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In silico Pharmacokinetic, Bioactivity and Toxicity study of Some Selected Anti-asthmatic Agents

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ABSTRACT

Asthma is a disease affecting the airways that carry air to and from lungs. Exposure to various irritants and substances that trigger allergies (allergens) can trigger signs and symptoms of asthma. The prevalence of asthma varies widely in different regions of the world due to distinct genetic, environmental and occupational risk factors. In this research investigation, we study the pharmacokinetic, drug-likeness, bioactivity profile and toxicity profile of some selected anti-asthmatic agents 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 anti-asthmatic agents with more potency and lesser toxicity.

Keywords: QSAR, TPSA, GPCR, Teratogenicity, GERD.

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INTRODUCTION

Asthma is a disease affecting the airways that carry air to and from lungs. People who suffer from this chronic condition (long-lasting or recurrent) are said to be asthmatic. The inside walls of an asthmatic's airways are swollen or inflamed. This swelling or inflammation makes the airways extremely sensitive to irritations and increases your susceptibility to an allergic reaction. As inflammation causes the airways to become narrower, less air can pass through them, both to and from the lungs. Symptoms of the narrowing include wheezing (a hissing sound while breathing), chest tightness, breathing problems, and coughing. Asthmatics usually experience these symptoms most frequently during the night and the early morning. [1]

An asthma episode, or an asthma attack, is when symptoms are worse than usual. They can come on suddenly and can be mild, moderate or severe. [2] The prevalence of asthma varies widely in different regions of the world due to distinct genetic, environmental and occupational risk factors. However, this disparity appears to be closing as the prevalence in high-income countries is reaching a plateau whereas the prevalence in low and middle-income countries continues to rise.

Worldwide, it is estimated that approximately 334 million people currently suffer from asthma, and 250,000 deaths are attributed to the disease each year. The prevalence of the disease is continuing to grow, and the overall prevalence is estimated to increase by 100 million by 2025. [3-4]

Medications for treating an asthma attacks are categorized into two types namely quick-relief medications and long-term control medicines. Quick relief bronchial asthma medicines open the swollen & blocked airways and help to promote breathing. While long-term asthma drugs reduce inflammation caused to airways. [5]

Despite the various research efforts towards anti-asthmatic drugs, no drugs are available having better pharmacokinetics and non-toxic. So, there is essential need to design new potent molecule with better pharmacological profile and non-toxic. This research investigation involves the search of pharmacokinetic, drug-likeness, toxicity and bioactivity profile of available anti-asthmatic agents on the basis of several physico-chemical parameters by computational methods. To design a new molecule having good pharmacological profile, this study will provide the lead information.

MATERIALS AND METHODS

In silico Pharmacokinetic Studies

By applying computational methods, there are various physicochemical features and pharmacokinetic descriptors were calculated for some selected anti-asthmatic agents through the online tool Molinspiration Cheminformatics server (http://www.molinspiration.com). [6]

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. 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. [7]

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. 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. [8]

In silico Bioactivity Studies

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). [9]

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). [10]

In silico Toxicity Studies

The toxicity of the selected anti-asthmatic 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. [11]

RESULTS AND DISCUSSION

There some anti-asthmatic agents were selected and analyzed to ADME properties and drug likeness (Lipinski's rule of five) which are given in Table 1. All selected agents have molecular weight in the acceptable range (MWT ≤ 500) except montelukast and ciclesonide. 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. [12]

Table 1: ADME Properties of Anti-asthmatic Agents

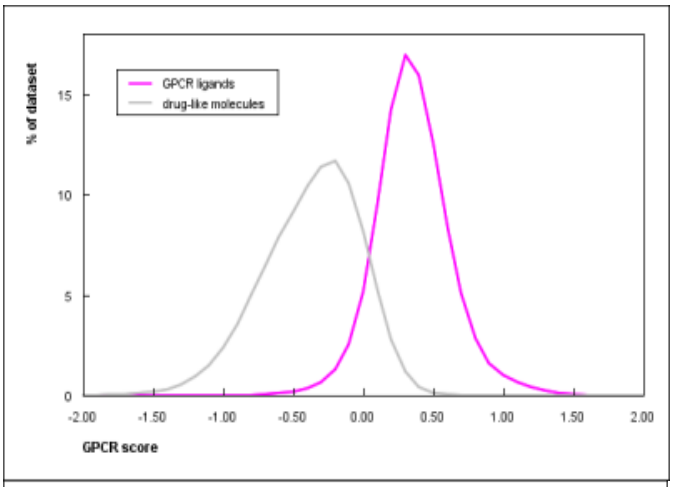
Name	Molecular formula	Molecular weight	LogP	TPSA	nON	nOHNH	nrotb	volume	*In silico* % absorption
Salbutamol	$C_{13}H_{21}NO_3$	239.31	1.35	72.71	4	4	5	237.12	83.91
Terbutaline	$C_{12}H_{19}NO_3$	225.29	1.07	72.71	4	4	4	220.31	83.91
Ipratropium bromide	$C_{20}H_{30}BrNO_3$	332.46	-1.47	46.53	4	1	6	332.39	92.94
Theophylline	$C_7H_8N_4O_2$	180.17	-0.01	72.69	6	1	0	150.69	83.92
Montelukast	$C_{35}H_{36}ClNO_3S$	586.20	7.89	70.42	4	2	12	533.72	84.70
Fluticasone	$C_{22}H_{27}F_3O_4S$	444.51	3.54	74.60	4	2	3	378.07	83.26
Ciclesonide	$C_{32}H_{44}O_7$	540.70	5.65	99.14	7	1	6	512.74	74.79
Salmeterol	$C_{25}H_{37}NO_4$	415.57	3.94	81.94	5	4	16	419.34	80.73

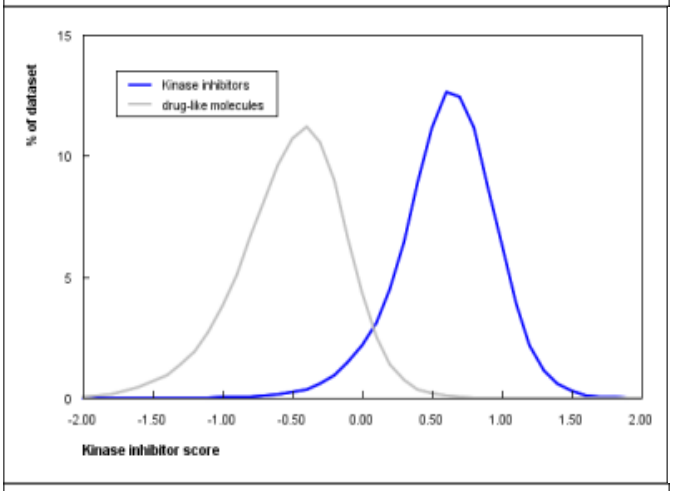
Table 2: Bioactivity of Anti-asthmatic Agents

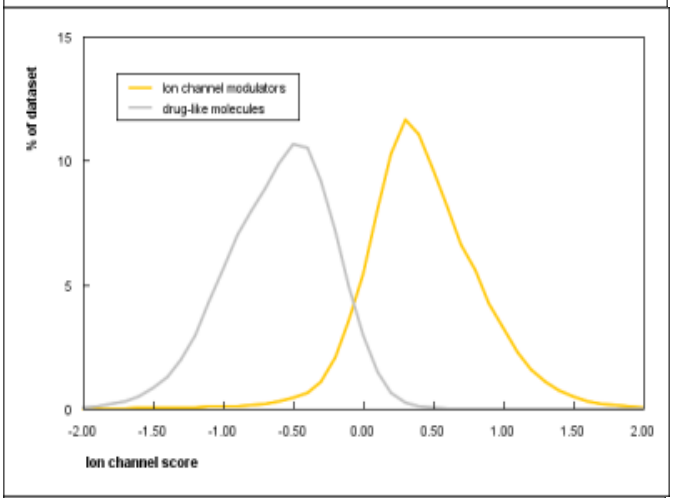
Name	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Salbutamol	0.23	-0.03	-0.27	-0.21	0.07	0.19
Terbutaline	0.15	-0.07	-0.39	-0.31	-0.15	0.07
Ipratropium bromide	0.56	0.35	-0.29	-0.37	-0.07	0.17
Theophylline	-0.40	-0.79	-1.24	-2.56	-1.46	-0.12
Montelukast	0.67	-0.16	-0.18	0.18	0.21	0.22
Fluticasone	0.16	0.02	-0.65	2.00	1.04	0.90
Ciclesonide	-0.03	-0.53	-0.74	0.78	0.11	0.33
Salmeterol	0.38	0.05	0.08	0.15	0.29	0.27

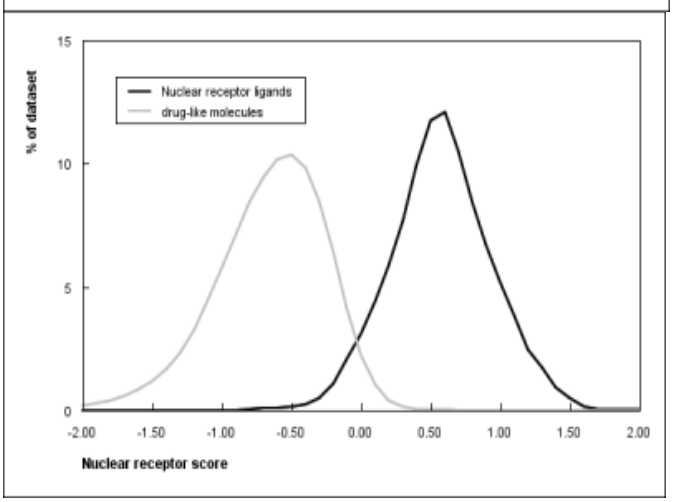
Table 3: Toxicity Profile of Anti-asthmatic Agents

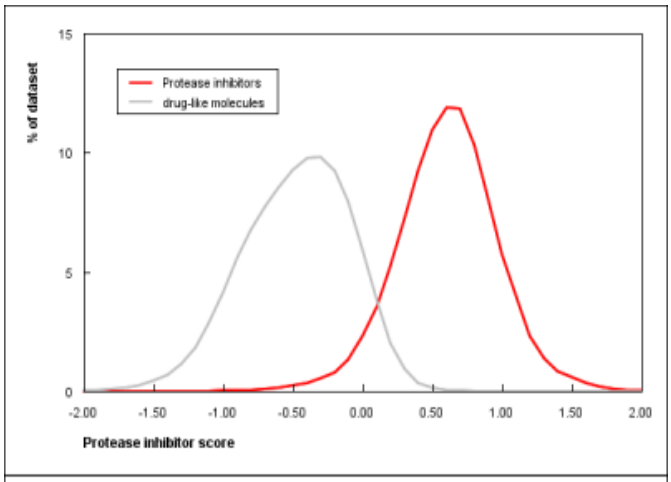
Name	Toxicity	Overall toxicity	Oncogenicity	Mutagenicity	Teratogenicity	Irritation	Sensitivity	Immunotoxicity	Neurotoxicity
Salbutamol	Probable	53	0	29	19	53	0	0	29
Terbutaline	Probable	53	0	29	19	53	0	0	29
Ipratropium bromide	Highly Probable	76	76	0	19	0	0	0	0
Theophylline	Highly Probable	81	76	81	0	0	0	0	0
Montelukast	Highly Probable	76	76	53	19	0	0	0	0
Fluticasone	Highly Probable	76	76	51	33	44	0	0	0
Ciclesonide	Highly Probable	76	76	49	33	29	0	0	0
Salmeterol	Highly Probable	71	0	71	19	53	0	0	29











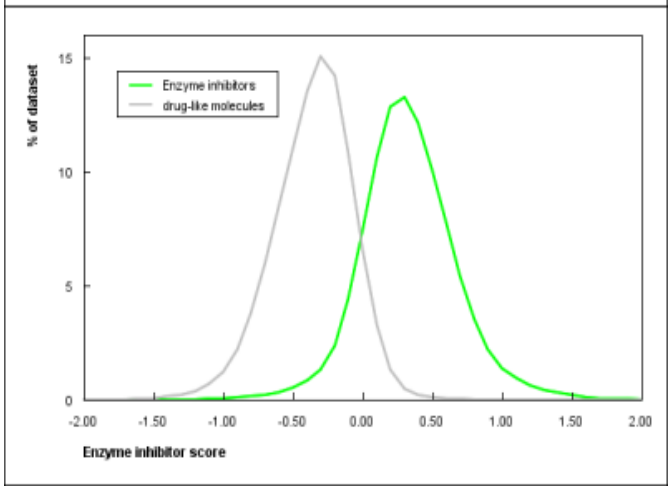


Fig. 1: The bioactivity score graph of Salbutamol for different proteins

Among selected anti-asthmatic agents, montelukast and ciclesonide have one violation according to Lipinski's rule of five. Montelukast has molecular weight 586.20 and also has logP value 7.89 which are higher from acceptable range. The MLogP (octanol/ water partition coefficient) of all agents were calculated and found to be within acceptable range according to Lipinski's rule except montelukast. 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. 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. Percent absorption were also evaluated for all selected anti-asthmatic agents by %ABS = 109- (0.345 * TPSA). 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. [13]

Bioactivity of all selected anti-asthmatic 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. [14]

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 graph of salbutamol for different protein is given in figure 1.

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-asthmatic agents were evaluated to toxicity profile and given in Table 3. All of the drugs were found to be highly probable to toxicity except salbutamol and terbutaline.

The interesting fact about toxicity is all selected anti-asthmatic agents were found to be exhibited teratogenicity except theophylline.

These research findings provide the lead for the design and development of new potent anti-asthmatic agents. Computational study of all selected anti-asthmatic agents 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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