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"Designing of Potent Drug to Target Alpha Synuclein in Parkinson's Disease"

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***Abstract**: Parkinson disease is a chronic and progressive neurodegenerative disorder characterized by muscle rigidity, tremor and bradykinesia. The central aspect of Parkinson disease involves dysmetabolism of specific proteins resulting in aggregation, aborted protein degradation and/or formation of Lewy bodies. Parkinson disease involves the progressive loss of dopamine-containing neurons from the substantia nigra. The study of involvement of a protein named alpha synuclein in disease and the ligands targeting it, to possibly find a drug to cure the disease. Mutation in α-synuclein can lead to misfolding, aggregation and resistance to protein degradation. In silico approach to design a drug for Parkinson's disease is employed to obtain the outcome. Alpha synuclein (PDB id :1XQ8) ,the receptor molecule, is docked with the ligands that sustained the screening procedure exerted by the software suite. Ligands are screened on the basis of numerous criteria such as hepatotoxicity, absorption level, carcinogeniticity and so on. The drug with the lowest docking energy is considered ideal. It may be chosen for further clinical trials and can finally go for FDA approval.*

***Keywords:** Parkinson disease , Alpha synuclein, Docking, ADME/Tox,*

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I. Introduction

Parkinson's disease is a degenerative disorder of the central nervous system. It results from the death of dopamine-containing cells in the substantia nigra, a region of the midbrain; the cause of cell-death is unknown. Early in the course of the disease, the most obvious symptoms are movement-related, including shaking, rigidity, slowness of movement and difficulty with walking and gait. Later, cognitive and behavioural problems may arise, with dementia commonly occurring in the advanced stages of the disease. Other symptoms include sensory, sleep and emotional problems.

PD is more common in the elderly with most cases occurring after the age of 50. Parkinson's disease is often defined as a parkinsonian syndrome that is idiopathic (having no known cause), although some atypical cases have a genetic origin. Many risk and protective factors have been investigated: the clearest evidence is for an increased risk of PD in people exposed to certain pesticides and a reduced risk in tobacco smokers. The pathology of the disease is characterized by the accumulation of a protein called alpha-synuclein into inclusions called Lewy bodies in neurons, and from insufficient formation and activity of dopamine produced in certain neurons of parts of the midbrain. Diagnosis of typical cases is mainly based on symptoms, with tests such as neuroimaging being used for confirmation. Estimates suggest that approximately 750,000 Americans have PD.

Signs and symptoms

Numerous symptoms are witnessed in Parkinson's disease. The various signs and symptoms are Motor Symptoms-Cardinal,Non motor symptoms- Neuropsychiatric ,Sleep,Autonomic, Gastro intestinal , Neuro- opthalmological

Diagnosis

Parkinson's disease is diagnosed by a careful neurological examination, testing movements, coordination, reflexes, and other aspects of function. Several specialized tests may be used, including imaging of the brain with magnetic resonance imaging (MRI) or positron emission tomography (PET). These are not essential to diagnosis in most cases, but may help to confirm the diagnosis in difficult cases and to distinguish PD from similar diseases such as progressive supranuclear palsy.

In-silico approach opens up the perspective to target the particular protein that plays a crucial role in the causation of PD. The major protein involved in the disease is **alpha-synuclein.** Alpha-Synuclein is a 140 amino acid protein abundantly expressed in presynaptic terminals of vertebrates. One of its normal functions is

to regulate dopamine transporter activities as shown in **Fig 1** .This protein contains an NAC region that is prone to aggregate, especially under oxidative stress. The aggregated a-synuclein can inhibit the function of 26S proteasome which is important for the clearance of misfolded proteins and other target molecules. The dysfunction of proteasome will contribute to cell death. Two mutations, A53T and A30P, in a-synuclein have been identified in families with early-onset familial Parkinson's disease. These mutations may accelerate the aggregation of a-synuclein.

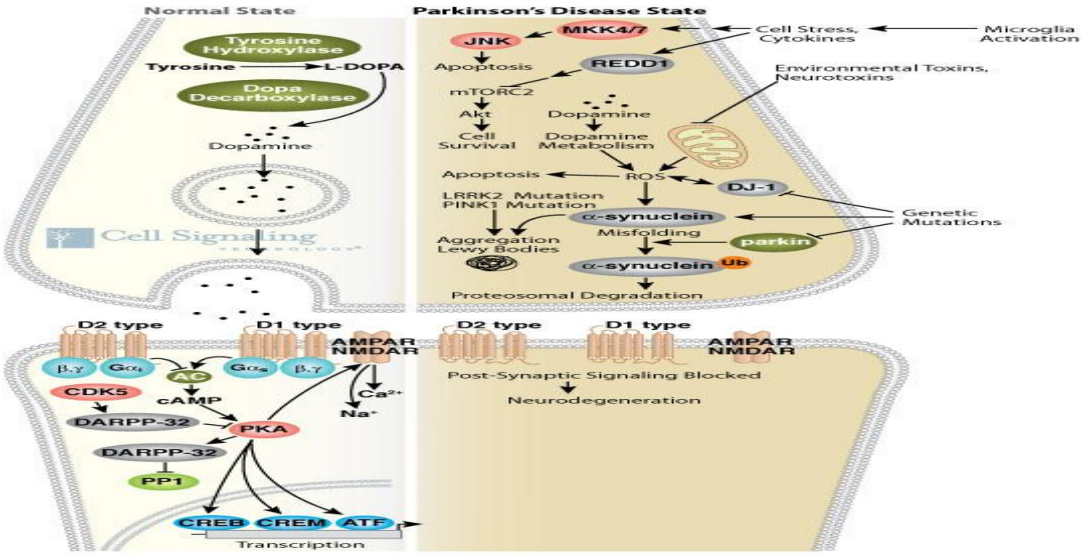

Fig 1

II. Experimental

Protein analysis

Proteins involved in disease are explored through **GeneCards**(provided gene-centric information, automatically mined and integrated from a myriad of data sources) and the most commonly diagnosed protein (alpha synuclein) is selected .The sequence, function and structure of alpha-synuclein is extracted from **NCBI**. **BLAST** is performed employing numerous model organisms. BLOSUM matrix used in BLAST is in accordance with the hierarchy of organisms i.e. BLOSUM 80 with higher vertebrates, BLOSUM 62 with invertebrates and lower vertebrates and BLOSUM 45 in case of microbes. Evolutionary relatedness of model organisms to the query protein is estimated with the help of **SDSC Biology Workbench (**The SDSC Workbench is a web-based tool for biologists that allows to search many popular protein and nucleic acid sequence databases) .Color coded representation of the phylogenetic tree can also be obtained in the form of texshade and boxshade. Conformatory tools like SOPMA, PROTPARAM, PHYRE, JPred, CPH Model were used to derive the structurally based information of the query protein. PDB ids are validated through different tools and the pdb id 1XQ8 is confirmed. So **1XQ8** is found to be the receptor protein.

Simulation of Receptor

Energy minimization of receptor takes place in **Accelrys Discovery Studio** is a software suite of life science molecular design solutions for computational chemists and computational biologists that makes it easier to examine the properties of large and small molecules, study systems, identify leads and optimize candidates). Binding site of the receptor (1XQ8) is edited and charmM and forcefield is applied. Algorithm used in minimization process is Conjugate Gradient. Steps are increased with an increment of 200 until the energy stabilizes. The final value of energy of receptor after minimization is: -6886.47162 kcal/mol.

Creation of library of compounds and Virtual Screening

Myriad of compounds are selected from natural sources and GeneCards. Reviewing the literature and related articles about the disease and treatment assists in selecting the compound from natural sources. The chosen compounds are enlisted and then screened on the basis of Lipnk. 5 Rule.(Bioassay Activity).

ADME Test/TOPKAT on screened compounds

Compounds are screened on the basis of the values of hepatotoxicity and absorption level in ADME in **Accelrys Discovery Studio**. ADME is the test for Absorption Distribution Metabolism Excretion capacities of drugs. If the values of ADMET Hepatotoxicity and ADMET Absorption level are equal to zero, then the compound is selected further for TOPCAT .Non carcinogenicity is the foremost criteria of this screening test. Other parameters are that are considered for testing are**:** Rat Oral LD50, Developmental Toxicity Potential (DTP),

Skin Irritation, Ocular Irritancy SEV/MOD vs MLD/NON. Drug candidates are thus finalized for energy minimization on the basis of these results.

Simulation of drugs

Energy optimization of candidate molecules that survive the pre-mentioned screening tests takes place in **Accelrys Discovery Studio**. Algorithm used in minimization process is Conjugate Gradient. Steps are increased with an increment of 200 until the energy stabilizes.

Docking

Drug candidates that qualify the mentioned tests are docked with the receptor (1XQ8) using CDOCKER available on **Accelrys Discovery Studio** 50 poses were obtained (10 for each ligand).One with the minimum cdocker energy is considered to be suitably the best out of the five candidates. Interaction of receptor with that particular drug is visualized and analyzed.

III. Result And Discussion

Based on docking energies of potential drug candidates as shown in **Table 1**, one with the lowest CDOCKER energy is considered ideal. As per the study conducted, **Delonal** is the potent drug target for the cure of the disease.

NAME	TOP HITS	CDOCKER ENERGY	CDOCKER INTERACTION ENERGY	POSE NUMBER
Atropine	10	-14.4708	27.1402	10
Delonal	10	-45.6144	23.9657	10
fatty_acid	10	32.6051	31.8937	10
Levamfetamine	10	21.8091	25.7744	10
Q10	10	-30.6298	23.6332	10

Table 1

The results of TOPCAT and ADMET of delonal are shown in fig 2 and fig 3 respectively .

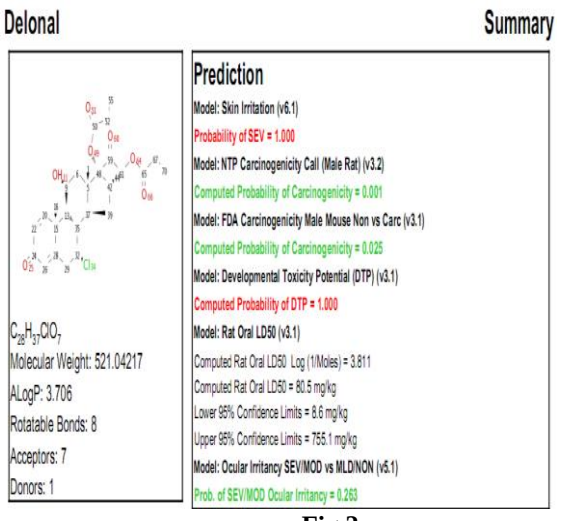

Fig 2

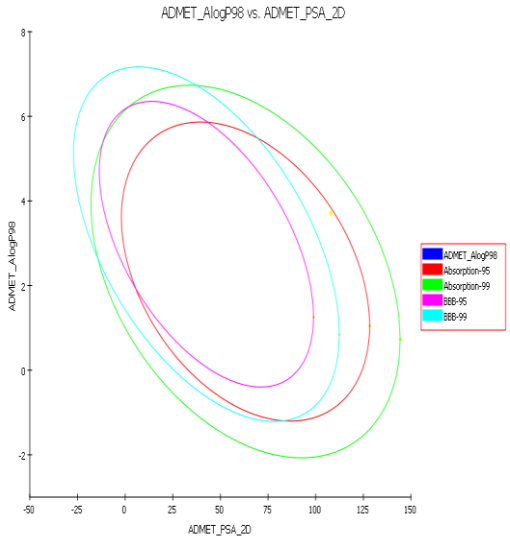

Fig 3

Docking of Delonal with 1XQ8 shows the degree or extent of their interaction. Docking as in **Accelrys Discovery Studio** is shown in fig 4.

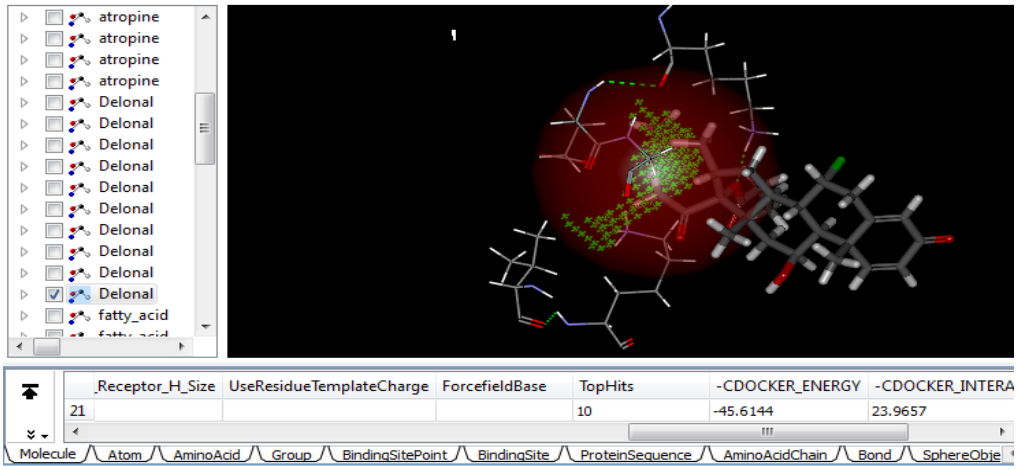

Fig 4

IV. Conclusion

Parkinson's disease is a neurodegenerative disease whose treatment is possible with drugs like levodopa, anti-anticholinergic drugs and dopamine agonists. In–silico approach to drug designing can result in more drugs that could be possibly used to cure the disease. It was found that alpha synuclein plays a vital role in causing the disease so it was selected as the receptor molecule.PDB id of receptor was 1xq8.Docking was performed in **Accelrys Discovery Studio** to filter out the best drug on the basis of docking energy. Thus paper successfully found a drug named Delonal that could undergo clinical trials and other screening procedures.

Acknowledgement

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[7] α-Synuclein and Parkinson's disease, alessandra recchia,patrizia debetto, aless andro negro ,diego guidolin, stephen d. skaper and pietro giusti·Alpha-synuclein (α-syn) is a small soluble protein expressed primarily at presynaptic terminals in the central nervous system.

TABLE OF FIGURES

S.No.	Abbreviation	Explanation
1.	Accl. Dis.	Accelrys Discovery
2.	Lipnk.	Lipinski's

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