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DOCKING STUDY OF SOME GLUTAMIC ACID DERIVATIVES AS POTENT ANTINEOPLASTIC AGENTS

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ABSTRACT

Objective: In the paper we have taken the protein Histone Deacetylase and identified the glutamic acid analogs that were used against Cancer.Here, out of 90 glutamic acid analogs, 20 better active analogs energy value was shown.

Methods: For the bioinformatics study of glutamic acid analogs, Histone Deacetylase protein preparation and optimization, ligand preparation and optimization and docking simulations was carried out by using biological databases like PubChem, Drug Bank, Protein Data Bank and software's like Arguslab, Weblab viewer lite program, molinspiration, FROG ADME Tox.

Results: It was observed using RasMol that the amide groups present in the analogs was the site of binding to the receptor and methyl group present in the analogs, which resulted in a decrease in the energy values.When the modified drugs were docked against the protein Histone Deacetylase (HDAC) the energy value obtained was ANALOG 1 (-10.370504) and ANALOG 2 (-10.218276).

Conclusion: Among the 90 analogs of glutamic acid, 20 analogs showed an increase in the energy values (-10.370504 to -7.833821) which means these analogs were more compatible with the receptor and required less energy to binding with the receptor.

Keywords: Glutamic acid, Anti-cancer, Docking, Bioinformatics

INTRODUCTION

Cancer known medically as a malignantneoplasm, is a broad group of various diseases, all involving unregulated cell growth. In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body. The cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream. Most cancers form a tumor but some, like leukemia, do not. Cancer affects people at all ages with the risk for most types increasing with age [1]. Cancer caused about 13% of all human deaths in 2007 (7.6 million) [2, 3].

Glutamic acid is critical for proper cell function, but it is not considered an essential nutrient in humans because the body can manufacture it from simpler compounds [4, 5]. In addition to being one of the building blocks in protein synthesis, it is the most widespread neurotransmitter in brain function, as an excitatory neurotransmitter and as aprecursor for the synthesis of GABA in GABAergic neurons. It increases the brain function and mental activity. It detoxifies the brain from ammonia by attaching itself to nitrogen atoms in the brain and also helps in the transportation of potassium across the blood–brain barrier. It is conjectured that glutamate is involved in cognitive functions like learning and memory in the brain, though excessive amounts may cause neuronal damage associated with diseases like amyotrophic lateral sclerosis, lathyrism and Alzheimer's disease [6]. Glutamate activates both ionotropic and metabotropic glutamate receptors [7].

Glutamine is the respiratory fuel of tumor cells. Glutamic acid and glutamine both are inter convertible. Glutamic acid plays an important role in the biosynthesis of purine and pyrimidine bases of DNA and RNA [8]. It is metabolized to L-glutamine by L-glutamine synthetase and this metabolic process is essential for normal maintenance of cells. The synthesis of L-glutamine is hindered in neoplastic cells due to lower reactivity of L-glutamine synthetase. Thus antagonists of this enzyme can interfere with the metabolic role of L-glutamine and act as anti-cancer agents [9]. The importance of non-essential amino acid glutamine in proliferation of human tumor cells was studied extensively [10. 11]. L-glutamine is not only the precursor of the biosynthesis of purine and pyrimidine bases of DNA as well as used us a building block of proteins. Thus, the structural variants of glutamine attracted our attention to develop possible anticancer agents, which may act through glutamine and/or folic acid antagonism. Computational Biology and bioinformatics have the potential not only of speeding up the drug discovery process thus reducing the costs, but also of changing the way drugs are designed. Rational Drug Design (RDD) helps to facilitate and speedup the drug designing process, which involves variety of methods to identify novel compounds. One such method is the docking of the drug molecule with the receptor (target). The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor. Docking is the process by which two molecules fit together in 3D space [12].

MATERIALS AND METHODS

Tools and materials used

For our present study we used biological databases like PubChem, Drug Bank, PDB (Protein Data Bank) and software's like Arguslab, Weblab viewer lite program, molinspiration, FROG [13] ADME Tox. Drug Bank is a unique Bioinformatics/Cheminformatics resource that combines detailed drug (*i.e.*, chemical) data with comprehensive drug target (*i.e.*, protein). Each Drug Card entry contains greater than 80 data fields with half of the information being devoted to drug/chemical data and the other half devoted to drug target or protein data [14]. The PDB (Protein Data Bank) is the single worldwide archive of Structural data of Biological macromolecules, established in Brookhaven National Laboratories (BNL) in 1971. It contains Structural information of the macromolecules determined by X-ray crystallographic, NMR-methods *etc.* Molinspiration is an independent research organization focused on development and application of modern cheminformatics techniques, especially in connection with the internet. Arguslab offers quite good on-screen molecule-building facilities, with a moderate library of useful molecules. It is a free molecular modeling package that runs under

Windows [15]. The program reads in molecular coordinate files and interactively displays the molecule on the screen in variety of representations and color schemes. RASMOL [Raster Display of Molecules] is a molecular graphics program intended for the structural visualization of proteins, nucleic acids and small biomolecules. The program reads in molecular coordinate files and interactively displaysthe molecule on the screen in variety of representations and color schemes [16]. TOX is an acronym in pharmacokinetics and pharmacologyfor absorption, distribution, metabolism and excretion, and describes the deposition of a pharmaceutical compound within an organism. The four criteria all influence the drug levels and kinetics of drug exposure to the tissues and hence influence the performance and pharmacological activity of the compound as a drug (http://www.pharma-algorithms.com/webboxes/). ACD/ChemSketch is the powerful all-purpose chemical drawing and graphics package from ACD/Labs developed to help chemists quickly and easily draw molecules, reactions and schematic diagrams, calculate chemical properties and design professional reports and present at ions. ACD Chemsketch can convert SMILES notations to Structure and vice versa.

Methodology

Bioinformatics is seen as an emerging field with the potential to significantly improve how drugs are found, brought to the clinical trials and eventually released to the marketplace. Computer-Aided Drug Design (CADD) is a specialized discipline that uses computational methods to simulate drug-receptor interactions. CADD methods are heavily dependent on bioinformatics tools, applications and databases [17].

Protein preparation and optimization

The crystal structure of Histone Deacetylase (HDAC) taken in this study was retrieved from RCSB protein databank (http://www.rcsb.org/pdb). The missing residues were corrected and the complexes bound to receptor molecule removed using Accelrys Discovery Studio Visualizer 2.5.5. The PDB files were energy minimized using ArgusLab. The non-essential water molecules were removed and polar hydrogens were merged.

Ligand preparation and optimization

Using Chemsketch Software the structures of the drugs and analogs were sketched draw and generated their MOL File followed subsequent generation of their 3-D structures by using tool Weblab viewer lite program a molecule format converter in to PDB. Appropriate force field applied to them and then optimization was carried out using Argus Lab 4.0 (http://www.arguslab.com).

Docking simulations

The docking analysis of glutamic acid analogs, Histone Deacetylase (HDAC) protein and all the analogs with Histone Deacetylase (HDAC) protein was carried by Argus lab docking software. Docking allows the scientist to virtually screen a database of compounds and predict the strongest binders based on various scoring functions. It explores ways in which two molecules, such as drugs and Histone Deacetylase (HDAC) protein fit together and docks to each other well. The molecules binding to a receptor inhibit its function and thus act as drug [18]. The collection of glutamic acid analogs and receptor complexes were identified via docking and their relative stabilitieswere evaluated using molecular dynamics and their bindingaffinities, using free energy simulations. All the parameters used for Arguslab docking are selected by default.The parameters used for the docking process were correlation type, FFT mode, grid dimension, receptor range, ligand range, twist range and distance range. The drug and its analogues were docked with the receptor using the above parameters.

RESULT AND DISCUSSION

Docking results tabulated between Histone Deacetylase (HDAC) protein and the 20 better conventional glutamic acid analogs (Table 1) as well as with the structure of protein and modified analogs are shown in Figure no. 1 through 5.

Based on the literature it has been shown clearly that glutamic acid analogs have been used to target the Histone Deacetylase (HDAC) protein. Out of 90 glutamic acid analogs on docking with Histone Deacetylase (HDAC) protein produced an energy value ranges from -10.370504 to -0.421512.

In all 90 glutamic acid analogs, it was observed using RasMol that the amide groups present in the analogs was the site of binding to the receptor and methyl group present in the analogs, which resulted in a decrease in the energy values. These modifications were made using Chemsketch and the energy values were calculated using Arguslab. This way the pharmacophoric part of the drug was partially identified.

Docking results of the drug and its derivatives via Arguslab docking software reveals that the e-value of glutamic acid ANALOG 1 (-10.370504) is better as compared to that of the other glutamic acid analogs. All the analogswere prepared virtually using ChemSketch. However, among the 90 analogs of glutamic acid, these particular 20 analogs showed an increase in the energy values (-10.370504 to -7.833821). This particular ANALOG 2 and 3 showed an increase in the energy values (-10.218276 and -10.053551) which means these analogs were more compatible with the receptor and required less energy to binding with the receptor. However, the binding site of the analog was similar to that of its other analogs, which means that functional groups involved were the same and by preparing the analog only the steric compatibility was increased.

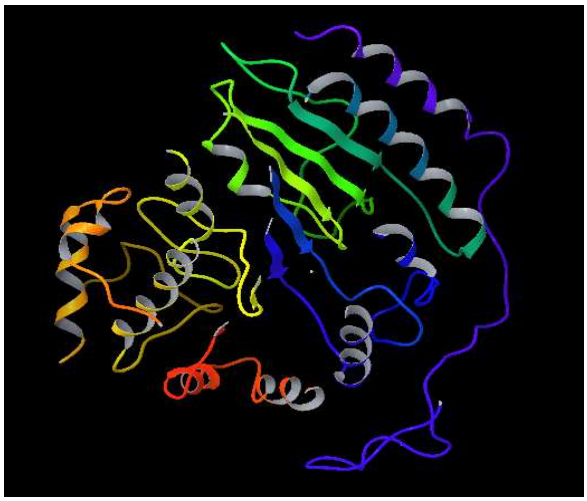

Fig. 1: Structure of Histone Deacetylase (HDAC) protein

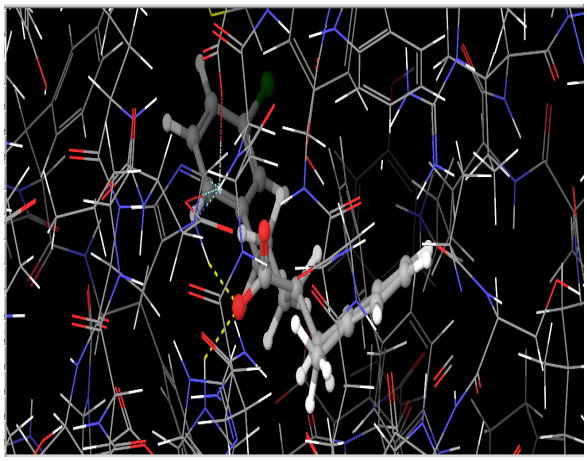

Fig. 2: Docking of ANALOG 1 with Histone Deacetylase (HDAC) protein

Table 1: Docking results of Histone Deacetylase (HDAC) receptor with glutamic acid analogs

Compound	Docking score	Glide score	Glide metal	Glide E-model	Glide energy
ANALOG 1	-10.370504	-10.370504	-2.3	-73.090349	-54.594004
ANALOG 2	-10.218276	-10.218276	-2.3	-45.192229	-48.210089
ANALOG 3	-10.053551	-10.053551	-2.3	-75.955287	-53.37163
ANALOG 4	-10.029615	-10.029615	-2.3	-72.143399	-51.420012
ANALOG 5	-9.126992	-9.126992	-2.3	-55.418917	-45.385994
ANALOG 6	-8.338884	-8.338884	-2.3	-28.419622	-16.805575
ANALOG 7	-8.314506	-8.314506	0.00E+00	-73.378346	-53.609475
ANALOG 8	-8.270166	-8.270166	0.00E+00	-73.934908	-56.102194
ANALOG 9	-8.146894	-8.146894	0.00E+00	-76.362223	-55.743061
ANALOG 10	-8.144146	-8.144146	0.00E+00	-70.600109	-52.609303
ANALOG 11	-8.120721	-8.120721	0.00E+00	-73.416972	-52.829025
ANALOG 12	-8.116124	-8.116124	0.00E+00	-87.360346	-65.076888
ANALOG 13	-8.019647	-8.019647	0.00E+00	-83.386952	-64.699483
ANALOG 14	-7.968454	-7.968454	0.00E+00	-76.932891	-57.663357
ANALOG 15	-7.914943	-7.914943	0.00E+00	-85.139812	-64.588913
ANALOG 16	-7.90738	-7.90738	0.00E+00	-84.549457	-64.279021
ANALOG 17	-7.903412	-7.903412	0.00E+00	-73.60706	-56.894295
ANALOG 18	-7.884024	-7.884024	0.00E+00	-86.639578	-65.459477
ANALOG 19	-7.859739	-7.859739	0.00E+00	-77.293827	-59.373958
ANALOG 20	-7.833821	-7.833821	0.00E+00	-83.888337	-64.103485

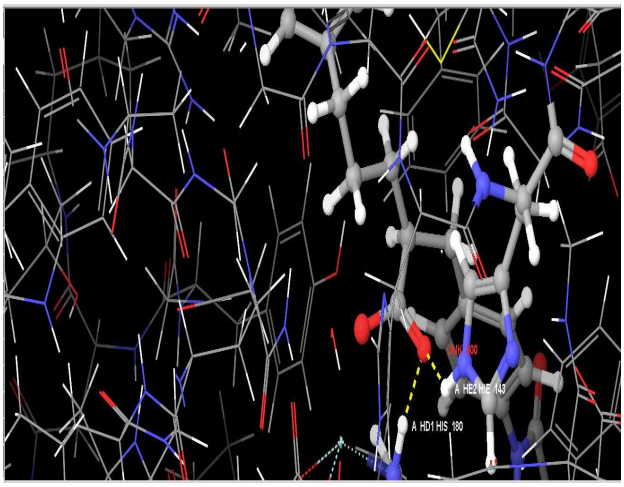

Fig. 3: Docking of ANALOG 2 with Histone Deacetylase (HDAC) protein

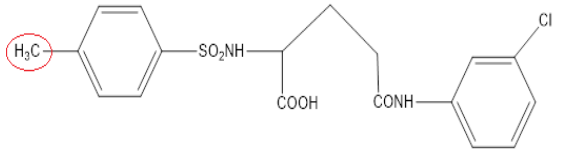

Fig. 4: Structure of ANALOG 1

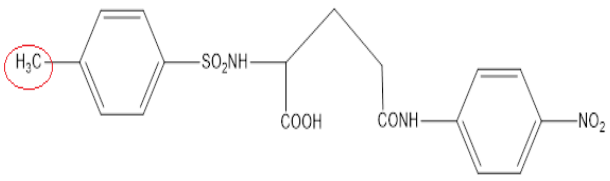

Fig. 5: Structure of ANALOG 2

CONCLUSION

The Protein-Ligand interaction plays a significant role in structural based drug designing. In the present work we have taken the protein Histone Deacetylase (HDAC) and identified the glutamic acid analogs that were used against Cancer. Here, out of 90 analogs, 20 better active analogs energy value was shown. When the modified drugs were docked against the protein Histone Deacetylase (HDAC) the energy value obtained was ANALOG 1 (-10.370504) and ANALOG 2 (-10.218276). Hence it is explicit that when compared to synthetic anticancer drugs, glutamic acid and its derivatives will be more promising in its action against cancer with minimal side effects as they are endogenic in nature.In future research work the ADME/T (Absorption, Distribution, Metabolism, Excretion/Toxicity) properties of these compounds can be calculated using the commercial ADME/T tools available thus reducing the time and cost in drug discovery process.

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