Available online at www.ijpsdronline.com

International Journal of Pharmaceutical Sciences and Drug Research 2016; 8(5): 254-258

Research Article

ISSN: 0975-248X
CODEN (USA): IJPSPP

In silico ADME, Bioactivity and Toxicity prediction of Some Selected Anti-Epileptic Agents

Neeraj Kumar[1*], Shashank Shekhar Mishra[2], C S Sharma[2], H P Singh[2]

[1]*Department of Pharmaceutical Chemistry, Geetanjali Institute of Pharmacy, Udaipur-313002, Rajasthan, India*
[2]*Department of Pharmaceutical Chemistry, Bhupal Nobles' College of Pharmacy, Udaipur-313001, Rajasthan, India*

ABSTRACT
Epilepsy is a brain disorder characterized by partial or generalized spontaneous (unprovoked) recurrent epileptic seizures and often, comorbidities such as anxiety and depression. Epilepsy is fourth most common neurological disorder. In developed countries, new cases occur of epilepsy in babies and elderly due to the differences in the frequency of disease causes. All available antiepileptic drugs have antiepileptogenic effects; they only prevent the development or progression of epilepsy. However, no drugs have been reported with epileptogenesis effect. This computational research investigation provides the pharmacokinetic, bioactivity and toxicity profiles of some selected antiepileptic agents that would be useful for development of new antiepileptic molecule having good pharmacological profile.

Keywords: ILAE, GABA, ADMETox, GPCR, QSAR.

INTRODUCTION

Epilepsy is one of the major life-shortening brain diseases affecting approximately 1% of the worldwide population. [1] Epilepsy is fourth most common neurological disorder which affects people of all ages and characterized by unpredictable seizures. [2] The cause of epilepsy is unknown in most cases but in some cases epilepsy develops as the result of brain stroke, brain injury, brain tumors and genetic defects. Globally, about 22 million people had affected from epilepsy according to 2013 report. Most of the cases occur in developing countries approx 80%. [3] Although, in developed countries, new cases occurs of epilepsy in babies and elderly due to the differences in the frequency of disease causes.

***Corresponding author: Dr. Neeraj Kumar,**
Department of Pharmaceutical Chemistry, Geetanjali Institute of Pharmacy, Udaipur-313002, Rajasthan, India; **E-mail:** neerajkumarkamra@gmail.com
Received: 10 September, 2016; **Accepted:** 22 September, 2016

According to the ILAE commission 2011 (International league against epilepsy), epilepsies have been classified into three ways [4]-

1. Unknown cause (genetic or presumed genetic origin)
   (i) Pure epilepsies due to single gene disorders
   (ii) Pure epilepsies with complex inheritance
2. Symptomatic (pathologic abnormalities)
   (i) Genetic causes
      (a) Childhood epilepsy syndromes
      (b) Progressive myoclonic epilepsies
      (c) Neurocutaneous syndromes
      (d) Other neurologic single gene disorders
      (e) Disorders of chromosome function
      (f) Developmental anomalies of cerebral structure
   (ii) Acquired causes
      (a) Hippocampal sclerosis
      (b) Perinatal and infantile causes
      (c) Cerebral trauma, tumor or infection
      (d) Cerebrovascular disorders
      (e) Cerebral immunologic disorders

(f) Degenerative and other neurologic conditions

3. Provoked (associated with specific systemic or environmental factors)

(a) Provoking factors

(b) Reflex epilepsies

4. Crytogenic (presumed symptomatic nature in which the cause has not been identified)

There are several management approaches available today but usually epilepsy cannot be cured. Medication drugs are most common approach to treat seizures as compared to other available methods such as epilepsy surgery, neurostimulation. Conventional medicated drugs treat epilepsy by various mechanisms such as blockage of sodium or calcium channels; enhance the GABA function by targeting $GABA_A$ receptors, GABA transaminase. But all available antiepileptic drugs have antiepileptogenic effects; they only prevent the development or progression of epilepsy. However, no drugs have been reported with epileptogenesis effect. So, the design of a new antiepileptic drug which prevents the development of epileptic-seizures in an individual at risk having good pharmacological, toxicological profiles is a valuable approach.

The scope of this work is to search the pharmacokinetic, drug-likeness, toxicity and bioactivity profile of available antiepileptic drugs on the basis of several physic-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 ADME prediction

By applying computational methods, there are various physicochemical properties and pharmacokinetic descriptors were calculated for some selected antiepileptic agents through the tool MolinspirationCheminformatics server (http://www.molinspiration.com).

MolinspirationCheminformatics 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 qualitative concept used for drug like ability 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 ≤ 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. 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.

In silico Bioactivity prediction

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). 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 prediction**

The toxicity of the selected antiepileptic 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.

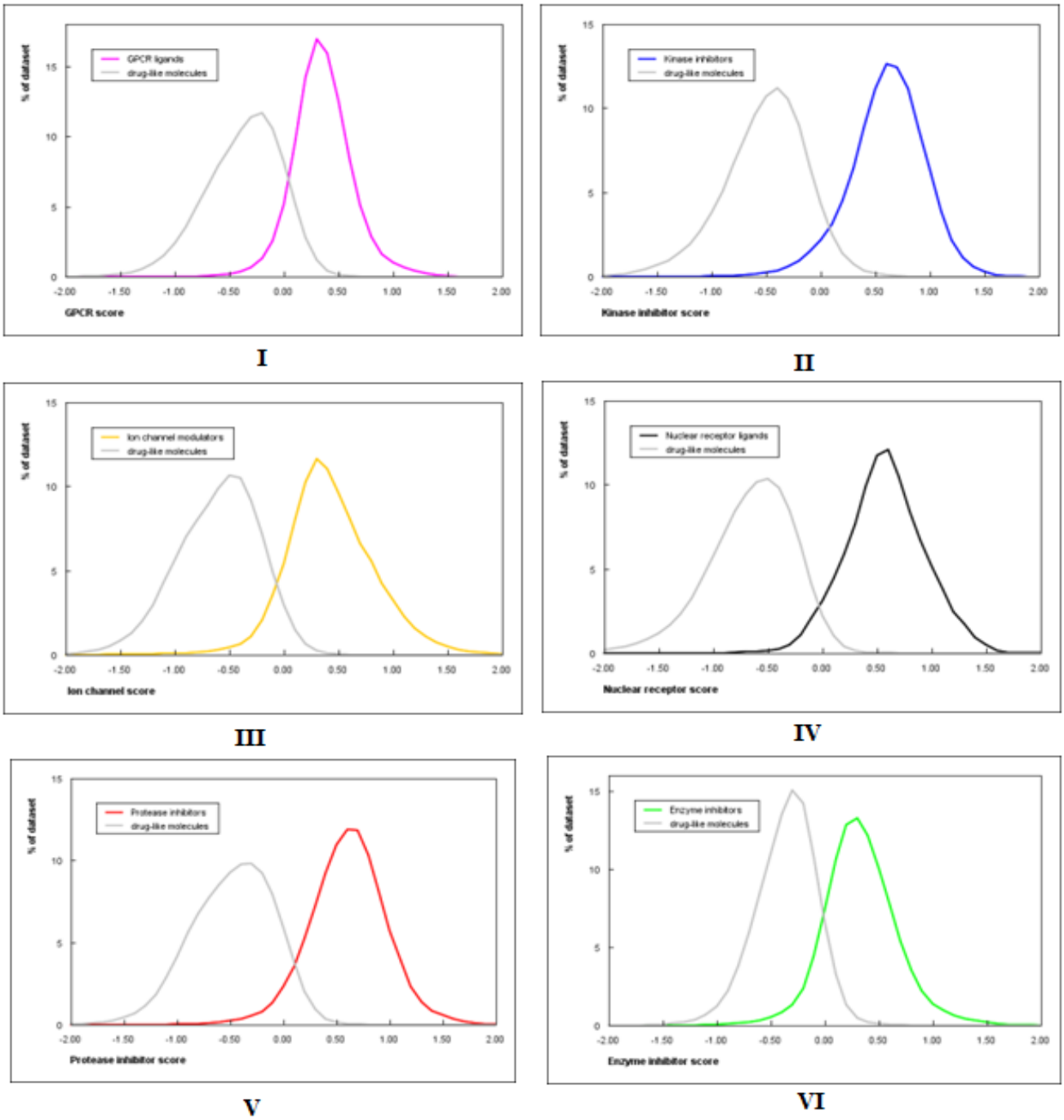

Fig. 1: The bioactivity score graph of phenytoin for different proteins

Table 1: ADME Properties of Antiepileptic agents

Name	Molecular formula	Molecular weight	LogP	TPSA	nON	nOHNH	nrotb	volume	*In silico* % absorption
Phenytoin	$C_{15}H_{12}N_2O_2$	252.27	2.18	58.20	4	2	2	223.89	88.92
Phenobarbitone	$C_{12}H_{12}N_2O_3$	232.24	0.80	75.27	5	2	2	204.82	83.03
Carbamazepine	$C_{15}H_{12}N_2O$	236.27	2.84	48.03	3	2	0	215.08	92.42
Trimethadione	$C_6H_9NO_3$	143.14	0.18	46.61	4	0	0	127.72	92.91
Phensuximide	$C_{11}H_{11}NO_2$	189.21	1.18	37.38	3	0	1	174.14	96.10
Vigabatrin	$C_6H_{11}NO_2$	129.16	-0.39	63.32	3	3	4	129.09	87.15
Clobazam	$C_{16}H_{13}ClN_2O_2$	300.75	2.55	40.62	4	0	1	255.04	94.98
Diazepam	$C_{16}H_{13}ClN_2O$	284.75	2.74	32.67	3	0	1	246.54	97.72

Table 2: Bioactivity of Adrenergic agents

Name	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Phenytoin	0.07	-0.14	-0.47	-0.32	0.01	-0.02
Phenobarbitone	-0.30	-0.01	-0.46	-0.50	-0.12	-0.13
Carbamazepine	0.01	0.35	-0.10	-0.54	-0.32	0.24
Trimethadione	-0.59	-0.14	-1.44	-1.53	-0.54	-0.60
Phensuximide	-0.52	-0.72	-1.27	-1.27	-0.90	-0.33
Vigabatrin	-1.58	-0.99	-2.41	-1.99	-1.43	-1.18
Clobazam	-0.01	-0.23	-0.00	-0.31	-0.45	-0.15
Diazepam	0.37	0.53	-0.45	-0.20	0.01	0.15

Table 3: Toxicity Profile of Antiepileptic agents

Name	Toxicity	Overall toxicity	Oncogenicity	Mutagenicity	Teratogenicity	Irritation	Sensitivity	Immunotoxicity	Neurotoxicity
Phenytoin	Highly Probable	76	76	0	0	0	0	0	0
Phenobarbitone	Highly Probable	76	76	0	0	0	0	0	0
Carbamazepine	Highly Probable	81	76	81	17	0	0	0	0
Trimethadione	Highly Probable	76	76	0	0	0	0	0	0
Phensuximide	Highly Probable	76	76	0	0	0	0	0	0
Vigabatrin	Highly Probable	76	76	47	19	0	0	0	0
Clobazam	Highly Probable	81	76	81	18	0	0	0	0
Diazepam	Highly Probable	81	76	81	18	0	0	0	0

RESULT AND DISCUSSION

There were some antiepileptic agents 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. [7]

All selected antiepileptic agents have number of H-bond acceptors and number of Hbond donors is within range according to Lipinski's rule of five, so selected agents have no violations. 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. [8] 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. [9] Percent absorption were also evaluated for all selected antiepileptic agents by %ABS = 109- (0.345 * TPSA). [10] 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 antiepileptic 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. [11]

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.

Phenytoin, carbamazepine, trimethadione, phensuximide having bioactivity score against GPCR ligand which indicates they could bind more effectively with GPCR. The bioactivity score graph of phenytoin 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 antiepileptic agents were evaluated to toxicity profile and given in Table 3. All of the drugs were found to be highly probable to toxicity.

The interesting fact about toxicity is all selected antiepileptic agents were found to be exhibited oncogenecity. These research findings provide the lead for the design and development of new potent antiepileptic drugs. Computational study of all selected antiepileptic 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. Schmidt D, Sillanpää M. Evidence-based review on the natural history of the epilepsies. Current opinion in neurology. 2012; 25(2):159-163.
2. http://www.epilepsy.com/
3. Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, Duan L. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2015; 386(9995): 743-800.
4. Zeng QY, Fan TT, Zhu P, He RQ, Bao YX, Zheng RY, Xu HQ. Comparative long-term effectiveness of a monotherapy with five antiepileptic drugs for focal epilepsy in adult patients: a prospective cohort study. PloS one. 2015; 10(7): e0131566.
5. Sharma CS, Mishra SS, Singh HP, Kumar N. In silico ADME and Toxicity Study of Some Selected Antineoplastic Drugs. International Journal of Pharmaceutical Sciences and Drug Research. 2016; 8(1):65-67.
6. Lipinski CA. Lead-and drug-like compounds: the rule-of-five revolution. Drug Discovery Today: Technologies. 2004; 1(4):337-341.
7. Srimai V, Ramesh M, Parameshwar KS, Parthasarathy T. Computer-aided design of selective Cytochrome P450 inhibitors and docking studies of alkyl resorcinol derivatives. Medicinal Chemistry Research. 2013; 22(11):5314-5323.
8. Abraham DJ. Burger's medicinal chemistry and drug discovery. Wiley Interscience, 2003.
9. Palm K, Stenberg P, Luthman, K, Artursson P. Polar molecular surface properties predict the intestinal absorption of drugs in humans. Pharmaceutical research. 1997; 14(5):568-571.
10. Sharma CS, Verma T, Singh HP, Kumar N. Synthesis, characterization and preliminary anticonvulsant evaluation of some flavanone incorporated semicarbazides. Medicinal Chemistry Research 2014; 23(11):4814-4824.
11. Verma A. Lead finding from *Phyllanthus debelis* with hepatoprotective potentials. Asian Pacific Journal of Tropical Biomedicine. 2012; 2(3): S1735-S1737.

Source of Support: Nil, Conflict of Interest: None declared.