RESEARCH ARTICLE

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IN SILICO PHARMACOKINETIC AND TOXICITY EVALUATION OF SOME SELECTED NONSTEROIDAL ANTI-INFLAMMATORY AND ANTIPYRETIC-ANALGESIC AGENTS

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ABSTRACT

According to the World Health Organization, 90 % of diseases are associated with pain. The World Health Organization published an analgesic ladder model for pain management that states that the therapy is based on assessment of pain intensity. Thus NSAIDs are the drug of choice for mild pain. Due to widespread use of NSAIDs, the adverse effects of these drugs have become increasingly common. The most common adverse effects associated with NSAIDs are gastrointestinal assault, inflammatory bowel disease, hypersensitivity reactions and renal dysfunction. In this research investigation, we study the pharmacokinetic, drug-likeness, bioactivity profile and toxicity profile of some selected non-steroidal anti-inflammatory drugs by computational methods. The study provides the information about the pharmacokinetic and toxicity of existing drugs that can be used for design and development of new NSAIDs with more potency and lesser toxicity.

Keywords: - Non-steroidal anti-inflammatory drugs, TPSA (Total polar surface area), GPCR Ligand, MLogP, QSAR.

INTRODUCTION

Pain is the most common reason that patients seek advice from pharmacists and other health professionals and represent important therapeutic and economic cost for the community [1]. According to the World Health Organization, 90 % of diseases are associated with pain [1]. So, pain management by the use of opioids in patients with chronic pains, is one of the most difficult public health issues for patients, doctors and other health professionals [2]. The World Health Organization published an analgesic ladder model for pain management that states that the therapy is based on assessment of pain intensity. Thus NSAIDs are the drug of choice for mild pain. NSAIDs are the non-selective inhibitors of cyclooxygenase enzyme that

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catalyzes the formation of prostaglandins and thromboxane from arachidonic acid. Due to widespread use of NSAIDs, the adverse effects of these drugs have become increasingly common. The most common adverse effects associated with NSAIDs are gastrointestinal assault, inflammatory bowel disease, hypersensitivity reactions and renal dysfunction [3].

The scope of this investigation is to study the ADME, drug-likeness, toxicity profile of current existing drugs on the basis of several physiochemical descriptors by computational approaches. The study provides the information about the pharmacokinetic and toxicity of existing drugs that can be used for design and development of new NSAIDs with more potency and lesser toxicity.

Materials and Methods-

***In silico* Pharmacokinetic Evaluation-**

By applying computational approaches, there are several physicochemical properties and pharmacokinetic descriptors were evaluated for some selected NSAIDs using the tool MolinspirationCheminformatics server (http://www.molinspiration.com).

MolinspirationCheminformatics 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 QSAR, molecular modeling and drug design, high quality molecule depiction, molecular database tools supporting substructure and similarity searches. This software also supports fragment-based virtual screening, bioactivity prediction and data visualization. Molinspiration tools are written in Java, therefore can be used practically on any computer platform [4].

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 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. The Lipinski rule of five deals four simple physicochemical parameter ranges (MWT $\leq$ 500, log P $\leq$ 5, H-bond donors $\leq$ 5, H-bond acceptors $\leq$ 10) associated with 90% of orally active drugs that have passed phase II clinical status [5].

There are several scoring methods such as ligand efficiency and lipophilic efficiency can be used to express drug likeness as measure of potency. These physicochemical descriptors are associated with aqueous solubility and intestinal permeability within acceptable range.

In silico Toxicity Evaluation-

The toxicity of the NSAIDs 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.

RESULT AND DISCUSSION

There were some Non-steroidal anti-inflammatory drugs were selected and analyzed to ADME properties and drug-likeness (Lipinski's rule of five) which are given in Table 1. All NSAIDs have molecular weight in the range (MWT $\leq$ 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 [6]. All selected NSAIDs have number of H-bond acceptors and number of H-bond donors is within range according to Lipinski's rule of five, so selected NSAIDs have no violations. The MLogP (octanol / water partition co efficient) of all agents were calculated and were found to be within 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 [7]. 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 [8]. Percent absorption were also evaluated for all selected NSAIDs by %ABS = 109- (0.345 * TPSA) [9]. 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 NSAIDs was evaluated against six different protein structures. Biological activity is predicted 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 [10].

The result of this investigation was found that the selected NSAIDs are biologically active and have physiological effect. The bioactivity score profile of the all selected agents is given in Table 2. Piroxicam, diclofenac, ketorolac, ibuprofen, naproxen having bioactivity score against GPCR ligand which indicates they could bind more effectively with GPCR. In the selected NSAIDs, Piroxicam, diclofenac, ibuprofen, naproxen, fenoprofen also having moderate enzyme inhibiton activity with good bioactivity score. 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 Non-steroidal anti-inflammatory drugs were evaluated to toxicity profile and given in Table 3. All of the drugs were found to be highly probable to toxicity. The interesting fact about toxicity is all selected Non-steroidal anti-inflammatory drugs were found to be teratogenic and exhibits teratogenicity.

These research findings provide the lead for the design and development of new Non-steroidal anti-inflammatory drugs. Currently, all existing Non-steroidal anti-inflammatory drugs having serious toxicity profile. Therefore, it is essential that the development of new Non-steroidal anti-inflammatory molecules with lesser gastro-intestinal side effects and toxicity. Computational study of all selected Non-steroidal anti-inflammatory 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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Table-1 ADME Properties of Non-steroidal anti-inflammatory drugs

Name	Molecular formula	Molecular weight	LogP	TPSA	nON	nOHNH	nrotb	volume	In silico % absorption
Aspirin	$C_9H_8O_4$	180.16	1.43	63.60	4	1	3	155.57	87.05
Piroxicam	$C_{15}H_{13}N_3O_4S$	331.35	2.06	99.60	7	2	2	268.05	74.63
Diclofenac	$C_{14}H_{11}Cl_2NO_2$	296.15	4.57	49.33	3	2	4	238.73	91.98
Ketorolac	$C_{15}H_{13}NO_3$	255.27	2.20	59.30	4	1	3	226.39	88.54
Ibuprofen	$C_{13}H_{18}O_2$	206.28	3.46	37.30	2	1	4	211.19	96.13
Fenoprofen	$C_{15}H_{14}O_3$	242.27	3.89	46.53	3	1	4	224.83	92.94
Naproxen	$C_{14}H_{14}O_3$	230.26	3.38	46.53	3	1	3	213.97	92.94
Lumiracoxib	C15H13ClFNO2	293.73	4.48	49.33	3	2	4	246.69	91.98

Table-2 Bioactivity of Non-steroidal anti-inflammatory drugs

Name	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor Ligand	Protease inhibitor	Enzyme inhibitor
Aspirin	-0.76	-0.32	-1.06	-0.44	-0.82	-0.28
Piroxicam	-0.42	-0.57	-0.50	-0.73	-0.04	0.18
Diclofenac	0.14	0.20	0.17	0.09	-0.10	0.25
Ketorolac	0.29	-0.04	-0.09	-0.03	-0.29	0.62
Ibuprofen	-0.17	-0.01	-0.72	0.05	-0.21	0.12
Fenoprofen	-0.02	0.02	-0.25	0.29	-0.07	0.20
Naproxen	-0.11	-0.06	-0.38	0.14	-0.25	0.15
Lumiracoxib	-0.02	-0.06	0.05	0.10	-0.22	0.08

Table-3 Toxicity Profile of Non-steroidal anti-inflammatory drugs

Name	Toxicity	Overall toxicity	Oncogenicity	Mutagenicity	Teratogenicity	Irritation	Sensitivity	Immunotoxicity	Neurotoxicity
Aspirin	Highly Probable	76	76	0	17	0	0	0	0
Piroxicam	Highly Probable	81	76	81	34	0	0	0	0
Diclofenac	Highly Probable	76	76	47	29	0	0	29	0
Ketorolac	Highly Probable	91	77	91	17	0	0	0	0
Ibuprofen	Highly Probable	76	76	0	19	0	0	0	0
Fenoprofen	Highly Probable	76	76	0	19	0	0	0	0
Naproxen	Highly Probable	76	76	0	19	0	0	0	0
Lumiracoxib	Highly Probable	76	76	47	29	0	0	0	0