{15}N_7O_2S_3$	337.46	-0.11	175.85	9	8	7	262.24	48.33
Nizatidine	$C_{12}H_{21}N_5O_2S_2$	331.47	-0.26	86.01	7	2	10	293.96	79.32
Omeprazole	$C_{17}H_{19}N_3O_3S$	345.42	2.41	77.11	6	1	5	302.81	82.39
Pantoprazole	$C_{16}H_{15}F_2N_3O_4S$	383.38	1.95	86.35	7	1	7	305.36	79.20
Lanzoprazole	$C_{16}H_{14}F_3N_3O_2S$	369.37	2.88	67.88	5	1	6	292.24	85.58
Rabeprazole	$C_{18}H_{21}N_3O_3S$	359.45	2.20	77.11	6	1	8	320.09	82.39

Table 2: Bioactivity of Anti-ulcer agents

Name	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor Ligand	Protease inhibitor	Enzyme inhibitor
Cimetidine	0.58	0.14	-0.32	-1.72	-0.02	0.54
Ranitidine	-0.01	-0.59	-0.51	-1.01	-0.21	0.30
Famotidine	0.06	-0.84	-0.80	-1.08	0.22	0.38
Nizatidine	0.03	-0.49	-0.54	-1.25	0.01	0.17
Omeprazole	0.24	-0.22	0.08	-0.21	-0.23	0.43
Pantoprazole	0.07	-0.23	0.06	-0.28	-0.55	0.37
Lanzoprazole	0.27	-0.13	0.13	-0.03	-0.09	0.42
Rabeprazole	0.26	-0.19	0.13	-0.14	-0.08	0.38

Table 3: Toxicity Profile of Adrenergic agents

Name	Toxicity	Overall toxicity	Oncogenicity	Mutagenicity	Teratogenicity	Irritation	Sensitivity	Immunotoxicity	Neurotoxicity
Cimetidine	Not Probable	0	0	0	0	0	0	0	0
Ranitidine	Highly Probable	76	76	0	0	0	0	0	0
Famotidine	Highly Probable	76	76	0	0	0	0	0	0
Nizatidine	Highly Probable	76	76	0	0	0	0	0	0
Omeprazole	Highly Probable	76	76	53	19	0	0	0	0
Pantoprazole	Highly Probable	76	76	53	19	0	0	0	0
Lanzoprazole	Highly Probable	100	100	53	0	0	0	0	0
Rabeprazole	Highly Probable	100	100	53	0	53	0	0	29

All selected agents have molecular weight in the acceptable range (MWT ≤ 500). Low molecular weight containing molecules are easily absorbed, diffused and transported as compared to high molecular weight compounds. As molecular weight increases except certain limit, the bulkiness of the molecules are also increases comparably. [5]

In selected anti-ulcer agents, famotidine have one violation according to Lipinski's rule of five. Famotidine has 8 hydrogen bong donors which are higher from acceptable range. The MLogP (octanol / water partition co efficient) of all agents were calculated and found to be within acceptable range according to Lipinski's rule. The MLogP value is used to calculate the lipophilic efficiency that measures the potency of drug. Therefore Octanol-water partition coefficient logP value is essential in rational drug design and QSAR studies. In the pharmacokinetic study, hydrophobicity of the molecule is assessed by evaluating logP value because hydrophobicity plays a vital role in the distribution of the drug in the body after absorption. [2] TPSA (Topological Polar Surface Area) is a very useful physiochemical parameter of molecule that gives the information about polarity of compounds. This parameter was evaluated for analyzing drug transport properties. Polar surface area is the sum of all polar atoms mainly oxygen and nitrogen including attached hydrogen. [6] Percent absorption were also evaluated for all selected antiepileptic agents by %ABS = 109- (0.345 * TPSA). [7] Molecular volume assesses the transport properties of the molecule such as blood-brain barrier penetration. The number of rotatable bond was calculated and have found relevant. A molecule which have more number of rotatable bond become more flexible and have good binding affinity with binding pocket.

Bioactivity of all selected antimalarial agents was evaluated against six different protein structures. Biological activity is measured by bioactivity score that are categorized under three different ranges-

1. If bioactivity score is more than 0.00, having considerable biological activity.
2. If bioactivity score is 0.5 to 0.00, having moderately activity.
3. If bioactivity score is less than -0.50, having inactivity. [8]

The result of this study was found that the selected agents are biologically active and have physiological effect. The bioactivity score profile of the all selected agents is given in Table 2.

The bioactivity score provide the information about the binding cascade of the drugs that is used for the development of a new functional drug with increased binding selectivity profile and less undesirable effects. All selected anti-ulcer agents were evaluated to toxicity profile and given in Table 3. All of the drugs were found to be highly probable to toxicity except cimetidine.

These research findings provide the lead for the design and development of new potent antimalarial drugs. Computational study of all selected antimalarial drugs gives the information about the pharmacokinetics of the existing drugs that provide the lead for development of functional drug with more effectiveness and lesser toxicity.

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