Develop The New Carbidopa Derivatives For Parkinson's Disease Through Protein-Ligand Interactions Studies

V.Uma Rani[1], K Sarath Chandra[2], A.Maheshwar[3]
[1]Associate Professor, Dept of Information technology
[2]Lecturer, Dept of Information technology
Dept of Information technology
[1, 2, 3] Kukatpally, Hyderabad,India3

Abstract- *Parkinson's disease is a long term disease which mainly affects the motor system that is central nervous system. Some of the symptoms are rigidity, thinking problems, slowness in movement and difficulty with walking. Carbidopa is identified as potential target protein for Parkinson's disease and carbidopa analogs are identified as a potential inhibitors for Parkinson's disease. Carbidopa analogs will be developed through Molecular Modeling techniques including Molecular Dynamics, Geometry optimization, Physio-chemical properties and Monte-carlo simulations.*

Keywords- Parkinson's disease, Carbidopa, Hyperchem

I. INTRODUCTION

Parkinson's disease is a long term disorder of the central nervous system that affects the motor system. In the beginning phases of ailment a few side effects happen such are for the most part unbending nature, shaking, trouble with strolling, and gradualness in development, behavioral and figuring issues may likewise happen. Dementia turns into the most widely recognized in the beginning phases of the infection. Tension and Depression are additionally normal happening in more than 33% of individuals with Parkinson's sickness. Different side effects incorporate rest, passionate and tangible issues. Every one of these side effects together are called "Parkinsonism", or a Parkinsonian disorder".

II. METHODOLOGY

2.1 Computer Aided Drug Design Approaches:

Computational appraisal of the coupling fondness of compound inhibitors preceding amalgamation is an imperative part of PC supported medication outline (CADD) ideal models. In this examination, the molecular mechanics (MM) technique is utilized for the estimation of relative restricting affinities of inhibitors to a catalyst. Subjective forecasts of relative restricting affinities of Beta Secretase inhibitors utilizing MM technique are talked about. The outcomes demonstrate that the MM based strategy is valuable in the subjective estimation of relative restricting affinities of protein inhibitors preceding synthesis.

2.2 COMPUTER AIDED DRUG DESIGN:

High determination X-ray structure of 1W6F is utilized to examine the interactions of potential ligands with the allosteric binding site and plan new analogs. Techniques used to outline inhibitors range from graphical perception of the ligand in the binding site cavity for the estimation of relative binding affinities utilizing molecular mechanics strategy in conjunction with the approach.

2.3 LEAD GENERATION:

The following three methods are often used for discovery of lead compounds.

2.3.1 De novo drug design methods:

This technique requires a 3D structure of the objective protein. In a large portion of the cases successes are accounted for however general De nova drug design decides an objective and not reality.This strategies have been utilized to produce another structure by along these lines including particle pieces to a creating structure, by joining usefulness to a splendidly measured atom scaffold.These techniques can be utilized making different molecular structures.

2.3.2 Database search methods:

In a portion of the cases, new lead compounds have been perceived by examining structures that are found in surely understood standard databases for a specific structure includes by applying 3D structure of target protein with perceived active site.

2.3.3 Combinatorial methods:

Combinatorial techniques doesn't require target protein structure which is for the most part fundamental for other two strategies. Combinatorial science makes it simpler to deliver an expansive library of structures with large great arrangement of assorted variety.

III. PERFORMING MOLECULAR MECHANICS FOR THE MOLECULES

Finding the energy of the molecules using various techniques in hyperchem 7.5, such as:

3.1 Molecular dynamics,
3.2 Langevin dynamics and
3.3.Monte carlo dynamics.

3.1 MOLECULAR DYNAMICS:

Molecular elements is predominantly used to acquire the naturally visible information by testing a tiny reproduction over a drawn out stretch of time. It is valuable additionally to track geometric amounts and vivacious as the reproduction continues to check whether the framework has sufficiently settled for examining to be measurably legitimate or not.

3.2 LANGEVIN DYNAMICS:

A Langevin with little contrasts because of the presentation of the friction coefficient. The Langevin Dynamics technique makes the development of particles subjected to arbitrary frictional forces and collisions number of rotatable bonds in the inhibitor. Quantitative descriptors in view of atomic Flow reenactment is composed similarly as a Sub-atomic Progression reproduction, with little contrasts because of the presentation of the friction coefficient. The Langevin Flow technique makes the development of atoms subjected to irregular frictional powers and collision number of rotatable bonds in the inhibitor. Quantitative descriptors in view molecular.

3.3 MINIMIZATION METHODS:

At times expectations of inhibitor binding has been construct exclusively in light of a visual analysis of structures with no force field counts. These strategies depended on graphical analysis of highlights, for example, steric and electronic correlative of the docked inhibitor to the objective protein, the degree of covered hydrophobic surface and can be utilized to demonstrate solvated frameworks without unequivocally including dissolvable particles. It gives data on the development time of the atomic framework. The Monte Carlo technique is utilized to reenact balance properties strategies have been utilized to produce observational scoring capacities got from crystal structure information and trial shape and network based energetics have demonstrated helpful in drug design. Further developed strategies have been utilized to produce exact scoring capacities derived from crystal structure information and trial binding affinities.

TARGET STRUCTURE:

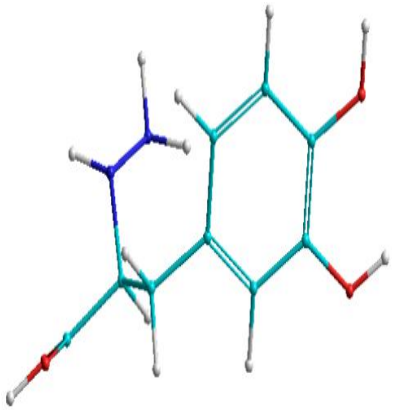

Fig 1. STANDARD LIGAND - (CARBIDOPA)

Total Energy = 139.789932 Kcal/mol ,
Gradient = 12.239537
Minimized energy = 13.612422 Kcal/mol,
Gradient = 0.0811382
Molecular Dynamics:
Time = 60ps,
Ekin = 44.9225 Kcal/mol ,
Epot = 40.8434 Kcal/mol,
Temp = 308.104k

The result of target protein that is Carbidopa is obtained by performing minimization method using the computer application hyperchem.

List of ligands

Sl.no.	Inhibitor	R1
1	Inhibitor-1	BR
2	Inhibitor-2	CF3
3	Inhibitor-3	CH2CH3
4	Inhibitor-4	CH2OH
5	Inhibitor-5	CL
6	Inhibitor-6	H
7	Inhibitor-7	I

Table 1: List of ligands used as carbidopa derivatives

IV. PROJECT RESULTS (Docking)

_____Ligands	Fitness	S(hb_ext)	S(vdw_ext
BR	48.11	15.59	32.51
CF3	40.26	12.28	24.05
CH2CH3	60.26	16.79	38.62
CH2OH	42.33	7.76	26.64
CL	19.20	1.23	10.23
H	25.01	8.64	15.35
I	16.63	0.6	14.01
standard	42.18	13.20	21.27

TABLE 2: PROTEIN-LIGAND INTERACTIONS

Above results are obtained after performing Protein-ligand interactions (Docking)

where Fitness = S(hb_ext) + 1.3750*S(vdw_ext) + S(hb_int) + 1.0000*S(hb_ext)

V. CONCLUSION

A comparison of the calculated binding energies for structurally similar inhibitors to carbidopa molecule, indicates that the protein-ligand interaction (docking) studies would help better in identifying the suitable analogues.

In this project, the inhibitor 3 with the substituents R1-CH2CH3 is identified as the most suitable analogues of Carbidopa in the present study. This need to be further analysed and evaluated in laboratory to successfully discover a new drug for the deadly disease, Parkinson's disease.

REFERENCES

[1] Purification and biochemical characterization of hepatic arylamine N- acetyltransferase from rapid and slow acetylator mice: identity with arylhydroxamic acid N, O-acyltransferase and N-hydroxyarylamine O-acetyltransferase,SS Mattano, S Land, CM King and WW Weber,Department of Pharmacology, University of Michigan Medical School, Ann Arbor 48109

[2] Disseminated tuberculosis with multiple intracerebral tuberculomas in a patient with anorexia nervosa.Int J Eat Disord. 2007 Jan 29 Ahn JY, Chang JH, Kim KS, Kim WJ.58

[3] The Glycosyltransferases of Mycobacterium tuberculosis; Roles in the SynthesisofArabinogalactan ipoarabinomannan and other gyc oconjugate Berg S, Kaur D, Jackson

[4] Crawford JT. New technologies in the diagnosis of tuberculosis. Semin Respir Infect 9 : 62-70, 1994.

[5] Centers for Disease Control and Prevention. Update: nucleic acid amplification tests for tuberculosis Morb Mortal Wkly Rep 49:593-594