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IN SILICO PHARMACOKINETIC, BIOACTIVITY AND TOXICITY STUDY OF SOME SELECTED ANTI-ANGINAL AGENTS

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ABSTRACT

Angina pectoris is the major cardio-vascular disease that occurs due to the imbalance between blood supply and demand that results obstruction of coronary arteries. WHO reports states that 1.6% of population affects from angina pectoris. In this research investigation, we study the pharmacokinetic, toxicity and bioactivity profile of few selected anti-anginal agents by computational methods. All selected anti-anginal agents showed excellent pharmacokinetic and bioactivity profile and highly probable to toxicity. These research investigations provide the lead for the development of new antihypertensive agents with lesser toxicity and more effectiveness.

Key-words- ADME, Kinase inhibitor, Ion channel modulator, TPSA, Log P

INTRODUCTION

Angina pectoris is referred to sensation of chest pain that occurs due to imbalance between blood supply and demand to the heart muscles that results obstruction of coronary arteries. Stable and unstable angina is the two forms of anginal pain [1]. Smoking, hypertension, diabetes mellitus, kidney disease, physical inactivity, psychological stress is the various risk factors for angina pectoris [2]. The treatment approach focused on the relief of symptoms that slowing the future events of heart attack [3]. According to WHO report, angina affects 112 million people (1.6% of population) due to ischemic heart disease which found more common in men as compared to men [4].

Modern drug design is based on modern computational chemical techniques; it also uses sophisticated knowledge of disease mechanisms and receptor properties. A good understanding of how the drug is transported into the body, distributed throughout the body compartments, metabolically altered by the liver and other organs, and excreted from the patient is required, along with the structural characteristics of the receptor.

MATERIALS AND METHODS

In silico ADME prediction

By applying computational methods, there are various physicochemical properties and pharmacokinetic descriptors were calculated for some selected anti-anginal agents through the 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 QSAR, molecular modelling 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. [5] Drug-likeness is described as a complex balance of various molecular properties and structural features which determine whether particular molecule is similar to the known drugs. 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 [6]. Other calculation methods such as ligand efficiency and lipophilic efficiency can also be used to express drug-likeness as parameters of potency.

***In silico* Bioactivity score calculation**

The bioactivity score of selected agents were also evaluated using the tool Molinspiration Cheminformatics server (http://www.molinspiration.com). In this technique large chemical databases are analyzed in order to identify possible new drug candidates.

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 [7]. 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 [8]. 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 [9].

***In silico* Toxicity analysis**

The toxicity of the selected anti-anginal 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 [10, 11 and 12].

RESULT AND DISCUSSION

There were eight anti-anginal agents selected and analyzed to pharmacokinetic parameters 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). 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. [13, 14]

The MLogP (octanol / water partition co efficient) of all agents were calculated and found to be within acceptable range except perhexiline 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. 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-anginal agents by %ABS = 109- (0.345 * TPSA) [15]. 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.

Table-1 Pharmacokinetic parameters of Anti-anginal agents

Name	Molecular formula	Molecular weight	LogP	TPSA	nON	nOHNH	nrotb	volume	*In silico* % absorption
Nitroglycerin	$C_3H_5N_3O_9$	227.09	2.19	165.17	12	0	8	160.02	52.01
Felodipine	$C_{18}H_{19}Cl_2NO_4$	384.26	4.80	64.64	5	1	6	323.32	86.69
Propranolol	$C_{16}H_{21}NO_2$	259.35	2.97	41.49	3	2	6	257.82	94.68
Atenolol	$C_{14}H_{22}N_2O_3$	266.34	0.72	84.58	5	4	8	260.90	79.81
Nifedipine	$C_{17}H_{18}N_2O_6$	346.34	3.07	110.46	8	1	6	302.78	70.89
Nicorandil	$C_8H_9N_3O_4$	211.18	0.52	97.05	7	1	5	177.19	75.51
Perhexiline	$C_{19}H_{35}N$	277.50	6.21	12.03	1	1	4	311.85	104.84
Dipyridamole	$C_{24}H_{40}N_8O_4$	504.64	1.59	145.43	12	4	12	475.37	58.82

Bioactivity of all selected anti-anginal 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. [16]

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.

Table-2 Bioactivity parameters of Anti-anginal agents

Name	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Nitroglycerin	-0.20	-0.48	-0.71	-0.89	-0.94	0.32
Felodipine	-0.34	-0.09	-1.04	-0.19	-0.63	-0.51
Propranolol	0.12	0.06	-0.17	-0.19	-0.04	0.04
Atenolol	0.13	-0.00	-0.27	-0.31	0.08	0.03
Nifedipine	-0.45	-0.13	-1.08	-0.25	-0.73	-0.50
Nicorandil	-0.01	-0.29	-0.36	-0.91	-0.53	0.37
Perhexiline	0.26	0.28	-0.12	-0.09	0.24	0.17
Dipyridamole	0.17	0.10	0.28	-0.12	-0.08	0.24

All selected anti-anginal agents were evaluated to toxicity profile and given in Table 3. All of the drugs were found to be highly probable to toxicity except clonidine and losartan.

Table-3 Toxicity parameters of Anti-anginal agents

Name	Toxicity	Overall toxicity	Oncogenicity	Mutagenicity	Teratogenicity	Irritation	Sensitivity	Immunotoxicity	Neurotoxicity
Nitroglycerin	Highly Probable	76	76	0	0	0	0	0	0
Felodipine	Highly Probable	76	76	42	38	0	0	29	40
Propranolol	Highly Probable	100	100	0	53	0	0	29	0
Atenolol	Highly Probable	76	76	0	53	0	0	29	0
Nifedipine	Highly Probable	76	76	67	34	0	29	0	0
Nicorandil	Highly Probable	76	76	0	17	0	0	0	0
Perhexiline	Highly Probable	71	0	71	0	0	0	0	0
Dipyridamole	Highly Probable	71	53	71	19	0	0	0	0

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