

Research Journal of Pharmaceutical, Biological and Chemical Sciences

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

Jayalakshmi T¹*, and Thanulika P².

¹School of Bio-Engineering, Dept. of Genetic Engineering, Bharath University, Chennai, Tamil Nadu, India. ²Department of Bioinformatics, Bharath University, Chennai, Tamil Nadu, India.

ABSTRACT

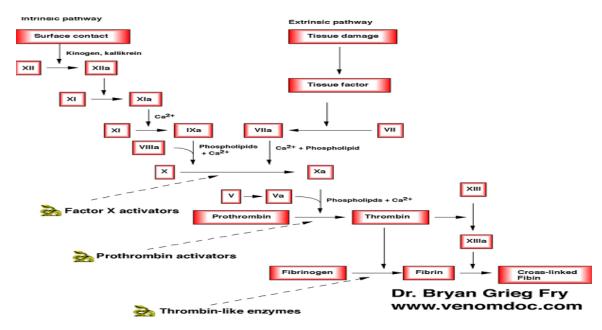
The aim of this Project work was based on structure Based Drug Designing and Pharmacophore analysis on blood coagulation Factor Xa, Factor Xa, a Hydrolase, is the converting enzyme of Prothrobin to Thrombin in blood clotting. The development of specific inhibitors of blood coagulation enzymes can lead 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.

*Corresponding author



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 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.

November - December 2015 RJPBCS 6(6)

Page No. 140



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.

Accelrys Discovery Studio							Send Feedbac	:k 🗖 🖗
File Edit View Chemistry Structure Se	quence Chart	Scripts Windo	ow Help					
😂 🖬 🥥 🔊 🚿 🗶 🛍 🗄 🍋	🐨 🔶 😪 📊	3 in in 1900.		· 0 0. 0	0r 6a 6 🕨 🕨	O B. # 1		
				10 00 00			<u> </u>	
							N.	
Tools 🔀		- 3D Window	Dock Ligand	s (LibDock) - Htm	I Window Mo	lecule - Table Browse	er ×	
⊨ ⇔ Close eceptor-Ligand Interactions		<cell></cell>						
Molecule not typed		2P95	auence.			Ser STE	TXXXI.	
More	⊳	V CO A	quence					<
100 000	⊳	🔽 🐟 L			1		A Charles	₹
ding Site ? - ×		☑ 👄 A ☑ 👄 Water			156		* XAR	X- and CE
Definition		Vater			. L / 200		T-DEAL	A A A
	⊳	👿 🚀 Protein G	roups	~	A VY			- 13 - 13 - 13 - 13 - 13 - 13 - 13 - 13
Define Selected Molecule as Receptor	⊳	Site 1			JA MD			
Define Sphere from Selection		🔲 🌌 Site 2			A TOT -		ANT LAND	
Find Sites from Receptor Cavities		🔲 🚀 Site 4		~		137 035	SP C CAR	EP ALK
Find Sites as Volume of Selected Ligand	⊳	🔲 🎻 Site 5			YAR SKI	Sec. St. S.		15 (P
This sites as volume of selected eights	⊳	Site 6 SBD_Site	Sphere	A		Starks and	CET-AR	-71 12
Site Editing		SBD_Receptor	spriere					
Contract Binding Sites		Molecule-1		~~~			Mars San	
Expand Binding Sites		Molecule-1 Molecule-1			Carl Star			Crease.
		Molecule-1		-		KL WILL		A MAL
Delete Binding Sites Points	D 🔽 🖍	Molecule-1			L F(M)	HUPSAK.	VERAL 21	
Partition Sites		Molecule-1		\sim			S SKA	THE Y
Convert to Atoms		Molecule-1 Molecule-1					125-25-	
		Molecule-1		-7			A CARLER AND	
Display						~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	YAR X	
Show/Hide Site Spheres					- K-R		Children C	
Color/Decolor Residues Inside Spheres	Struct			Index	AbsoluteEnergy		RelativeEnergy	MOL_NUMB
Show/Hide Residues Outside Spheres	6	Molec		-	96.315	123	16,48	- 1
Next Site	7	Molec		7	93, 167	68	13,332	1
	8	Molec		8	92.104	54	12.268	1
Previous Site	9	Molec	ule-1	9	94.028	80	14.193	1
Interaction Filters				m				,
							S	erver: localhost
							 	() 9:21 PN
							- 12	- ()-)

RESULTS AND DISCUSSION

File		ys Disc						Chart Carleta		11-1-			
	Edit	View		emistry		ructure	Sequence		Window	Help			
Þ		ه 😂	2	$ \times$	X		3 🛛 🗯 🖉	la lo la le	@ 11	▶ 🛛	S. 🖏 🗄 🖸 🕨		
tocols		Files		< >		Dock Lig	jands (CDOCk	ER) - Html Window	f	xa - Table	Browser ×		
			ė. (Struc	ture	Name	Index	TopHits	-CDOCKER_ENERGY	-CDOCKER_INTERA	POS
					13	3	328-2	Molecule-2	13	10	16.309	33.789	з
					14	+	nggi ^o	Molecule-2	14	10	13.104	27.433	4
					15	5	zzho	Molecule-2	Molecul	e-2	12.425	30.474	5
					16	5	3. Ar	Molecule-2	16	10	12.379	30.886	6
					13	7	3.4.0	Molecule-2	17	10	12.246	30.403	7
					18	3 "	je j	Molecule-2	18	10	12.172	30.493	8

Figure 1: Visualizaton of CDOCKER

ISSN: 0975-8585



			· · · ·							
× .	1. N 🖓 🖍	24 🔛								
ds	model - 3D Window	Dock Lig	ands (LibDock) - Hi	tml Window Mo	ecule - Table Browse	er Molecule	- Table Browser (1)	×		
	Structure	Name	Index	AbsoluteEnergy	ConfNumber	RelativeEnergy	MOL_NUMBER	POSE_NUMBER	LibDockScore	HotSpots
	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	Molecule-1	1	96.315	123	16.48	1	1	107.139	7.41,59.09
										10.21,55.8
	~d*									10.81,67.8
	and the	Molecule-1	2	94.886	103	15.051	1	2	105.237	6.61,60.8
	10									
		Molecule-1	3	94.419	115	14.583	1	3	104.497	3.81,59.4
	nes q									8.01,59.2
	. ÷Ż.	Molecule-1	4	94,799	120	14.964	1	4	104,435	6.61,60.8
	mon of	, interesting a		5		1.001			2011100	9.41,61.0
										11.61,67.
	maring	Molecule-1	5	94.886	103	15.051	1	5	101.319	4.81,59.8 6.61,61.2
	1									9.01,59.8
	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	Molecule-1	6	96.315	123	16.48	1	6	100.782	8.01,58.2
	· ~ V									
7) Ø 🗔				m				his copy of Windo	: localhost:9 ws is not ge
	celrys Discovery S	tudio		Chart Scripts V					his copy of Windo	: localhost:9 wws is not ge >) 9:12 PN
2	celrys Discovery S Edit View Cl 🔲 🍲 🕼 🦄	tudio nemistry Struc	ture Sequence	Chart Scripts V 중 교 교 (제)	Vindow Help	0 0 0 0	· 6 0 0		his copy of Windo	: localhost:9 wws is not ge >) 9:12 PN
*	celrys Discovery S Edit View Cl IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII	tudio nemistry Struc X & Pa X X	iture Sequence		Vindow Help		r ∂es ∂es ► €		his copy of Windo	: localhost:9 wws is not ge >) 9:12 PN
*	celrys Discovery S Edit View Cl 🔲 🍲 🕼 🦄	tudio nemistry Struc X & Pa X X	iture Sequence	Chart Scripts V → ☆ ☆ ☆ ☆ ☆ ☆ ☆ imi Window Mit AbsoluteEnergy	Vindow Help 해 순 또 문화				his copy of Windo	e localhost:9 www.is.not.ge) 9:12 PN
*	Edit View Cl Edit View Cl I I I I I I I I I I I I I I I I I I I	tudio nemistry Struc X & D : A SPC Dock Li	ture Sequence (1) R & (2) pands (LibDock) - Hi	> S⊋ ∰ 1∎0 1∎0 tml Window Me	Vindow Help 해 순 또 문화	r Molecule	- Table Browser (1) >		his copy of Windd	HotSpots
*	Celitys Discovery S Edit View Cl Cl St Cl St Cl Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St St Cl St Cl St St Cl St	tudio nemistry Struc X & D : A SPC Dock Li	ture Sequence (1) R & (2) pands (LibDock) - Hi	> S⊋ ∰ 1∎0 1∎0 tml Window Me	Vindow Help 해 순 또 문화	r Molecule	- Table Browser (1) >		his copy of Windd	HotSpots
*	Celitys Discovery S Edit View Cl Cl St Cl St Cl Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St St Cl St Cl St St Cl St	tudio nemistry Struc X & D : A SPC Dock Li	ture Sequence (1) R & (2) pands (LibDock) - Hi	· 중 소 또 또 ml Window Me AbsoluteEnergy	Vindow Help III 🚓 📉 🗍 🕫 Diecule - Table Browse ConfNumber	RelativeEnergy	- Table Browser (1) > MOL_NUMBER	Pose_NUMBER	his copy of Windo	HotSpots
*	Celitys Discovery S Edit View Cl Cl St Cl St Cl Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St St Cl St Cl St St Cl St	tudio nemistry Struc X & D : A SPC Dock Li	ture Sequence (1) R & (2) pands (LibDock) - Hi	Se (2) (m) (m) Mu Modew AbsoluteEnergy 96.315	Vindow Help III 🚓 📉 🗍 🕫 Diecule - Table Browse ConfNumber	r Molecule RelativeEnergy 16.48	- Table Browser (1) > MOL_NUMBER	Pose_NUMBER	his copy of Windc	HotSpots 9,01,59,85 9,01,59,85 9,01,59,85
*	Celitys Discovery S Edit View Cl Cl St Cl St Cl Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St St Cl St Cl St St Cl St	tudio nemistry Struc X & D : A SPC Dock Li	ture Sequence (1) R & (2) pands (LibDock) - Hi	· 중 소 또 또 ml Window Me AbsoluteEnergy	Vindow Help III 🚓 📉 🗍 🕫 Diecule - Table Browse ConfNumber	RelativeEnergy	- Table Browser (1) > MOL_NUMBER	Pose_NUMBER	his copy of Windo	HotSpots 9,01,59,87 4,81,59,87 4,81,59,87
*	Celitys Discovery S Edit View Cl Cl St Cl St Cl Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St St Cl St Cl St St Cl St	tudio nemistry Struc > X E Dock Lin Name Molecule-1	ture Sequence (1) R & (2) pands (LibDock) - Hi	Se (2) (m) (m) Mu Modew AbsoluteEnergy 96.315	Vindow Help III A Y P Necule - Table Browse ConfNumber 123	r Molecule RelativeEnergy 16.48	Table Browser (1) > MOL_NUMBER	Pose_NUMBER	his copy of Windc	HotSpots 9 0.1 59.88 4 8.19.88 9 0.1 59.88 9 0.1 59.88 9 0.1 59.88 9 0.1 59.88 9 0.1 59.88 9 0.1 59.88 9 0.1 59.88
*	Celitys Discovery S Edit View Cl Cl St Cl St Cl Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St St Cl St Cl St St Cl St	tudio nemistry Struu × X ⊡ ⊃ock Li Name Molecule-1 Molecule-1	ture Sequence (1) R & (2) pands (LibDock) - Hi	AbsoluteEnergy 96.315 93.167	Vindow Help III an Y P olecule - Table Browse ConfNumber 123 68	r Molecule RelativeEnergy 16.48 13.332	- Table Browser (1) > MOL_NUMBER 1	Pose_NUMBER	his copy of Windc	HotSpots 9,0199,85 0,0199,95 0,000,000,000,000,000,000,000,000,000,
*	Celitys Discovery S Edit View Cl Cl St Cl St Cl Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St Cl St Cl St Cl St Cl St Cl St St Cl St Cl St St Cl St Cl St St Cl St	tudio nemistry Struc > X Ib > Dock Lin Name Molecule-1	ture Sequence (1) R & (2) pands (LibDock) - Hi	Se (2) (m) (m) Mu Modew AbsoluteEnergy 96.315	Vindow Help III A Y P Necule - Table Browse ConfNumber 123	r Molecule RelativeEnergy 16.48	Table Browser (1) > MOL_NUMBER	Pose_NUMBER	his copy of Windc	HotSpots HotSpots HotSpots HotSpots HotSpots HotSpots HotSpots HotSpots
*	Edit View Cl Edit View Cl I I I I I I I I I I I I I I I I I I I	tudio nemistry Struu × X ⊡ ⊃ock Li Name Molecule-1 Molecule-1	ture Sequence (1) R & (2) pands (LibDock) - Hi	AbsoluteEnergy 96.315 93.167	Vindow Help III an Y P olecule - Table Browse ConfNumber 123 68	r Molecule RelativeEnergy 16.48 13.332	- Table Browser (1) > MOL_NUMBER 1	Pose_NUMBER	his copy of Windc	HotSpots 9,0199,85 0,0199,95 0,000,000,000,000,000,000,000,000,000,
*	Edit View Cl Edit View Cl I I I I I I I I I I I I I I I I I I I	tudio nemistry Structure X & Co. Pot Structure Dock Lit Name Molecule-1	ture Sequence (1) R & (2) pands (LibDock) - Hi	Image: Second	Vindow Help SIII A V S Secule - Table Browse ConfNumber 123 68 54	x Molecule RelativeEnergy 16.48 13.332 12.268	- Table Browser (1) > MOL_NUMBER 1 1	Pose_NUMBER	his copy of Winds	HotSpots 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,61,61,61,61,61,61,61,61,61,61,61,61,61
*	Edit View Cl Edit View Cl I I I I I I I I I I I I I I I I I I I	tudio nemistry Struu × X ⊡ ⊃ock Li Name Molecule-1 Molecule-1	ture Sequence (1) R & (2) pands (LibDock) - Hi	AbsoluteEnergy 96.315 93.167	Vindow Help III an Y P olecule - Table Browse ConfNumber 123 68	r Molecule RelativeEnergy 16.48 13.332	- Table Browser (1) > MOL_NUMBER 1	Pose_NUMBER	his copy of Windc	HotSpots 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,59,65 9.01,61,61,61,61,61,61,61,61,61,61,61,61,61
: >) ~	Edit View Cl Edit View Cl I I I I I I I I I I I I I I I I I I I	tudio nemistry Structure X & Co. Pot Structure Dock Lit Name Molecule-1	ture Sequence (1) R & 4	Image: Second	Vindow Help SIII A V S Secule - Table Browse ConfNumber 123 68 54	x Molecule RelativeEnergy 16.48 13.332 12.268	- Table Browser (1) > MOL_NUMBER 1 1	Pose_NUMBER	his copy of Winds	: localhost:99 wws is not ge)) 9:12 PN
*	Edit View Cl Edit View Cl I I I I I I I I I I I I I I I I I I I	tudio nemistry Structory Structory le 2 & Dock Li Name Molecule-1 Molecule-1 Molecule-1	Lure Sequence 23 ls v6///s 10 ls v6///s 10 rds rds 6 7 8 9	Image: Second	Vindow Help III con V 99 Jecule - Table Browse ConfNumber 123 68 54 80	r Molecule RelativeEnergy 16.48 13.332 12.268 14.193 14.193	- Table Browser (1) > MOL_NUMBER 1 1	POSE_NUMBER 6 7 8 9	LibDockScore 100.378 98.362	HotSpots Hot
*	Edit View Cl Edit View Cl I I I I I I I I I I I I I I I I I I I	tudio nemistry Structure X & Co. Pot Structure Dock Lit Name Molecule-1	ture Sequence (1) R & 4	Image: Second	Vindow Help SIII A V S Secule - Table Browse ConfNumber 123 68 54	x Molecule RelativeEnergy 16.48 13.332 12.268	- Table Browser (1) > MOL_NUMBER 1 1 1	Pose_NUMBER	his copy of Winds	HotSpots 9,01,59,85 8,01,59,25 9,01,59,85 9,01,59,85 9,01,59,85 9,01,59,85 9,01,59,85 9,01,59,85 9,01,59,85 9,01,59,85 8,01,59,85 9,01,59,85 8,01,59,15 9,01,59,85 8,01,59,15 9,01,59,85 8,01,59,15 9,01,59,85 8,01,21,01,01 9,01,59,85 8,01,21,01,01 9,01,59,85 8,01,21,01,01 9,01,59,85 8,01,21,01,01 9,01,59,85 8,01,21,01,01 9,01,59,85 8,01,21,01,01 9,01,59,85 8,01,21,01,01 9,01,59,85 8,01,21,01,01 9,01,59,85 8,01,21,01,01 9,01,59,85 8,01,59,
*	Edit View Cl Edit View Cl I I I I I I I I I I I I I I I I I I I	tudio nemistry Structory Structory le 2 & Dock Li Name Molecule-1 Molecule-1 Molecule-1	Lure Sequence 23 ls v6///s 10 ls v6///s 10 rds rds 6 7 8 9	Image: Second	Vindow Help III con V 99 Jecule - Table Browse ConfNumber 123 68 54 80	r Molecule RelativeEnergy 16.48 13.332 12.268 14.193 14.193	- Table Browser (1) > MOL_NUMBER 1 1 1	POSE_NUMBER 6 7 8 9	LibDockScore 100.378 98.362	HotSpots Hot

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.



REFERENCES

- [1] http://online.wsj.com/article/SB119725064671318856.html.
- [2] Mark Brooker. "Registry of Clotting Factor Concentrates". Eighth Edition, 2008, World Federation of Hemophilia, 2008.
- [3] Hoffman M, Monroe MM. Hematology/Oncology Clinics of North America 2007;21 (1):1-11.
- [4] Turpie AG. Arterioscl Thromb Vasc Biol, 2007;27 (6):1238-47.
- [5] Broze G J, Warren L A, Novotny W F, Higuchi D A, Girard J J, Miletich J P. Blood (UNITED STATES) 1988;71 (2): 335–43.