Review Article

# Docking study targeting 3CYY protein using Alzheimer drugs

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**ABSTRACT**

Mirror neurons are the type of neurons that mimic the action of bystander. They are present in the premotor and primary motor cortex, rostral division of the ventral premotor cortex. They help in understanding, speech, social cognition, etc., Alzheimer disease is a neurodegenerative disorder which leads to loss of memory in elderly adults. It is caused mainly by two types of abnormalities such as beta-amyloid plaques and tau proteins. It is hypothesized to have a link with motor function and known as cognition hypothesis. In this study, Alzheimer drugs donepezil, rivastigmine, and memantine are chosen to estimate the binding efficiency using Autodock1.5.6 software which is a suite of automated docking tools. It is designed to predict how small molecules, such a substrate or drugs bind to receptor of known three-dimensional structure. From the result obtained we have concluded that Donepezil helps to treat Alzheimer more effectively than other drugs when it is combined with 3CYY protein.

**KEY WORDS:** 3CYY protein, Alzheimer disease, AutoDock 1.5.6, Discovery studio visualizer 4.0, Mirror neurons

## INTRODUCTION

Mirror neuron was first discovered in the ventral premotor region of the macaque monkey.[1] It is the neurons that mimic the action of bystander. These type of neurons is responsible for the observation of motor acts performed by others. Its main functions are matching observations of hand and mouth motor acts with the execution of the similar motor acts.[2] In humans, mirror neurons are present in the dorsal premotor and primary motor cortex, rostral division of the ventral premotor cortex.[3] The main functions of mirror neurons are action understanding, imitation, speech, and language, theory of mind, social communication, empathy, and social cognition.[4]

Alzheimer disease is a neurodegenerative disorder characterized by progressive deterioration of memory.[5] It is commonly found to affect women population than men; it is due to the improper or imbalance secretion of estrogen hormone after menopause.[6]

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Alzheimer disease is caused by a combination of genetic, lifestyle, and environmental factors. This disease leads to significant shrinkage of the brain. Alzheimer's brain tissue under the microscope shows two types of hallmark abnormalities.

1. Plaques: Clump of β-amyloid.
2. Tangles: Thread of tau protein twist into abnormal tangles.

Alzheimer disease is hypothesized to have a link with motor function and this hypothesis is termed as embodied cognition hypothesis. In AD, mirror neurons are extremely damaged. Hence, mirror neurons may be the underlying cause of Alzheimer disease.

AutoDock Tools: An interactive graphical tool for coordinate preparation, docking, and analysis.[6]

## DONEPEZIL

**IUPAC**

1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl) methylpiperidine hydrochloride.

Molecular formula: $C_{24}H_{29}NO_3$

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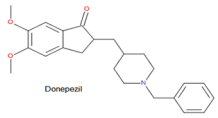
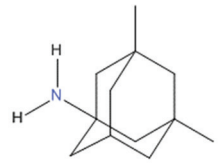
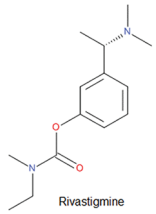
**Table 1: Structure of Alzheimer drugs**



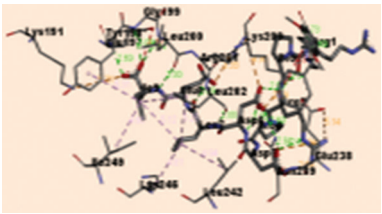
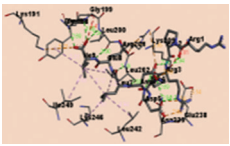
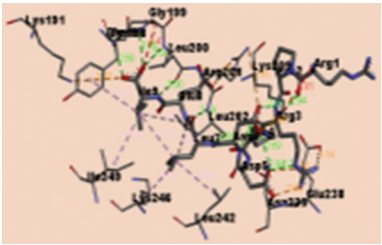




Memantine




Rivastigmine

**Table 2: Molecular docking analysis with the 3CYY protein for the drugs-donepezil, memantine, and rivastigmine**

| S. no | Compound | Docking structure |
|---|---|---|
| 1 | Donepezil |  |
| 2 | Memantine |  |
| 3 | Rivastigmine |  |

It helps to treat all stages of Alzheimer Disease. It prevents the breakdown of Ach in the brain. The common side effects are nausea, vomiting, muscle cramps, weight loss.[7]

## MECHANISM

Donepezil

↓

Acetylcholinesterase inhibitor

↓

Inhibit hydrolysis by acetylcholine

↓

Increase cortical acetylcholine

## MEMANTINE

**IUPAC**

1,3-Dimethyl-5-aminoadamantane.

Molecular formula: $C_{12}H_{21}N$

It helps to treat moderate to severe Alzheimer. It blocks the toxic effects associated with excess glutamate and regulates glutamate activation. The common side effects are dizziness, headache, and constipation.

## MECHANISM

Memantine

↓

NMDA receptor antagonist

↓

Acting of glutamatergic transmission

↓

Slow neurodegenerative

## RIVASTIGMINE

**IUPAC**

(S)-N-ethyl-3-((1-dimethylamino)ethyl)-N-methylphenylcarbamate.

Molecular formula: $C_{14}H_{22}N_2O_2$

It helps to treat mild to moderate Alzheimer. It helps to prevent the breakdown of Ach and Butyrylcholine. The common side effects are nausea, vomiting, and indigestion.

## MECHANISM

Rivastigmine

↓

Binds reversibly with inactivate cholinesterase

↓

Hydrolysis of acetylcholine

↓

Increased concentration of acetylcholine

**Table 3: Binding energies of docked compounds-3CYY with the donepezil, memantine, and rivastigmine**

| Drug | ΔG (Kcal/Mol) | Ki (Mm) | Internal energy | Vdw-Hb-desolv energy | Electrostatic energy | Total internal | Torsional energy |
|---|---|---|---|---|---|---|---|
| Donepezil | −7.37 | −0.26 | −9.16 | −7.51 | −1.65 | −0.93 | 1.79 |
| Memantine | −6.24 | −0.48 | −6.54 | −4.82 | −1.72 | 0.07 | 0.3 |
| Rivastigmine | −4.82 | −0.27 | −6.31 | −5.93 | −0.38 | −0.45 | 1.49 |

↓

Acetylcholinesterase and butyrylcholinesterase with peripheral tissues

## MATERIALS AND METHODS

3CYY is the tetrameric connexin protein. Connexins are proteins that can form gap junctions channels and hemichannels. As in AD, it has shown that there is increased expression in astrocytes that contact amyloid plaques *in vivo*. Amyloid plaques are aggregates of the amyloid protein, which is present in AD patient.[8].

The reactive gliosis has been associated with changes in the function of connexins (i.e. proteins). This causes an increase in astrocyte and astrocytes get contact with amyloid plaques and divides improperly to form βamyloid protein (i.e. Toxic to neurons).[9]

Docking is the method which concludes the orientation of ligand to a receptor when bound to each other of known three-dimensional structure to form a stable complex and to predict the binding energy between two molecules, i.e. ligand and receptor.

## PROCEDURE

### Protein (3CYY)

Protein from PDB Bank (RCSB) was retrieved from the AutoDock worksheet. Water molecules and hydrogen are deleted. Charges are computed by Gasteiger.

### Ligands

(Donepezil, Rivastigmine, and Memantine).

Ligand files are generated by selecting the atomic coordinates, selecting root, detecting the torsion tree, and number of torsions.

### Set Up the Grid Box

Grid parameter files are generated with the X, Y, and Z coordinated to form grid box with respect to the protein and the ligand.

### To Perform Docking

Docking has been done by selecting the ligand and the protein with the generated AutoGrid output file. For commanding or to run the AutoDock, Cygwin terminal was used with the necessary inputs for the generation of AutoGrid and AutoDock.[10]

## RESULTS AND DISCUSSION

In this study, Alzheimer drugs are chosen to estimate the binding efficiency by targeting 3CYY protein. The structures of Alzheimer Drugs are given in the Table 1 and the drugs are docked with the compound 3CYY protein represented in Table 2. The binding affinity of Donepezil was −7.37kcal/mol and when compared with other ligands Donepezil shows most significant binding energy with the target 3CYY and the results are tabulated in Table 3. The results are visualized using Discovery Studio Visualizer 4.0.

## CONCLUSION

From the results obtained we have concluded that Donepezil helps to treat Alzheimer more effectively than other drugs when it is combined with 3CYY protein. In further studies, we can perform docking with the various receptor and also we can design new compounds from existing Donepezil, Rivastigmine, and Memantine by addition or removal of the functional group to increase the efficiency of binding by QSAR (Quantitative Structural Activity Relationship) studies.

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