Chemistry Research Journal, 2017, 2(1):42-45

Available online www.chemrj.org

Research Article

ISSN: 2455-8990
CODEN(USA): CRJHA5

In silico Pharmacokinetic and Toxicity study of Some Selected Antidepressant Drugs

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Abstract Major depressive disorders affect the general health and reduce the life quality. The treatments approaches are used to treat major depressive disorders are counselling and antidepressant medication. Due to occurrence of serious but low adverse events, there is essential need to design and develop new drug with lesser toxic and higher potency. In this work, we performed the evaluation of pharmacokinetic descriptors, bioactivity score and various types of toxicities through computational methods.

Keywords Anxiety, Drug-likeness, Nuclear receptor ligands, Teratogenicity

Introduction

Major depressive disorders also known as depression is characterized by dysthymia, anxiety and low mood state at least two weeks. This depressive disorder negatively affects the general health as well as person's personal work, school life. Major people who die by suicide had depression or other mood disorders [1]. 253 million people are affected from major depressive disorder according to global burden of disease study 2013 [2]. The chances of depressive condition are enhanced with neurological diseases such as stroke, psychosis and parkinson's disease. The interesting fact about this major depressive disorder is it found more in urban areas as compared to rural areas [3]. The pathophysiology of depression is not clearly understood but the cause of depression includes the genetic, environmental and mostly psychological factors. The treatments approaches are used to treat major depressive disorders are counselling and antidepressant medication. In comparison with counselling approach, antidepressant medication appears to be more effective but causes serious adverse events. So, it is quite essential to make new potent antidepressant agents which have lesser adverse events with higher antidepressant activity.

Materials and Methods

In silico ADME analysis

There are various physicochemical features and pharmacokinetic descriptors were calculated for some selected antidepressant 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 [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 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 $\leq$ 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 [5]. 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. Only SMILES or SD file 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 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.

Result and Discussion

There some antidepressant agents were selected and analyzed to pharmacokinetic 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 $\leq$ 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].

Table 1: ADME Properties of Antidepressant agents

Name	Molecular formula	Molecular weight	LogP	TPSA	nON	nOHNH	nrotb	volume	*In silico* % absorption
Isocarboxazide	$C_{12}H_{13}N_3O_2$	231.25	1.23	67.16	5	2	4	210.01	85.82
Phenelzine	$C_8H_{12}N_2$	136.20	0.45	38.05	2	3	3	141.34	95.87
Pargyline	$C_{11}H_{13}N$	159.23	1.90	3.24	1	0	3	169.25	107.88
Imipramine	$C_{19}H_{24}N_2$	280.42	4.16	6.48	2	0	4	287.31	106.76
Doxepine	$C_{19}H_{21}NO$	279.38	3.85	12.47	2	0	3	277.32	104.69
Bupropion	$C_{13}H_{18}ClNO$	239.75	3.42	29.10	2	1	4	228.54	98.96
Fluoxetine	$C_{17}H_{18}NOF$	309.33	4.53	21.26	2	1	7	275.13	101.66
Sertraline	$C_{17}H_{17}Cl_2N$	306.24	3.98	12.03	1	1	2	267.90	104.84

Among selected antidepressant agents, all are found to be within 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 [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 antiepileptic agents 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 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 [10].

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.

Imipramine, Doxepine, Fluoxetine and Sertraline having good bioactivity score against GPCR ligand which could indicates they could bind more effectively with GPCR.

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 of Antidepressant agents

Name	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Isocarboxazide	-0.46	-0.63	-0.74	-1.10	-0.60	-0.41
Phenelzine	-1.14	-1.07	-1.32	-1.81	-0.94	-0.40
Pargyline	-0.44	-0.21	-0.78	-0.98	-0.63	-0.09
Imipramine	0.25	0.16	0.10	0.00	-0.08	0.13
Doxepine	0.70	0.34	0.08	0.58	0.11	0.65
Bupropion	-0.29	0.04	-0.86	-0.61	-0.19	-0.28
Fluoxetine	0.38	0.04	0.13	0.37	0.18	0.19
Sertraline	0.23	0.27	-0.37	-0.16	-0.12	0.02

All selected antidepressant agents were evaluated to toxicity profile and given in Table 3. All of the drugs were found to be highly probable to toxicity except sertraline, doxepine and pargyline.

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.

Table 3: Toxicity Profile of Antidepressant agents

Name	Toxicity	Overall toxicity	Oncogenicity	Mutagenicity	Teratogenicity	Irritation	Sensitivity	Immunotoxicity	Neurotoxicity
Isocarboxazide	Highly Probable	72	72	67	29	53	0	0	29
Phenelzine	Highly Probable	72	72	67	29	47	0	0	0
Pargyline	Not Probable	0	0	0	0	0	0	0	0
Imipramine	Highly Probable	71	0	71	0	0	0	0	0
Doxepine	Not Probable	0	0	0	0	0	0	0	0
Bupropion	Highly Probable	76	76	0	18	0	0	0	0
Fluoxetine	Highly Probable	71	0	71	0	0	0	0	0
Sertraline	Not Probable	42	40	42	38	0	0	29	40

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