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IDENTIFICATION OF COMPETITIVE POTENT DRUG TARGET TO FACTOR X IN HAEMOPHILIA

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ABSTRACT

A congenital blood clotting disorder of factor X deficiency in clotting hemophilia has several diverse mutations that produce different clinical phenotypic patterns varying from mild to severe. The target of this studying is to develop a new drug capable to preventing bleeding and haemorrhage but still maintain the usefulness of coagulation factor XI. An encompassing library is developed using different areas and methodologies. e.g. the drug's compounds are reviewed for ADMET attributes. The docking studies targeting the most appropriate medication candidate which proves to be the most promising one is carried out next. This spliceosome candidate has a good binding affinity with the region of the receptor that makes the artery stop discharging when the vessel is damaged.

KEYWORDS: docking, serine protease, pharmacophore

INTRODUCTION

The word "hemophilia" describes a group of inherited birth defects that complicates our body's clotting process, which is necessary to stop damages and bleeding when a blood vessel is cut. Haemophilia bleed internally in the joints and bleeding is observed to be longer after the injury or an accident. The case could be persistent. The X chromosome is known for its genes that code for the coagulation factor X, which is a protein necessary for healthy oxidation processes. In hemophilia, where the level of factor X is either completely absent or is definitely lower than normal, the X chromosome is believed to be the likely place of gene location. This protein which is a blood artery's safeguard remains in its suspended state in the blood until the artery is injured. It unites with another molecule von Willebrand factor which takes the form of a double as this protein. Factor Xa is subsequently prompted to begin the clotting off after being injured.

The gene which is responsible for coding coagulation factor X, an important part of the built-in process of blood clotting, is this one.The path of change of factor X into its active form of Xa contains phospholipids. One transcript with alternative splicing and a second transcript not containing anything from this section of the gene will be made by the gene. There are gene variations 1 which tend to have a transcript of isoform a which is a big glycoprotein that circulates in plasma and binds to von Willebrand factor via a non-covalent approach.

MATERIAL AND METHODS

Bioinformatics represents an emerging field of science that applies informatics techniques to resolve problems of biological nature. This step can rise up above other usual manners of carrying out laboratory experiments so as to provide a new idea in scientific basic research methods.

DATABASES USED:

- PDB (www.pdb.com)
- Gene card (www.genecard.org)
- Drug bank (www.drugbank.ca)
- Pubchem (www.ncbi.nlm.nih.gov)

METHOD

The serine protease that is the target protein of factor X was retrieved from NCBI style. I employed a 96-well plate in those experiments and utilized these agents and the serine protease as three ligands. Each ligand molecule is subjected to Swiss docking analysis subsequently receives screening by ADMET test. Swiss dock technique shows ligand molecules that have been purported to have no toxic or carcinogenic tendency in the process of being put in the drugs.

DRUG Library

In order to do the careful choosing of the ligands, the ligands were set up in a drug library. Then, we have considered some things in common among all the ligands such as their basic structure elements. The following table provides an overview of each ligand's characteristics:The following

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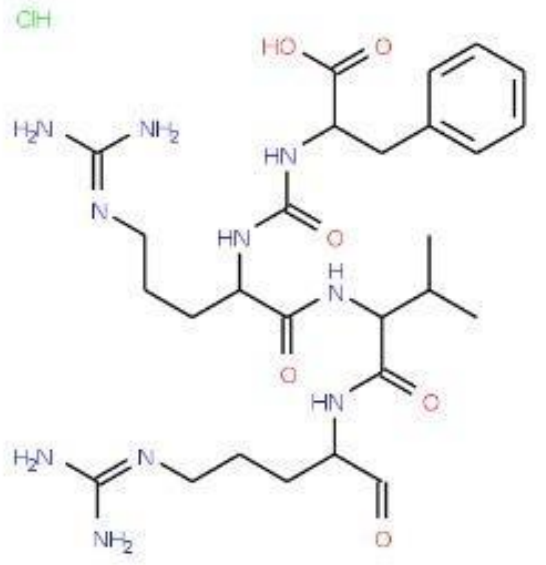
Table 1: Drug library with molecular properties

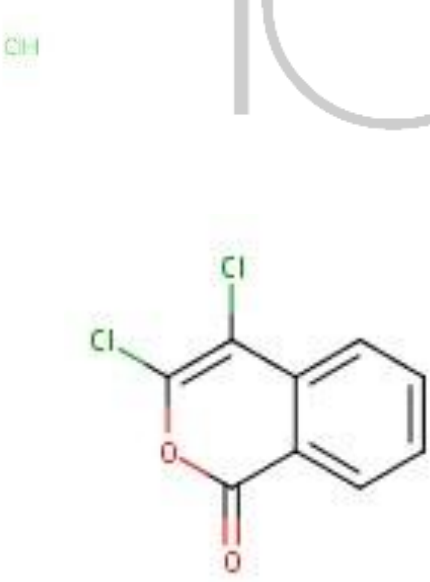
LIGANDS	MOL FORMULA	MOL Wt.	Num. H donor	Num. H accept
Chymostatin	$C_{31}H_{41}N_7O_6$	607.70054g/mol	7	7
Antipaindihydrochloride	$C_{27}H_{46}Cl_2N_{10}O_6$	677.62354g/mol	11	8
3,4-dichloroisocaumarin	$C_9H_4Cl_2O_2$	2150.3286	0	2

RESULT AND DISCUSSION

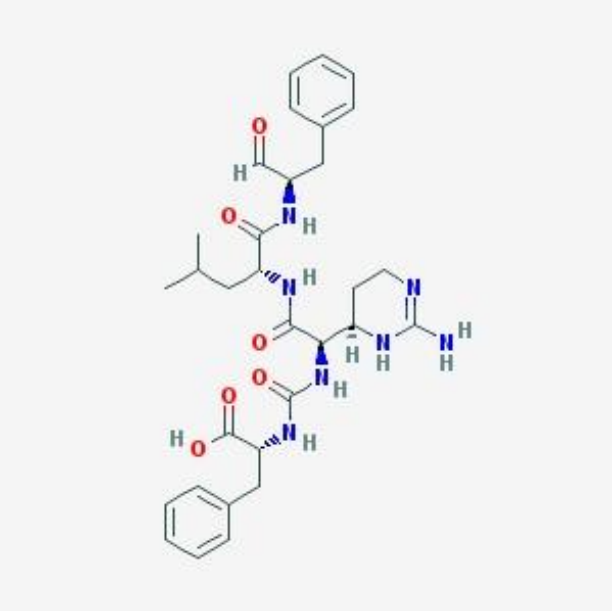
A target protein structural analysis performed by the Protein Data Bank (PDB ID) was a foundation of approach. Serine protease was selected from other factors known for its amazing ligand-binding properties. With every ligand taken into consideration there was a high binding energy every time. In our process water removal of the molecules called ligands was carried out. Q SITE finder and PDB SUM were used to hunt down receptors and their active sites through web sources.



Antipaindihydrochloride



3,4-dichloroisocaumarin



Chymostatin

Fig 1: Structures of the selected ligands

ADMET PROPERTIES

ADMET properties of the ligands are given in table 2.

Table 2: ADMET properties of the ligands

	CHYMOSTATIN	
Properties	**Value**	**Probability**
Ames test	Non ames toxic	0.7162
Carcinogenicity	Non carcinogenic	0.9257
Biodegradation	Not ready biodegradable	0.8206
hERG	Weak inhibitor	0.9813
	ANTI-PAIN DIHYDROCHLORIDE	
Carcinogenicity	Non carcinogenic	0.9322
Ames test	Non ames toxic	0.6
Biodegradation	Not ready biodegradation	0.7732
hERG	Weak inhibitor	0.8132
	3,4-DICHLOROISOCAUMARIN	
Ames test	Non amestoxix	0.7865
Carcinogenicity	Non carcinogenic	0.9227
Biodegradation	Not ready biodegradation	0.9632
hERG	Weak inhibitor	0.87052

SWISS DOCK

SwissDock *in-silico*experiments can predict interactions between protein and ligands. In the process of a binding set the docking algorithm will be performed in order to find the most matching pose by the conformational search which would eventually fit the binding regions of the protein. The ligands and their best docking outcomes are listed below.

Table 3: The ligands and their best docking outcomes

Ligands	**Clusters**	**Elements**	**Fullfitness(kcal/mol)**	**Estimated**
Chymostatin	0	0	-892.13	-11.51
	0	1	-877.89	-10.27
3,4-dichloroisocaumarin	0	0	-892.25	-11.15
	0	1	-891.76	-11.12
Antipaindihydrochloride	0	0	-894.21	-11.00
	0	1	-865.24	-10.12

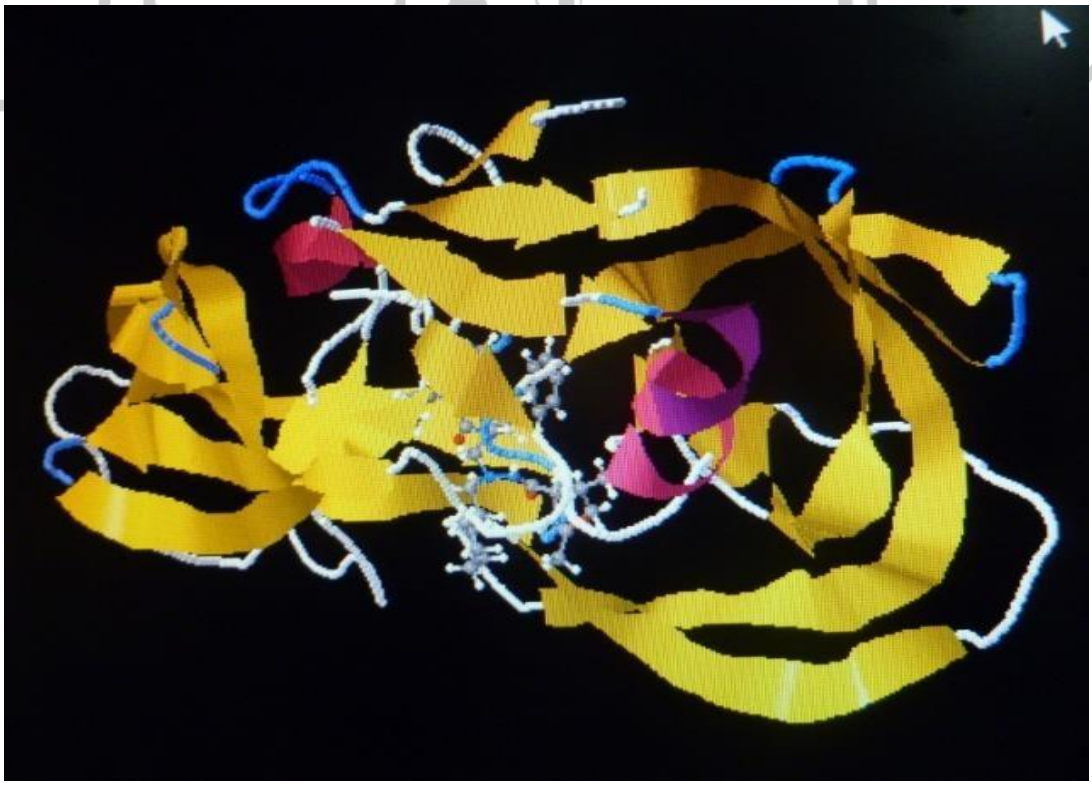


Fig 2: Ligand-target interaction

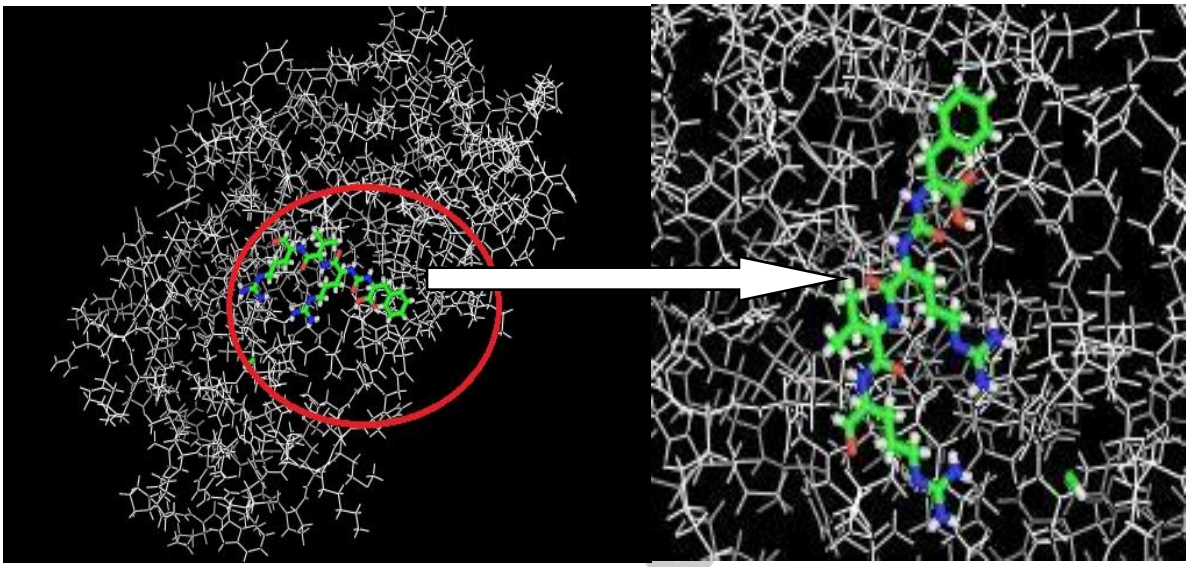


Fig 3:Antipaindihydrochloride

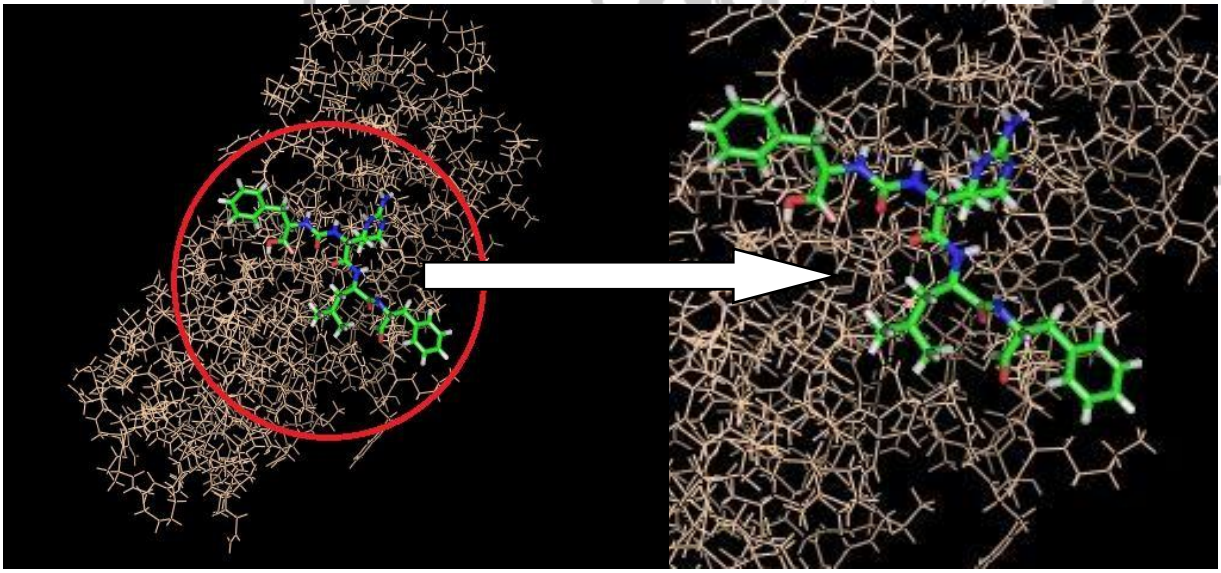


Fig 4 (chymostatin)

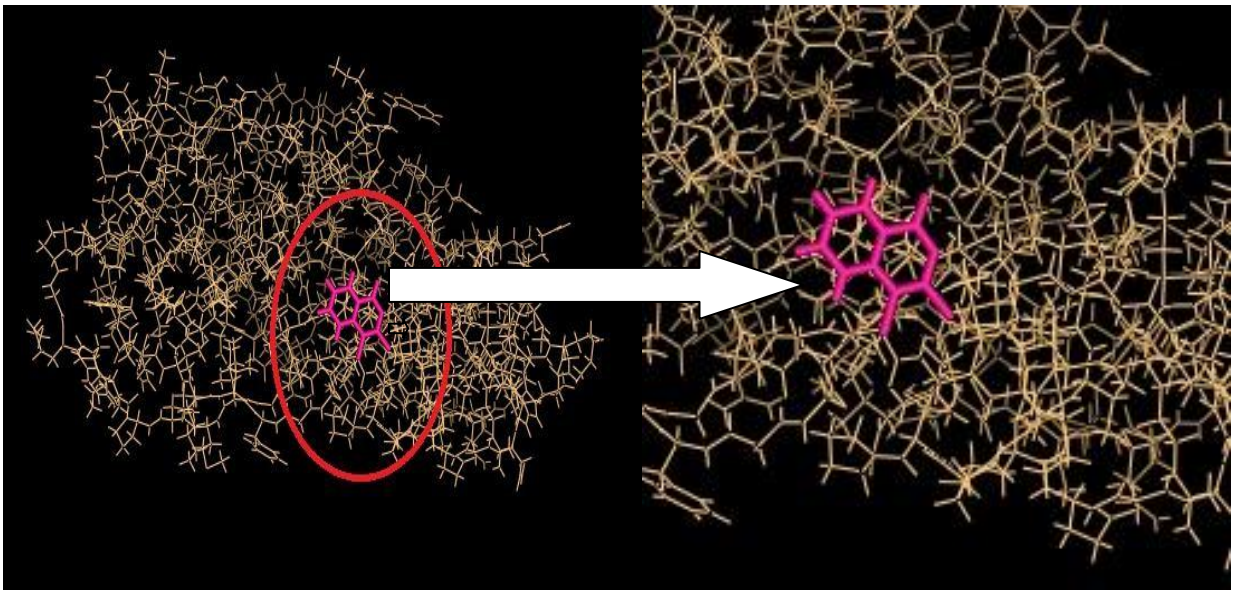


Fig 5 (3,4 dichloroisocaumarin)

CONCLUSION

Through the process of molecule-protein interactions, the discovery and creation of medicines during the steps of molecular docking are made possible. The protein known as serine protease exhibits the best docking results in this study when it interacts with three different ligands: (i) chymostatin,(ii) antipaindihydrochloride,(ii) and 3,4-dichloroisocoumarin. These interactions serve the purpose to appraise the efficiency of their ligands and as a result provide remarkable proof that they can be more powerful or effective than the licensed medicines.

REFERENCES

1) Basilico F, Nardini I, Mori F, Brambilla E, Benazzi L, De Palma A, Rosti E, Mauri P. charaterization of factor X pharmaceutical preparations by means of MuPIT proteomic approach. J Pharm Biomed Anal. 2010;53(1):50-7. Epub .
2) Catherine J. Rea, M.B., B.Chir, Jonathan H. Foley, FactorXIII in the treatment of hameophilia A N Engl J Med 2012; 366:281-283, 2012
3) Esquilin J, Takemoto C, Green N. Female factor IX deficiency due to maternally inherited Xinactivation. Clin Genet. 2012 Jan 10 doi: 10. 1111/j.1399-0004.2012.0184.x
4) Margaritis P, Gene-based continuous expression of FVIIa for the treatment of haemophilia A – spontaneous disappearence and no recurrence of the inhibitor after re-challenge.2012 jan 18.
5) Mannucci P M The Safety and Efficacy History of B-dominless Factor X. journal of Coagulation Disorders, July 2010;2(2): 7-9
6) Hain M Steinbech .Updokon the use of orthotic in hemophilia.Orthop Rev. 1988 oct;17(10):975-8
7) Rodriguez-merchan EC, Jimenez-yuste V, Aznar JA, Hedner U, Knobe K, Lee CA,LjungR,QueolF,Santagostino E,

Valentino LA, CaffariniA,Joint protection in haemophilia. 2011 sep ;17 Suppi 2:1-23. Doi 10.1111/j.1365-2516.2011.02615.x.

8) Lin Y, Stanwort S, Birchall J, Doree C, Hyde C., Recombinant factor Xa for the prevention and treatment of bleeding in patient without haemophilia. Cochrane Database SystRev . 2011 feb16;(2):CD005011.

9) Salek SZ, Benson GM Elezovic I, Krenne V, Ljung RC, Morfini M, Remoe E, Santagostino E, Sorensw B. The need for speed in the management of haemophilia patients with inhibitors. 2011 jan;17(1):95-102 doi: 10.1111/j.1365-2516.2010.02265.x.

10) Goun SC van den Berg HM, Oldenburg J, astermark J, de Groot PG ,Margaglione M ,Thompos AR van Heerde W, Boekhorst J, Miller CH.inhibitor development in patient with haemophilia factor X . Blood 2012 Jan 30.