Computational Screening for Novel Drug Target for Treatment of JME (Juvenile Myoclonic Epilepsy)

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Abstract

JME is a type of epilepsy caused either by inheritance or by some unknown reason. The first line of treatment for this includes drugs like lamotrigine, brivaracetam, and clonazepam, out of which clonazepam is a benzodiazepine. It not only acts as an anti-epileptic drug but also as an antidepressant due to which it causes drowsiness. We are trying to find novel compounds through computational screening that can target JME without having side effects of current therapeutics which may not be sleep-inducing or do not meddle with a patient's daily routine. We screened many compounds against a target protein mutation from various databases to identify which has the lowest free energy.

Keywords: virtual screening, novel drug target, JME.

Introduction

JME, or Juvenile Myoclonic Epilepsy, is a longstanding disorder of which the main cause has been unknown. Unlike other epileptic episodes, it includes three stages: absence seizure, petit mals, and grand mals. The onset of JME is around the pre-adolescent stage but the symptoms start to show around the age of 15 years. Many research studies have been conducted to find the root cause of JME, but the closest we have gotten to it is by narrowing down the receptors that may be involved in the expression of JME. Some of them are
JABA/R, sodium channels and calcium channels, TRPM2, Myoclonic!/EFHC1and its mutation like F229L and D210N, etc. The most effective drug to cure JME is Sodium valproate. However, Valproate cannot be administered to girls of childbearing years as it makes them susceptible to having ovarian cysts which in turn causes infertility. We have chosen the protein mutation of EFHC1 i.e., D210N.

Materials and Methods

Materials: Autodock Vina, Biovia Discovery, Open Babel, Command Prompt, RCSB PDB, ZINC, Swiss UniProt.

Methods: We have used protein mutation of EFHC1 I.e, D210N. We have docked seven different compounds: CBD, THC, Mysoline, Valproaic, Taurine, Curcumin, and Gingerol.

Procedure:

- First, we downloaded the D210N protein in PDB format from RCSB PDB, in Human APE1 E96Q/D210N mismatch substrate complex form.
- Then we downloaded our ligands from zinc.docking.org in an SDF format, which we further converted into the PDB format using Open Babel.
- Then we prepared the protein using Biovia Discovery, where we removed the unnecessary ligands and chains from it and further created an SBD site sphere at the assumed binding site, where we are supposed to bind our chosen ligand.
- Then we docked our chosen ligand with our protein in Autodock Vina, where we further extracted them in PDBQT format.
- We used Command Prompt to generate the output i.e., a tabulated summary of the calculated free binding energy of each ligand in different torsions.

Discussion

After calculating the free energy of every ligand using Command Prompt, we then further visualised them and inferred that other than THC no other ligand had any bonding affinity towards chain A.

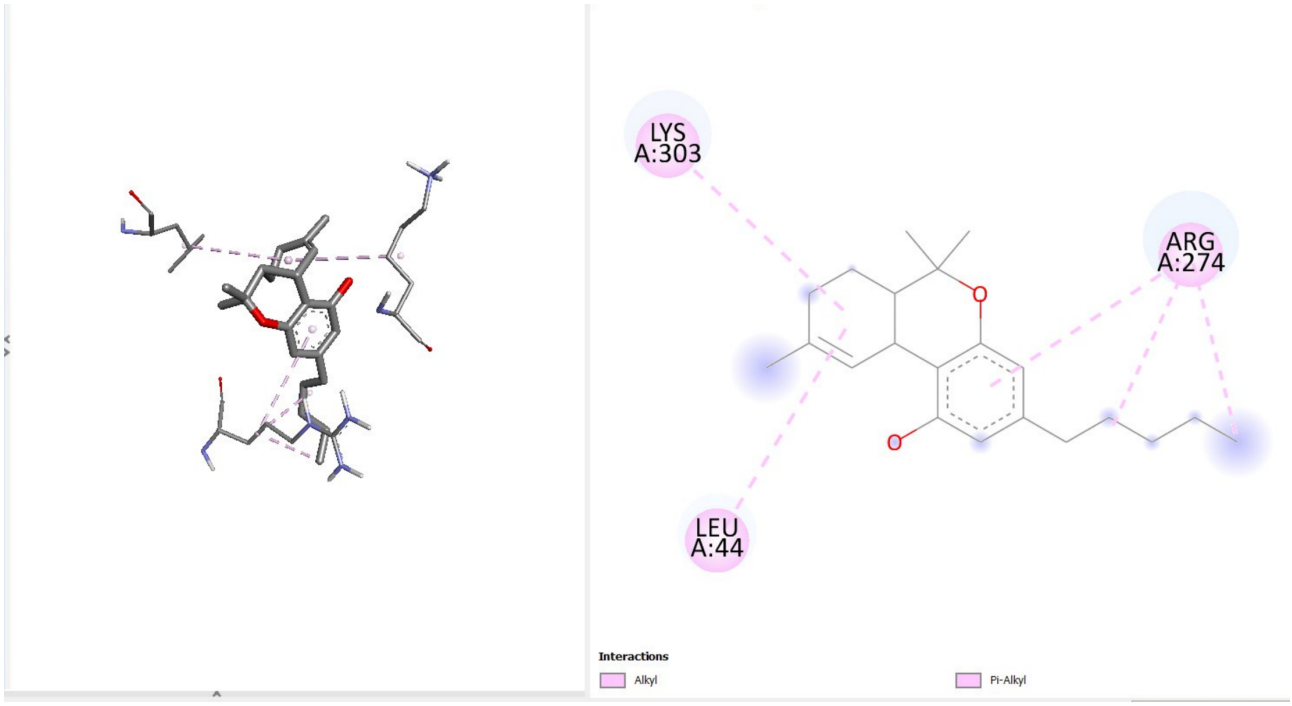

Fig1. Shows 3-D and 2-D protein(D210N) and ligand(THC) interaction.

Result

We have concluded that of all the chosen ligands THC turned out to be the one having the most bonding affinity towards our protein with with a maximum calculated free energy of -6.4 kcal/mol.

```
#############################################################
# If you used AutoDock Vina in your work, please cite:      #
#                                                           #
# O. Trott, A. J. Olson,                                    #
# AutoDock Vina: improving the speed and accuracy of docking #
# with a new scoring function, efficient optimization and   #
# multithreading, Journal of Computational Chemistry 31 (2010) #
# 455-461                                                   #
#                                                           #
# DOI 10.1002/jcc.21334                                     #
#                                                           #
# Please see http://vina.scripps.edu for more information.  #
#############################################################

Detected 12 CPUs
WARNING: at low exhaustiveness, it may be impossible to utilize all CPUs
Reading input ... done.
Setting up the scoring function ... done.
Analyzing the binding site ... done.
Using random seed: -89649664
Performing search ... done.
Refining results ... done.

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1         -6.4      0.000      0.000
   2         -6.4      1.230      1.825
   3         -6.3      2.703      6.464
   4         -6.3      2.053      5.719
   5         -6.1      2.090      3.336
   6         -6.1      1.806      2.497
   7         -6.1      2.307      6.316
   8         -6.0      2.499      4.747
   9         -6.0      2.430      4.264
Writing output ... done.
```

Fig2. Shows a log of free energy of ligand THC in different torsions.