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Insilico Studies of Potential Inhibitors on Factor Xa by Pharmacophore Analysis.

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ABSTRACT

The aim of this Project work was based on structure Based Drug Designing and Pharmacophore analysis on blood coagulation Factor Xa , Factor Xa, a Hydrolase, is the converting enzyme of Prothrobin to Thrombin in blood clotting. The development of specific inhibitors of blood coagulation enzymes can lead to new anticoagulant/antithrombotic agents that could be useful for prophylaxis and/or treatment of thromboembolic disorders. With an Inhibitor bound to the Active site are made with Computer aided Drug Designs Inhibitors with all the guidelines used for the later to derive a relevant data or activities in a similar procedure. The Computational study, that are CDOCKER ,LIBDOCK,LIGAND FIT,LUDI &PHARMACAPHORE generation.In all these docking studies and pharmacophore analysis the compound we have got least energy with highest fit score 17bns(Sulphonamide derivative) compound,the The ligand molecule in all the methods it mostly interacted with amino acids GLY-216, TRY-99, SER-195, GLN-192 &CYS-191 respectively.

Keywords: Proteins, Docking, Drug designing, Bioinformatics tools.

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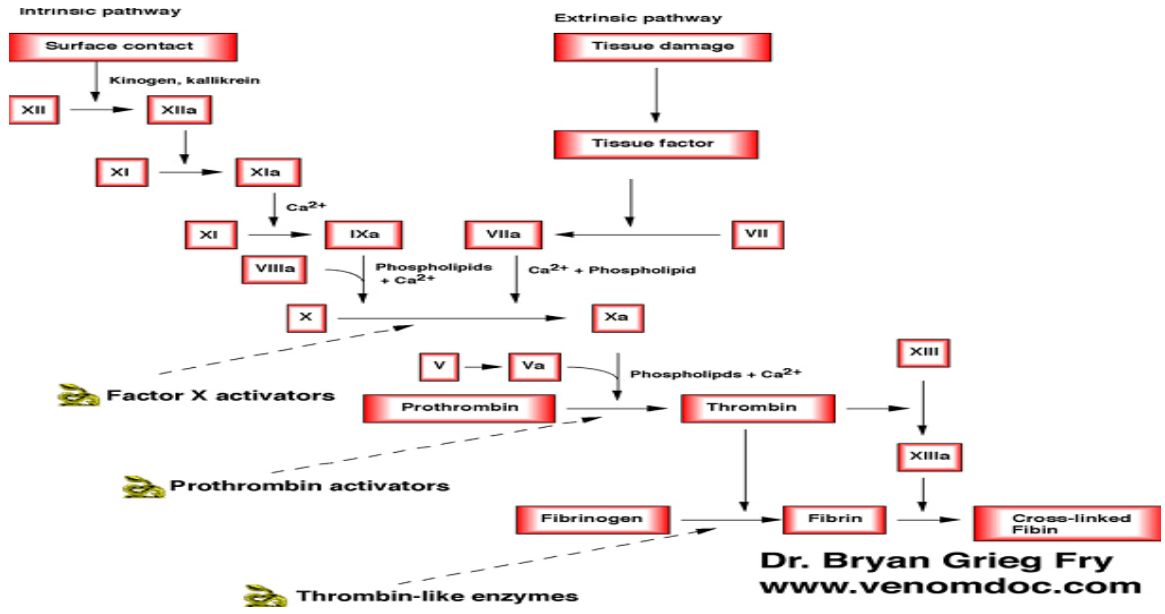
INTRODUCTION

Factor X, also known by the eponym Stuart-Prower factor or as prothrombinase, is an enzyme (EC 3.4.21.6) of the coagulation cascade. It is a serine endopeptidase. Factor Xa is the activated form of the coagulation factor thrombokinase, known eponymously as Stuart-Prower factor. Factor X is an enzyme, a serine endopeptidase, which plays a key role at several stages of the coagulation system. Factor X is synthesized in the liver. The most commonly used anticoagulants in clinical practice, warfarin and the heparin series of anticoagulants and fondaparinux, act to inhibit the action of Factor Xa in various degrees.Traditional models of coagulation developed in the 1960's envisaged two separate cascades, the extrinsic (tissue factor (TF)) pathway and the intrinsic pathway[1]. These pathways converge to a common point, the formation of the Factor Xa/Va complex which together with calcium and bound on a phospholipids surface generate thrombin (Factor IIa) from prothrombin (Factor II).A new model, the cell-based model of anticoagulation appears to explain more fully the steps in coagulation. This model has three stages: 1) initiation of coagulation on TF-bearing cells, 2) amplification of the procoagulant signal by thrombin generated on the TF-bearing cell and 3) propagation of thrombin generation on the platelet surface[2].

THE INTRINSIC AND EXTRINSIC CASCADES OF BLOOD CLOOTING:



MATERIALS AND METHODS

Databases:

1. PDB
SWISS-PROT
1. UNIPROT CONSORTIUM

Discovery Studio

CATALYST
CHEMSKETCH
SDF

SDF is one of a family of file formats from MDL holding chemical data, especially structure information. "SDF" stands for structure-data file and SDF files actually wrap the molfile (MDL_Molfile) format. Multiple compounds are separated by a delimiter, a line of four dollar signs ($$$$). A feature of SDF is the possibility of storing associated data items.

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Multiple data items are possible on multiple lines. The MDL SDF format specifications require a hard carriage return to be inserted in any text field exceeding 200 characters in length. This is frequently violated in practice [3].

STRUCTURE BASED DRUG DESIGN:

MOLECULAR DOCKING:

In the field of molecular modelling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using for example scoring functions.

RESULTS AND DISCUSSION

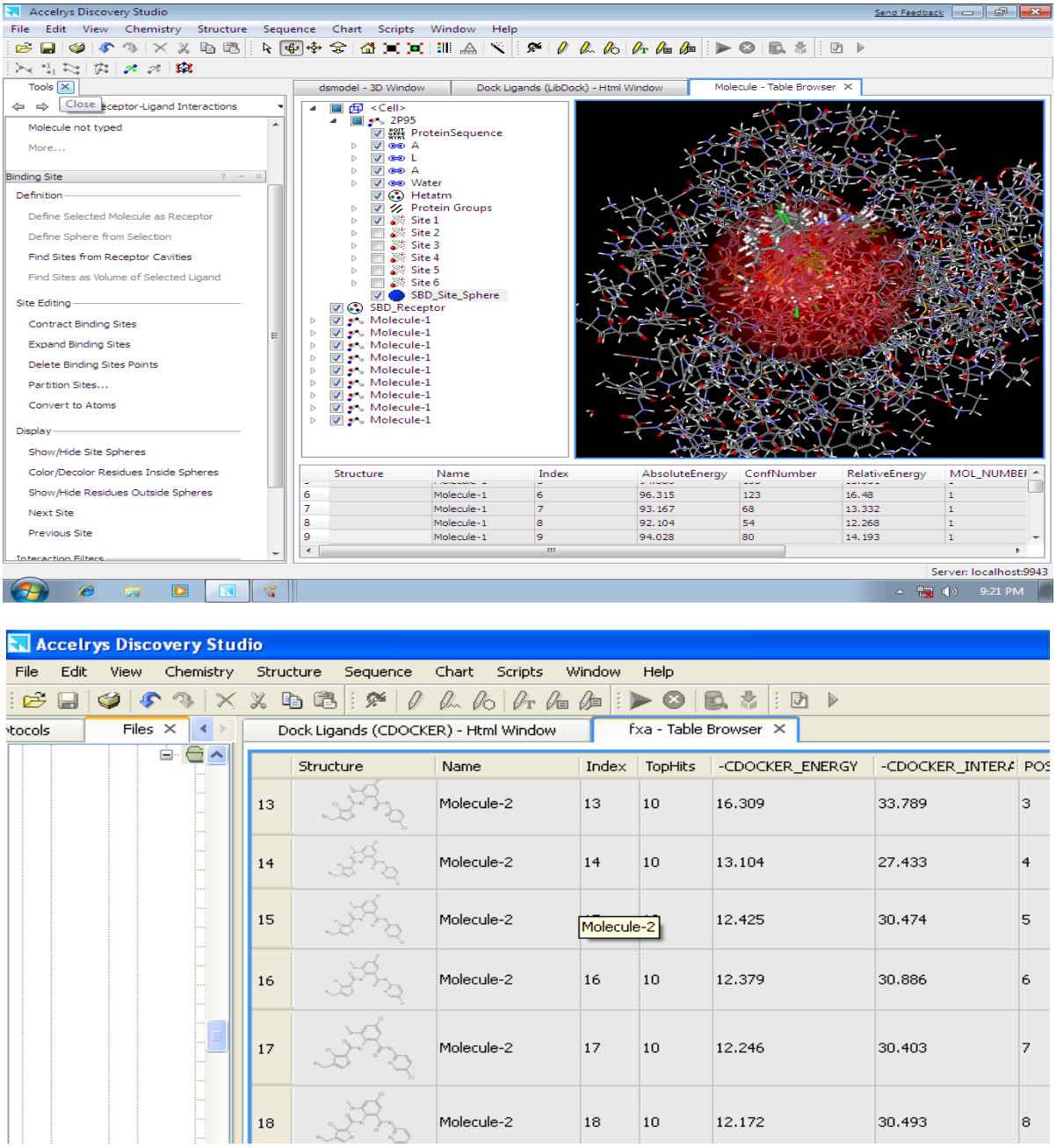

Figure 1: Visualizaton of CDOCKER

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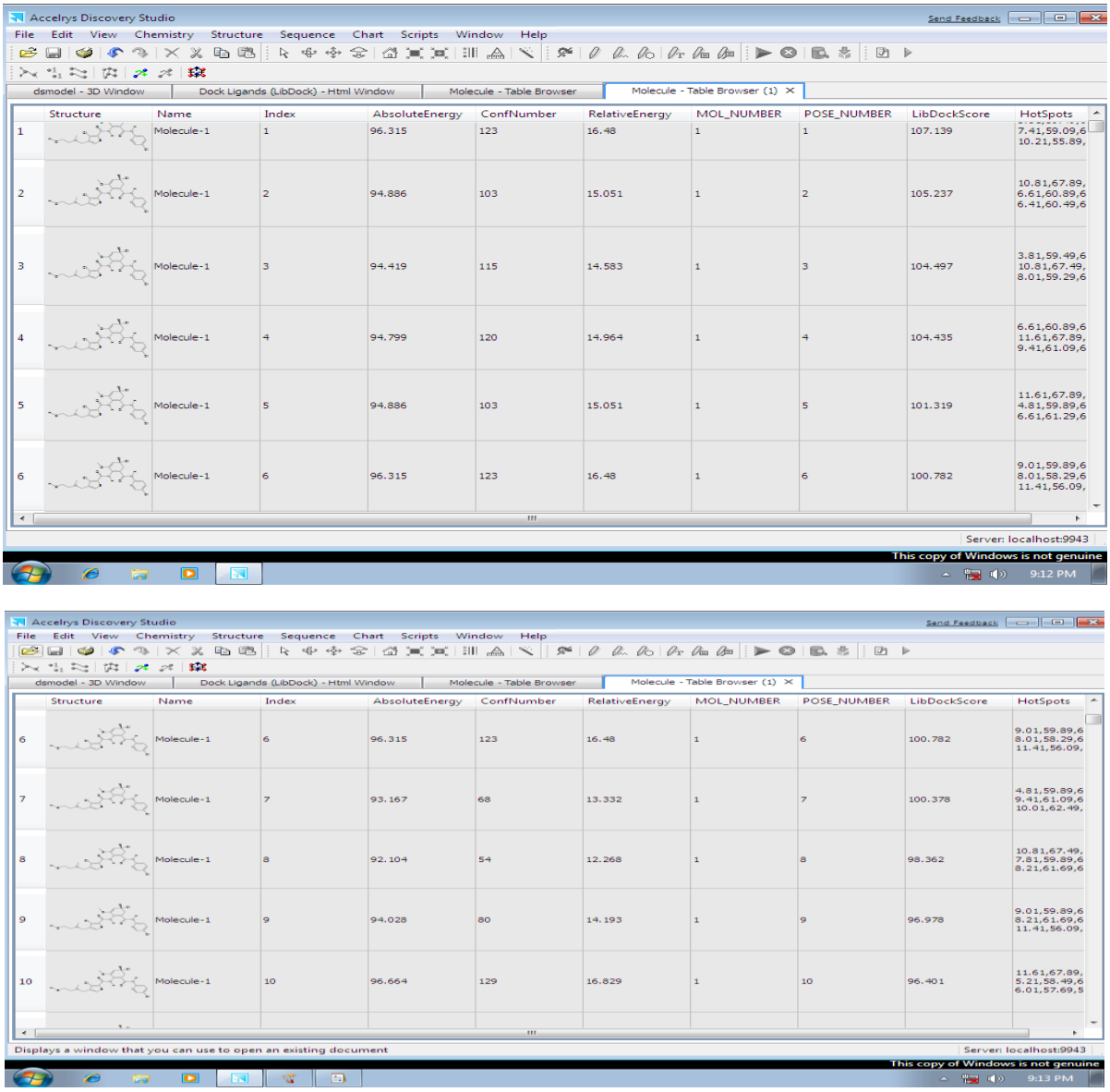

Figure 2: Visualization of Libdock results

CONCLUSION

In docking studies it was found that the molecule which showed best dock score was not the active molecule according the IC50 values. This could be explained by the fact that probably that particular conformation of the molecule Crystal ligand was the more potent than the best active molecule. Using the LUDI one new molecule was generated which was docked in the active site of FXa, Which showed highest dock score than the highest active molecule and crystal ligand [4].

From the pharmacophore studies a more accurate considerations have been made. This computational method is able to account for major structure activity relationships associated with new compounds, like HBA, HBD and HA. I common for highly active FXa inhibitors. Thus by enhancing these functions the potency of the molecules could further be increased Finally, the scope of this project was limited and hence more elaborate, meticulous and comprehensive work has to be done to come to any judicious conclusions. But definitely these results will provide some valuable information in understanding the structural features of FXa inhibitors and in designing new potential compounds [5]. The scope of this kind of studies can be infinite especially when process of tedious research has been simplified to literally the click of the mouse by the cutting edge technology of Insilco studies.

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