Fall 2023 CS123A Bioinformatics Project Report

PROJECT TITLE: Comprehensive Quantitative Structure-Activity Relationship model utilizing Machine Learning to predict the bioactivity of molecular inhibitors against Thrombin.

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Page 1 of

Page 2 of

Page 3 of

Page 4 of

Page 5 of

INTRODUCTION

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Description automatically generatedFor a long time, Vitamin K antagonists were the sole oral anticoagulants available commercially but their limitations like narrow therapeutic window, delayed onset of action among others render them tedious to administer [1]. A protein molecule thrombin arose as the alternative target molecule for anticoagulant medication. The function of thrombin is to help in the clotting mechanism, as shown in Fig.1, of the human body by converting fibrinogen to fibrin and activating clotting factors XIII, V, VIII, XI and platelets [2][3] rendering it essential in hemostasis. The therapeutic window of a drug is specific to its concentration and is the product of a delicate balance between thrombosis and bleeding [4]. Drug discovery and associated development are convoluted, painstaking procedures. Immense advances in technology and the advent of artificial intelligence (AI) provide the pharmaceutical industry with a plethora of opportunities to ease this process. The world of AI has had a significant shift from studies to actual industrial applications. Machine learning (ML) in its essence, is the utilization of algorithms created by programmers to parse through, comprehend, master, and make predictions off data. The quality and accuracy of results are directly proportional to the amount of training data input into the model. ML finds application in pharmaceuticals especially in the identification of drug targets [5]. Quantitative structure activity relationship (QSAR) is a statistical process of applying models that relate the chemical structure of compounds to their bioactivity. Variables in the form of numerical descriptors are used to represent the chemical structure and then analyze the relationship between the same with the bioactivity of the compound in question using predictive models [6]. QSAR models grant us the power to create safe, potent, and efficacious drugs replacing the need to create new testable compounds cutting labor, time, and monetary losses [7]. Hence, our project chose to apply this important, interesting, high impact bioinformatics tool to identify drug targets for thrombin in the hopes of collecting and categorizing compounds as active or inactive which could then serve as the basis for potential anticoagulant medication in the pharmaceutical space. Thrombin, though having wound healing properties by partaking in the coagulation cascade, also has numerous pathogenicities linked to it. Widespread accumulation of thrombin in the form of plaques, amyloid deposits, neurofibrillary tangles is noticed in the brains of patients suffering from Alzheimer's disease [8]. Animal models of Multiple Sclerosis displayed axonal loss associated with fibrin accumulation in cranial vessels [9]. Low quantities of the compound protect the neurons and astrocytes from stressors like hypoglycemia while higher concentrations promote death of the hippocampal and motor neurons [10,11,12]. This compound also makes the body more susceptible for central nervous system (CNS) infections like meningitis and human immunodeficiency virus related nervous complications, as it increases the ability of pathogens to cross the blood brain barrier [13]. Thrombosis, formation of an endogenous blood clot, when coupled with atherosclerotic plaques, especially unstable ones, lead to an increased predisposition to myocardial infarctions (MI) [14]. Thrombosis affects both veins (Deep Vein Thrombosis) and arteries (Ischemic stroke, Acute limb Ischemia) alike. Hormonal therapy, pregnant and postpartum women, long hours of travel, pre-existing conditions like Diabetes, Hypertension, obesity are associated with thrombosis in the deep veins of the leg especially the calf [15,16]. Conditions like DVT increase the predilection of ischemic stroke due to transfer of a dislodged clot into the cerebral vasculature. Thrombin inhibition is crucial to ameliorate such disastrous events. Thrombin inactivation is either direct or indirect based on the involved binding site. Heparin induces indirect activation by binding at the exosite no. 2 of thrombin but requires cofactors like antithrombin and additional saccharides to maximize its effect. Direct thrombin inactivators can bind to both free and fibrin-bound thrombin molecules. They also do not require any cofactor like antithrombin to function. Both parenteral (Bivalirudin, Lepirudin) and oral (Dabigatran etexilate) variants of anticoagulant medication are available. As with any drug the process involved in discovery and development goes through many phases namely target discovery, target validation, lead compound identification, lead compound optimization, preclinical development, and clinical trials as shown in Fig. 2. Depending on the type of drug and the disease in question these processes could sometimes span over a decade. Lead compound identification takes a long time and requires screening hundreds of potential candidates to find a few molecules that could then progress to the next phase. The expense incurred runs into millions. Addressing this problem with the help of artificial intelligence is thus necessary to cut costs while also ensuring the quicker release of a much-needed drug to combat the conditions linked to thrombosis. A diagram of a process

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Fig 1. Coagulation cascade in the human body

Source: DOI:[10.1016/j.bbrep.2015.11.011](http://dx.doi.org/10.1016/j.bbrep.2015.11.011)

Fig 2. Typical flowchart depicting steps in drug development and discovery.

Source: doi: [10.1111/j.1476-5381.2010.01127.x](https://doi.org/10.1111%2Fj.1476-5381.2010.01127.x)

Machine learning is increasingly being used in numerous stages of drug design such as identifying targets [5], improving small-molecule compound design and optimization [17] and develop new markers for drug efficacy [18]. There are two main types of ML techniques: supervised and unsupervised learning. Supervised learning methods develop training models for predictive purposes on a known input dataset, whereas unsupervised methods are used for exploration and clustering of the data. This project aims to create a QSAR model with supervised machine learning to identify and categorize potential drug candidates for thrombin. One of the major benefits of this proposed solution is significant enhancement in efficiency, particularly when dealing with substantial volumes of data. Robust machine learning models can analyze thousands of data points in a condensed timeframe enabling high throughput screening of potential drug candidates against thrombin. Compounds with a reduced probability of success are eliminated at a very early stage leading to huge economic gains. QSAR models provide the researcher with a comprehensive insight into the relationship between bioactivity of a compound and its structure which is key in designing new drug candidates. ML also eases the burden on the researchers by alleviating the need to create physical testable samples. Another benefit of utilizing ML is the fact that databases everywhere are curated with the latest advancements ensuring researchers access to state-of-the-art developments in real time. This tool also behaves as an aid to invitro testing by providing data-driven actionable insights, thus optimizing, and enhancing the whole drug development process from the initial stage. QSAR models also considerably increase the chances of identifying novel drug candidates by allowing scientists to explore structurally eclectic compounds which might be difficult to find traditionally. Machine learning also assists in the idea of making personalized precision medication a reality as these algorithms function on a diverse range of input variables. There is no restriction on the number and type of data and accuracy essentially improves to provide the best possible results. Medication can be tailor made to suit the patient’s specific genetic and molecular makeup thus increasing chances of better drug interaction and improved efficacy in treatment of disease. QSAR models can be integrated with differing data sources such as omics data improving the understanding of the complex biochemical interactions involved in thrombin inhibition and guides in identifying multi-target drug candidates.

BACKGROUND

Quantitative structure activity relationship (QSAR) was developed over 60 years ago and continues to be a very important aspect of drug discovery and development till date [19]. QSAR has persisted as an efficacious methodology for constructing mathematical models. These models aim to establish a statistically meaningful correlation between the chemical structure and continuous attributes (such as pIC50, pEC50, Ki, etc.) or categorical/binary descriptors (including active, inactive, toxic, nontoxic, etc.) of biological or toxicological relevance. This correlation is pursued through the application of regression techniques for continuous properties and classification techniques for categorical attributes [20]. In machine learning, a diverse array of methodologies is generally contemplated, encompassing techniques such as Random Forest, Naive Bayesian Classification (NBC), Multiple Linear Regression (MLR), Logistic Regression (LR), Linear Discriminant Analysis (LDA), Probabilistic Neural Networks (PNN), Multi-Layer Perceptron (MLP), Support Vector Machine (SVM), among others [21]. Computational intelligence provides several methods of analysis and learning in the context of drug development, highlighting the AI driven procedures used to find a range of drugs methodically and seamlessly [22]. In recent times, QSAR modeling encompasses the adept application of various machine learning techniques to model and conduct virtual screening on extensive datasets, featuring a multitude of diverse chemical structures [23,24]. Modern QSAR models implement auxiliary features like set of empirical rules (eg. Lipinski’s rules) [25], chemical feasibility [20] among others. Random forest QSAR models were built to predict ligand activity toward targets and rank the targets for a specific ligand [26]. Antagonists and agonists of Epidermal growth factor receptor, a cancer drug target, were categorized utilizing random forest QSAR models for a vast set of compounds spanning diverse classes [27]. 4-aminopyrimidine-5-carbaldehyde oxime with potent inhibition of vascular endothelial growth factor receptor 2 (VEGFR2) has been found utilizing QSAR associated with an SVM model [28]. QSAR models utilizing SVM have also been implemented to predict HIV protease inhibitors and were revealed to be superior to Multiple linear regression (MLR) models [29]. A gradient boosting algorithm for QSAR models to predict drug blockade of the Human Ether a-go-go related Gene (hERG1) channel has been built [30]. Comparative analysis of various machine learning QSAR models has been carried out to predict the inhibitory constant of thrombin antagonists among which SVM emerged superior [31]. A two-stage machine learning model composed of several classifier and regression models have been deployed to predict peptide thrombin inhibitors resulting in the creation of a dataset of potential direct thrombin inhibitor drug candidates [32]. Our project differs in the fact that we are utilizing QSAR along with a combination of support vector regression, random forest regression and gradient boosting to predict and classify thrombin inhibitors accessing the CHEMbl database, an integrative repository which incorporates the chemical, bioactivity, and genomic data of drug-like compounds under a singular framework.

DATA COLLECTED/ACCESSED

For a project with the objective of finding thrombin antagonists with QSAR machine learning models we decided on a few key features for the type of dataset to be used. One of them included comprehensive molecular descriptors. These descriptors represent the chemical structure of the potential drug candidates and the set of descriptors we chose for this purpose was the Lipinski descriptor array. Biological activity denoting structure-activity relationship within the dataset displayed as quantitative units was the second feature we decided on. For our project IC50 (half maximal inhibitory concentration) was chosen as the bioactivity measure. A third feature we believed was crucial to forming our dataset was consistency of input data into the QSAR models. This would establish the fact that same molecular structures would deliver the same input ensuring the reliability, accuracy and reproducibility of the machine learning models in use. To fulfil this need we resolved to choose compounds with canonical smiles representations. Finally, we wanted to incorporate a chemically diverse set of compounds that would improve the model’s predictive abilities while also recording a broad spectrum of biochemical compounds. Considering the complexity of our models, number of input features, diversity in chemical structures, bioactivity measure and limited computational resources our team believed a few thousand compounds would be sufficient to conduct the tests on. The Lipinski rule of 5 is recognized as the standard for medicinal chemists and is especially relevant to our project as factors like molecular weight, lipophilicity, hydrogen bond donors, and acceptors help assess drug-likeness. These properties guide researchers in the direction of compounds that are suitable for administration. Compounds that flout the Lipinski rule tend to have poorer absorption and distribution within the human body. IC50 is relevant to our objective as it indicates the concentration of the compound required to antagonize 50% of thrombin activity. It also helps map out the fluctuations in inhibitory effects versus substrate concentration and is pivotal in predicting the therapeutic benefits a specific compound may potentially have. Canonical SMILES (Simplified Molecular Input Line Entry System) is a standard representation of the structure of any molecule using ASCII characters. As compared to SMILES, canonical SMILES certify a unique representation of each molecule thus contributing to consistency in the data. This in turn, is essential in maintaining the standardization of input data into QSAR machine learning models and thus is relevant to our project. Hence, the CHEMbl database [33] was our directory of choice to query, collate and create the dataset utilized in this project. After a programmatic search of this database for our target of interest we isolated bioactivity data of thrombin target with ChEMBL ID `CHEMBL204` reported as IC50 values in nM (nanomolar) unit. We dropped null and duplicate rows for canonical smiles. The final dataframe composed of 1985 potential drug leads is saved as a csv file which has the following columns: -

1. `molecule\_chembl\_id`: Unique ChEMBL ID of the molecule

2. `canonical\_smiles`: Information about the chemical and molecular structure

3. `standard\_value`: quantitative IC50 measures.

4. `class`: IC50 values binned into `active`, `inactive` and `intermediate`

In this project we will only consider active and inactive compounds.

APPROACH AND METHOD

EVALUATION OF RESULTS

CONCLUSON AND DISCUSSION

FUTURE WORK

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Page 6 of

Page 7 of

Page 8 of

Page 9 of

Page 10 of

Page 11 of

Page 12 of

Page 13 of

Page 14 of

Page 15 of

Page 16 of

Page 17 of

Page 18 of

Page 19 of

Page 20 of

Page 21 of

Page 22 of