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In-silico characterization for Multiple sclerosis: A special emphasis on Tetrakis (4-aminopyridine-$_k$N^1) dichloridocopper (II) monohydrate with sphingosine 1-phosphate lyase

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ABSTRACT

This Molecular docking study aimed to identify the binding site of protonated ligand Tetrakis (4-aminopyridine-$_k$N^1) dichloridocopper (II) monohydrate with sphingosine 1-phosphate lyase (S1PL) for the treatment of multiple sclerosis. With the aid of MGL Tools – 1.4.6, the molecular docking analysis shows that the oxygen atom of phenolic O-H group of tyrosine TYR526 interacts with the hydrogen atom of NH group of the ligand. Oxygen atom of water molecule present in the ligand interacts with hydrogen atom of NH group present in glutamine GLN476. In-silico docking study of a protein ligand interaction resulted in -6.11 kcal mol^{-1} and -6 kcal mol^{-1} free energy values for the GLN476 - ligand and TYR526 – ligand respectively and the corresponding median Inhibition concentration IC_{50} value found to be 8µg/ml. This molecular docking study show good inhibitory interaction effect for ligand for the treatment of multiple sclerosis.

Introduction

In the year 2004, Strupp M et al., said that the Patients with episodic ataxia type 2 (EA2) can often be successfully treated with acetazolamide. The authors report three patients with EA2 (two with proven mutations in the CACNA1A gene) whose attacks were prevented with the potassium channel blocker 4-aminopyridine [1]. *In the year 2006*, Susan I.V. Judge and their coworkers suggested that the Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) characterized by demyelination, with a relative sparing of axons. In MS patients, many neurologic signs and symptoms have been attributed to the underlying conduction deficits [2].

Mayo L and their team suggested that although the cause of this disease remains unknown, it is evident that lymphocytes cross the blood brain-barrier and cause inflammation around the axons of the brain and the spinal cord, leading to demyelination, neuro axonal injury, astrogliosis, and finally neuro degeneration [3]. Based on this, Sinthiya A and their coworkers in 2008 reported the structure of Tetrakis (4-aminopyridine-κ*N* ^{1}) dichloridocopper (II) monohydrate [4]. In the year of 2014, Weiler S and their team identified that the Sphingosine 1-phosphate (*S1P*) *lyase* has recently been implicated as a therapeutic target for the *treatment of multiple sclerosis* (MS) [5]

Here we report a novel compound that inhibit enzyme activity of purified sphingosine-1-phosphate lyase, as seen in the co-crystal structure with human sphingosine-1-phosphate lyase, bind to the active site of the Tetrakis (4-aminopyridine-κ*N* ^{1}) dichloridocopper (II) monohydrate [4] using molecular docking. The software MGL Tools – 1.4.6 helps to predict the protein – ligand interaction.

Materials and Methods

The bioactive ligand [4] involved in this work is shown in figure 1. The protein structure Figure 2 of Spingosine 1-phosphate lyase (PDB ID: 4Q6R) is retrieved from PDB database. All water molecules removed from all protein structure and add with Koll Mann charges was assigned. Through which hydrogen were added, side chains are optimized for hydrogen bonding. The energy minimized protein is then saved in PDB format. Using MGL Tools – 1.4.6 nonpolar hydrogen are merged. AutoDock atom type AD4 and Gasteiger charges are assigned and finally saved in protein.pdbqt format [6].

In the present case, a grid of regularly spaced points is defined for optimized protonated ligand molecule by the AutoDock in order to perform the interaction of the protein-ligand. The defined grid must be within the region of interest in the macromolecule. The potential energy got from the interaction is stored in one grid point for each atom in the ligand [7]. In this present investigation, the S1PL pore forms the central cavity for allowing the ligand to enter. *The grid parameters*: 80, 80 and 60 points in the x, y and z dimensions respectively with *Grid point spacing* : 0.375 Å .

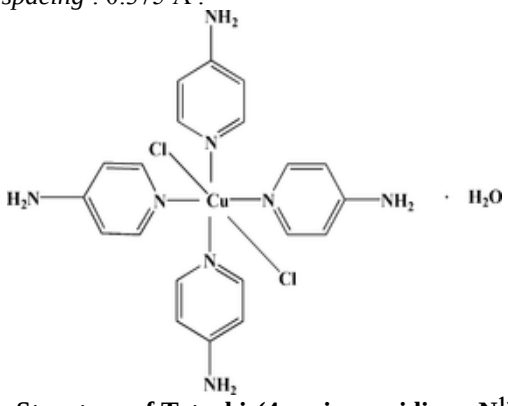

Fig 1. Structure of Tetrakis(4-aminopyridine-$_\kappa$N^1) dichloridocopper(II)monohydrate ligand

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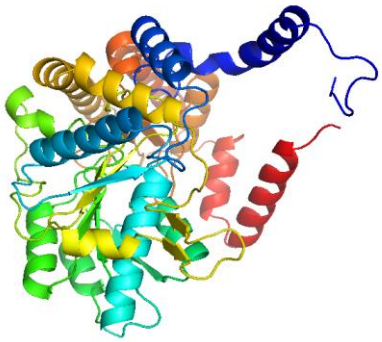

Fig 2. The three dimensional structure of S1PL

Docking of macromolecules are performed using an empirical free energy function and Lamarckian Genetic Algorithm, with an initial population of 250 randomly placed individuals, a maximum number of 106 energy evaluations, a mutation rate of 0.02, and a crossover rate of 0.80. One hundred independent docking runs are performed for each ligand. Results differing by 2.0 Å in positional root-mean square deviation (RMSD) are clustered together and represented by the result with the most favorable free energy of binding. AutoDock default values are used for the remaining parameters.

Result and discussion

Among the several bonding sites, only two common binding sites within the pore appear in S1PL after applying the molecular docking. Figure 3 shows the three dimensional structure of the complex between Tetrakis (4-aminopyridine-$_kN^1$) dichloridocopper (II) monohydrate and the sphingosine-1-phosphate lyase. Figure 4 shows the Binding mode and hydrogen bond interaction of ligand Tetrakis (4-aminopyridine-$_kN^1$) dichloridocopper (II) monohydrate in the active site of Human sphingosine 1-phosphate lyase along with interacting amino acids residues. The first binding zone is corresponds to glutamine residue (residual number 476). The second binding zone corresponds to tyrosine residue (residue number 526). Thus we identified that these two are the putative receptor site on the basis of electronic and structural data.

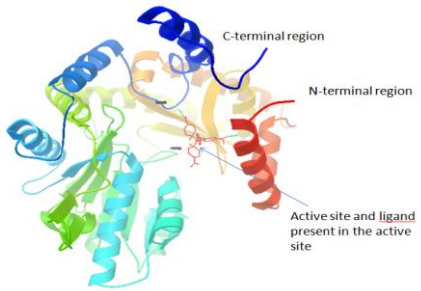

Fig 3. Three dimensional structure of the complex between protein and ligand

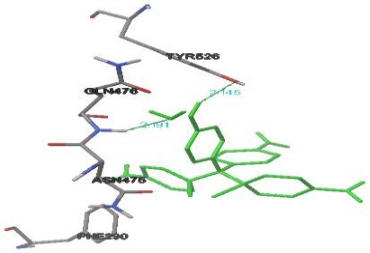

Fig 4. The Binding mode and hydrogen bond interaction of ligand Tetrakis (4-aminopyridine-$_kN^1$) dichloridocopper (II) monohydrate in the active site of Human sphingosine 1-phosphate lyase along with interacting amino acids residues.

Table 1 show that the Hydrogen bonding interaction with ligand studied during molecular docking. The oxygen atom of phenolic O-H group of tyrosine TYR526 interact with the hydrogen atom of NH group of the ligand with H…O distance 2.145Å and oxygen atom of water molecule present in the ligand interacts with hydrogen atom of NH group present in glutamine GLN476 with H…O distance 2.191Å. Table 2 shows the binding energies in (kcal mol^{-1}) of the protonated ligand for two binding sites. The data corresponds to the minimum energy conformations located by a Lamarckian genetic algorithm on the AutoDock force field and the ligand bind preferentially to the GLN476 and TYR526 site with IC_{50} value inhibition constant 8 µg / ml.

Table 1. Hydrogen bonding interaction with ligand studied during molecular docking exercise

S.No	Interacted Amino acid	Bonding	Donor	Acceptor	d(H…O)Å
1	Tyrosine TYR526	N-H…O	Nitrogen atom of ligand	Oxygen atom of TYR526	2.145
2	Glutamine GLN476	N-H…O	Nitrogen atom of GLN476	Oxygen atom of water molecule in ligand	2.191

Table 2. Binding energies of the protonated ligand for two binding sites

Putative receptor	Docking score (kcal mol^{-1}) Lowest binding energy
Glutamine GLN476	-6.11
Tyrosine TYR526	-6

Conclusion

In this present investigation, a molecular docking is performed to investigate the binding site of Tetrakis (4-aminopyridine-$_kN^1$) dichloridocopper (II) monohydrate ligand to the sphingosine 1-phosphate lyase. The N-H group is well suited to act as hydrogen donors in hydrogen bonded complexes. The present result suggests that the ligand binds with sphingosine-1-phosphate lyase by forming two hydrogen bonds. In-silico docking study of a protein ligand interaction resulted in -6.11 kcal mol^{-1} and -6 kcal mol^{-1} free energy values for the GLN476 - ligand and TYR526 – ligand respectively and the corresponding median Inhibition concentration IC_{50} value found to be 8µg / ml. This molecular docking study show good inhibitory interaction effect for ligand for the treatment of multiple sclerosis.

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