https://doi.org/ 10.33472/AFJBS.6.9.2024.839-859

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Computational Pharmacokinetic Analysis and Molecular Docking Studies for FXa Inhibitors as Thrombolytic Agents

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Article History

Volume 6,Issue 9, 2024

Received:21 Mar 2024

Accepted : 22 Apr 2024

doi: 10.33472/AFJBS.6.9.2024.839-859

Abstract:

Background: As world economy develops, with advance and updated lifestyle profoundly, the chronic diseases happenings rise continually. Cardiovascular diseases (CVD), is group of disorder and leading cause of mortality from last three decades. Despite significant advances in cardiovascular disease in prevention and treatment, the morbidity and mortality increase continually in developed countries. Underlying causes of cardiovascular disease are multiple factors, complex mechanisms and some common components at end stage that carries thrombosis. Number of safe and effective antithrombotic drugs plays critical role in the treatment of cardiovascular diseases.

Objective: The *Insilco* methodologies are in use now-a days can impacts the entire drug development process as identifying and discovering new potential drug is time and cost effective. Here, we are using different *Insilco* methodologies to study FXa inhibition activity.

Methods: In our present work, we screened and assesses the toxic profile of the selected ligands by OSIRIS property explorer and TOXTREE web server online source in order to obtain the novel or potent molecule for designing.

Result: In our present work, total seven compounds were taken and using in-silico approach only three L1, L4 and L5 showed a remarkable binding energy, therapeutics activity in addition to pharmacological activity.

Conclusion: Further, directional approach is also need in clinical trials and commercialization. All the selected ligands satisfactorily accepted and developing a new agent.

Keywords: ADME, Drug likeliness, thrombolytics, QSAR studies, biological activity, toxicity

1. Introduction

Globally, over the last few decades an estimated 17.9 million peoples dies due to cardiovascular diseases (CVD) and has been growing exponentially among developed and developing nations [1]. As world economy develops, with advance and updated lifestyle profoundly, the chronic diseases happenings rise continually. Cardiovascular diseases (CVD), is group of disorder and leading cause of mortality from last three decades [2,3]. As per the GBR report, the occurrence of CVD in men is more as compared to women, men mortality was 9,346,335 [9,173,337–9,526,547] and in women 8,444,614 [8,266,536–8,615,992] [4].

Technological advancements automate the world and transforming healthcare system via innovations, new devices but emergence of chronic disorders is still increases [5]. Despite significant advances in cardiovascular disease in prevention and treatment, the morbidity and mortality increase continually in developed countries. Underlying causes of cardiovascular disease are multiple factors, complex mechanisms and some common components at end stage that carries thrombosis. Number of safe and effective antithrombotic drugs plays critical role in the treatment of cardiovascular diseases [6].

On pathogenesis basis, thromboembolic events play a pivotal role for occurrence of via Acute Coronary Syndrome (ACS), Unstable angina, Pulmonary Embolism (PE), Deep Venous Thrombosis (DVT), Venous Thromboembolism (VTE) and Ischemic stroke [7,8]. Traditionally, warfarin and heparin were used as pharmacotherapies and have been extensively in use but carries some limitations as interactions with other drugs and foods, monitoring clotting time [9]. With reference to anticoagulant, FXa (Coagulation enzyme factor Xa) is located at conglomerate point between coagulation cascade (intrinsic and extrinsic) and works as a promising target for converting fibrinogen to fibrin (soluble) [10]. From last decades, number of oral, Selective and Direct FXa inhibitors include: Apixaban, Betrixaban, Edoxaban, Rivaroxaban These are all approved and are currently in clinical studies [11,12]. All factor Xa (FXa) inhibitors are more specific and lowers the risk of bleeding time by preventing the conversion of prothrombin to thrombin [13]. On the available data, apixaban becomes the novel scaffold and further developments as combating the complications of bleeding and reducing the overdose and quantity of administer dosage then series of derivatives were synthesized and step forwards towards the drug discovery and drug development [14,15].

In the design of novel drug, conventional drug discovery and development processes (discovery for novel molecule and its optimization, target finding and its validation, preclinical and clinical trials and its approval) are time consuming, risky, costly [16-18]. Recently developed and first approach in terms of drug design, CADD (Computer-aided

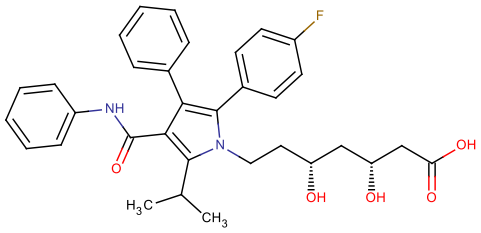
drug design) in collaboration with wet laboratory structure elucidation, mechanism and active site or target irrespective of novel and known targets becomes boon for researchers and academicians [19]. The *Insilco* methodologies are in use now-a days can impacts the entire drug development process as identifying and discovering new potential drug is time and cost effective [20-25]. Computer-aided drug design, utilizes the available information and knowledge for screening of novel drug candidates and estimates the hazardous effects by interacting the one bond with other including toxicity. In our present work, we screened and assesses the toxic profile of the selected ligands by OSIRIS property explorer and TOXTREE web server online source in order to obtain the novel or potent molecule for designing [26,27].

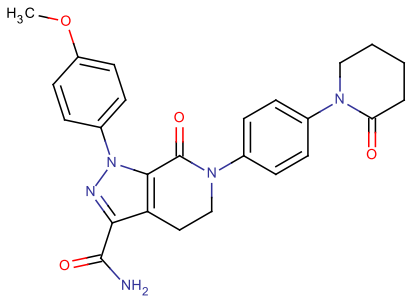
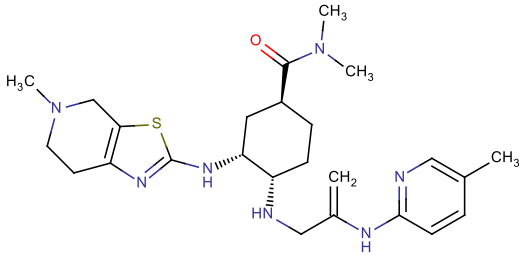
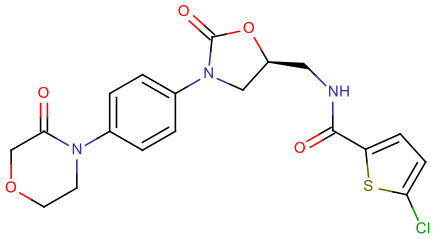
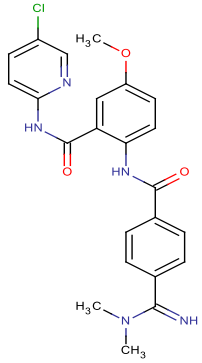
2. Methods

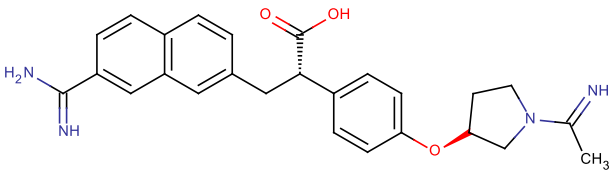
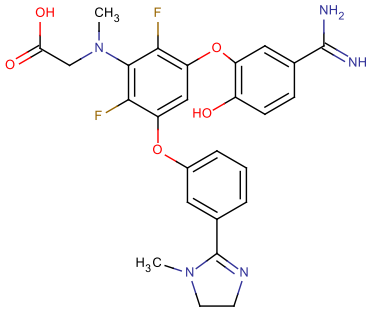
2.1. Protein Preparation for FXa inhibitor and Optimization of Ligands

For clarification of binding site of compounds, in detailed docking studies was carried out. The protein structure for human FXa inhibitors (PDB Id:2P16) was downloaded from Protein data Bank (https://www.rcsb.org) in pdb format with resolution between 2.1 to 2.5A. From literature survey, ligands(L1-L6) (Table 1) with specific binding site were searched and downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov) in Structured Data Format (SDF) format then these were drawn by using Chem Draw Ultra (Cambridge Soft Corporation, USA) and their smiles were generated and saved in .mol file in order to carry out docking. For theoretical validation, the structures were optimized for ADME and in silico investigations were also performed in order to get minimum energy by Avogadro Software v1.2.0. Furthermore, all ligands were evaluated for biological activities and ADME properties as a result of structural input.

Table 1: Description of selected Ligands

Ligand	Chemical Structure	Molecular Weight (g/mol)
L(Atorvastatin)		558.6

L1 (Apixaban)		459.5
L2 (Edoxaban)		548.1
L3 (Rivaroxaban)		435.9
L4 (Betrixaban)		451.9

L5 (DX-9065a)		571.1
L6 (ZK-807834)		526.5

2.2. Evaluation of ADME and Docking studies

SwissADME algorithm (http://www.swissadme.ch) was used to perform the analysis of ADME properties of selected ligands. Within screening, SMILES format was used for analysis of bioavailability and major pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the selected ligands [28]. The drug's absorption depends on Gastro-Intestinal absorption (GSI), membrane & skin permeability, water solubility and P-gp substrate. The Blood-Brain Barrier (BBB) take hold of the drug distribution.

The volume of distribution and metabolism evaluation is carried out by using CYP models such as CYP3A4, CYP2C9 and CYP1A2 inhibitor [29]. At last, excretion depends on renal OCT2 substrate and total clearance and results are in Table 2.

2.3. Drug score and toxicity prediction of selected compounds

In the drug discovery and development process, the designing of compounds by computational based designing especially in molecular structural compounds to the biopharmaceutical formulation for installation into retail should be safe for oral usage drugs. For medications to enter the bloodstream by oral absorption, they must demonstrate GI tract absorption. Hence, for drug-likeliness prediction, drug dissolution i.e., Solubility (Log S) is the important parameter. Furthermore, by OSIRIS tool [30], the simulation was also performed as solubility, drug –likeliness, Drug score and toxicity predictions (skin irritations, tumorigenic, mutagenic and reproductive effect) of selected or studied compounds (L1- L6) were noted in tabular form. Highly toxic (Red color), medium (Yellow color) and no toxicity (Green color).

Additionally, for comparison, we added the SMILES of ligands in Toxtree (3.1.0.1851 version) openly accessible software, wherein the decision-tree method for evaluating toxic risks covers factors such as Cramer's rule, eye irritation, genotoxicity, carcinogenicity, corrosion, and skin sensitivity, among others. and results are obtained in table after processing [31]. Furthermore, CLC (Cell Line Cytotoxicity predictor) is a web-based service was used for Cytotoxicity prediction to evaluate the hazardous or cytotoxic effects of organic compounds [32-35].

2.4. Target prediction and Bioactivity prediction

For docking, the targeted site and active site plays an important role in simulation studies. The specific site prediction and binding site for protein binding with selected compounds (FXa inhibitors) is crucial for structure-based docking. For target prediction, Swiss target prediction (http://www.swisstargetprediction.ch) was use [36]. Molinspiration, a web-based tool for bioactivity score prediction. From drug score overall potential of the drug molecule were checked and the from its bioactivity score of the selected compounds were evaluated against human receptors i.e., kinases, nuclear receptors, ion channels, GPCRs, proteases and enzymes. Molinspiration Cheminformatics Online Server shows the biological characteristics of the selected ligands [37].

2.5. Docking studies of selected ligands (L1-L6)

From ADME profile, drug score, target prediction and toxicity profile of the selected compounds, the best drug score and best targeted site predicted and then after toxicity prediction software least toxic compounds were selected for docking. We utilized CB-Dock 2 Online platform (a user–friendly, freely available and used for blind docking) for binding energies prediction automatically. This web server can be accessed at https://cadd.labshare.cn/cb-dock2/ and provides interactive 3D visualization of results. CB-Dock 2, is an improved version that detects the cavities on proteins on basis of clustering of solvent-accessible surface and calculates automatically the active centers and size of cavity [38].

3. Results

During new drug development/ processing, various types of unfavorable absorption, distribution, metabolism, and elimination properties are the main cause of new drug molecules being rejected. Computer-Aided Drug Design (CADD) is a systematic approach that uses ADME properties to predict the properties of high-quality drugs [39,40]. However, there is unexpected rise in demand for the *In-silico* prediction tools for ADME properties before planning of synthesis of any novel drug molecule. Within this context, ADME or physicochemical properties for all selected ligands i.e., L1-L6 ligands

were assayed on the basis of their water-solubility, lipophilicity, drug-likeliness, pharmacokinetics and in reference to medicinal chemistry as Lipinski's rule of 5 for all drug candidates such as no. of H-bond acceptors is less than 10, H-bond donors is less than 5, molecular weight less than 500Da and log P value is less than 5 in the reference with standard drug (L). Swiss dock- ADME analysis is illustrated in Table 2. It can be observed from table 2, significant ADME analysis results and docking results of selected ligands as binding energies were evaluated individually for all ligands [41-44].

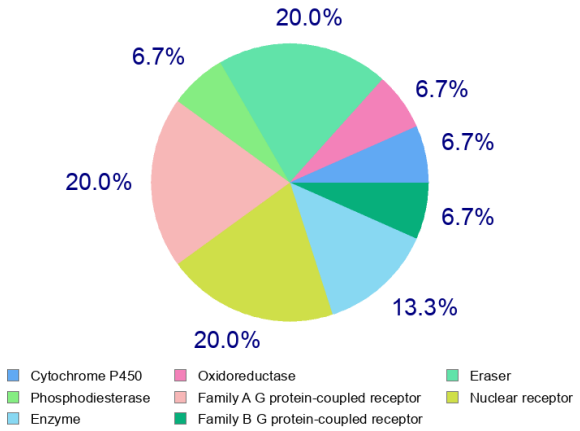
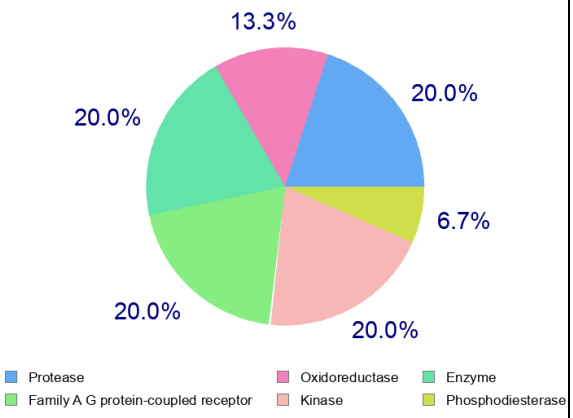
Table 2: Results of ADME and docking studies

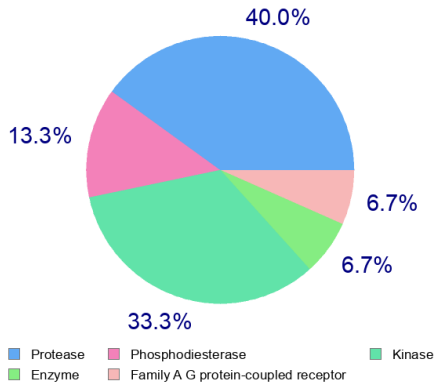
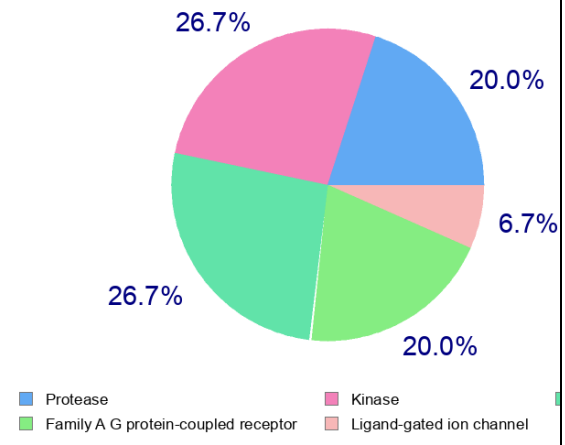
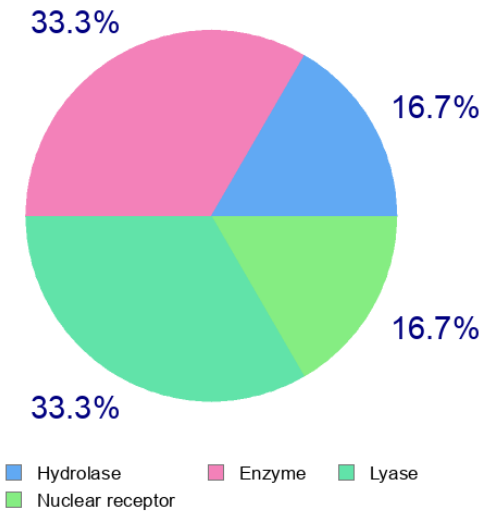
Ligands	Physicochemical Properties#	Lipophilicity	Water Solubility	Pharmacokinetics	Drug likeness	Medicinal Chemistry	Docking results Binding energies (kcalMol^{-1})
L (Atorvastatin)	MF = $C_{33}H_{35}FN_2O_5$ MW =558.64g/mol nHA =41 nArHA =23 Fraction (Csp3) = 0.27 nRB = 13 nHBA = 6 nHBD = 4 MR = 158.26 TPSA = 111.79A2	Log $P_{o/w}$ (iLOGP) = 3.81 Log $P_{o/w}$ (XLOGP3) = 4.96	Log S (ESOL) = -5.99 Solubility = 1.03e-0.6 mol/l Class = Soluble	GI absorption = Low BBB permeant = No P-gp substrate = Yes CYP1A2 inhibitor = No CYP2C19 inhibitor = Yes	Lipinski = Yes; 1 violation Ghose = No Veber = No Egan = No Muegge = Yes Bioavailability Score = 0.56	PAINS = 0 alert Lead likeness = No; 3violation: Synthetic accessibility = 4.95	-7.8
L1 (Apixaban)	MF = $C_{25}H_{25}N_5O_4$ MW = 459.50 g/mol nHA = 34 nArHA = 17 Fraction (Csp3) = 0.28 nRB = 5 nHBA =5 nHBD = 1 MR = 132.70 TPSA =110.76 A^2	Log $P_{o/w}$ (iLOGP) = 3.62 Log $P_{o/w}$ (XLOGP3) = 2.24	Log S (ESOL) = -4.14 Solubility = 7.24e-0.5 mol/l Class = Moderately soluble	GI absorption = High BBB permeant = No P-gp substrate = Yes CYP1A2 inhibitor = No CYP2C19 inhibitor = Yes	Lipinski = Yes; 0 Violation Ghose = Yes Veber = Yes Egan = Yes Muegge = No; 2 violations: MW<200; XLOGPS<-2 Bioavailability Score = 0.55	PAINS = 0 alert Lead likeness = No Synthetic accessibility = 3.48	-10.1

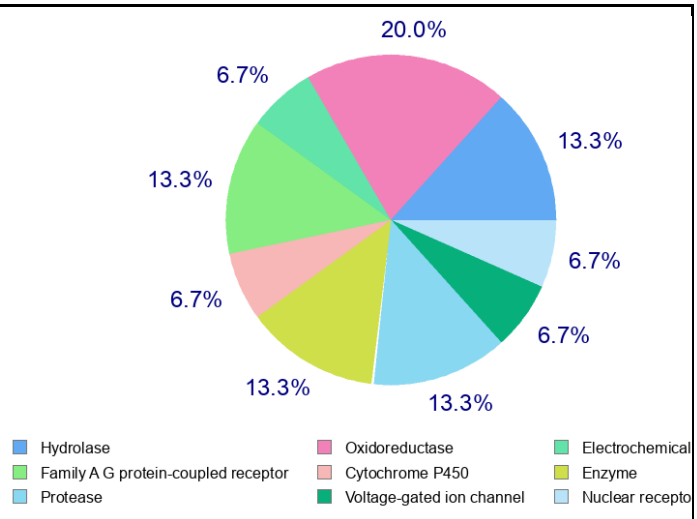
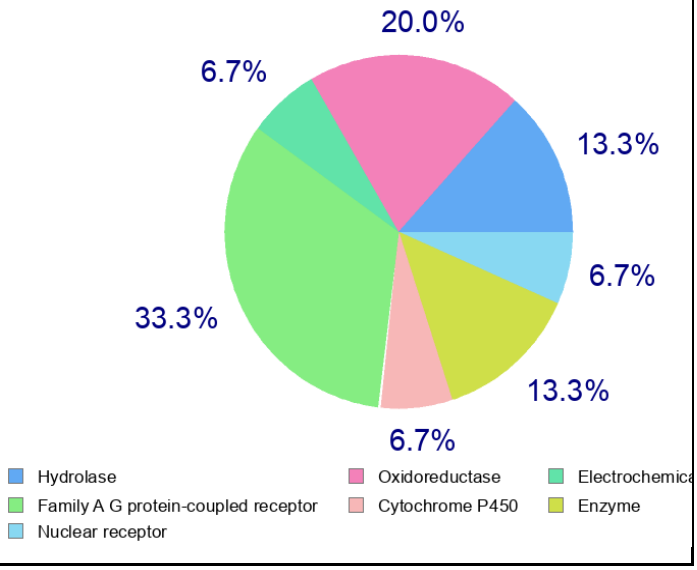
L2 (Edoxaban)	MF = $C_{24}H_{30}ClN_7O_4S$
	MW = 548.06 g/mol
	nHA =37
		Log $P_{o/w}$ (iLOGP) = 2.97
		Log $P_{o/w}$
			Log S (ESOL) = -3.69
			Solubility = 2.03E-04 mol/l
				GI absorption = Low
				BBB permeant = No
				P-gp substrate = Yes
				CYP1A2
					Lipinski = No; 2 Violation
					Ghose = No; 2 violations: #atoms<20
					Veber = No
						PAINS = 0 alert
						Lead likeness = No; 2 violations
							-8.7

	nArHA =11 0Fraction (Csp3) = 0.50 nRB = 10 nHBA = 7 nHBD = 3 MR = 143.24 TPSA = 164.87 A^2	(XLOGP3) = 1.42	Class = soluble	inhibitor = No CYP2C19 inhibitor = No	Egan = No Muegge = No; 1 violation: MW<200 Bioavailability Score = 0.55	Synthetic accessibility = 5.04	
L3 (Rivaroxaban)	MF = $C_{19}H_{18}ClN_3O_5S$ MW = 435 g/mol nHA = 29 nArHA = 11 Fraction (Csp3) =0.32 nRB = 6 nHBA =5 nHBD = 1 MR = 114.09 TPSA =116.42 A^2	Log $P_{o/w}$ (iLOGP) = 2.66 Log $P_{o/w}$ (XLOGP3) = 2.49	Log S (ESOL) = -.4.00 Solubility = 1.01e-04 mol/l Class = Soluble	GI absorption = High BBB permeant = No P-gp substrate = Yes CYP1A2 inhibitor = No CYP2C19 inhibitor = Yes	Lipinski = Yes; 0 violation Ghose = Yes Veber = Yes Egan = Yes Muegge = Yes Bioavailability Score = 0.55	PAINS = 0 alert Lead likeness = No; 1 violation: MW<350 Synthetic accessibility = 3.63	-8.8
L4 (Betrixaban)	MF = $C_{23}H_{22}ClN_5O_3$ MW = 451.91 g/mol nHA = 32 nArHA = 18 Fraction (Csp3) = 0.13 nRB = 9 nHBA =5 nHBD = 3 MR = 125.23 TPSA =107.41 A^2	Log $P_{o/w}$ (iLOGP) = 2.72 Log $P_{o/w}$ (XLOGP3) = 3.56	Log S (ESOL) = -4.71 Solubility = 1.96e-05 mol/l Class = Moderately soluble	GI absorption = High BBB permeant = No P-gp substrate = No CYP1A2 inhibitor = No CYP2C19 inhibitor = Yes	Lipinski = Yes; 0 violation Ghose = Yes Veber = Yes Egan = Yes Muegge = Yes Bioavailability Score = 0.55	PAINS = 0 alert Lead likeness = No; 3 violations: MW<250 Synthetic accessibility = 3.05	-9.9
L5 (DX-9065a)	MF = $C_{26}H_{39}ClN_4O_8$ MW =571.06 g/mol nHA =39 nArHA =16 Fraction (Csp3) = 0.27 nRB = 8 nHBA =10 nHBD = 9 MR = 157.07 TPSA = 169.64 A^2	Log $P_{o/w}$ (iLOGP) = 0.00 Log $P_{o/w}$ (XLOGP3) = 1.78	Log S (ESOL) = -4.28 Solubility = 5.28e-05 mol/l Class = Moderately Soluble	GI absorption = Low BBB permeant = No P-gp substrate = No CYP1A2 inhibitor = No CYP2C19 inhibitor = No	Lipinski = No; 3 Violation Ghose = No; 3 violations: Veber = No Egan = No Muegge = No; 2 violations: MW<200 Bioavailability Score = 0.17	PAINS = 0 alert Lead likeness = No; 2 violations Synthetic accessibility = 4.51	-11.5
L6 (ZK-807834)	MF = $C_{25}H_{24}F_2N_6O_5$	Log $P_{o/w}$ (iLOGP) = 2.87	Log S (ESOL) = -4.28 Solubility	GI absorption = Low BBB permeant = No	Lipinski = No; 2 violations Ghose = No;	PAINS = 0 alert Lead likeness =	-9.6

	MW =526.49 g/mol nHA =38 nArHA =18 Fraction (Csp3) = 0.20 nRB = 9 nHBA = 10 nHBD = 4 MR = 142.35 TPSA = 157.59 A^2	Log $P_{o/w}$ (XLOGP3) = 2.25	= 5.27e-05 mol/l Class = Moderately soluble	P-gp substrate = Yes CYP1A2 inhibitor = No CYP2C19 inhibitor = No	2 violations: Veber = No Egan = No Muegge = No; 1 violation: Bioavailability Score = 0.55	No. 2 violation Synthetic accessibility = 4.03	

Ligands	**Anatomical Therapeutic Chemical (ATC) Classification**	**Class (Best)**	**Pie Chart**
L (Atorvastatin)	**C10AA:** HMG CoA reductase inhibitors, plain lipid modifying drugs **C10A:** lipid modifying agents, plain **C10:** lipid modifying agents	Cardiovascular system drugs	
L1 (Apixaban)	**B01af:** Direct Factor Xa Inhibitors **B01a:** Antithrombotic Agents **B01:** Antithrombotic Agents	Blood And Blood Forming Organ Drugs Enzymes Family A G-protein-coupled receptor	

L2 (Edoxaban)	**B01AF:** Direct factor Xa inhibitors **B01A:** ANTITHROMBOTIC AGENTS	Blood and blood forming organ drugs Protease Kinase	
L3(rivaroxaban)	**B01AF (95%)**	Lyase Hydrolase Enzyme	
L4 (Betrixaban)	**B01AF:** Direct factor Xa inhibitors	Lyase	

L5 (DX-9065a)	**B01AF:** Direct factor Xa inhibitors	Oxidoreductase	
L6 (ZK-807834)	**B01AF:** Direct factor Xa inhibitors	Family A G protein-coupled receptor	

In order to carry out docking, binding energies of ligand and receptors plays an important role to bind specifically to show specific biological activity. From table 2, the binding energies of ligands as L1, L4 and L5 showed remarkable binding energies as -10.5, -9.9 and -11.5 respectively from all selected ligands (L, L1- L6). Docking results of chosen ligands i.e., L, L1-L6 outlined in Table 7. SwissADME, and docking studies showed that only the three L1, L4 and L5 showed the highest performance and were chosen for further processing, and were also considered suitable for high-grade FXa inhibitors.

In order to check biological activity score, results from Molinspiration in table 3 showed L1, L4 and L5 magnificent biological activity score. Furthermore, the ATC (Anatomical Therapeutic Chemical) classification system showed the relationship of drug's therapeutic, chemical properties and pharmacological activities of selected drugs. ATC classification system is a drug classification system that categorizes a drug's directing activity to a specific organ based on its

therapeutic, chemical and pharmacological properties [45,46]. It serves as a tool to track the usage of drugs as well as to enhance the quality of drug use for research. Figured results for different cell line cytotoxicity's for selected ligands (L, L1- L6) were illustrate in Table 4. In combination with the Pa values and Pi values, the bioavailability score demonstrated good drug-like properties and also has great potential for the development of an oral drug for its therapeutic use. Our study displayed, the L1, L4 and L5 considered to be safe and effective for FXa inhibitors. Although, L1, L4 and L5 having minute toxicities as per OSIRIS property explorer, Toxtree and cell-lines cytotoxicity investigations but can be further investigated for better ADME and reduction of toxicities, efforts to be carried out.

Table 3: Molinspiration-predicted biological characteristics of L1-L6

Ligand	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
L(Atorvastatin)	0.13	-0.14	-0.07	0.18	0.27	0.21
L1 (Apixaban)	-0.00	-0.29	-0.15	-0.31	-0.01	0.01
L2 (Edoxaban)	0.11	-0.31	-0.24	-0.70	0.34	-0.04
L3 (Rivaroxaban)	0.40	-0.25	-0.32	-0.14	0.43	0.11
L4 (Betrixaban)	0.19	-0.04	0.17	-0.39	0.40	-0.01
L5 (DX-9065a)	0.77	0.52	0.05	0.24	1.21	0.49
L6 (ZK-807834)	0.77	0.36	0.15	-0.10	0.97	0.48

Table 4: Drug score and toxicity prediction of studied ligands using OSIRIS freeware

Ligand	Log S	Drug likeliness	Drug score	Mutagenic	Tumorigenic	Reproductive effect	Irritant
L(Atorvastatin)	-6.92	-4.036	0.15	1		0.6	1
L1 (Apixaban)	-4.317	-0.372	0.168	0.6	0.6	1	1
L2 (Edoxaban)	-2.801	7.361	0.644	1	1	1	1
L3 (Rivaroxaban)	-4.558	-2.413	0.129	0.6	0.6	1	1
L4 (Betrixaban)	-3.946	-0.815	0.564	1	1	1	1
L5 (DX-9065a)	-3.369	5.391	0.672	1	1	1	1
L6 (ZK-807834)	-5.722	-1.277	0.282	1	1	1	1

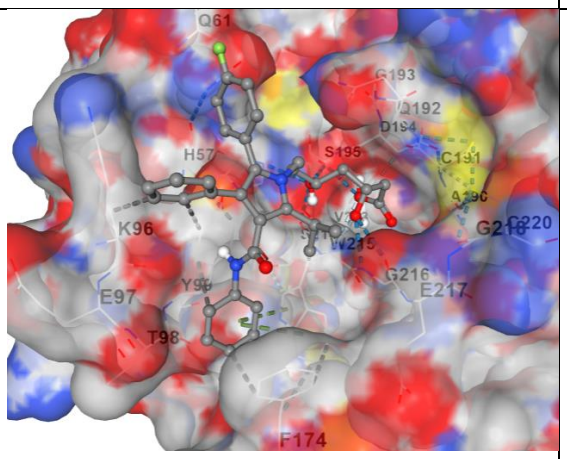
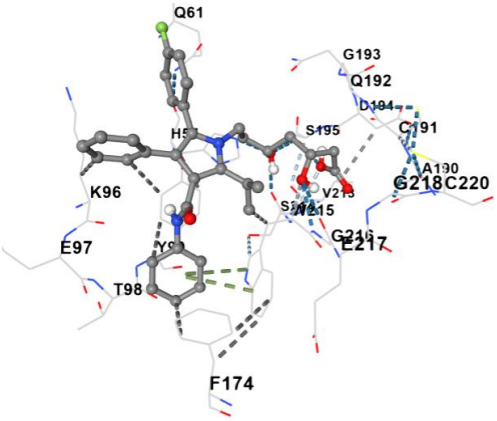
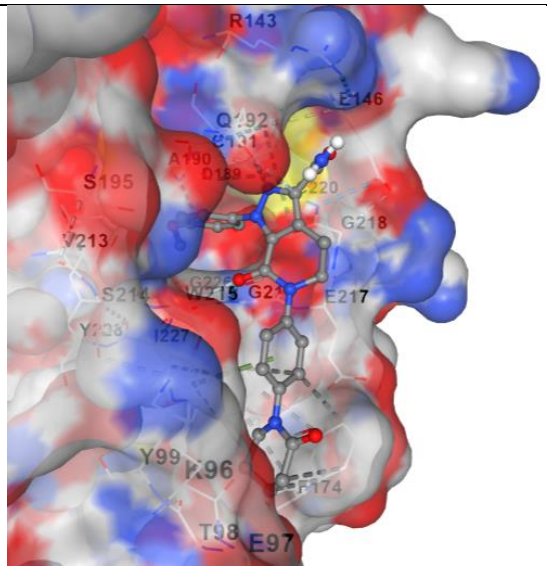
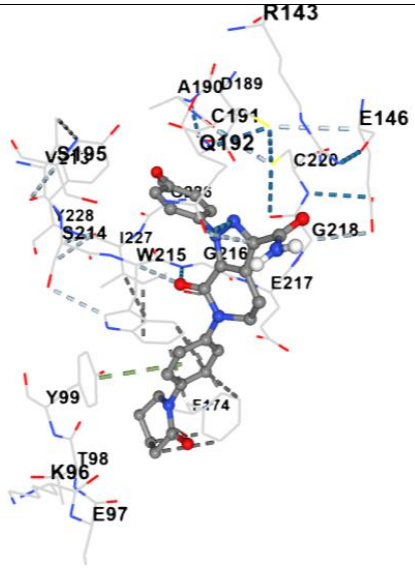
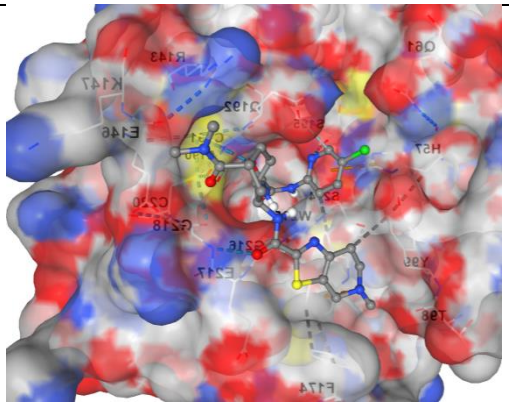
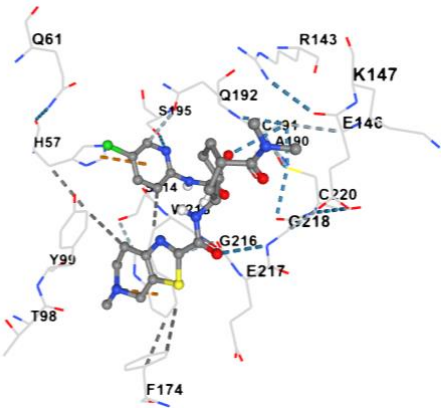
Table 5: Prediction of cell line cytotoxicity's of L, L1-L6

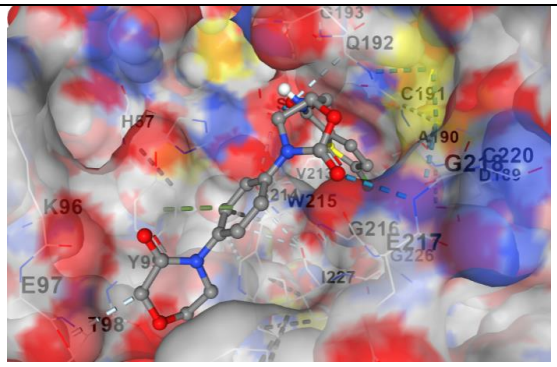
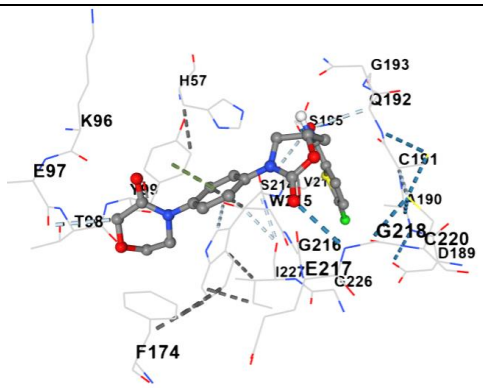
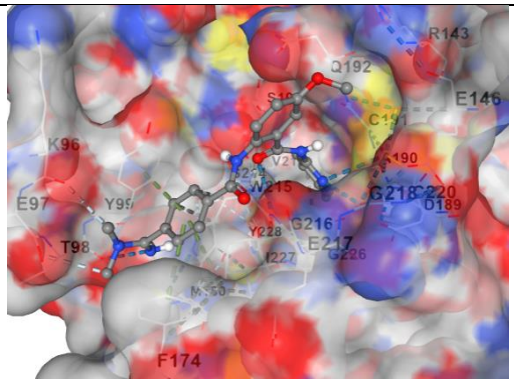
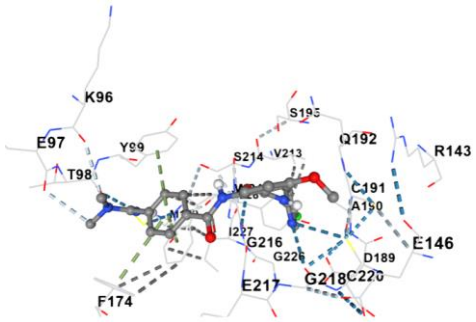
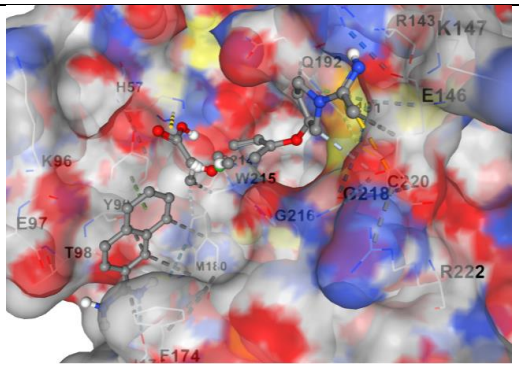
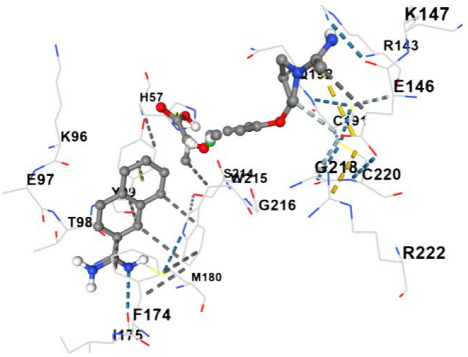
Ligand	Pa values	Pi values	Cell -line details
L(Atorvastatin)	0.390	0.085	Hep G2, Hepatoblastoma
L1 (Apixaban)	0.575	0.009	A2780. Ovarian carcinoma
L2 (Edoxaban)	0.398	0.064	Kasumi-1, Acute myeloblastic leukemia
L3 (Rivaroxaban)	0.307	0.171	CAKI-2, Kidney carcinoma
L4 (Betrixaban)	0.363	0.037	MDA-MB-468, Breast adenocarcinoma
L5 (DX-9065a)	0.438	0.191	A2780cisR, Cisplatin-resistant ovarian carcinoma
L6 (ZK-807834)	0.350	0.173	MCF7, Breast carcinoma

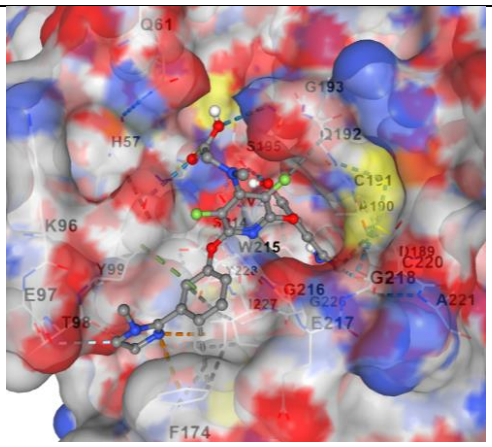
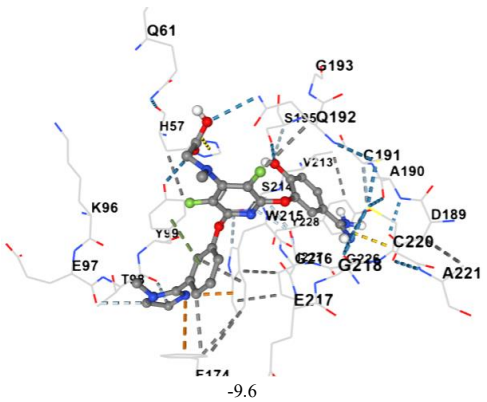
Table 6: Toxicity prediction of studied ligands using toxtree freeware

Ligand	Crammer's rule	Kroes TTC decision tree	Skin sensitivity	Genotoxic carcinogenicity	Potential carcinogen based on QSAR
L(Atorvastatin)	High class	Low risk	No	No	No
L1 (Apixaban)	High class	Low risk	No	Yes	No
L2 (Edoxaban)	High class	Low risk	No	No	No
L3 (Rivaroxaban)	High risk	low risk	No	No	No
L4 (Betrixaban)	High risk	Low risk	No	No	No
L5 (DX-9065a)	High risk	Low risk	Yes	Yes	No
L6 (ZK-807834)	High risk	Low risk	Yes	No	No

Table 7: Representation of Docking studies of ligands (L, L1-L6)

Ligand	Representation of Docking studies	Dock Score
L (Atorvastatin)		 -7.8
L1 (Apixaban)		 -10.1
L2 (Edoxaban)		

		-8.7
L3 (rivaroxaban)		 -8.8
L4 (Betrixaban)		 -9.9
L5 (DX-9065a)		 -11.5

L6 (ZK-807834)		

4. Discussion

Computer-Aided Drug Design (CADD) is a systematic approach that uses ADME properties to predict the properties of high-quality drugs. ADME or physicochemical properties for all selected ligands i.e., L1-L6 ligands were assayed on the basis of their water-solubility, lipophilicity, drug-likeliness, pharmacokinetics and in reference to medicinal chemistry as Lipinski's rule of 5 for all drug candidates in the reference with standard drug (L). SwissADME, and docking studies showed that only the three L1, L4 and L5 showed the highest performance and were chosen for further processing, and were also considered suitable for high-grade FXa inhibitors.

5. Conclusion

From the last few decades, the research focused on the cheap, potent, safe and sustainable products for world. In our present work, total seven compounds were taken and only three L1, L4 and L5 showed a remarkable binding energy, therapeutics activity in addition to pharmacological activity. In our in-silico approach, L1, L4 and L5 showed remarkable binding energies as -10.5, -9.9 and -11.5 respectively and significant bioavailability score as well as good drug-likeness properties. Further, directional approach is also need in clinical trials and commercialization. All the selected ligands satisfactorily accepted and developing a new agent.

6. Acknowledgement

Authors are acknowledged Department of Pharmaceutical Sciences and Drug Research, Punjabi University Patiala for moral support and some critical suggestions.

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