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COMPUTATIONAL PREDICTION OF BLOOD-BRAIN PARTITIONING OF DRUGS

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ABSTRACT: Increasing use of bioinformatics made very easy to researchers in biological and drug discovery field. Bioinformatics is involved at each and every step of drug discovery to drug development. The first step of the drug discovery is a question about disease and the treatment by drugs and whenever term drug comes, means something has to be given and the second question arises the given compound is drugable or not. To check any drugable compound the compound has to be cleared by the ADME studies and the main sensitive parameter blood brain barrier. Bioinformatics made it easy without use of model organism and waste of time. In this study we aimed to predict the blood brain barrier parameters on 87 drugs about their drug ability.

INTRODUCTION: Information technology becomes the boon in all the fields. It saves time as well as money also. If we talk about the biomedical field, it proved a its essential role in drug discovery in treatment of the diseases because life science in addition with the information technology gave birth a new subject named as the bioinformatics. Now days use of bioinformatics is everywhere and by every type, because the process taking years in the drug discovery is completed in days by the use of bioinformatics.

Traditional drug discovery process is taking years to test a drugability of a compound. The first step of a drugable compound is to check whether the compound is drugable or not?

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That is a very important part of drug discovery and it consumes a huge amount of money and time. While with bioinformatics is shortens the time and money expenditure also. Several online tools are available for the ADME prediction about the drugability of compounds [1]. The main part of the ADME properties is blood brain barrier (BBB) that links to the study of drug toxicity. For designing new molecules that target components of the CNS or, on the other hand, to find new substances that should not penetrate the barrier.

Several studies in the literature have attempted to predict BBB penetration, so far with limited success and few, if any, application to real world drug discovery and development programs [2]. The blood brain barrier is regulation of drug transport from entering and leaving the brain. There are several physico-chemical barriers established by brain capillaries to restrict drug or chemical transport into the brain. Tight membrane junctions act as physical barrier separating the capillary endothelial cells resulting in limited paracellular

transport, while the chemical barrier is due to the expression of multidrug transporters that mediate the efflux of a broad range of hydrophobic chemicals. The metabolic demand of brain leads to unusual nutrient demands this provides limited permeability and compensated by the expression of a large number of transporters that are responsive. Brain function is also regulated by the blood brain barriers indirectly and directly controlling the uptake of nutrients [3].

Traditionally two widely used methods for studying the blood brain are a cell culture model using rat, pig, or cow brain endothelial cells and isolated microvessels. Cell culture model is more popular likely because it is easier to use and less costly compared to isolated microvessels [4]. Here the disadvantage is that the laborious preparation, animals required, and a shorter lifespan in vitro. Better alternatives as machine learning schemes seemingly to develop *in silico* models to predict the BBB permeation since mathematically and may able to handle such nonlinear relationship. For instance, the descriptors required to describe the efflux transport by p-glycoprotein are different from those used to depict the influx transport by organic cation transporter [5]. Here bioinformatics comes in use to skip all these animal experimentation by using the *in silico* tools. The present *in silico* study approach to predict the blood brain permeability/penetration of the drug.

MATERIALS AND METHODS: The *in silico* procedure considered superior to other methods such as blood to brain drug partition measurements at steady state (logBB), as it lacks systemic distribution effects, which distort brain penetration substantially [6]. logPS is a complex parameter, because it encompasses passive transcellular diffusion across the BBB as well as a possible contribution by active transport. Small lipophilic agents (e.g., ethanol) cross the endothelial cell membrane by passive diffusion [4]. lipophilicity, molecular weight, and measures of molecular polarity are the major physico-chemical determinants for the process of membrane binding and diffusion [4]. There are several anticancer drugs, corticosteroids, and anti-epileptics examples and well-documented for high passive cellular permeability by an active drug efflux transport [7, 8]. Despite favorable molecular properties, central nervous system (CNS) concentrations of these drugs are significantly lower than expected. This results in suboptimal exposure and therefore poor pharmacological activity in the target tissue.

Physico-chemical properties can be calculated or measured to give signal about BBB permeability of a test compound. These properties range as compounds with a molecular weight less than 400–600 Da [4], a polar surface < 70 Å2 [9] and an octanol to water partition coefficient close to 3.4 [10].

The present study was completed at Department Pharmacology and Therapeutics, King George's Medical University, Lucknow. Study was conducted with objective to compile comprehensive and consistent data set of a complex but highly predictive biological endpoint (logPS) from literature data. Data was drawn from several resources. Experimental protocols were analyzed and standard protocols were used. Dataset of 87 compounds was used for the study [11, 12, 13]. Next step to use machine learning algorithms in prediction of logPS values from calculated physico-chemical descriptors. This is in line with current practice, for example in the prediction of enzyme-drug interactions [14] or the discrimination between substrates, inhibitors, and inducers of P-glycoprotein [15]. Computational tools and algorithms were used with focused ease of use.

RESULTS AND DISCUSSION:

Data Set: High quality dataset needed as prerequisite for any QSAR modeling approach. In the present study, a dataset of 87 small molecules was compiled using more reliable in vivo BBB permeability-surface area (logPS) products, which are obtained by direct internal carotid artery perfusion. This method has the advantage of high sensitivity, as there is no systemic exposure of the test compound prior to its transport across the blood-brain barrier (BBB).

Chemical Space and Compound Classification: The low level of chemical similarity (Tanimoto coefficient = 0.282 for our dataset of n = 87 compounds used for classification learning) reflects the broad chemical space covered by our dataset. Range of physico-chemical properties of the dataset (n = 87) used for classification learning as Molecular weight 46–1201 Da; Partition coefficient

(aLogP) −4.3–2.4; Polar surface area (tPSA) 3.2–279 $Å^2$; Rotatable bonds count 0–18; Hydrogen bond acceptor count 1–23. The distinction of positively (CNSp+) and negatively (CNSp.) classified molecules refers to compounds with logPS values ≥ -2 and ≤3, respectively. To achieve better separability and due to the scarcity of data points in this range, logPS values between -2.1 and -2.9 were exempt from classification learning.

Descriptors and Modeling: BBB permeability was represented by logPS values with the use of modern machine learning algorithms. Decision tree built with the chi-squared automatic interaction detector (CHAID) on CDK descriptors. Prediction of strong (CNSp+) or weak (CNSp−) blood-brain barrier permeation is based on the splitting criteria of the partition coefficient (aLogP), rotatable bonds count, charge weighted partial positive surface area divided by total molecular surface area (fPSA3), and hydrogen bond acceptor count (hBondAcceptors). All the parameters used in the BBB prediction were under the drugability criteria defined before.

CONCLUSION: Day by day the use of *in silico* studies is increasing with advancement of technology. In medical and drug discovery field computational studies are proving itself a boon for the researchers because computational studies are saving time and money with better results. So here the by predicting the drugability of compounds by the important parameter blood brain barrier proved all the drugs were under drugability range. It also recommended more studies to advancement of tools used in drug discovery process.

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