

Analysis and treatment of neurodegenerative disease

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Abstract

Tau-protein kinase (EC 2.7.11.26) is an enzyme that catalyzes the transferring a phosphate group to the side chain oxygen atom of serine or threonine residues. Tau-protein is an important protein that stabilizes microtubules of neurons in the central nervous system. Abundant neurofibrillary lesions made of hyperphosphorylated Tau protein constitute one of the defining neuropathological features of Alzheimer's disease. Tau proteins interact with tubulin to stabilize microtubules. Hyperphosphorylation of the tau protein (tau inclusions), however, can result in the self-assembly of tangles of paired helical filaments and straight filaments, which are involved in the pathogenesis of Alzheimer's disease. Defective Tau protein causes the dementia leading to Alzheimer's disease.

Keywords: neurons, dementia, lesions, helical filaments.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease of the central nervous system named for German physician Alois Alzheimer, who first described it in 1906. Alzheimer's disease (AD), also called Alzheimer disease, Senile Dementia of the Alzheimer Type (SDAT) or simply Alzheimer's, is the most common form of dementia^[1]. This incurable, degenerative, and terminal disease was first described by German psychiatrist and neuropathologist Alois Alzheimer in 1906 and was named after him. Generally, it is diagnosed in people over 65 years of age, although the less-prevalent early-onset Alzheimer's can occur much earlier. In 2006, there were 26.6 million sufferers worldwide. The prevalence of Alzheimer's is thought to reach approximately 107 million people by 2050^[1].

Although the course of Alzheimer's disease is unique for every individual, there are many common symptoms^[2]. The earliest observable symptoms are often mistakenly thought to be 'age-related' concerns, or manifestations of stress. In the early stages, the most commonly

recognised symptom is memory loss, such as difficulty in remembering recently learned facts^[14]. When a doctor or physician has been notified, and AD is suspected, the diagnosis is usually confirmed with behavioural assessments and cognitive tests, often followed by a brain scan if available^[3].

As the disease advances, symptoms include confusion, irritability and aggression, mood swings, language breakdown, long-term memory loss, and the general withdrawal of the sufferer as their senses decline^[10]. Gradually, bodily functions are lost, ultimately leading to death. Individual prognosis is difficult to assess, as the duration of the disease varies. AD develops for an indeterminate period of time before becoming fully apparent, and it can progress undiagnosed for years^[4]. The mean life expectancy following diagnosis is approximately seven years. Fewer than three percent of individuals live more than fourteen years after diagnosis^[9].

The cause and progression of Alzheimer's disease are not well understood. Research indicates that the disease is associated with plaques and tangles in the brain.^[11] Currently used treatments offer a small symptomatic benefit; no treatments to delay or halt the progression of the disease are as yet available^[13]. As of 2008, more than 500 clinical trials have been conducted for identification of a possible treatment for AD^[5], but it is unknown if any of the tested intervention strategies will show promising results^[15]. A number of non-invasive, life-style habits have been suggested for the prevention of Alzheimer's disease, but there is a lack of adequate evidence for a link between these recommendations and reduced degeneration^[7]. Mental stimulation, exercise, and a balanced diet are suggested, as both a possible prevention and a sensible way of managing the disease^[6].

MATERIALS AND METHODS:

Web based Tools used:

BLAST

BLAST is actually a family of programs (all included in the blastall executable). BLAST searches for high scoring sequence alignments between the query sequence and sequences in the database using a heuristic approach that approximates the Smith-Waterman algorithm^[18]. The exhaustive Smith-Waterman approach is too slow for searching large

genomic databases such as GenBank^[8]. Therefore, the BLAST algorithm uses a heuristic approach that is slightly less accurate than Smith-Waterman but over 50 times faster. [16-24]

ARGUS LAB:

ArgusLab is a molecular modeling program that runs on Windows 98, NT, and 2000^[12]. ArgusLab consists of a user interface that supports OpenGL graphics display of molecule structures and runs quantum mechanical calculations using the Argus compute server^[16]. The Argus compute server is constructed using the Microsoft Component Object Model^[17]

GOLD (Genetic optimization for ligand docking):

GOLD is a program for calculating the docking modes of small molecules in protein binding sites and is provided as part of the *GOLD Suite*, a package of programs for structure visualisation and manipulation (Hermes), for protein-ligand docking (GOLD) and for post-processing (GoldMine) and visualisation of docking results^[7]. Hermes acts as a hub for many of CCDC's products, for more information please refer to the Hermes product page.

RESULTS:

QUERY SEQUENCE OF TAU-PROTEIN KINASE:

```
>Q5TCY1|34-297
WKVLKKIGGGGGEIYEAMDLLTRENVALKVESAQQPKQVLKMEVAVLKKLQGGKHVCRF
IGCGRNEKFNYVVMQLQGRNLADLRRSQPRGTFTLSTTLRLGKQILESIEAIIHSVGF LHR
DIKPSNFAMGRLPSTYRKCYMLDFGLARQYTNNTGDVRP PRNVAGFRGTVRYASVNAHKN
REMGRHDDLWSLFYMLVEFAVGQLPWRKIKDKEQVGMIEKEYEHRMLLKHMPSEFHL FLD
HIASLDYFTKPDYQLIMSVFENSM
```

PRIMARY SEQUENCE ANALYSIS BY BIOEDIT

Protein: Q5TCY1|34-297
 Length = 264 amino acids
 Molecular Weight = 30578.10 Daltons

Amino Acid	Number	Mol%
Ala A	13	4.92
Cys C	3	1.14
Asp D	12	4.55
Glu E	15	5.68
Phe F	14	5.30
Gly G	20	7.58
His H	9	3.41
Ile I	11	4.17
Lys K	21	7.95
Leu L	28	10.61
Met M	12	4.55
Asn N	10	3.79
Pro P	9	3.41
Gln Q	12	4.55
Arg R	20	7.58
Ser S	13	4.92
Thr T	11	4.17
Val V	18	6.82
Trp W	3	1.14
Tyr Y	10	3.79

Figure.1: The above graph is showing amino acid composition of Query sequence, The amino acid LEU is [25-29] present highest percentage compared to other residues and the molecular weight of the protein is 10.61.

Amino acid composition:

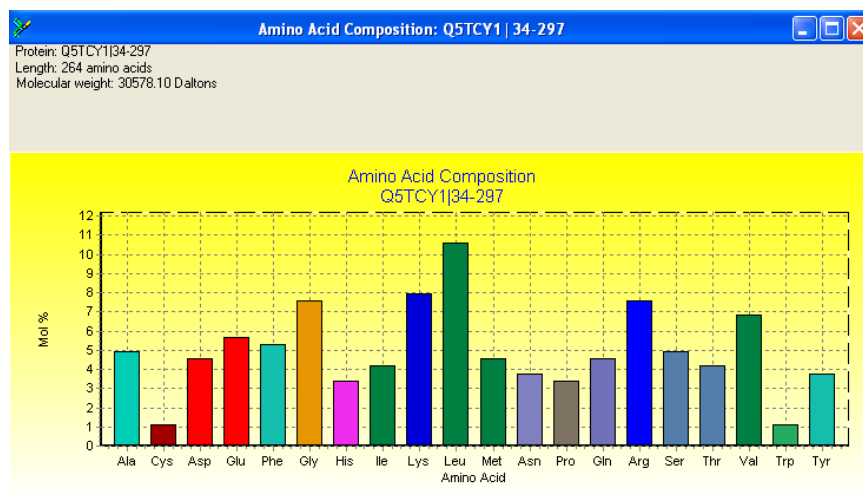


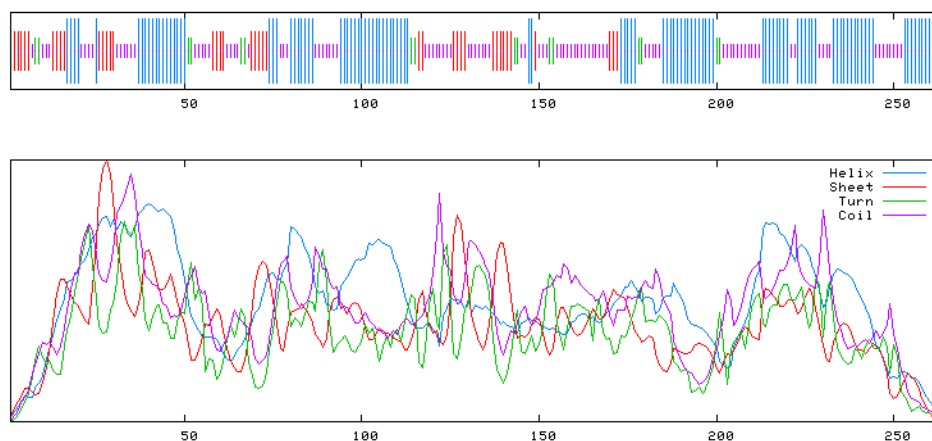
Figure.2: The above graph is showing amino acid composition of Query sequence, The amino acid Leu is present highest percentage compared to other residues.

SECONDARY STRUCTURE PREDICTION: SOPMA

SOPMA RESULT:

SOPMA :

Alpha helix	(Hh) :	108 is 40.91%
3 ₁₀ helix	(Gg) :	0 is 0.00%
Pi helix	(Ii) :	0 is 0.00%
Beta bridge	(Bb) :	0 is 0.00%
Extended strand	(Ee) :	41 is 15.53%
Beta turn	(Tt) :	16 is 6.06%
Bend region	(Ss) :	0 is 0.00%
Random coil	(Cc) :	99 is 37.50%
Ambiguous states	(?) :	0 is 0.00%
Other states	:	0 is 0.00%



Parameters :

Window width : 17

Similarity threshold : 8

Number of states : 4

GOLDRESULTS:

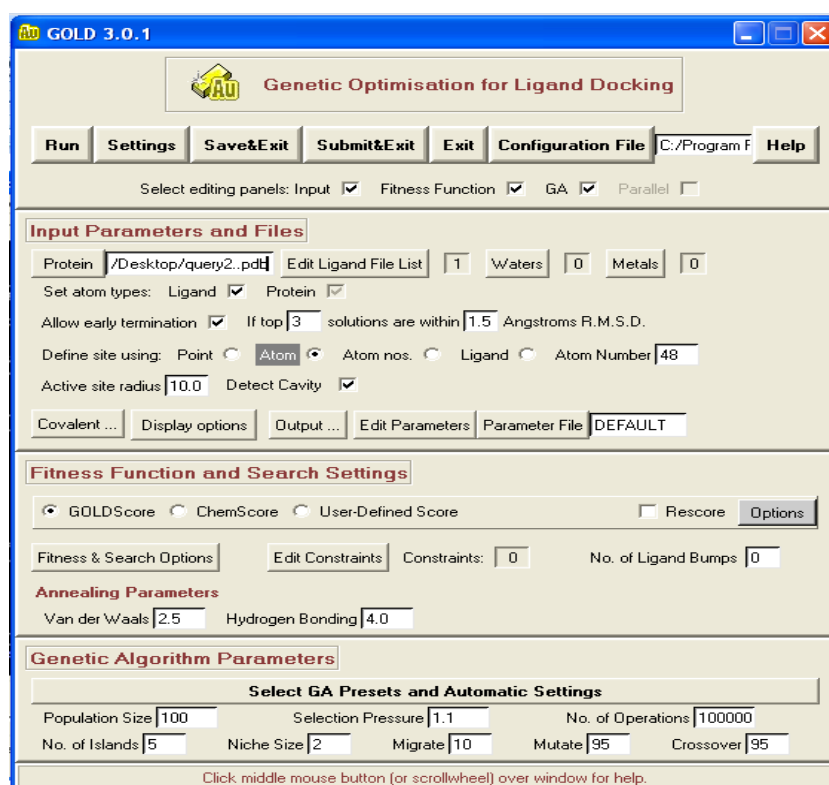


Figure.3: SOPMA results

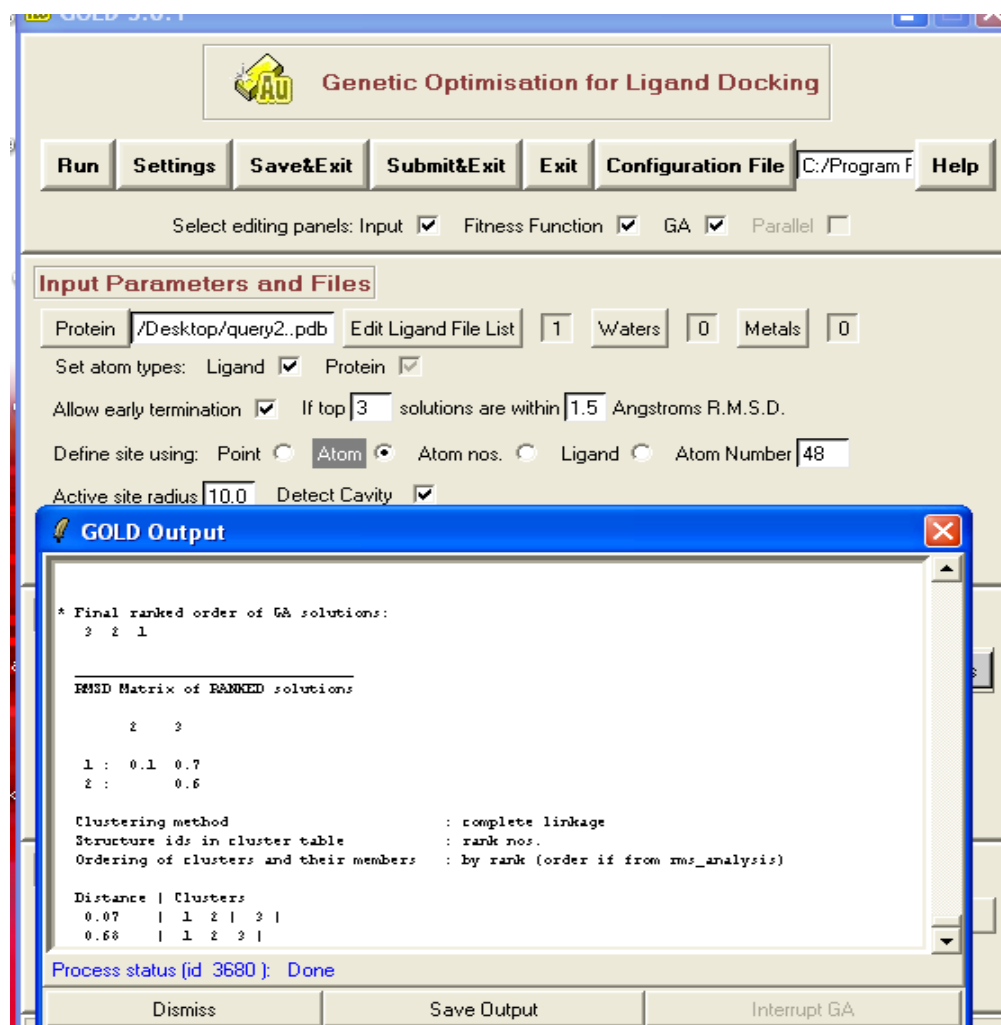


Figure 4: best ligand pose were found based on Rank order ,in the above diagram indicating 3 is the best one

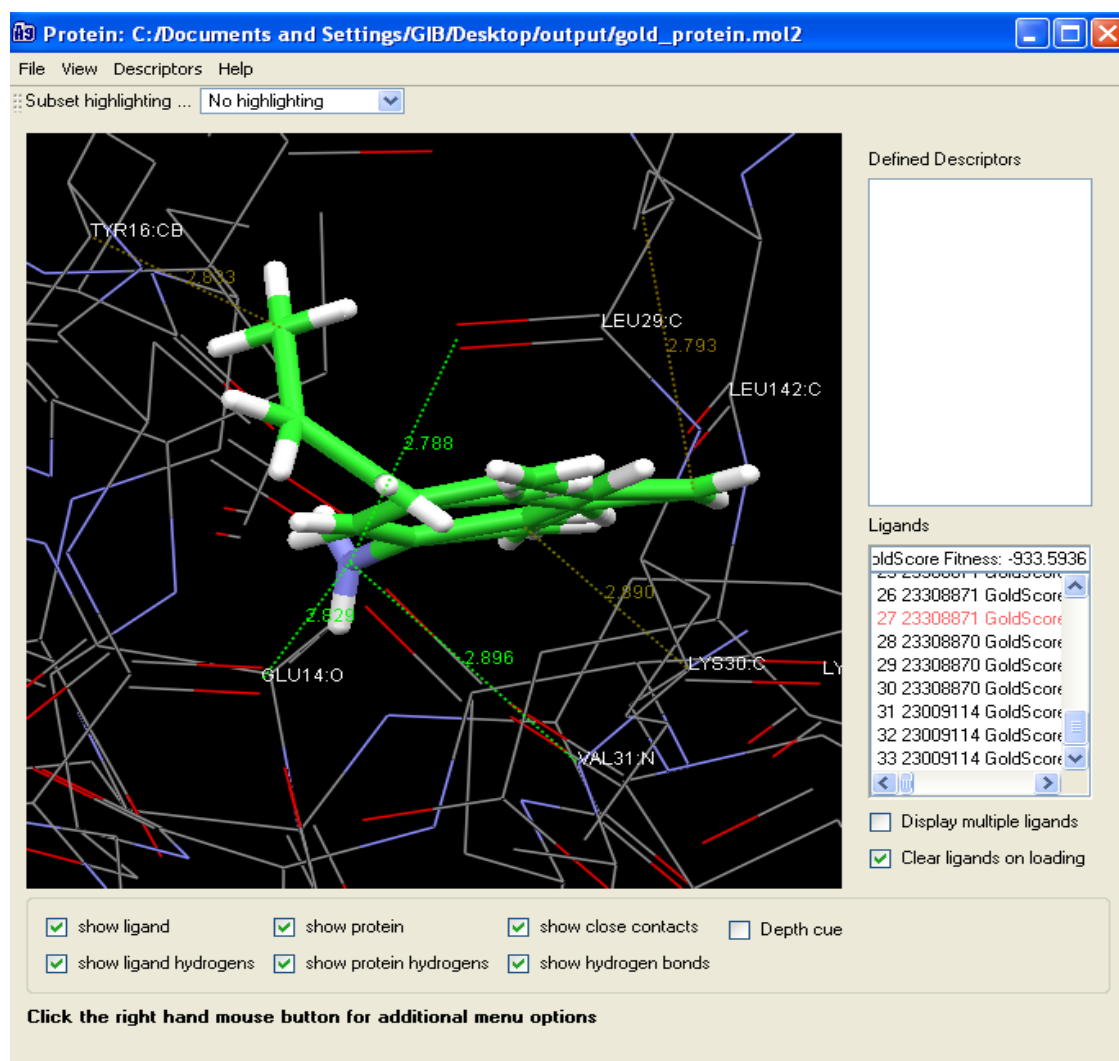


Figure 5 : The drug molecule was interacting with active site residues Hbonds interaction formed between Glu14,Val 31,Leu29 [29-45]

Conclusions

Present study we have modeled TAU-PROTEINKINASE which has key functional role in causing the Alzheimer disease. We selected the template by using BLAST tool and the template shown high similarity with its template 1CKA shows high accuracy. The modeled structure was validated stereo chemically after the energy minimization process by NAMD and modeled structure was shown very less RMSD with its template. The stable structure is used for docking studies with L-Glutamic acid, Memantine, Tacrine, Ropinirole in ARGUS LAB. Among all of them Memantine got least energy (-51.31263) and high affinity. Further studies we have taken similar compounds of Memantine (40 compounds) and performed

flexible docking studies in GOLD, there we got better drug molecule (5R,7R)-3-propyladamantan-1-amine it was shown strong hydrogen bonding interactions with Glu14, Val 31, Leu 29 .

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