Identification of a Chlorogenic Ester as a Monoamine Oxidase (MAO-B) Inhibitor by Integrating “Traditional and Machine Learning” Virtual Screening and In Vitro as well as In Vivo Validation: A Lead against Neurodegenerative Disorders?

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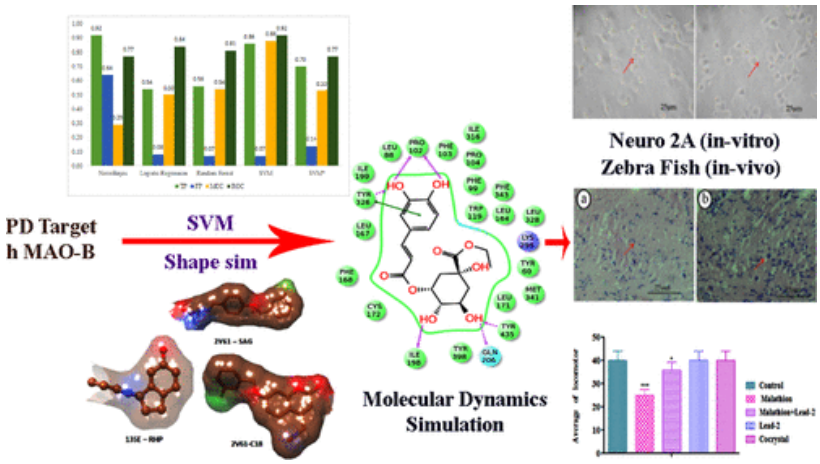
SI Supporting Info (1) »

SUBJECTS: Inhibitors, Mathematical methods, Screening assays, Computational chemistry, Drug discovery

Abstract



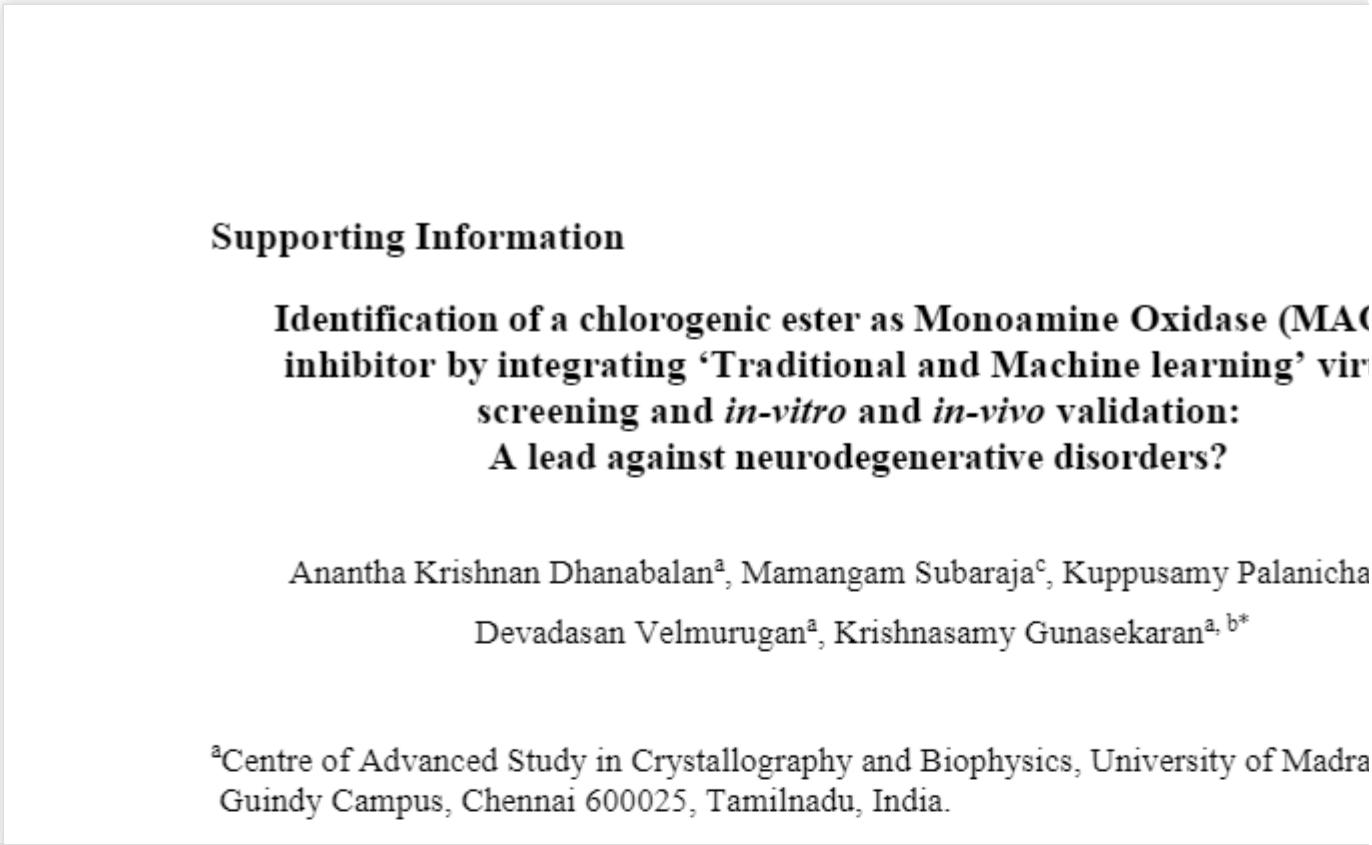
Parkinson’s disease (PD) is the furthermost motor disorder of adult-onset dementia connected to memory and other cognitive abilities. Monoamine oxidases (MAOs) have gained significant attention in recent years owing to their possible therapeutic use against PD. Expression of MAO-B has been found to be elevated in PD patients for increased uptake of dopamine, producing hydrogen peroxide and finally causing neuronal injury. In this work, two new compounds have been identified as leads against MAO-B, and one of those compounds has been validated in vitro and in vivo. From the Protein Data Bank, MAO-B protein structures complexed with selegiline, 6-hydroxy-*N*-propargyl-1(*R*)-aminoindan, or a chromen derivative have been selected as templates for shape-based virtual screening (SB-VS) against the Traditional Chinese Medicinal (TCM) natural database. In parallel, using machine learning, a molecular-descriptor-based support vector model (SVM) was prepared and screened. For this purpose, naïve Bayesian, logistic regression, and random forest strategies were employed with the best specific molecular descriptor, which yielded a model with an overall accuracy (*Q*) of 0.81. Two common hit compounds lead-1 and lead-2 resulting from

could be observed. An experimental zebra fish model confirms the neuroprotection by lead-2 by assessing the locomotor activities under malathion influence and treatment of lead-2. Also, histopathology analysis revealed that lead-2 could slow down degeneration in the brain. The present study emphasizes that integrating machine learning in parallel with traditional virtual screening may be useful to identify effective lead compounds for a given target.

KEYWORDS: MAO-B, PD, shape screening, SVM, molecular simulation, RINs, chlorogenic ester

(Figure S5); Tanimoto coefficient (ECFP) analysis on identified best leads with respect to known MAO-B inhibitors (Figure S6); MD trajectory analyses of RMSD, RGYR, and RMSF (Figure S7); overall RMSD map for each MD frame (Figure S8); conformational analysis of all three complexes from the MD trajectory (Figures S9–S11); overall and comparison of the residual interaction network (Figures S12 and S13); hydrogen bond and hydrophobic occupancy (Figure S14); per residual decomposed energy of three complexes (vdW, electrostatics, total) for polar and nonpolar solvation (Figures S15 and S16); representative photomicrograph showing morphological changes of Neuro-2A cells (Figure S17); mRNA levels of MAO and α-syn (Figure S18); activities of SOD experimental groups of zebra fish (Figure S19); ligand interaction profile of identified lead compounds (Table S1); ADME properties of lead compounds (Table S2); shape screening of top 10 hits (Table S3); and training set and test set of known active and inactive data for the SVM model (Tables S4 and S5) (PDF)

as well as in vivo validation: A Lead against Neurodegenerative Disorders?



Supporting Information

Identification of a chlorogenic ester as Monoamine Oxidase (MA(inhibitor by integrating 'Traditional and Machine learning' vir screening and *in-vitro* and *in-vivo* validation: A lead against neurodegenerative disorders?

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