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PROTEIN LIGAND INTERACTION USING AUTODOCK IN BIO-COMPUTING

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ABSTRACT
Protein is made up of Amino acids. A protein contains one long peptide. Ligand is an ion or molecule . Ebola virus causes severe fever in humans there is no proper treatment for infection caused by this protein Hence there is a need for new drugs .Auto Dock is the software which carries out molecular docking studies .Docking enables us understanding the molecular interactions those take place between a ligand and corresponding protein. . It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure. Ligand is a small molecule and protein is bigger one. Auto Dock is used to find the binding energy and Inhibition constant values .This values are used to get drug against Ebola virus.

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General Terms
Autodock,openbabel,NCBI,RCSB(PDB).

Keywords
ligand,protein

1. INTRODUCTION
Auto Dock is an excellent non-commercial docking program that is generally used. Auto-Dock offer the advantage of delivering new drug candidates more quickly and at a lower cost . AutoDock 4 actually consists of two main programs: *autodock* performs the docking of the ligand to a set of grids describing the target protein; *autogrid* pre-calculates these grids. It is very fast, provides high quality predictions of ligand conformations, and good correlations between predicted inhibition constants and experimental ones. AutoDock has also been shown to be useful in blind docking, where the location of the binding site is not known. AutoDock is free software and version 4 is distributed under the GNU General Public License: it employs a stochastic Lamarckian genetic algorithm for computing ligand conformations and simultaneously minimizing its scoring function which approximates the thermodynamic stability of the ligand bound to the target protein .In this project to 4IBK(EBOLA) as protein with Nicotine,Cotinine,Nornicotine,Myosmine,Anabasine,Anatabine as Ligand. To interact with autodock to get best Drug.

1.1 Information about Protein and Ligand.

Protein:

- **4IBK** :
  4IBK(Ebola virus VP35) protein .It is a 2 chain structure with sequence from EBOZM(VP35)(Ebola virus is a deadly pathogenic virus. It is classified under Filoviridea Family.

Ligand:

- **Nicotine:**
  Nicotine is a potent parasympathomimetic alkolaid found in the night shade family of plants(solanaceae) and a stimulant drug.
- **Cotinine:**
  Cotinine is an alkaloid function in tobacco and is also the predominant metabolite

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of nicotine.the word "cotinine" is an anagram of "nicotine".

- **Nornicotine:**
  Nornicotine is an alkaloid found in various plants including nicotiana,the tobacco plant.it is chemically similar to nicotine,but does not contain a methyl group.
- **Myosmine**:
  Myosmine is an alkaloid found in tobacco and other plants.chemically,it is closely related to nicotine.
- **Anabasine**:
  Anabasine Is A Pyridine And Piperidine Alkaloid Found In The Tree Tobacco Plant.
- **Anatabine:**
  Anatabine Is One Of The Minor Alkaloids Found In Plants In The Solanaceae Family ,Which Includes Tabacco Plant And Tomato

2. REQUIREMENTS:

1)Windows XP or Windows 7
2) MGL tools
http://mgltools.scripps.edu/downloads
3)Open Babel
4) Cygwin
http://www.cygwin.com/install.html
5) Discovery Studio Visualizer
http://accelrys.com/products/discovery-studio/visualization-download.php
6) Autodock
/autodock-4-0-1-and-autogrid-4-0.0

3 .METHODS

3.1 ***Retrieving protein.pdb files from major protein databases:***

http://www.rcsb.org/pdb/home/home.do

- Type the query protein (4IBK)
- Select (4IBK)
- Select download files
- Click PDB files(.gz) and download it.
- Open (.gz) with notepad.and click find box and give TER find A chain and then delete other chain and save as .pdb file

3.2Retrieving Ligand.pdb files from major ligand databases:

http://pubchem.ncbi.nlm.nih.gov/

- Search your Ligand
- Click on ligand
- Click 3D image
- Save 3D .SDF file
- Open .SDF file in open Babel convert output as cotinine .pdb file

3.3 Preparing target protein

- *File->Read Molecule .*

Polar hydrogens are added to the target structure

- *Edit->Hydrogens->Add->Polar only->Ok*

Kollman charges are added to the peptide

- *Edit->Charges->Add Kollman Charges*

The structure is saved

- *File->Save->Write PDB*

3.4 - Initializing ligand for docking

The Protein is hidden from the view

- *Display->Show/Hide Molecule*

The ligand file is loaded

- *Ligand->Input->Open...*

Change the file type to '.pdb', choose the ligand file saved in '.pdb' format-> *Open*
Detecting the root of the ligand.

- *Ligand->Torsion Tree->Detect Root...*

View rotatable bond

- *Ligand->Torsion Tree->Choose Torsions...*

The Ligand is saved in PDBQT file format as 'Ligand.pdbqt'.

- *Ligand->Output->Save as PDBQT*

3.5 - Preparing Grid map

- *Grid->Macromolecule->Choose*

Setting the Map types that will be used for the grid.

- *Grid->SetMapTypes->Choose Ligand.*

Setting the Grid Box position and size.
Grid Box... (Dimension: 60X60X60; Spacing 0.408; X centre: 15.438,Y centre : 23.703, Z centre : 4.245)

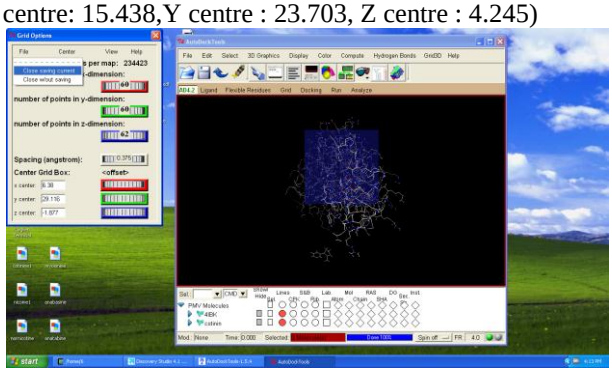

Fig 3.1: Grid options widget

Saving the current grid positioning

- *File->Close Saving Current*

Saving Grid file

- *Grid->Output->Save GPF*

3.6- Setup docking parameter file

Setting the protein target to be docked

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- *Docking->Macromolecule->Set filename->protein.pdbqt*

Ligand is selected which is to be docked

- *Docking->Ligand->Choose… (Ligand)*

Setting search parameters

- *Docking->Search Parameters->Genetic Algorithm...*

Docking parameters are set to default
Setting the Docking output parameter file

- *Docking->Output->Lamarckian GA.*

Docking Parameter file is explicitly saved as "a..dpf".

3.7 Using Cygwin for Molecular Docking

(cd..)(ls) (cd 1)

(autogrid4.exe -p a.gpf -l a.glg &)
(tail -f a.glg &) (autodock4.exe -p a.dpf -l a.dlg & (tail-f a.dlg &)

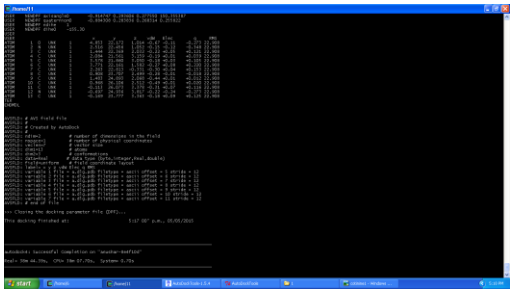

Fig 5.1 Docking molecular

(grep '^DOCKED' a.dlg | cut -c9- >a.pdbqt)(cut -c-66 a.pdbqt> a.pdb) (catTarget.pdb a.pdb | grep -v '^END ' | grep -v '^END$' > complex.pdb).

- *Analyze ->Dockings->Open->a..dlg*

Macromolecule is loaded into view

- *Analyze->Macromolecule->Choose..(protein)* Viewing the conformations
- *Analyze->Conformations->Play, ranked by energy…*

Choose best conformation

- *Set Play Option*

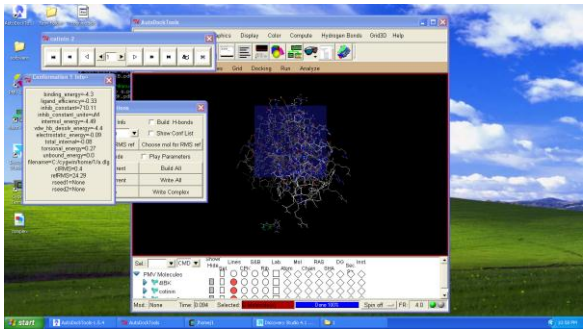

Fig 5.2 conformations

Open complex.pdb in Discovery Studio

- *Scripts->Click Ligand Interactions->Click Show Ligand Binding Site Atoms*
- *Label->Select Object: AminoAcid->Select Attributes: 1 Letter & ID insertion code*

Save as Image files.

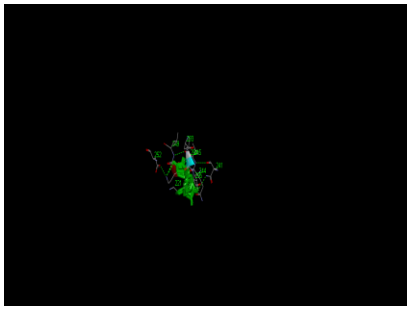

Fig 5.2 4IBK-COTININE

TABLE 1:TABLE OF PROTEIN LIGAND CHART

s.no	Protein_ligand	Binding_energy	Inhibitation_constant
1.	4IBK-COTININE	-4.3	710.11
2.	4IBK-NICOINE	-3.59	2.35
3.	4IBK-NORNICOTINE	-3.66	2.07
4.	4IBK-MYOSMINE	-4.01	1.15
5.	4IBK-ANABASINE	-4.11	976.83
6.	4IBK-ANATABINE	-4.1	983.03

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6.RESULTS

6.1 PROTEIN-LIGAND CHARTS

6.1.1 4IBK-COTININE

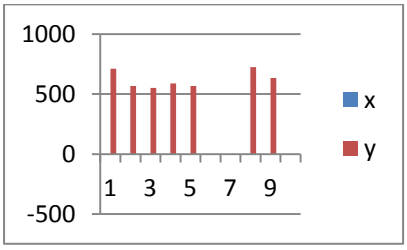

Fig 6.1.1 4IBK- COTININE

6.1.2 4IBK-NICONINE

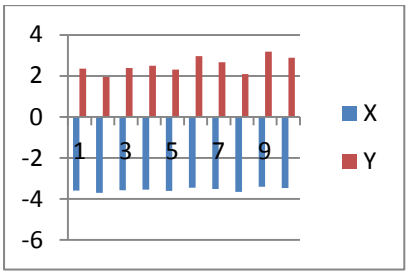

Fig 6.1.2 4IBK- NICONINE

4IBK-NORNICOTINE

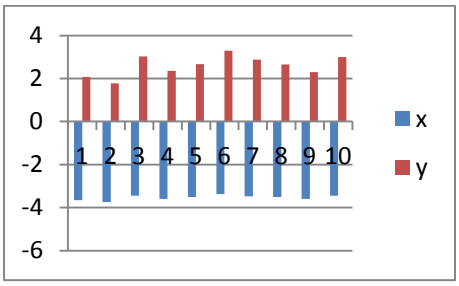

Fig 6.1.3 4IBK- NORNICOTINE

4IBK-MYOSMINE

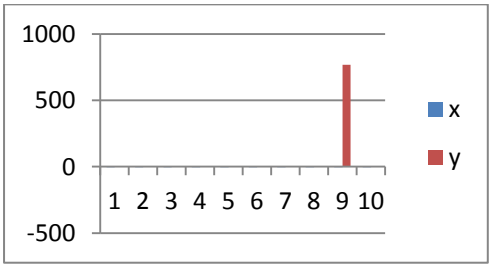

Fig 6.1.4 4IBK- MYOSMINE

6.1.5 4IBK-ANABASINE

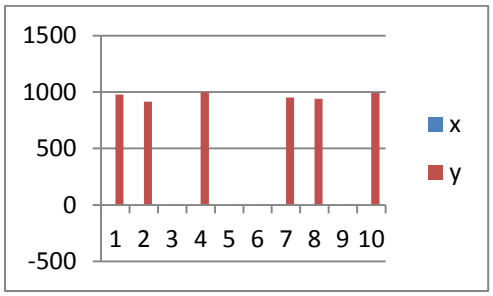

Fig 6.1.5 4IBK- MYOSMINE

6.1.6 4IBK-ANABASINE

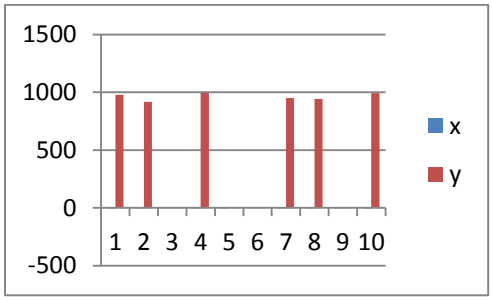

Fig 6.1.6 4IBK- ANABASINE

6.1.7 4IBK-ANATABINE

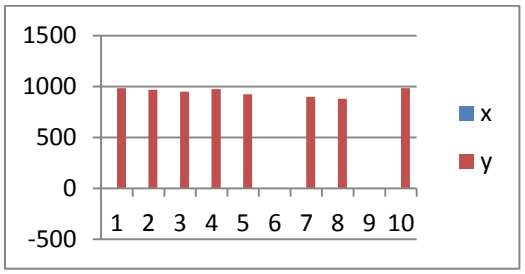

Fig 6.1.7 4IBK-ANATABINE

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10.3 CONCLUSION

Auto Dock is a popular non-commercial docking program that docks a ligand to its protein and performs well (accurate and computationally fast)..it is user-friendly for docking ligands with target protein that utilizes Ebola cause severe fever in humans and nonhuman primates, since it causes high mortality rate and currently no drugs are available, there is an urgent need for novel antiviral against Ebola virus infections.Auto Dock helps in reducing the cost and time for drug discovery process which otherwise takes many years. Virtual screening and docking studies helped to obtain ligand molecules that can inhibit the important proteins involved in the pathogenesis of ebola virus. Auto Dock is used to find the binding energy and Inhibitation constant values to get Best drug against EBOLA virus

11. REFERENCES

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