Ligand based screening of chemical constituents from African medicinal plants for the identification of MAOB inhibitors

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Abstract: Ligand based virtual screening (LBVS) is based on the hypothesis that similar structures have similar biological functions. In this research paper, ligand based virtual screening has been performed in order to predict the inhibitors for monoamine oxidase (MAO-B), an enzyme specifically involved in the metabolism of non-hydroxylated amines such as benzylamine and beta-phenylethylamine (PEA), thus, could be the target to treat various neurodegenerative disorders like Parkinson's disease. For this purpose, Afro Database, a subset of ZINC natural compound database has been screened using Random Forest Modeling (RF). For the training of RF model, 36 reference molecules, the known inhibitors of MAO have been collected from Duke's phyto-chemical and ethno-botanical database. As an outcome of this screening, 31 compounds out of 968 compounds from Afro Database (compounds from African medicinal plants) are predicted to be active as MAO-B inhibitor, Out of the 31 predicted active compounds, Norlichexanthone (ZINC05765089) is predicted to be most active against MAO-B with highest RF score 0.795181, along with the other top hits, could be the putative drug candidates for the prevention/ treatment of Parkinson's disease.

Keywords: Ligand based virtual screening, MAO-B, Random Forest Model, AfroDb.

INTRODUCTION

Monoamine oxidases, an intra-mitochondrial enzyme, belong to a family of enzymes those catalyses the breakdown of dopamine, norepinephrine and serotonin and tyramine (Livingston and Livingston, 1996; Amsterdam and Chopra, 2001; Youdim *et al*., 2006).

The enzyme has two isoenzymes, MAO-A and MAO-B, consist of three binding domains, for FAD, substrate and membrane. The FAD binding domain of both the isoenzymes is present towards the outer mitochondrial membrane and is involved in the metabolism of intracellular amines (Colibus *et al*., 2005).

The MAO-A and MAO-B, mainly differ in their substrate specificity and inhibitor selectivity (Choi *et al*., 2015). MAO-A shows greater affinity for hydroxylated amine like serotonin and nor-epinephrine and inhibited by clorgyline, whereas, MAO-B has higher affinity for non-hydroxylated amines such as benzylamine and phenylethylamine and inhibited by selegiline and rasagiline (Fisar 2016; Malik *et al*., 2018; Saglik *et al*., 2018). Therefore, impaired activity of MAO-A and MAO-B are involved in distinct clinical conditions (Duncan *et al*., 2012; Bortolato *et al*., 2008).

Disturbance in the MAO-A activity results in a variety of neuropsychiatric disorders such as depression and anxiety, therefore, inhibition of MAO-A is linked with the antidepressant and anti-anxiety activity (Amsterdam and Chopra, 2001; Fiedorowicz and Swartz, 2004; Ilgın *et al*., 2017) whereas, MAO-B activity that increase with age, is mainly linked with the neurodegenerative defects, such as Parkinson's disease (PD) (Duncan *et al*., 2012), that mainly affect the motor system. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) a neurotoxin produced during the reaction catalyzed by MAO-B may produce a condition resembling to idiopathic Parkinson's disease (Mellick 2001).

Selective inhibition of MAO-B has neuroprotective action against the neurodegeneration and effective to treat the movement disorders including Parkinson's and Alzheimer's disease (Fiedorowicz and Swartz, 2004 ; Riederer and Laux 2011; Teo and Ho, 2013; Robakis and Fahn, 2015;Wang *et al*., 2016; Ilgın *et al*., 2017; Dezsi and Vecsei, 2017).

Therefore, the identification of novel compounds that can inhibit MAO-B reversibly and selectively with less side effects is still required not only for the prevention from neurodegeneration but to treat Parkinson's disease.

Traditionally, people only depend on plants/herbs for the cure of diseases but as time passed drugs were designed using High Throughput Screening (HTS) (Harvey, 2008). Earlier, drug discovery process uses *in-vitro* testing of biological activity of large number of molecules against a target protein. This process was time consuming and costly. This problem was overcome by the use of computational methods that reduces the cost and time of the process (Guido *et al*., 2008).

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Nowadays with the advancement in the technology computational (*in-silico)* methods plays an integral part in the various stages of modern drug discovery process, Large datasets of compounds can be screened computational in search of potential hits/drug candidates against a target protein (Wolf *et al*,, 2010). It reduces the number of compounds to be tested in wet lab experiments, thus, it is less time consuming and less costly as compared to HTS (Shoichet, 2004).

During this study, ligand-based virtual screening has been performed by Random Forest (RF) modelling, using two data sets, a test dataset, consisting of compounds with known activity against the MAO enzyme and a target dataset, Afro DB (Ntie-Kang *et al*., 2013) a subset of ZINC database (Irwin and Shoichet, 2005), consisting of phyto-chemicals from African Medicinal plants, in search of compounds active against MAO-B

MATERIALS AND METHODS

During this study, RF model was used to identify the compounds from AfroDB that could be active against MAO-B as the development of MAO inhibitors could be the target in order to treat of variety of neurodegenerative disorders such as Parkinson's disease. To perform LBVS two datasets were compiled: a test dataset and a target dataset

Test dataset

To indentify the compounds that could be the inhibitors for MAO-B through RF model, compounds with reported biological activity against the MAO enzyme were required, that is, reference molecules. These reference molecules, the test dataset, have been compiled using the Duke's phytochemical and ethnobotanical databases. It is a database that stores information of naturally derived compounds that are used in drug discovery.

Target dataset

The phyto-chemicals from the African medicinal plants were screened during this study. For this purpose, 986 compounds from the AfroDb (Ntie-Kang *et al*., 2013), a subset of ZINC database (Sterling and Irwin 2015), were downloaded.

Molecular descriptors

To build the RF model, molecular descriptors were calculated for each of the entry in the test and target dataset using the DRAGON software (Mauri, 2006), that requires structure in sdf format. For each of the compounds in the test dataset, were obtained from PubChem (Kim *et al*., 2016), a database of small molecules. These SMILES are then be converted to 2D structure and saved in the SDF format. Whereas, SDF file for each compound in the Afro dataset, has been downloaded from ZINC database (Sterling and Irwin 2015), Hydrogens were then added to SDF file by using Open Babel (O'Boyle *et al*., 2011) a computer software, chemical expert system mainly used to interconvert chemical file formats. SDF file is now ready for both the two datasets for the calculation of descriptors by Dragon software.

Five set of molecular descriptors, Constitutional, RDF, Randic, 3D Morse and 2D autocorrelations were calculated for each compound in both test and target data sets by Dragon. It is software that calculates molecular descriptors for chemical compounds, it is capable of calculating 3224 descriptors in a single run.

Random forest (RF) model

RF, a form of multiple decision trees, consist of an ensemble of classification trees. It is of great significance in virtual screening as it can use a small set of active compounds to search a much larger dataset of new compounds. In the next step five Rf models were constructed using the set of five descriptors as discussed earlier. In each model multiple classification trees (100 trees) were constructed from the input data, and each tree has given a classification or vote for a compound depending on that compound is predicted to be active or inactive

RESULTS

RF is the best form of multiple decision trees as it is capable of using small sets of active compounds for screening large datasets of new drug candidates.

In this study, RF-based classifier have been constructed in order to predict the activity of 968 compounds from AfroBD (target set) against the target protein MAO-B.

For that purpose, five RF models were trained on a training set that consist of 36 compounds present in the test dataset (table 1). Each model was trained based upon the five set of molecular descriptors, Constitutional, RDF, Randic, 3DMorse and 2D autocorrelations. Finally, the constructed models were then used to predict the activity of the 986 compounds from Afro Database against the enzyme MAO-B.

Among these five, Randic model was selected with the highest predicted accuracy (89%), where 32 test compounds were predicted as active out of 36, where as the predicted accuracy for constitutional and 2D autocorrelation RF model was 63% and 75% respectively.

The results of Randic RF model are presented in the table 2. Here, in the Rf model if the compounds have achieved the score of 0.5 or above, they were classified as active, that is, 50% of the tees have voted for the compound, thus, 31 compounds from 968 compounds in the target dataset were predicted to be active against the MAO-B, with RF score greater than 0.5.

Table 1: List of compounds with known activity against MAO in the test dataset

S. No.	Name	S. no.	Name
1	Medicarpin	19	Isoliquiritigenin
2	Bellidifolin	20	Isoliquiritin
3	Bellidifoline	21	Kaempferol
4	Chrysin	22	Licochalcone-A
5	Cleomiscosin-C	23	Licochalcone-B
6	Demethylbellidifolin	24	Licocoumarone
7	Genistein	25	Licofuranone
8	Gentiacaulein	26	Licopyranocoumarin
9	Glicoricone	27	Liquiritigenin
10	Glycycoumarin	28	Mangiferin
11	Glycyrrhisoflavone	29	Myristicin
12	Glycyrrhizin	30	Polyphenols
13	Harmaline	31	Quercitrin
14	Harman	32	Scopoletin
15	Harmine	33	Strictamine
16	Hypericin	34	Swerchirin
17	Isoathyriol	35	Tannin
18	Isogentisin	36	Xanthones

Table 2: List of 31 compounds from AfroDb predicted to be active against MAO-B with ZINC ID and RF score.

S. no.	ZINC ID	Predicted RF Score	S. no.	ZINC ID	Predicted RF Score
1	ZINC05765089	0.795181	17	ZINC14417338	0.613333
2	ZINC05765091	0.746988	18	ZINC14815320	0.592593
3	ZINC05765093	0.741176	19	ZINC00608186	0.569767
4	ZINC05765094	0.730337	20	ZINC05765103	0.567901
5	ZINC95486193	0.726027	21	ZINC87493012	0.561798
6	ZINC05765095	0.722892	22	ZINC00001785	0.547945
7	ZINC05765096	0.719101	23	ZINC03871576	0.539474
8	ZINC01721693	0.703125	24	ZINC95486326	0.534884
9	ZINC05765097	0.701149	25	ZINC95485971	0.533333
10	ZINC05765098	0.695652	26	ZINC18825330	0.531646
11	ZINC05765099	0.670588	27	ZINC14557836	0.526316
12	ZINC05765100	0.659091	28	ZINC05765104	0.524390
13	ZINC05765101	0.658537	29	ZINC71791185	0.518072
14	ZINC05765102	0.648352	30	ZINC95486057	0.507692
15	ZINC95485906	0.635135	31	ZINC02578057	0.506494
16	ZINC85996205	0.621622			

Among these 31 Norlichexanthone (ZINC05765089) is found to be most active with highest RF score 0.795181, along with other top scored compounds ZINC05765091, ZINC05765093, ZINC05765094, thus, these compounds could be the inhibitors of MAO-B.

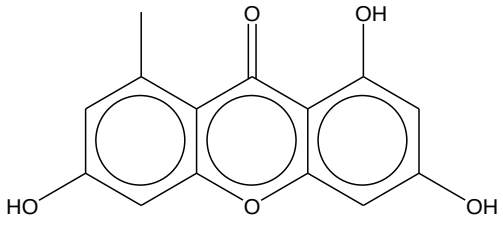
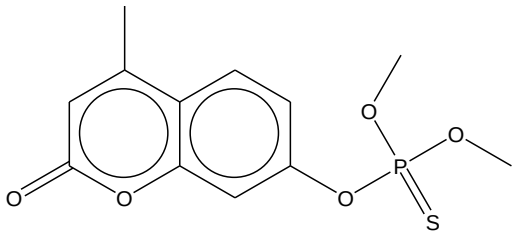
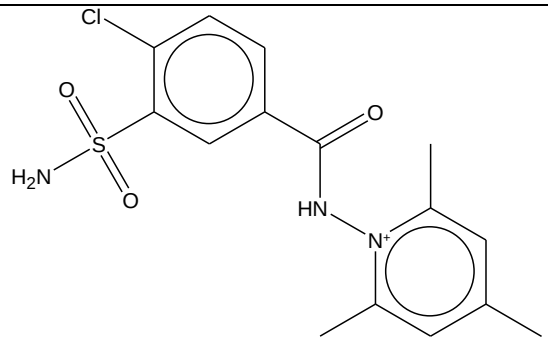
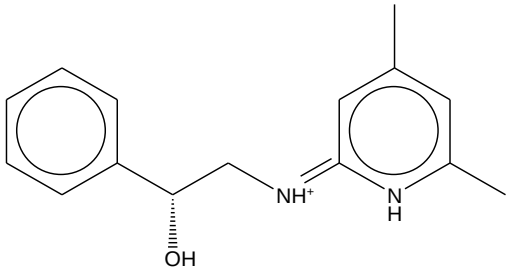
In future studies, these 31 compounds that have been predicted to be active against the enzyme MAO-B can be tested experimentally, thus, could be the potential drug candidates to treat the Parkinson's disease and other neurodegenerative disorders.

DISCUSSION

Currently approximately 10 million people are affected by Parkinson's disease worldwide and still there is no effective treatment of this disease. There are many reported studies about the role of natural products for the prevention and treatment of PD due to their antioxidant and neuro-protective activity (Fu *et al.,* 2015; Ding *et al*., 2018 Solayman *et al*., 2017; Patil *et al*., 2013). Role of MAO-B inhibitors in the treatment for PD and as possible neuro-protective agent have also been studied.

Currently many MAO inhibitors are in use to treat depression, Alzheimer's and Parkinson's disease and other neurodegenerative disorders, but most of them are causing serious side effects, therefore, many researchers are working in this field to design new potent MAO inhibitors with lesser side effects. For this purpose, many scientist have successfully used computational methods for the identification of MAO inhibitors especially from natural

Table 3: Structures of top four hits obtained from RF modeling

 1) ZINC05765089 (Norlichexanthone) RF Score: 0.795181	 2) ZINC05765091 Phosphorothioic acid RF Score: 0.746988
 3) ZINC05765093 (Besulpamide) RF Score: 0.741176	 4) ZINC05765094 (5-methyl-2,3-dihydrofluoranthene-2,3-diol) RF SCORE: 0.730337

sources (Pisani *et al*., 2015; Dhiman *et al*., 2018; Saglik *et al.,* 2019; Sivaraman *et al*., 2015). These studies suggest that virtual screening proved to be effective mean to identify new chemical class and compounds with appropriate predicted activities and only selective compounds then can be investigated experimentally.

Ligand based virtual screening (LBVS)**,** one of the virtual screening method**,** is based on the hypothesis that similar structures have similar biological functions. It works by building a concept model of ligand structure, the classification algorithms of virtual screening method then use this model as the training data. These algorithms learn the model parameters from the input training data that are the molecules with known activities against the target protein (Gertrudes, *et al.,* 2012; Senanayake *et al*., 2013). The algorithm is then classifying the new molecules as active or inactive based upon the learnt properties from this training data. Use of this method reduces the number of compounds to be tested experimentally (Schierz, 2009).

For virtual screening, the most widely used classification algorithms in the field of bioinformatics and medicinal chemistry (Chen *et al*., 2007) are Support Vector Machines (SVM) (Burbidge *et al*., 2001), Random Forest (RF) Model (Svetnik *et al*., 2003; Boulesteix *et al*., 2012).

Many scientists are using various *in-silico* methods for the identification of inhibitors against MAO from natural products (Dhiman P *et al*. 2018; Pisani *et al*., 2015). Random forest (Breiman, 2001), one of the classification algorithm, has been used here as a Ligand Based VS tool for the identification of active compounds against the MAO-B (Svetnik *et al*., 2003).

Random Forest, among the various methods used for ligand-based virtual screening, is used commonly in the field of cheminformatics and computational chemistry to design new drugs (Boulesteix *et al.*, 2012). As it is easier to use, flexible and can handle even unbalanced data. Specially, it can be trained when only limited number of active compounds of diverse structures is available.

It is the best form of multiple decision trees and it is capable of using a small set of active compounds for screening large datasets of new candidates. RF model predicts the molecules in the test dataset as active (similar to known ligands) or inactive (dissimilar to known ligands) by forming decision trees and by giving RF score accordingly (Ehrman *et al.*, 2007). Compounds having RF score between 0.5-1 are considered to be active. The top hits obtained by this method can be further be evaluated by structure based virtual screening or by other methods.

Earlier, Ehrman *et al.*, (2007), screened the Chinese Herbs against the various target proteins using this Random

Forest model, here, similar approach have been used here to identify the inhibitors of MAO-B from African medicinal plants. During this study, out of 968 compounds from AfroDb, 31 compounds are predicted to be active against MAO-B

Norlichexanthone (1,3,6-trihydroxy-8-methylxanthen-9-one) (ZINC05765089), the top hit with Rf score (0.795) (table 3) is the derivative of xanthone. It has been demonstrates that various xanthone derivatives inhibited MAO in a competitive and reversible manner (Ohishi *et al*., 2000; Carradori *et al*., 2014)

These xanthone derivatives also have shown inhibitory activities towards amyloid beta aggregation and acetylcholinesterase (Urbain *et al*., 2008), along with MAO, which have crucial role in the development of neurodegenerative diseases, thus, Norlichexanthone, from African medicinal plant could be a potent inhibitor of MAO-B and a putative drug candidate for the prevention and treatment of neurodegenerative disorders including Parkinson's disease

ZINC01721693 (Afzelechin), is a flavan-3-ol, a type of flavonoid, is among the top ten hits and scored 0.703125 in Rf model. This compound have reported neuroprotective activity (Li *et al*., 2005) and antioxidant activity (Ruiz *et al*., 2017).Among the top ten hits, ZINC95486193 ((2S)-2-(2,4-dihydroxyphenyl)-5-hydroxy -6-(3-methylbut-2-enyl)chroman-4-one) , also a flavonoid derivative.

In general flavonoids have reported activity for the treatment Parkinson's disease as they protect the neuronal cells from undergoing neurodegeneration by activating the endogenous antioxidant status of the cell (Magalingam *et al*., 2015) along with their anticholinesterase, metal-chelators, free radical scavengers, neuroprotective, anti-inflammatory, ameliorating learning and memory properties, antidepressant and antiamyloidogenic properties, therefore, flavonoids provide conventional cure against neurodegenerative diseases, thus, ZINC01721693 (Afzelechin) and ZINC95486193, novel hits obtained during this study, are flavonoid derivatives, can effortlessly can further be evaluates as possible drug for the cure/ treatment of neurodegenerative diseases.

Whereas, among the top ten hits, ZINC05765091, ZINC05765093, ZINC05765094, ZINC05765095 and ZINC05765096 (table 3) are novel compounds and do not have any reported activity against the MAO enzyme. Thus, the results presented in this study are helpful in identifying potential drug candidates from natural products to treat neurodegenerative disorders.

The hits obtained during this study can further be evaluated molecular docking method in order to get the detailed analysis of binding mode of these compounds within the active site of MAOB and can further be tested *in vitro* for determination of the biological activity against the MAO B enzyme. Thus, the results presented in this study are helpful in identifying potential drug candidates from natural products to treat neurodegenerative disorders

CONCLUSION

Natural products play an important part to improve the quality of life for persons suffering from neurological diseases. The aim of this study was to predict the effective MAO-B inhibitors from natural recourses, as there are reported evidences that MAO-B inhibitors have neuro-protective properties For this purpose, compounds from African medicinal plants were screened against the MAO-B enzyme for their biological activity by using the Rf Model, a ligand based virtual screening method.

According to these *in-silico* studies, compounds ZINC05765089, ZINC05765091, ZINC05765093 predicted to be most active against MAO-B with highest Rf score, therefore, could be the promising lead compounds against MAO-B.

Based on these results, in future, the compounds predicted to be active and their improved derivatives can further be tested *in-vitro* for evaluation of their inhibitory activity against the MAO-B enzyme and clinically, thus, provide more potent and safer MAO inhibitors for treatment of Parkinson's disease.

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