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Computational Analysis of Pharmacokinetic, Bioactivity and Toxicity Parameters of Some Selected Antihypertensive Agents

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ABSTRACT

Hypertension is generally defined as mild when the diastolic pressure is between 90 and 104 mm Hg, moderate when it is 105 to 114 mm Hg, and severe when it is above 115 mm Hg. The increasing prevalence of hypertension is attributed to population growth, ageing and behavioral risk factors, such as unhealthy diet, harmful use of alcohol, lack of physical activity, excess weight and exposure to persistent stress. In this research work, we study the pharmacokinetic, toxicity and bioactivity profile of few selected antihypertensive agents by computational methods. These research investigations provide the lead for the development of new antihypertensive agents with lesser toxicity and more effectiveness.

Keywords: - QSAR, Ion channel modulator, Nuclear receptor Ligand, Teratogenicity.

INTRODUCTION

Hypertension is a consequence of many diseases. Haemodynamically, blood pressure is a function of the amount of blood pumped by the heart and the ease with which the blood flows through the peripheral vasculature. Hypertension is generally defined as mild when the diastolic pressure is between 90 and 104 mm Hg, moderate when it is 105 to 114 mm Hg, and severe when it is above 115 mm Hg [1]. It is estimated that about 15% of the adult population in the United States are hypertensive [2]. Hypertension is a risk factor for coronary heart disease and the single most important risk factor for stroke. It causes about 50% of ischaemic strokes and increases the risk of hemorrhagic stroke. Hypertension stresses your body's blood vessels, causing them to clog or weaken. Hypertension can lead to atherosclerosis and narrowing of the blood vessels making them more likely to block from blood clots or bits of fatty material breaking off from the lining of the blood vessel wall [3]. The

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increasing prevalence of hypertension is attributed to population growth, ageing and behavioural risk factors, such as unhealthy diet, harmful use of alcohol, lack of physical activity, excess weight and exposure to persistent stress [4]. Despite the many years of experience, treatment remains empiric because the etiology of the principal form of hypertension, primary hypertension, is unknown.

MATERIALS AND METHODS

Pharmacokinetic study through computational approaches

There are various physicochemical descriptors and pharmacokinetic relevant properties of the adrenergic agents were evaluated by using 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 $\leq$ 500, log P $\leq$ 5, Hbond donors $\leq$ 5, H-bond acceptors $\leq$ 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 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.

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 study

The toxicity of the selected antidepressant 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 twelve antihypertensive 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 $\leq$ 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. [13, 14]

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. 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 antiepileptic 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.

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. [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. All selected antihypertensive 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.

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

Table-1 ADME Properties of Antihypertensive agents

Name	Molecular formula	Molecular weight	LogP	TPSA	nON	nOHNH	nrotb	volume	In silico % absorption
Prazosin	$C_{19}H_{21}N_5O_4$	383.41	1.91	106.96	9	2	4	336.00	72.09
Clonidine	$C_9H_9Cl_2N_3$	230.10	2.61	36.42	3	2	2	181.94	96.43
Methyldopa	$C_{10}H_{13}NO_4$	211.22	-1.74	103.78	5	5	3	188.24	73.19
Minoxidil	$C_9H_{15}N_5O$	209.25	-0.86	93.64	6	4	1	192.77	76.69
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
Labetalol	$C_{19}H_{24}N_2O_3$	328.41	2.85	95.58	5	5	8	314.78	76.02
Captopril	$C_9H_{15}NO_3S$	217.29	-1.09	57.61	4	1	3	195.65	89.12
Nifedipine	$C_{17}H_{18}N_2O_6$	346.34	3.07	110.46	8	1	6	302.78	70.89
Losartan	$C_{22}H_{23}ClN_6O$	422.92	4.87	92.52	7	2	8	374.12	77.08
Chlorothiazide	$C_7H_6ClN_3O_4S_2$	295.73	0.02	118.70	7	3	1	196.55	68.04
Hydrochlorothiazide	$C_7H_8ClN_3O_4S_2$	297.75	-0.06	118.36	7	4	1	202.50	68.16

Table-2 Bioactivity score of Antihypertensive agents

Name	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor Ligand	Protease inhibitor	Enzyme inhibitor
Prazosin	0.09	-0.32	0.24	-0.70	-0.32	0.01
Clonidine	0.02	-0.01	-0.53	-1.64	-0.54	-0.25
Methyldopa	0.06	0.08	-0.53	-0.48	0.13	0.07
Minoxidil	0.21	0.11	0.24	-0.89	-0.15	0.42
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
Labetalol	0.38	-0.08	0.03	0.00	0.30	0.16
Captopril	-0.14	-0.08	-0.98	-0.55	0.97	0.50
Nifedipine	-0.45	-0.13	-1.08	-0.25	-0.73	-0.50
Losartan	0.96	0.06	0.01	0.02	0.24	0.37
Chlorthiazide	-0.69	-0.45	-0.95	-1.20	-0.22	0.18
Hydrochlorthiazide	-0.45	-0.25	-0.64	-1.21	-0.15	0.27

Table-3 Toxicity Profile of Antihypertensive agents

Name	Toxicity	Overall toxicity	Oncoge-nicity	Mutage-nicity	Teratoge-nicity	Irritation	Sensitivity	Immuno toxicity	Neurotoxi city
Prazosin	Highly Probable	76	76	53	19	0	29	0	0
Clonidine	Not Probable	40	40	35	29	0	0	29	0
Methyldopa	Highly Probable	76	76	29	19	53	0	0	29
Minoxidil	Highly Probable	71	0	71	0	0	0	0	0
Propranolol	Highly Probable	100	100	0	53	0	0	29	0
Atenolol	Highly Probable	76	76	0	53	0	0	29	0
Labetalol	Highly Probable	76	76	29	19	53	0	0	29
Captopril	Highly Probable	76	76	71	17	0	0	0	0
Nifedipine	Highly Probable	76	76	67	34	0	29	0	0
Losartan	Not Probable	18	0	0	18	0	0	0	0
Chlorthiazide	Highly Probable	76	76	0	18	0	0	0	0
Hydrochlor-thiazide	Highly Probable	76	76	0	18	0	0	0	0

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