In silico ADME, Bioactivity and Toxicity Prediction of Some Selected Anti-Parkinson Agents

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ABSTRACT

Parkinsonism, one of the most frequent CNS disorders characterized by tremor and hypokinesia. Several people affected from this disorder due to concurrent use of medications results as side effect. In this computational research investigation, we performed *In-silico* pharmacokinetic, bioactivity and toxicity study of some selected anti-parkinsonism agents. To design a new molecule having good pharmacological profile, this study will provide the lead information.

Key Words: QSAR, TPSA, *In Silico,* bioactivity, Log P

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INTRODUCTION

Parkinsonism is an extrapyramidal motor disorder characterized by rigidity, tremor and hypokinesia with secondary manifestations like defective posture and gait, mask like face and siolorrhoea; dementia may accompany [1]. Major pathology involved is the degeneration of dopamenergic neurone in substantial nigra and nigrostriatal tract of basal ganglia. The motor defect occurs due to the imbalance between dopaminergic (inhibitory) and cholinergic (facilitatory) system. Thus, the treatment approach of parkinsonism is –

1. Increase brain dopaminergic activity
2. Decrease brain cholinergic activity

Major people approx. 7% developed the symptoms with following medications. Various side effects of medications are increased and also drug-induced parkinsonism increases with age. In this research investigation, we performed computational evaluation of ADME, bioactivity and toxicity parameters of some selected anti-parkinsonism agents.

MATERIALS AND METHODS

ADME 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 [2]. 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.

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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 ≤ 500, log P ≤ 5, H-bond donor's ≤ 5, and H-bond acceptors ≤ 10) associated with 90% of orally active drugs that have passed phase II clinical status [3]. These physicochemical features are associated with acceptable aqueous solubility and intestinal permeability (Lead- and drug-like compounds: the rule-of-five revolution, Christopher A. Lipinski).

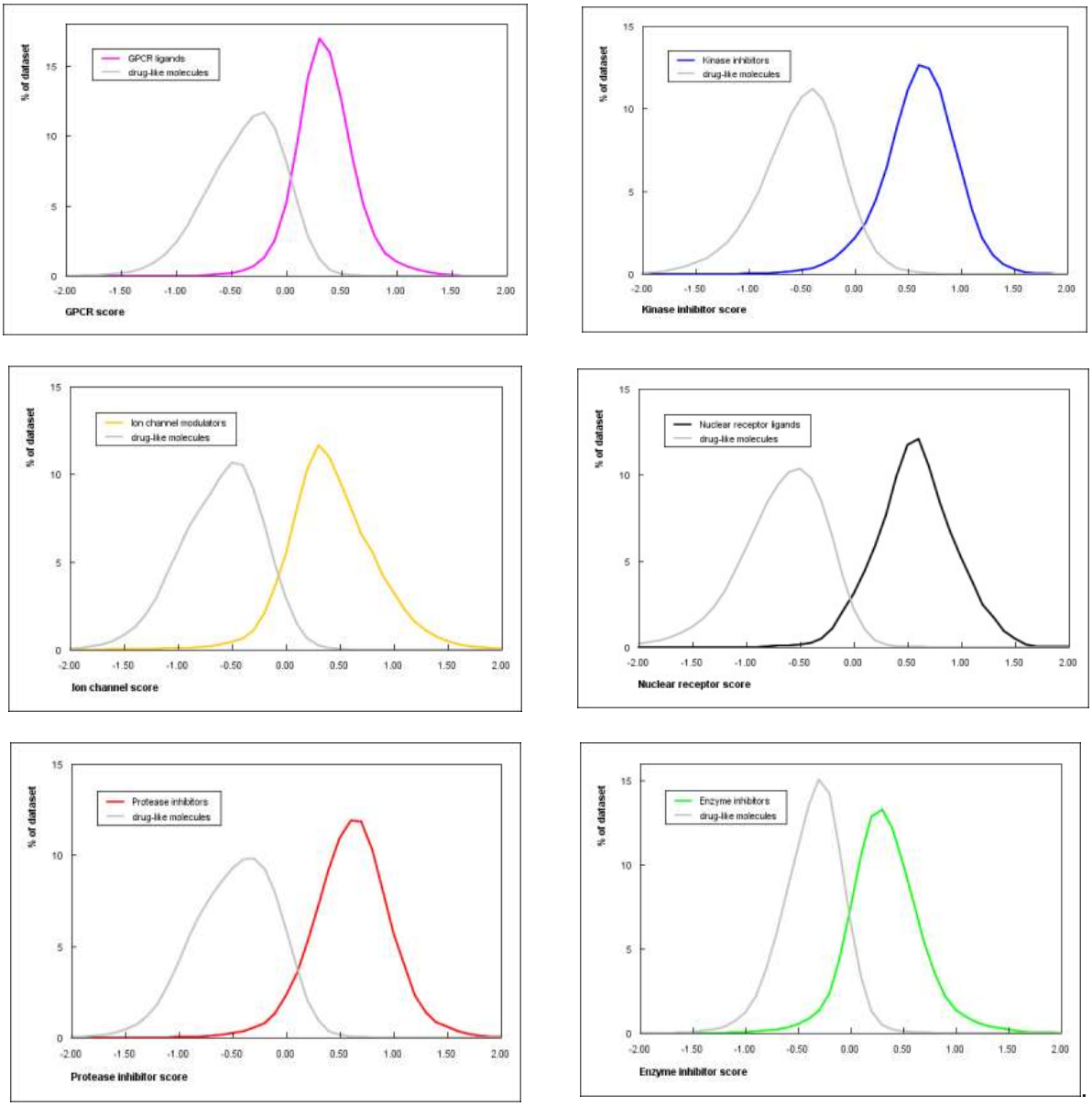

Figure 1. Bioactivity score graph of levodopa for various targets

In silico Toxicity study

The toxicity of the adrenergic agents was evaluated by computational method using Pallas version 3.1 ADME-Tox 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, 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 some anti-parkinsonism 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). 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 [4].

Table 1. ADME Properties of Anti-parkinsonism agents

Name	Molecular formula	Molecular weight	LogP	TPSA	nON	nOHNH	nrotb	volume	*In silico* % absorption
Procyclidine	$C_{19}H_{30}ClNO$	287.45	4.33	23.47	2	1	5	301.31	100.90
Orphenadrine	$C_{18}H_{23}NO$	269.39	3.90	12.47	2	0	6	277.33	104.69
Amantadine	$C_{10}H_{17}N$	151.25	2.65	26.02	1	2	0	159.20	100.02
Chlorphenoxamine	$C_{18}H_{22}ClNO$	303.83	4.00	12.47	2	0	6	290.55	104.69
Carbidopa	$C_{10}H_{14}N_2O_4$	226.23	-2.81	115.81	6	6	4	200.64	69.04
Levodopa	$C_9H_{11}NO_4$	197.19	-2.20	103.78	5	5	3	172.00	73.19
Ropinirole	$C_{16}H_{24}N_2O$	260.38	3.03	32.34	3	1	7	268.11	97.84

Table 2. Bioactivity of Anti-parkinsonism agents

Name	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor Ligand	Protease inhibitor	Enzyme inhibitor
Procyclidine	0.46	0.32	-0.16	-0.00	0.19	0.24
Orphenadrine	0.07	-0.04	-0.19	-0.25	-0.36	0.02
Amantadine	-0.50	-0.07	-0.85	-1.27	-0.54	-0.40
Chlorphenoxamine	0.17	0.05	-0.26	0.30	-0.15	0.02
Carbidopa	-0.19	-0.39	-0.63	-0.56	-0.12	0.04
Levodopa	-0.04	0.39	-0.60	-0.17	-0.01	0.29
Ropinirole	0.26	0.04	-0.11	-0.26	-0.11	0.00

Table 3. Toxicity Profile of Anti-parkinsonism agents

Name	Toxicity	Overall toxicity	Oncoge-nicity	Mutage-nicity	Teratoge-nicity	Irritation	Sensiti-vity	Immuno-toxicity	Neuro-toxicity
Procyclidine	Highly Probable	71	0	71	19	0	0	0	0
Orphenadrine	Not Probable	45	0	45	0	0	0	0	0
Amantadine	Not Probable	0	0	0	0	0	0	0	0
Chlorphenoxamine	Not Probable	18	0	0	18	0	0	0	0
Carbidopa	Highly Probable	76	76	67	29	53	0	0	29
Levodopa	Highly Probable	76	76	29	19	53	0	0	29
Ropinirole	Highly Probable	81	76	81	0	0	0	0	0
Pergolide	Probable	53	53	53	0	0	0	0	0

Among selected anti-parkinsonism agents, carbidopa have one violation according to Lipinski's rule of five. The MLogP (octanol / water partition co efficient) of all agents were calculated and found to be within acceptable range according to Lipinski's rule except carbidopa. 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 [5]. 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 [6]. Percent absorption were also evaluated for all selected antiepileptic agents by %ABS = 109- (0.345 * TPSA) [7]. 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 [8].

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 levodopa 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-parkinsonism agents were evaluated to toxicity profile and given in Table 3. All of the drugs were found to be highly probable to toxicity except amantadine, orphenadrine and chlorphenoxamine.

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

REFERENCES

[1] Fujiwara, Y., 2016. The Relationship of Clinical Treatment to Quality of Life in a Patient with Vascular Parkinsonism: A Case Report from a Pharmacist's Perspective.

[2] Sharma, C.S., Mishra, S.S., Singh, H.P. and Kumar N., 2016. In silico ADME and Toxicity Study of Some Selected Antineoplastic Drugs. *International Journal of Pharmaceutical Sciences and Drug Research, 8*(1), pp.65-67.

[3] Lipinski, C.A., 2004. Lead-and drug-like compounds: the rule-of-five revolution. *Drug Discovery Today: Technologies*, *1*(4), pp.337-341.

[4] Srimai, V., Ramesh, M., Parameshwar, K.S. and Parthasarathy, T., 2013. Computer-aided design of selective Cytochrome P450 inhibitors and docking studies of alkyl resorcinol derivatives. *Medicinal Chemistry Research*, *22*(11), pp.5314-5323.

[5] Abraham, D.J., 2003. Burger's Medicinal Chemistry and Drug Discovery Volume 5: Chemotherapeutic Agents.

[6] Palm, K., Stenberg, P., Luthman, K. and Artursson1, P., 1997. Polar molecular surface properties predict the intestinal absorption of drugs in humans. *Pharmaceutical research*, *14*(5), pp.568-571.

[7] Sharma, C.S., Verma, T., Singh, H.P. and Kumar, N., 2014. Synthesis, characterization and preliminary anticonvulsant evaluation of some flavanone incorporated semicarbazides. *Medicinal Chemistry Research*, *23*(11), pp.4814-4824.

[8] Verma, A., 2012. Lead finding from Phyllanthus debelis with hepatoprotective potentials. *Asian Pacific Journal of Tropical Biomedicine*, *2*(3), pp.S1735-S1737.

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