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Binding Affinity Analysis of Memory Enhancer Drugs in Amyloid Beta Protein in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia especially in older adults. AD is a progressive neurodegenerative brain disorder that causes a significant disruption of normal brain structure and function. Worldwide, nearly 44 million people have Alzheimer's. The global cost of Alzheimer's and dementia is estimated to be $605 billion, which is equivalent to 1% of the entire world's gross domestic product. It is one of the costliest chronic diseases to society. Amyloid Beta is one of the major proteins that cause the symptoms of this disease. It forms the plaques which block the transfer of signals in neurons and destroy the brain cells.

This study focuses on structure based drug designing of memory enhancing drug for Alzheimer's disease. In order to find the drug we first modeled the protein 'amyloid beta' using homology modeling. We further proceeded for the docking of the ligands for memory enhancing with the protein 'amyloid beta'. On the bases on binding affinity and interaction visualization the best ligand was selected and observed for memory enhancing drug. We conclude that Risperidone showed the minimum energy and therefore most stability. Hence, can be used as a very remarkable drug for memory enhancing.

Keywords: Alzheimer's disease, Neurodegenerative, Amyloid Beta protein, Risperidone

INTRODUCTION

Alzheimer's disease (AD) is the most common and well-known form of dementia affecting the increasingly elderly population, including families of those afflicted. Characterised by behavioural, psychological and cognitive degeneration, including memory loss, the disease affects the lives of patients and their families. With no effective treatments and no curative therapies, AD requires research to elucidate the mechanisms behind the disease [1].

Although AD is characterized by the progressive cognitive deterioration of a patient, each individual advances through the course of the disease uniquely. Initial symptoms are often mistaken for age-related problems or stress-induced indicators, including the inability to form new memories and recall recently learnt facts. These subtle problems in the 'pre-dementia' stage usually go unnoticed or may be identified as 'Mild Cognitive Impairment' (MCI). Early stages of the disease see behavioural, psychological changes, as well as a gradual inability to handle normal daily activities, including newly learned skills. Usually a patient is able to manage their own affairs, although their vocabulary and language fluency tend to be noticeably affected at this point of the disease. Later phases of AD require full-dependency on a caregiver, leading in some cases to a complete loss of speech and accompanied by a loss in muscle mass due to lack of mobility, ultimately causing the patient to become bedridden. Delusional symptoms and irritability, confusion, aggression and wandering tend to become less common than in the intermediate stages of the disease [2].

Clinical diagnosis of AD involves cognitive testing of patients; however diagnosis can only be confirmed at postmortem after neuropathological investigation. The golden standard involves measuring the characteristic brain lesions of Amyloid Beta (Aβ) peptide Senile Plaques (SP) and Neurofibrillary Tangles (NFT) consisting of hyper phosphorylated tau [3-5].

The accumulation of SP and the buildup of neurotoxic forms of the Aβ peptide such as protofibrils and oligomers, having been implicated in AD pathogenesis through familial genetic mutations of AD, are thought to lead to the cascade of neuro degeneration in AD [6].

Whilst this train of thought has sufficed for many years, the actual function of Aβ is still unknown, with researchers also believing it may be an acute phase protein or have another physiological role within the brain, such as an Apo lipoprotein involved in transporting metals, or regulating synaptic formation and transmission [7].

SP and Aβ peptide deposits are found also in cognitively normal elderly individuals, sometimes at the levels of those warranting an AD diagnosis, however without any cognitive decline SP are highly associated with age and emerge in early middle age, continuing to accumulate as an individual gets older. It is unknown what allows some individuals to remain free of cognitive deficits in the presence of high numbers of these brain lesions, although there are suggestions of 'cognitive reserve' obtained through the benefit of education [8].

Alzheimer's disease types

A minority (less than 1%) of those affected with AD are dominant familial forms caused by mutations in one of three genes and having an early age of onset before 65 years [9]. The more common sporadic version has no commonly acknowledged causes and the risks pertaining to the disease are not well understood.

Familial AD and genetic mutations

Familial AD, whilst rare, has provided researchers with much information about the causes of the disease, including the sporadic form. Discoveries of families with early onset, dominant forms of the disease lead researchers to connect the β-amyloid precursor protein (AβPP, the gene of which was found on chromosome 21) [10] and two enzymes that cleave it (Presenilin 1 – gene of PSEN1, found on chromosome 14 [11] and Presenilin 2–gene of PSEN2, found on chromosome 1, with the Aβ peptide found in SP within the brains of AD sufferers. Most mutations within the three genes (AβPP, PSEN1 and PSEN2) increase the levels of Aβ, thought to lead to excess amounts of toxic forms of Aβ peptide, which may aggregate into SP and supposedly disrupt neuronal messaging, ultimately causing the death of neurons. Further studies have also suggested that oligomers or protofibrils of Aβ peptide are to blame and disrupt synapses [12].

Sporadic AD

The more common sporadic form of AD has no directly known causes and is considered a multifactorial disease where many risk factors add up to instigate the dysfunction that results in the symptoms recognized as AD, as reviewed in [13]. There have been recent suggestions that there needs to be differentiation between subtypes of AD, which may have implications for treatments and progression of the disease. The levels and abundance of the characteristic hallmarks of AD–SP and NFT– have been observed occurring disproportionately in different cases, indicating there may be SP- or NFT- dominant forms. Others have proposed that there may be up to five subgroups of the disease [14], differing with regards to cerebrospinal fluid (CSF) levels of Aβ peptide, ubiquitin and tau, including early and late onset, high and low Aβ peptide and tau levels, prevalence of APOEİ4 allele, and incidence of concomitant neuropathological lesions such as Lewy bodies.

Risk factors for alzheimer disease

Environmental risks

A number of risks can be considered to environmental risks in the form of things that an individual exposes him or herself to over the period of their life. Longitudinal or retrospective studies [15] have produced many ideas for ways to maintain ones' cognitive reserve and allow an individual to live healthily into old age with intact brain function. Exercise is foremost thought to be the most beneficial way to retain cognitive function [16]. Beneficial in so many ways, exercise keeps the body operating effectively and keeps hormones and the immune system in check, as well as reducing body fat and keeping the cardiovascular system healthy.

Concomitant diseases

Epidemiological studies have raised questions as to why some individuals can survive to old age with intact cognition, yet at autopsy show numerous SP and NFT [17] suggesting that they should have presented with AD during their life. These issues have suggested that some persons have higher 'cognitive reserve [18] and handle brain insults better than those with lower cognitive reserve. This is a favoured theory, however it is also suggested that those who are unable to deal with large amounts of the neuropathological lesions may have other diseases present [19] which are either asymptomatic, or chronic, and contribute to the pathogenesis of AD.

Polymorphisms & genes

Studies of the disease have indicated that a large part of AD is hereditary and passed on through genetic polymorphisms or differences between individuals in genes. Up to 80% of disease risk is thought to be hereditary and affect disease occurrence and determine whether an individual will develop AD. The only accepted AD risk gene, APOE is claimed to account for approximately 65% of this genetic risk [20,21].

Drugs for prevention and disease modification

AD is a surreptitious disease; sometime symptoms become noticeable. Disease prevention, therefore may be beneficial, and may decrease the prevalence of AD. Studies assessing prevention are underway.

- The most widely accepted are donepezil (Aricept) and tacrine (Cognex). Both drugs are cholinesterase inhibitors that is they interfere with the cholinesterase enzyme, acetylcholinesterase, which breaks down the neurotransmitter acetylcholine.
- Nerve fibres, that is neurons, are stimulated or inhibited by the endless firing of signals across synapses (rated like electric switching centres). Such stimulating signals are often carried by acetylcholine and discontinued by the enzyme acetylcholinesterase, which breaks down acetylcholine. The Alzheimer's drugs donepezil and tacrine, therefore, seek to reduce the activity of the inhibitor acetylcholinesterase in order to increase the neurotransmitter acetylcholine [22].
- Memantine, a low- to moderate-affinity, noncompetitive N-methyl-D-asparate receptor antagonist has been used in German clinics for over 10 years to treat patients with dementia [23]. This drug often is used in combination with acetylcholinesterase inhibitors such as donepezil [24].
- The major value of memantine is that it is designed to protect against the excitotoxicity of low glutamate concentrations. As would be expected, addressing biochemical imbalances in the cholinergic and glutamatergic systems simultaneously appears to have some added value in the treatment of Alzheimer's disease.

- NSAIDS: One such prevention study is observed the use of NSAIDS (non-steroidal anti-inflammatory drugs) on AD. Preliminary results were promising, however AD researchers are reluctant to recommend NSAIDS given the toxicities (gastrointestinal ulcers, renal toxicity, and hypertension) associated with these NSAIDS medicines.
- Antioxidants: Pathological data indicates that oxidative stress and the accumulation of free radicals results in neuronal damage in AD. Vitamin E (α-tocopherol), vitamin C, and β-carotene are exogenous chain-breaking antioxidants, which decrease free-radical-mediated damage caused by toxic chain reactions in neuronal cells and help to inhibit dementia pathogenesis in mammalian cells. The most important lipid-phase antioxidant is α-tocopherol which is a powerful, lipid-soluble chain-breaking antioxidant found in lipid membranes, circulating lipoproteins and Low-density Lipoprotein (LDL) particles [25].
- Hormones: Research increasingly suggests that changes in estrogen levels during aging may increase risk for Alzheimer disease, the most common type of dementia. This update reviews the newest information about estrogen and cognitive aging, including information regarding the role of bioavailable estrogen in older women and men, use of selective estrogen receptor modulators (SERMs) to improve cognition, and studies of genetic risk factors to elucidate the effects of endogenous estrogen on aging and cognition [26].
- Other Agents: Various other pharmacological agents to treat AD are being studied. Gingko biloba, a plant extract that contains numerous pharmacological properties, some of which are thought to be antioxidative, anti-inflammatory or neurotransmitter modulators. Current research suggests that the use of gingko biloba provides smaller effects that that of cholinergics. Also, it is currently unknown which of the active components of this alternative compound contributes to cognitive enhancing effects. Furthermore, the compound is a non-regulated supplement in several countries and standardized preparations are not available [27,28].

MATERIALS AND METHODS

Databases and software's used

FASTA: FASTA is pronounced "fast A", and stands for "FAST-All", because it works with any alphabet, an extension of "FAST-P" (protein) and "FAST-N" (nucleotide) alignment. The current FASTA package contains programs for protein: protein, DNA: DNA, protein: translated DNA (with frame shifts), and ordered or unordered peptide searches. Recent versions of the FASTA package include special translated search algorithms that correctly handle frame shift errors (which six-frame-translated searches do not handle very well) when comparing nucleotide to protein sequence data. The FASTA output provides one more statistical parameter, the score. This describes the number of standard deviations from the mean score for the database search. FASTA also uses *E*-values and bit scores [29].

BLAST: BLAST uses heuristics to align a query sequence with all sequences in a database. The objective is to find high-scoring un-gapped segments among related sequences. The existence of such segments above a given threshold indicates pair-wise similarity beyond random chance, which helps to discriminate related sequences from unrelated sequences in a database. BLAST is a family of programs that includes BLASTN, BLASTP, BLASTX TBLASTN, and TBLASTX. BLASTN queries nucleotide sequences with a nucleotide sequence database. The BLAST web server (www.ncbi.nlm.nih.gov/BLAST/) has been designed in such away as to simplify the task of program selection. The programs are organized based on the type of query sequences, protein sequences, nucleotide sequences, or nucleotide sequence to be translated [30].

PubChem: PubChem is a database of chemical molecules and their activities against biological assays. The system is maintained by the National Center for Biotechnology Information (NCBI), a component of the National Library of Medicine, which is part of the United States National Institutes of Health (NIH). PubChem can be accessed for free through a web user interface. Searching the databases is possible for a broad range of properties including chemical structure, name fragments, chemical formula, molecular weight, XLogP, and hydrogen bond donor and acceptor count. PubChem is comprised of three linked databases -PubChem Compound, PubChem Substance and PubChem Bioassay that are within the NCBI's Entrez information retrieval system. Thus, PubChem can easily link its chemical structure records to biological property information in PubMed and to NCBI's Protein 3D Structure Resource (Entrez Databases, NIH Roadmap for Medical Research).

Swiss modeling: Swiss-Model (www.expasy.ch/swissmod/SWISS-MODEL.html) is an automated modeling server that allows a user to submit a sequence and to get back a structure automatically. The server constructs a model by automatic alignment (First Approach mode) or manual alignment (Optimize mode). In the First Approach mode, the user provides sequence input for modeling. The server performs alignment of the query with sequences in PDB using BLAST. After selection of suitable templates, a raw model is built. Refinement of the structure is done using GROMOS. Alternatively, the user can specify or uploads structures as templates. The final model is sent to the user by e-mail. In the Optimize mode, the user constructs a sequence alignment in Swiss Pdb Viewer and submits it to the server for model construction [31].

EXPERIMENTATION AND RESULTS

Data collections

FASTA

>gi|13325112|gb|AAH04369.1|APPprotein[Homosapiens]MLPGLALLLLAAWTARALEVPTDGNAGLLAEPQIAMFCGRLNMH
MNVQNGKWDSDPSGTKCIDTKEGILQYCQEVYPELQITNVVEANQPVTIQNWCKRGRKQCKTHPHFVIPYRCLVGEFVSD
ALLVPDKCKFLHQERMDVCETHLHWHTVAKETCSEKSTNLHDYGMLLPCGIDKFRGVEFVCCPLAEESDNVDSADAEED
DSDVWWGGADTDYADGSEDKVVEVAEEEEVAEVEEEEADDDEDDEDGDEVEEEAEEPYEEATERTTSIATTTTTTESVEE
VVREKWYKEVHSGQARWLML

BLAST

Using BLASTp tool of NCBI the alignment was done between the target sequence and the sequences in PDB. The sequence with maximum similarity was selected as template. Thus by this method sequence with accession ID AAH043691 was selected as template for model generation Figures 1 and 2.

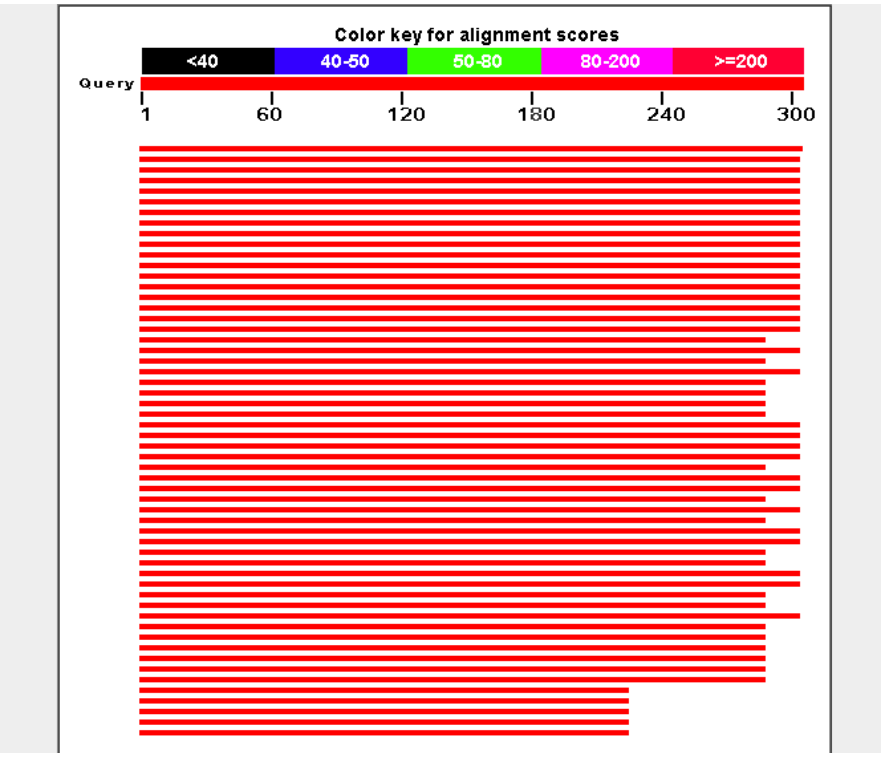


Figure 1: Showing similarity of target sequence with others.

Description	Max score	Total score	Query cover	E value	Ident	Accession
APP protein [Homo sapiens]	628	628	100%	0.0	100%	AAH04369.1
PREDICTED: amyloid beta A4 protein isoform X2 [Rhinopithecus roxellana]	608	608	99%	0.0	96%	XP_010381739.1
PREDICTED: uncharacterized LOC101926433 isoform X2 [Macaca fascicularis]	608	608	99%	0.0	96%	XP_005548941.1
PREDICTED: amyloid beta A4 protein-like [Macaca mulatta]	608	608	99%	0.0	96%	XP_002803216.1
PREDICTED: amyloid beta A4 protein isoform X2 [Colobus angolensis palliatus]	607	607	99%	0.0	96%	XP_011781878.1
PREDICTED: amyloid beta A4 protein isoform X1 [Colobus angolensis palliatus]	607	607	99%	0.0	96%	XP_011781877.1
PREDICTED: amyloid beta A4 protein isoform X1 [Rhinopithecus roxellana]	607	607	99%	0.0	96%	XP_010381738.1
PREDICTED: amyloid beta A4 protein isoform X7 [Pan troglodytes]	607	607	99%	0.0	96%	XP_009449632.1
amyloid beta A4 protein precursor [Pan troglodytes]	607	607	99%	0.0	96%	NP_001013036.1
amyloid beta A4 protein isoform a precursor [Homo sapiens]	607	607	99%	0.0	96%	NP_000475.1
amyloid beta A4 protein isoform h precursor [Homo sapiens]	607	607	99%	0.0	96%	NP_001191230.1
PREDICTED: uncharacterized LOC101926433 isoform X1 [Macaca fascicularis]	607	607	99%	0.0	96%	XP_005548940.1

Figure 2: Showing different sequences with the idnet % and query cover.

PubChem: Using PubChem, the information about the ligands was derived and observed. The ligands having hydrogen atom acceptor 6 or less than five were selected and preceded for docking (Tables 1-3).

II-MODELING

Swiss modeling: 3D Structure prediction of Amyloid Beta was done and best model on the basis of QMEAN4 and GMQE was selected (Figure 3).

These are energies values calculated by server (Figure 4).

GMQE (Global Model Quality Estimation) is a quality estimation of which combines properties from the target-template alignment. The resulting GMQE score is expressed as a number between zero and one, reflecting the expected accuracy of a model built with that alignment and template. Higher numbers indicate higher reliability. Once a model is built, the GMQE gets updated for this specific case by also taking into the account of QMEAN4 score of the obtained model in order to increase reliability of the quality estimation.

GMQE: 0.54

QMEAN is a combination scoring function for the quality estimation of protein structure models. QMEAN comprises of six structural descriptors. Four of them are statistical potentials analyzing torsion angles, solvation and non-bonded interactions. The other two terms represents the agreement between predicted and calculated secondary structure and solvent accessibility.

Table 1: List of Compounds selected for the memory enhancing drug.

S. No.	Compound name	Chem ID	XlogP	Molecular weight	Hydrogen bond acceptor	Hydrogen bond donor
1	GinsenosideRb1	9898279	0.3	1109.29448	23	15
2	Ginsenoside Rg1	1441923	2.7	801.01	14	10
3	Ginkolide B	6324617	-0.4	424.39856	10	3
4	Gikolide A	6419993	0.6	408.39916	9	2
5	Bilobalide	12308750	-0.3	326.29862	8	2
6	EGCG	65064	1.2	458.37172	11	8
7	Choline	305	-0.4	104.17076	1	1
8	Choline Chloride	6209	_	139062376	2	1
9	Phosphotidyl Choline	68616813	0.5	190.242902	1	0
10	DMAE	7902	-0.4	89.13624	2	1
11	Aricept	5741	_	415.9529	4	1
12	Rivastgmine	77991	2.3	250.33668	3	0
13	Aricept ODT	3152	4.3	379.49196	4	0
14	Galantamine	9651	1.8	287.35354	4	1
15	Memantine	4054	3.3	179.30184	1	1
16	Ebixa	181458	_	215.76278	1	2
17	Namzaric	76037163	_	631.71568	5	3
18	Haloperidol	3559	3.2	375.864223	4	1
19	Olanzapine	4585	208	312.4325	5	1
20	Risperidone	5073	2.7	410.484483	6	0
21	Quetiapine	5002	2.1	383.5071	5	1
22	Axon	447371	306	463.504043	5	2
23	Tacrine	1935	2.7	198.26366	2	1
24	ErgolyteMesylates	592735	3.5	591.7409	6	3
25	Hydergine	168870	_	659.7934	9	4
26	Razadyne	121587	_	368.265	4	1
27	BACE 1 inhibitor	135697681	_	_	_	_
28	Semagacest	9843750	1.3	361.43538	4	3
29	Tarenflurbil	92337	4.2	244.260923	3	1
30	Dimebon	197033	3.5	319.4433	2	0
31	Rember	4139	2.2	284.39922	2	0
32	PBT2	10016012	3	271.14248	3	1
33	Selengiline	26757	2.8	187.28078	1	0

Figure 3: Swiss model.

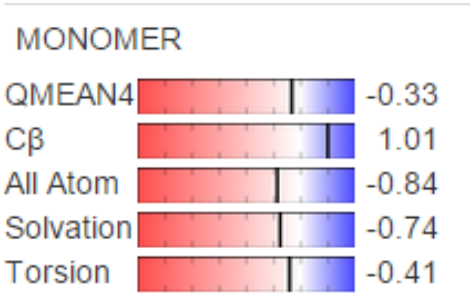


Figure 4: Energy values of the model.

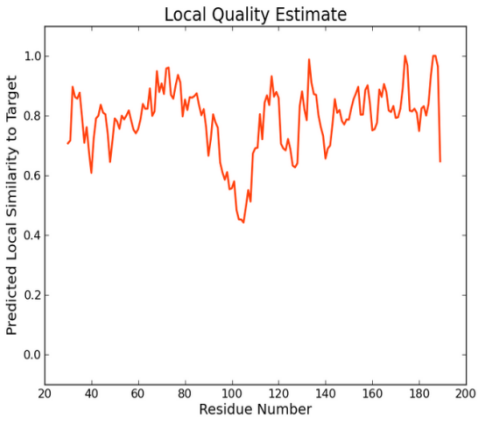


Figure 5: Local estimated value of the model.

QMEAN4: -0.33

Local Quality Estimate: This tool is provided to assess the quality and structural features of protein models and template structures. The quality estimate ranges between 0 and 1 with higher values for better models (Figure 5).

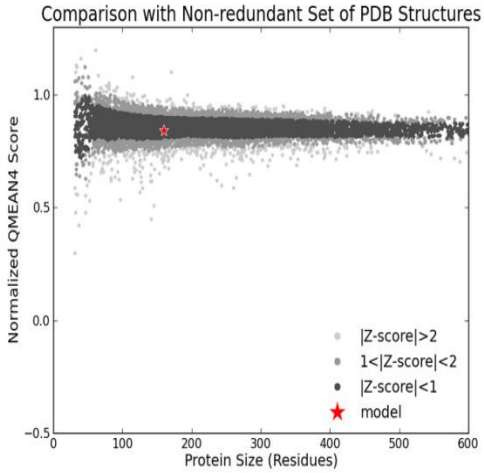


Figure 6: Z-score of the model, showing where the structure lies.

Z score ~0.85

Z-scores of the QMEAN composite score as well as all terms are provided relating the quality estimates to scores obtained for high-resolution reference structures. The QMEAN Z-score represents an measure of the absolute quality of a model by providing an estimate of the 'degree of nativeness' of the structural description observed in a model and by describing the likelihood that a given model is of comparable quality to experimental structures. Models of high quality are expected to have strongly positive QMEAN Z-scores (Figure 6).

Docking and visualization

After Protein ligand docking the following table was made showing all the energies. The Table 2 was arranged in increasing order of free energy. Free energy is inversely proportional to the stability of the compound; therefore the first ten compounds were chosen and further visualized Tables 3 and 4 (Figures 7-16).

Table 2: Result of docking of selected 20 compounds, arranged in ascending order of energy

S.NO	COMPOUND NAME	RUN	FREE ENERGY	Ki	FINAL INTERMOLECULR ENERGY	ELECTROSTATIC ENERGY	VDW + HBOND	TOTAL INTERNAL ENERGY	TORSIONAL FREE ENERGY	UNBOUND SYSTEM'S ENERGY
1	Risperidone	3	-5.42 kcal/mol	106.06 uM	-5.79 kcal/mol	-0.09 kcal/mol	-5.70 kcal/mol	-0.73 kcal/mol	+1.10 kcal/mol	+0.00 kcal/mol
2	Quetiapine	6	-4.95 kcal/mol	236.40 uM	-5.95 kcal/mol	-0.55 kcal/mol	-5.39 kcal/mol	-0.92 kcal/mol	+1.92 kcal/mol	+0.00 kcal/mol
3	Razadyne	7	-4.58 kcal/mol	440.01 uM	-4.98 kcal/mol	-0.41 kcal/mol	-4.57 kcal/mol	-0.15 kcal/mol	+0.55 kcal/mol	+0.00 kcal/mol
4	Galantamine	10	-4.48 kcal/mol	517.73 uM	-5.20 kcal/mol	-0.36 kcal/mol	-4.84 kcal/mol	-0.11 kcal/mol	+0.82 kcal/mol	+0.00 kcal/mol
5	Dimebon	8	-4.46 kcal/mol	541.97 uM	-4.60 kcal/mol	-0.04 kcal/mol	-4.56 kcal/mol	-0.68 kcal/mol	+0.82 kcal/mol	+0.00 kcal/mol
6	Semagacest	3	-4.23 kcal/mol	787.91 uM	-4.28 kcal/mol	-0.65 kcal/mol	-3.63 kcal/mol	-1.60 kcal/mol	+1.65 kcal/mol	+0.00 kcal/mol
7	Olanzapine	3	-3.95 kcal/mol	1.28 mM	-3.96 kcal/mol	-0.02 kcal/mol	-3.93 kcal/mol	-0.27 kcal/mol	+0.27 kcal/mol	+0.00 kcal/mol
8	Ebixa	2	-3.86 kcal/mol	1.48 mM	-4.20 kcal/mol	-1.21 kcal/mol	-3.00 kcal/mol	+0.07 kcal/mol	+0.27 kcal/mol	+0.00 kcal/mol
9	PBT2	2	-3.54 kcal/mol	2.52 mM	-4.35 kcal/mol	+0.28 kcal/mol	-4.63 kcal/mol	-0.02 kcal/mol	+0.82 kcal/mol	+0.00 kcal/mol
10	Rember	4	-3.52 kcal/mol	2.61 mM	-3.70 kcal/mol	+0.03 kcal/mol	-3.72 kcal/mol	-0.10 kcal/mol	+0.27 kcal/mol	+0.00 kcal/mol

DISCUSSION

Alzheimer disease is the most common type of dementia and possibly contributes to 60 to 70% of the patients. Alzheimer disease (AD) is characterized by a progressive decrease in cognitive operation. AD is substantially increased among people aged 65 years or more, with a progressive decline in memory, thinking, language and learning capacity. The pathophysiology of AD is related to the injury and death of neurons, initiating in the hippocampus brain region that is involved with memory and learning, then atrophy affects the entire brain.

Amyloid beta, also written Aβ, is a short peptide that is an abnormal proteolytic by product of the trans-membrane protein amyloid precursor protein (APP), whose function is unclear but thought to be involved in neuronal development. Amyloid beta monomers are soluble and contain short regions of beta sheet at sufficiently high concentration; they undergo a dramatic conformational change to form a beta sheet-rich tertiary structure that aggregates to form amyloid fibrils. These fibrils deposit outside neurons in dense formations known as senile plaques or neuritic plaques, in less dense aggregates as diffuse plaques, and sometimes in the walls of small blood vessels in the brain in a process called amyloid angiopathy or congophilicangiopathie. In Alzheimer disease abnormal aggregation of the tau protein, a microtubule-associated protein expressed in neurons is also observed. Tau protein acts to stabilize microtubules in the cell cytoskeleton. Like most microtubule-associated proteins, tau is normally regulated by phosphorylation. In AD patients, hyper-phosphorylated tau P-tau accumulates as paired helical filaments that in turn aggregate into masses inside the nerve cell bodies known as neurofibrillary tangles and as dystrophic neurites associated with the amyloid plaques.

Different types of drugs and vaccines are known for increasing the memory loss in this disease. In this report the compounds which are used in the memory enhancing drugs are made to dock with the protein amyloid beta. The protein-ligand docking interaction is observed and visualized on the bases of the energy. For docking Autodock tools 4.0 is used to predict the binding affinity, ligand efficiency and inhibitory constant. Which gives different conformations of the ligand molecule with amyloid beta in docking analysis ligand efficiency measures the ratio of free binding energy to the number of non-hydrogen atoms of the compounds and represents it in negative magtitude.

For docking analysis of 20 natural compounds against target amyloid beta, we retrieved the 3D structure of the amyloid beta having accession ID AAH04369.1. Fom RCSB databae, compounds were retrieved from pubchem. Protein optimization is done by adding H bonds and removing water atom under neutral pH.

Table 2 continued

S.NO	COMPOUND NAME	RUN	FREE ENERGY	Ki	FINAL INTERMOLECULR ENERGY	ELECTROSTATIC ENERGY	VDW + HBOND	TOTAL INTERNAL ENERGY	TORSIONAL FREE ENERGY	UNBOUND SYSTEM'S ENERGY
11	Rivastigmine	5	-3.22 kcal/mol	4.34 mM	-4.11 kcal/mol	-0.41 kcal/mol	-3.70 kcal/mol	-0.48 kcal/mol	+1.37 kcal/mol	+0.00 kcal/mol
12	Aricept	10	-3.08 kcal/mol	5.50 mM	-3.85 kcal/mol	-0.16 kcal/mol	-3.69 kcal/mol	-0.88 kcal/mol	+1.65 kcal/mol	+0.00 kcal/mol
13	AriceptODT	10	-2.77 kcal/mol	9.34 mM	-3.53 kcal/mol	+0.50 kcal/mol	-4.03 kcal/mol	-0.88 kcal/mol	+1.65 kcal/mol	+0.00 kcal/mol
14	Haloperidol	10	-2.72 kcal/mol	10.08 mM	-4.57 kcal/mol	-0.68 kcal/mol	-3.90 kcal/mol	-0.07 kcal/mol	+1.92 kcal/mol	+1.92 kcal/mol
15	Axon	7	-2.69 kcal/mol	10.59 mM	-4.40 kcal/mol	+0.17 kcal/mol	-4.57 kcal/mol	-0.49 kcal/mol	+2.20 kcal/mol	+0.00 kcal/mol
16	Selengiline	10	-2.58 kcal/mol	12.84 mM	-3.36 kcal/mol	-0.26 kcal/mol	-3.10 kcal/mol	-0.32 kcal/mol	+1.10 kcal/mol	+0.00 kcal/mol
17	Phosphotidylcholine	3	-2.35 kcal/mol	18.90 mM	-3.11 kcal/mol	-0.39 kcal/mol	-2.73 kcal/mol	-0.33 kcal/mol	+1.10 kcal/mol	+0.00 kcal/mol
18	DMAE	6	-1.91 kcal/mol	39.64 mM	-2.65 kcal/mol	-0.75 kcal/mol	-1.89 kcal/mol	-0.09 kcal/mol	+0.82 kcal/mol	+0.00 kcal/mol
19	Cholinechloride	5	-1.49 kcal/mol	80.81 mM	-2.18 kcal/mol	-1.11 kcal/mol	-1.07 kcal/mol	-0.13 kcal/mol	+0.82 kcal/mol	+0.00 kcal/mol
20	Choline	5	-1.13 kcal/mol	147.72 mM	-1.80 kcal/mol	-0.21 kcal/mol	-1.60 kcal/mol	-0.15 kcal/mol	+0.82 kcal/mol	+0.00 kcal/mol

Table 3: Visualization of selected compounds.

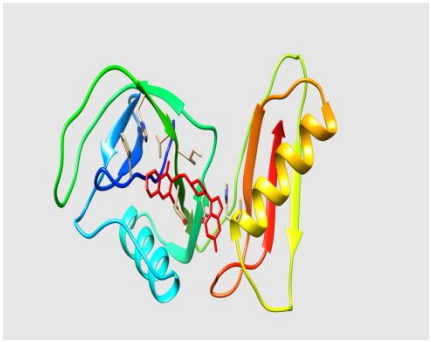
Visualization/Compound	Risperidone	Quetiapine	Razadyne	Galantamine	Dimebon	Semagacest	Olanzapine	Ebixa	PBT2	Rember
Free Energy of Binding	-5.42 kcal/mol	-4.95 kcal/mol	-4.58 kcal/mol	-4.48 kcal/mol	-4.46 kcal/mol	-4.23 kcal/mol	-3.95 kcal/mol	-3.86 kcal/mol	-3.54 kcal/mol	-3.52 kcal/mol
Inhibition Constant, Ki	106.06 uM	236.40 uM	440.01 uM	517.73 uM	541.97 uM	787.91 uM	1.28 mM	1.48 mM	2.52 mM	2.61 mM
Final Intermolecular Energy	-5.79 kcal/mol	-5.95 kcal/mol	-4.98 kcal/mol	-5.20 kcal/mol	-4.60 kcal/mol	-4.28 kcal/mol	-3.96 kcal/mol	-4.20 kcal/mol	-4.35 kcal/mol	-3.70 kcal/mol
vdW + Hbond + desolv Energy	-5.70 kcal/mol	-5.39 kcal/mol	-4.57 kcal/mol	-4.84 kcal/mol	-4.56 kcal/mol	-3.63 kcal/mol	-3.93 kcal/mol	-3.00 kcal/mol	-4.63 kcal/mol	-3.72 kcal/mol
Electrostatic Energy	-0.09 kcal/mol	-0.55 kcal/mol	-0.41 kcal/mol	-0.36 kcal/mol	-0.04 kcal/mol	-0.65 kcal/mol	-0.02 kcal/mol	-1.21 kcal/mol	+0.28 kcal/mol	+0.03 kcal/mol
Final Total Internal Energy	-0.73 kcal/mol	-0.92 kcal/mol	-0.15 kcal/mol	-0.11 kcal/mol	-0.68 kcal/mol	-1.60 kcal/mol	-0.27 kcal/mol	+0.07 kcal/mol	-0.02 kcal/mol	-0.10 kcal/mol
Torsional Free Energy	+1.10 kcal/mol	+1.92 kcal/mol	+0.55 kcal/mol	+0.82 kcal/mol	+0.82 kcal/mol	+1.65 kcal/mol	+0.27 kcal/mol	+0.27 kcal/mol	+0.82 kcal/mol	+0.27 kcal/mol
Unbound System's Energy	+0.00 kcal/mol	+0.00 kcal/mol	+0.00 kcal/mol	+0.00 kcal/mol	+0.00 kcal/mol	+0.00 kcal/mol	+0.00 kcal/mol	+0.00 kcal/mol	+0.00 kcal/mol	+0.00 kcal/mol

Further, the interactions and the binding of ligand were observed of the ten compounds with the least energy. For this ligplot and chimera was used. Ligplot shows the clear interaction and bonding of the ligand with protein. It tells about the proteins which are attached by hydrogen bonds and the proteins which are free. Chimera shows the location of the ligand in the protein structure.

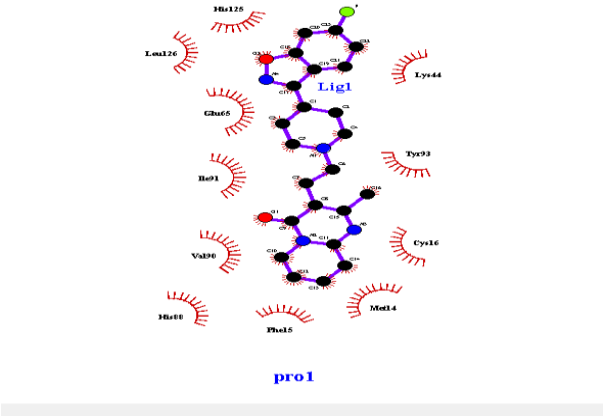
From protein-ligand docking Risperidone was observed to be the most potential target compound based on the minimum binding energy it showed. The binding energy was -5.42 kcal/mol, which was the least energy observed amongst the 20 compounds which were docked with the protein. Risperidone is the most stabled compound and can be used as the memory enhancing drug.

Table 4: Protein-ligand interaction.

S. No.	Compound	Energy	No. of hydrogen bonds	Distance and amino acids	Interacted amino acids
1	Risperidone	-5.42	0	-	His125, Leu126, Glu65, Ile91, Val90, His88, Phe15, Met14, Cys16, Tyr93, Lys44
2	Quetiapine	-4.95	3	His125 S-N(1.95), Met14 O-O(3.76), His88 N-O(3.50)	Ile91, His129, Leu126, Glu65, Tyr93, Val90
3	Razadyne	-4.58	4	Glu9 N-O(3.31) Ala8 N-O(2.72), N-O(2.61) N-O(3.14)	Gln11, Pro92, Ala66, Gln68, Pro69, Val70, Met23
4	Galantamine	-4.48	3	His88 N-O(2.92), Met14 O-O(2.82), Ile91 N-O(2.87)	Phe15, Cys16, Tyr93, Val90
5	Dimebon	-4.46	1	Ile91 N-N(3.11)	Tyr93, Asp42, Cys16, Phe15, Met14, Val90
6	Semagacest	-4.23	2	Glu65 O-O(2.52)	Asp155, Thr124, His123, Leu126, Tyr93, Ile91, Ile41, Met14
7	Olanzapine	-3.95	0	_	Val190, Met14, Phe15, Lys16, Cys40, Tyr93, Glu65, Ile91, Phe89
8	Ebixa	-3.86	2	Ile41 N-O(2.72), Asp42 N-O(2.71)	Met14, Cys16, Lys40
9	PBT2	-3.54	2	Ile91 O-O(2.83), N-N(3.07)	Phe89, Pro69, His88, Phe15, Val90, Met14, Tyr93
10	Rember	-3.52	2	Ile91 N-S(3.24), Phe89 N-O(2.82)	Met14, His88, Val90, Pro69

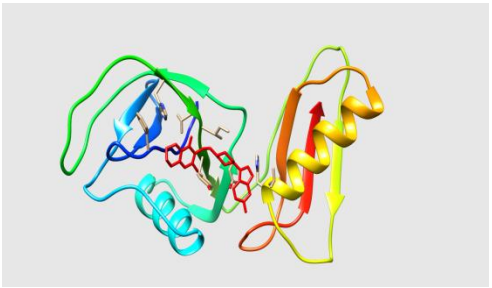


a) Shows the docking complex

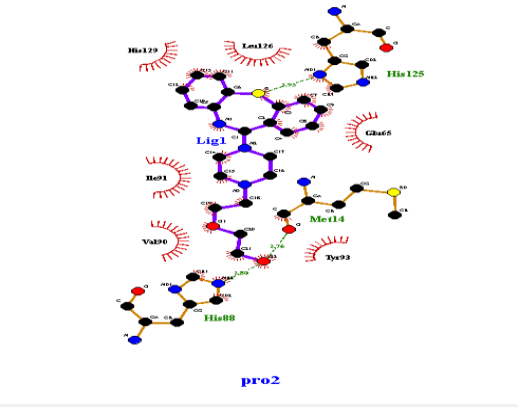


b) Shows the binding with proteins

Figure 7: Protein-ligand interaction with Risperidone.



a) Shows the docking complex

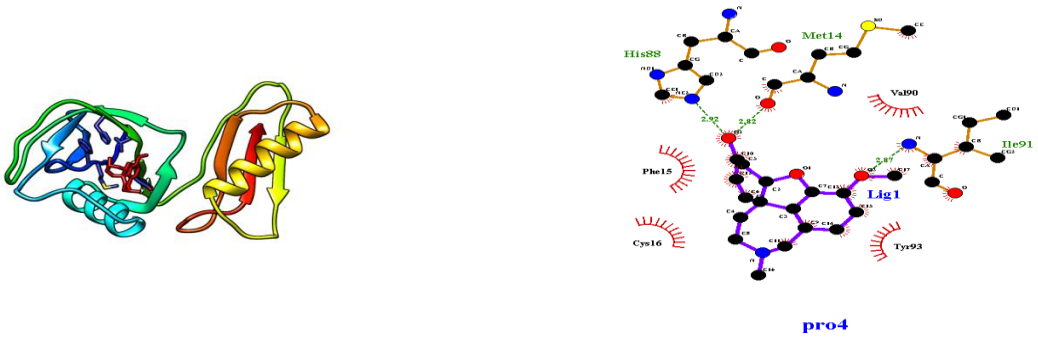


b) Shows the binding with proteins

Figure 8: Protein-ligand interaction with Quetiapine.

a) Shows the docking complex b) Shows the binding with proteins

Figure 9: Protein-ligand interaction with Razadyne.

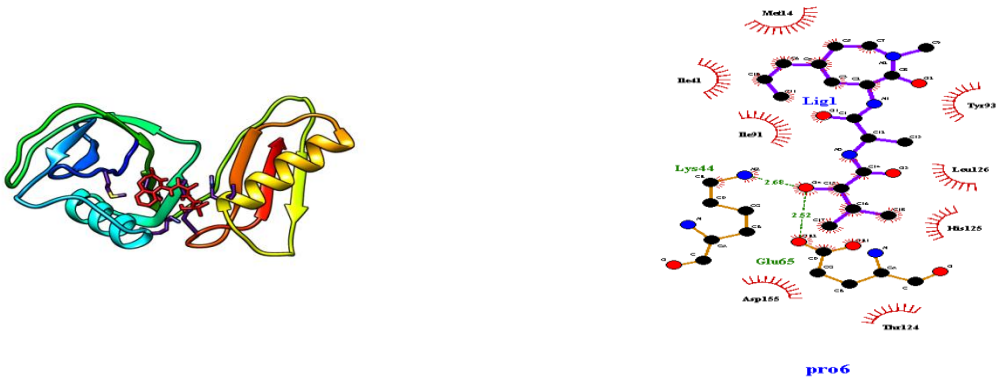


a) Shows the docking complex b) Shows the binding with proteins

Figure 10: Protein-ligand interaction with Galantamine.

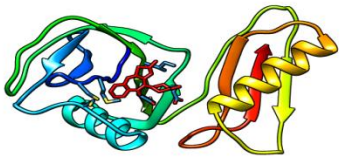
a) Shows the docking complex b) Shows the binding with proteins

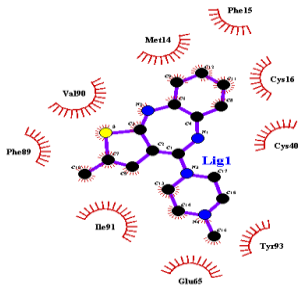
Figure 11: Protein-ligand interaction with Dimebon.



a) Shows the docking complex b) Shows the binding with proteins

Figure 12: Protein-ligand interaction with Semagacest.

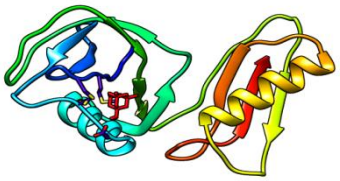


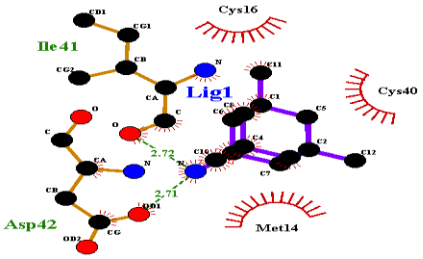


pro7

a) Shows the docking complex b) Shows the binding with proteins

Figure 13: Protein-ligand interaction with Olanzapine.

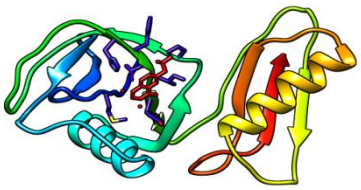


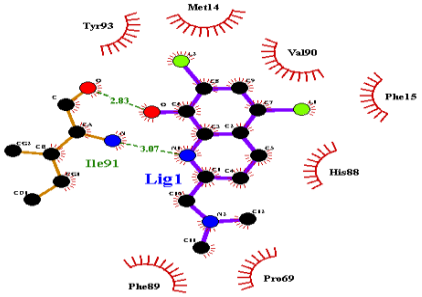


pro8

a) Shows the docking complex b) Shows the binding with proteins

Figure 14: Protein-ligand interaction with Ebixa.

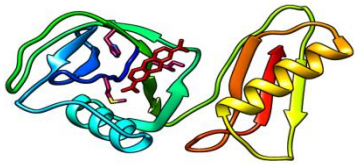


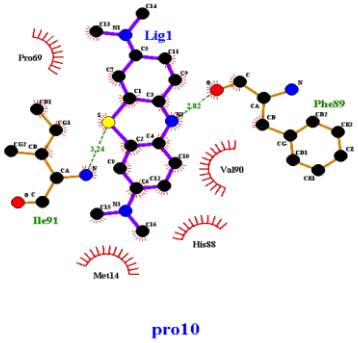


pro9

a) Shows the docking complex. b) Shows the binding with proteins

Figure 15: Protein-ligand interaction with PBT2.





pro10

a) Shows the docking complex. b) Shows the binding with proteins

Figure 16: Protein-ligand interaction with Rember.

CONCLUSION

From docking analysis we concluded that the binding energy of the ten compounds is remarkable for identifying target drug for memory enhancing in Alzheimer's disease. We conclude that Risperidone showed the minimum energy and therefore most stability. Hence, can be used as a very remarkable drug for memory enhancing. Visualization of the interaction showed no hydrogen bonds and free interactions with eleven proteins of the protein. Conclusively, our results strongly suggest that it is a worth compound for developing further as memory enhancing drug. However, this work is only a step forward towards understanding the interaction and binding of the ligand to the protein. To understand the mechanistic insights of the memory enhancing compound targeting on the protein amyloid beta. We finally obtained a stable ligand protein structure which can be further used for drug designing against Alzheimer's disease.

REFERENCES

[1] World Alzheimer Report. Alzheimer Disease International, London, **2009**.
[2] A.T. Jotheeswaran, J.D. Williams, M.J. Prince, *Alz. Dis. Assoc. Dis.*, **2010**, 24(3), 296-302.
[3] H. Braak, E. Braak, *Acta. Neuropathol*., **1991**, 82, 239-259.
[4] Z.S. Khachaturian, *Arch. Neurol.*, **1985**, 42, 11, 1097.
[5] I. Alafuzoff, T. Arzberger, S. Al-Sarraj, I. Bodi, N. Bogdanovic, H. Braak, O. Bugiani, K. Del-Tredici, I. Ferrer, E. Gelpi, G. Giaccone, M.B. Graeber, P. Ince, W. Kamphorst, A. King, P. Korkolopoulou, G.G. Kovács, S. Larionov, D. Meyronet, C. Monoranu, P. Parchi, E. Patsouris, W. Roggendorf, D. Seilhean, F. Tagliavini, C. Stadelmann, N. Streichenberger, D.R. Thal, S.B. Wharton, H. Kretzschmar, *Brain. Pathol.*, **2008**, 18, 4, 484.
[6] J.A. Hardy, G.A. Higgins, *Sci.*, **1992**, 256, 5054, 184.
[7] A. Kontush, *J. Alz. Dis.*, **2005**, 8, 2, 129.
[8] J. Dumurgier, C. Paquet, S. Benisty, C. Kiffel, C. Lidy, F. Mouton-Liger, H. Chabriat, J. Hugon, *Neurobiol. Dis.*, **2010**, 40, 2, 456.
[9] W.M. Van der Flier, Y.A.L. Pijnenburg, N.C. Fox, P. Scheltens, *Lancet. Neurol.*, **2011**, 10, 3, 280-288.
[10] K.E. Wisniewski, H.M, Wisniewski, G.Y. Wen, *Ann. Neurol.*, **1985**, 17, 3, 278.
[11] E. Levy-Lahad, E.M. Wijsman, E. Nemens, L. Anderson, K.A. Goddard, J.L. Weber, T.D. Bird, G.D. Schellenberg, **1995**, *Sci.*, 269, 5226, 970.
[12] G.K. Gouras, D. Tampellini, R.H. Takahashi, E. Capetillo-Zarate, *Acta. Neuropathol*., **2010**, 119, 5, 523.
[13] K. Iqbal, I. Grundke-Iqbal, *Alz. Dem.*, **2010**, 6, 5, 420.
[14] K. Iqbal, M. Flory, S. Khatoon, H. Soininen, T. Pirttila, M. Lehtovirta, I. Alafuzoff, K. Blennow, N. Andreasen, E. Vanmechelen, I. Grundke-Iqbal, *Ann. Neurol.*, **2005**, 58, 5, 748.
[15] W.A. Kukull, M. Ganguli, *Neurol. Clin.*, **2000**, 18, 4, 923.
[16] N. Scarmeas, J.A. Luchsinger, N. Schupf, A.M. Brickman, S. Cosentino, M.X. Tang, Y. Stern, *JAMA*, **2009**, 302, 6, 627-637.
[17] D. Iacono, *Neurol.*, **2009**, 73, 9, 665-673.
[18] Y. Stern, *Neuropsychol.*, **2015**, 47, 10.
[19] A. Martinez, M. Alonso, A. Castro, I. Dorronsoro, *Med. Res. Rev.*, **2002**, 22, 4, 373-384.
[20] L. Bertram, M.B. McQueen, K. Mullin, D. Blacker, R.E. Tanzi, *Nat. Genet.*, **2007**, 39, 1, 17.
[21] J. Wesson Ashford, J.A. Mortimer, **2002**, *J. Alz. Dis.*, 4, 3.
[22] http://www.aafp.org/afp/981101ap/sloane.html
[23] H.J. Koch, A. Szecsey, E. Haen, *Curr. Pharmaceut. Des.*, **2004**, 10(3), 253-259.
[24] P.N. Tariot, M.R. Farlow, G.T. Grossberg, S.M. Graham, S. McDonald, I. Gergel, *J. Am. Med. Assoc.*, **2004**, 291(3), 317-324.
[25] Y. Feng, X. Wang, *Oxid. Med. Cell. Longev*., **2012**, 472932.
[26] E.M. Ahmed, H.H. Estefan, S.F. Farrag, A.E. Salah, *Eur. Rev. Med. Pharmacol. Sci*., **2011**, 15(10):1131-1140.
[27] R. Bullock, *Br. J. Psychiat*., **2002**, 188, 135-139.
[28] R.W. Stackman, F. Eckenstein, B. Frei, D. Kulhanek, J. Nowlin, J.F. Quinn, *Exp. Neurol.*, **2003**, 184, 1, 510-520.
[29] T. Rognes, E. Seeberg, *Bioinformatics.*, **2000**, 16, 699-706.
[30] A.J. Mackey, T.A.J. Haystead, W.R. Pearson, *Mol. Cell. Proteomics*, **2002**, 1, 139-147.
[31] D. Xu, Y. Xu, E.C. Uberbacher, *Curr. Protein. Pept. Sci*., **2000**, 1, 1-21.