INTERNATIONAL JOURNAL OF ADVANCE RESEARCH, IDEAS AND INNOVATIONS IN TECHNOLOGY

ISSN: 2454-132X
Impact Factor: 6.078
(Volume 7, Issue 4 - V7I4-1868)
Available online at: https://www.ijariit.com

# Identification of novel compounds to treat Alzheimer's disease

*Swarnali Sarkar*
swarnali.sarkar2016@vitalum.ac.in
*Vellore Institute of Technology, Vellore, Tamil Nadu*

## ABSTRACT

***Alzheimer's disease or Alzheimer's is a brain disorder characterized by progressive loss of neural functions and dementia in elderly people. It has perilous effects on memory and other cognitive activities. Apolipoprotein (APOE) is responsible for delivering cholesterol-rich lipoproteins to the bloodstream. The maintenance of optimum levels of cholesterol is absolutely necessary as an imbalance might lead to cardiovascular and neurological diseases. Out of the four alleles for the APOE gene, the main causative agent for the onset of Alzheimer's is the e4 allele. APOE e4 allele leads to the production of amyloid plaques which further cause the accumulation of amyloid ß peptides. The excess build-up of such toxic products leads to neuronal death giving rise to early symptoms of the disease. Our research mainly focuses on the identification of potential inhibitors against Sortilin (SORT1) and APOE receptors associated with Alzheimer's. We have employed scientific software to identify the specific conformations of ligands that show the maximum interaction with the target compound and further analyzed these results by generating descriptors computationally for QSAR studies. The optimum model was generated with r2 = 0.794, s= 0.108. We have been able to select two ligands that can be used as potential drugs to treat Alzheimer's.***

***Keywords:*** *Alzheimer's, QSAR, APOE Protein*

## 1. INTRODUCTION

Alzheimer's is one of the most common neurodegenerative disease that affects a huge population every year. It is mainly characterized by impaired memory, mood swings, disorientation and personality changes. The exact cause of Alzheimer's is still not completely understood. However, it is quite certain that APP (Amyloid Precursor Protein) and Presenilin1 and Presenilin2 proteins significantly contribute to the aforementioned cause[1]. APP are known to arrest the transport of nuclear information encoded mitochondrial proteins[1] to the mitochondria and increase the production of Reactive Oxygen Species (ROS) by disrupting the electron-transport chain. Several evidences in the past have suggested that mutation in mitochondrial DNA (mt DNA) complicates the process of oxidative metabolism[3]. Mitochondrial DNA replicates independently without undergoing any recombination process and it is further segregated during cell division. The increased production of ROS causes mt DNA destruction because of amplified somatic mutations[3]. This is one of the important factors in the progression of Alzheimer's disease. Apolipoprotein E gene allele 4 (*ApoE4*) and gene mutation in sortilin-related receptor1 (SORT1) have been identified as the major factors[1] for the onset of Alzheimer's disease. SORT1 gene have previously been associated with cardiovascular diseases[2]

Alzheimer's more prominent in the age group of 40 and 90[3], including both men and women. A definite relationship between oxidative stress build-up and onset of Alzheimer's have not been well defined as of now. Thus, there is a need to identify compounds with inhibitory activities against SORT1 gene. In this study, we have considered a set of 47 compounds with prospective anti-oxidative properties that can be implemented to combat oxidative stress and mitochondrial dysfunction to a considerable extent. Inhibitors suppress the production of ROS and through our research we have been able to generate the models of two such compounds which fulfil biological parameters like solubility (logS), cardio-toxicity (hERG2) and metabolizing capacity ($2C9pK_i$), necessary for drug development. These compounds have been further reviewed by docking softwares and based on their interactive properties like dock score, binding efficiency, ligand efficiency it can be well established that they are vital in drug formulation for Alzheimer's disease.

## 2. REVIEW OF LITERATURE

Alzheimer's disease has mainly been reported in the population of older people[4]. The most prominent risk factor related to the development of Alzheimer's is increasing age. It is characterized by memory loss and dementia in the initial stages and the condition worsens over time where the individual is completely unaware of the surrounding environment[3]. Currently, no suitable drug has been identified for treating Alzheimer's yet certain formulations have been generated to combat dementia symptoms during the

 

early stages of progression. Several diagnostic studies[4] have been carried out in the recent past to examine the neurological, neuropsychological parameters of individuals affected by Alzheimer's. The main objective was to analyse the cognitive properties and understand the relation of age with the prevalence of disease[4]. The available biochemical, cellular and molecular biology data[1] from biological models have led to the conclusion that the accumulation of amyloid β protein in the synapses affects neurotransmission and can be the major cause for cognitive failure in elderly individuals. The brain of affected individuals exhibited amyloid deposits[1]. Of late, it has been established that mitochondrial dysfunction[5] and oxidative stress may lead to early onset of Alzheimer's in individuals. The most prominent factors include compromised metabolism, degradation of nucleic acid[5] because of excess oxidation and mutations in mitochondrial DNA (mt DNA). The mutations in mt DNA are heritable in nature and this gives rise to clinical complications at a very younger age. Therefore, it is necessary to generate compounds that can inhibit the activity of SORT1 receptor and arrest the disease at an early stage. In this study, we have considered a set of 47 compounds with anti-oxidative properties and evaluated their inhibitory activities by performing QSAR studies and two hit compounds have shown promising result in this regard.

## 3. MATERIALS AND METHODS

A set of 47 compounds was selected based on literature survey and biological assay. All these compounds showed inhibitory activities against SORT1 receptor. DPPH assay was taken into consideration during the collection of ligand molecules. A worksheet was prepared taking into account the IUPAC name, IC50 value and the bio-assay of these ligands. The crystal structure of SORT1 was retrieved from Protein Data Bank (PDB ID 3G2S[12] and 3WSY[13]). Structures of the ligand molecules were prepared using MarvinSketch[10] software in both 2D and 3D form. Another dataset was prepared for detailed study on targeted ligands keeping in mind its interaction with other amino acids, bio-availability and bio-assay.

The interaction of targeted ligands with the protein (3G2S[12] and 3WSY[13]) was determined by performing docking employing LeadIT[7] software. After conducting a literature survey of PubMed entries, 3G2S[12] was chosen as the target of interest. The two ligands which had interaction with Asn15 residue were considered for further docking studies using Auto-dock[8] tool. The protein molecule (in pdb format) and ligands (in sdf format) were loaded and the residues were selected based on protein data analysis for docking. The two ligands which had most optimum interaction were considered for further docking studies using Auto-dock[8] tool. The dock score for these compounds were noted down separately. The protein to be studied was retrieved in .pdb format and crystallographic water molecules and other heteroatoms were removed from the pdb file. The ligand molecules were exported from LeadIT[7] in .mol2 format. These ligands were converted to their respective pdb forms using specific commands and Openbabel[6] software. Docking was carried out by taking the protein and specific ligand file as the input, the ligand was suitably fit within the grid box so generated and required changes were saved. The docking parameters were entered and Genetic Algorithm was employed for optimization studies. Lamarckian[11] algorithm was used for generating the output and the number of iterations was set to 10. Auto-grid and auto-dock commands were entered to generate the glg and dlg files respectively. The grid and dock files so produced helped during result analysis.

This step was followed by the generation of descriptors for QSAR study. The dataset was divided into Test set, Training set and Validation sets for statistical analysis by StarDrop[9] software and the combination of descriptors that established maximum $r^2$ and optimum level standard error were chosen to be evaluated for log activity. Further, a comparative analysis was carried out with the log $IC_{50}$ values obtained from literature survey. Data of the best model was then visualized in graphical form to generate $r^2$ equations. The compounds were further tested for their ADME properties by making use of Stardrop[9] software to generate a drug model having high solubility, and minimum levels of cardio-toxicity and metabolizing capacity. Docking studies were aimed at analysing protein-ligand interactions, QSAR study was carried out to generate the best descriptors for optimum model development and StarDrop[9] was employed to study the biological parameters necessary for drug formulation. We expect to come up with the best ligand molecules that will fulfil the aforementioned criteria and can likely be used as potential drugs.

## 4. RESULTS

### 1) a) Molecular docking by Auto-dock[8]

The docking result was analysed based on binding energy, ligand efficiency, hydrogen bond interactions. The best results have been shown here:

| Compound ID | Binding energy (in kJ/mol) |
|---|---|
| S5000007 | -6.79 |
| S3000001 | -5.29 |
| S5000003 | -4.83 |
| S1000005 | -4.28 |

The following interactions have been observed after analysing the docking results:
H17:ASN15, H16:ASN19
H17:ASN19, H16:ALA12
H16:GLU62

### b) Molecular docking by LeadIT[7]

The four compounds that showed the most compelling results are shown as follows:

| Compound ID | Dock score |
|---|---|
| S5000007 | -13.385 |
| S3000001 | -6.526 |

 

| | |
|---|---|
| S5000003 | -13.5516 |
| S1000005 | -13.3186 |

**2) QSAR model prediction**

Statistical analysis were carried out and regression models were generated using StarDrop[9] software. After conducting a comparative analysis we came to a conclusion that RBF model with $r^2$ value of 0.794 and standard error value of 0.108 was the most optimized model.

**3) ADME property prediction**

ADME property prediction was carried out using StarDrop[9] software and the compounds that showed optimum solubility (logS), cardio-toxicity (herg2) and metabolizing capacity (2C9p$K_i$) were chosen as the most suitable drugs for anti-malarial therapy. A higher value of intrinsic solubility is desired so that the drug readily solubilizes in the body and it is one of the most sought after characteristic in the oral administration of drugs. A comparative lower value of herg2 parameter is desired so that the cardio-toxicity can be kept at a minimum value. Similarly, the metabolizing capacity should also be low inorder to prevent liver damage. S5000007 and S1000005 showed optimal activity in this regard.

Based on the above observation, S5000007 and S1000005 were chosen as hit compounds.

Fig 1 shows the docking result, Fig 2 show QSAR analysis for training set.

## 5. DISCUSSION

We have analysed the compounds based on the dock score, $IC_{50}$ values, binding energy and ADME properties. Now, we have to take the following cases into consideration-

**1) Docking study**

| Compound ID | $IC_{50}$ value (in µM) | Dock score | Binding energy (in kJ/mol) |
|---|---|---|---|
| S3000001 | 5 | -6.526 | -5.29 |
| S1000005 | 2 | -13.3816 | -4.28 |
| S5000003 | 19.8 | -13.5516 | -4.83 |
| S5000007 | 9.7 | -13.385 | -6.79 |

S3000001 and S5000007 shows high dock scores and binding energy. It can be concluded that the ligands are fitting appropriately in the pockets of protein molecule that has led to higher dock scores and binding efficiency. The minimum $IC_{50}$ values of both the compounds suggests that very less concentration is required for maximum inhibition activity.

**2) Analysis of docking result from LeadIT[7]**

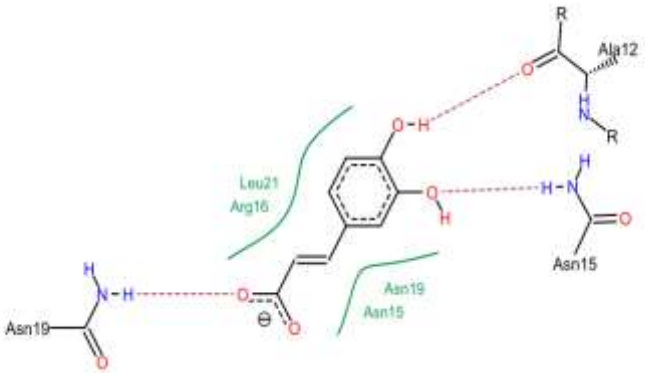


**Fig 1: Proposed interaction of ligand with Asn15 residue is depicted**

**3) QSAR model prediction**

The value of $r^2$ was determined to be 0.794 and minimum error rate of 0.108 was obtained when RBF model was employed for similarity analysis.

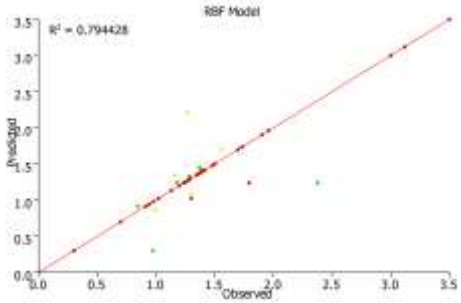


**Fig 2: Graph of the predicted log values vs experimentally derived log values for training set**

 

**4) ADME property prediction**

| Compound ID | logS | herg pIC50 | 2C9p$K_i$ |
|---|---|---|---|
| S3000001 | 3.988 | 4.414 | 4.239 |
| S5000007 | 2.92 | 4.411 | 4.895 |
| S1000005 | 5.094 | 3.235 | 3.848 |
| S5000003 | 4.26 | 3.419 | 4.057 |

S5000007 has lesser solubility and optimum cardio-toxicity and metabolizing capacity and S1000005 has optimum levels of all the biological parameters. The solubility of S5000007 can be increased by computationally altering its functional groups.

S3000001 shows high dock scores and binding energy, however the oral administration of drugs is not possible at such low solubility values so we cannot consider this ligand as a potential drug. S1000005 and S5000007 have been selected as potential drug candidates.

## 6. CONCLUSION

A total of 47 small molecules were taken into account during this study and two such compounds have been identified as potential inhibitors against SORT1 gene. The solubility of hit compounds can be enhanced by altering their functional groups for better oral drug administration. The drugs so developed should have appropriate bio-availability, metabolic activity and toxicity profile. It is believed that the prospective inhibitors which have been discussed here can assist in finding potent molecules capable of combating oxidative stress. The small molecules will further undergo optimization to aid in identification of promising lead compounds.

## 7. FUTURE WORK

Following hit confirmation, several compounds are chosen according to their specific characteristics to produce lead compounds based on selectivity, affinity, lipophilicity, efficacy, cytotoxicity and other physio-chemical parameters. In our case, further analysis is necessary to validate the *In-silico* results of the generated hits. If the lead compounds show favourable results with respect to clinical trials and obtain regulatory approvals, they can be further marketed as potential drugs to treat Alzheimer's.

## 8. REFERENCES

[1] Reddy, P. H. & Beal, M. F. Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease. *Trends Mol. Med.* **14,** 45–53 (2008).
[2] Andersson, C.-H. *et al.* A Genetic Variant of the Sortilin 1 Gene is Associated with Reduced Risk of Alzheimer's Disease. *J. Alzheimer's Dis.* **53,** 1353–1363 (2016).
[3] Carrieri, G. *et al.* Mitochondrial DNA haplogroups and APOE4 allele are non-independent variables in sporadic Alzheimer's disease. *Hum. Genet.* **108,** 194–198 (2001).
[4] Jadhav, S., Nikam, K., Gandhi, A., Shinde, N. & Salunkhe, K. Applications of computer science in pharmacy: An overview. *Natl. J. Physiol. Pharm. Pharmacol.* **2,** 1–9 (2012).
[5] Atamna, H. & Frey, W. H. Mechanisms of mitochondrial dysfunction and energy deficiency in Alzheimer's disease. *Mitochondrion* **7,** 297–310 (2007).
[6] O'Boyle, N. M. *et al.* Open Babel: An open chemical toolbox. *J. Cheminform.* **3,** 33 (2011).
[7] Kramer, B., Rarey, M. & Lengauer, T. Evaluation of the FLEXX incremental construction algorithm for protein-ligand docking. *Proteins Struct. Funct. Genet.* **37,** 228–241 (1999).
[8] Morris, G. M., Huey, R. & Olson, A. J. Using AutoDock for Ligand-Receptor Docking. in *Current Protocols in Bioinformatics* **24,** 8.14.1-8.14.40 (John Wiley & Sons, Inc., 2008).
[9] Peach, M. L. *et al.* Computational tools and resources for metabolism-related property predictions. 1. Overview of publicly available (free and commercial) databases and software. *Future Med. Chem.* **4,** 1907–1932 (2012).
[10] Csizmadia, P. MarvinSketch and MarvinView: molecule applets for the World Wide Web. *ECSOC-3, Third Int. Electron. Conf. Synth. Org. Chem.* 367–369 (1999).
[11] Jadhav, S., Nikam, K., Gandhi, A., Shinde, N. & Salunkhe, K. Applications of computer science in pharmacy: An overview. *Natl. J. Physiol. Pharm. Pharmacol.* **2,** 1–9 (2012).
[12] Cramer, J. F. *et al.* GGA autoinhibition revisited. *Traffic* **11,** 259–273 (2010).
[13] Jacobsen, L. *et al.* Molecular characterization of a novel human hybrid-type receptor that binds the $\alpha_2$-macroglobulin receptor-associated protein. *J. Biol. Chem.* **271**, 31379–31383 (1996).

 