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REVIEW OF SERINE PROTEASE INHIBITORS: DEVELOPMENT AND APPLICATIONS

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A class of enzymes known as proteases is responsible for catalyzing the breakdown of covalent peptide bonds. Proteases account for almost 2% of the genes in humans, infectious organisms, and other forms of life. Serine proteases, so named because they have a nucleophilic serine residue at the active site, make for nearly one-third of all proteases. Although digesting is their primary role in humans, they also play roles in immunological response, apoptosis, inflammation, blood coagulation, and signal transduction. They are therefore very attractive biological targets for the design of pharmacological molecules that can modulate their activity.

This review presents a description of the catalytic activity and structure of serine proteases, and the different strategies to develop inhibitors. Serine protease inhibitors targeting thrombin, FXa, and human neutrophil elastase (HNE), and dipeptidylprotease-4 (DPP4) will be described. It includes therapeutically applied, and those drugs which are still under investigation in clinical trials in the last two decades.

Keywords: *Serine protease inhibitor, Thrombin, FXa, HNE, DPP4*

INTRODUCTION

Serine proteases make up nearly a third of all proteases and play key roles in digestion, blood clotting, fibrinolysis, immune response, cleavage of pro-hormone, signal transduction, and complement fixation[1-3]. Serine proteases like other proteases are strictly regulated in the body. They are typically released in inactive forms or 'zymogenic' precursors, which become mature by cleaving the N-terminal end. Furthermore, endogenous inhibitors, which bind covalently or non-covalently to inactivate the protease ensure direct regulation of the proteases. For instance, a family of proteins known as serpins (serine protease inhibitor) has structural similarity that irreversibly inhibit serine proteases[4]. This regulation allows the maintenance of homeostasis in a variety of physiological systems.

Furthermore, their dysregulation is linked to a variety of illnesses including pulmonary diseases, cardiovascular disorders, inflammatory processes, cancer and Alzheimer's disease[5-7]. Serine proteases are thus appealing and viable targets for the development of enzyme inhibitors since they are involved in the pathogenesis of several disorders. The development of such compounds requires a thorough understanding of their catalytic mechanism and structure[8-10]. Protease inhibitors are extensively discussed in the literature demonstrating that academic and industry laboratories are particularly interested in them[11&12]. Selected serine protease inhibitors which are still in clinical trial phases and/or placed on the market are illustrated in Table (1)[13&14].

This study will address the characteristics of serine proteases as well as inhibitory techniques that target blood coagulation and inflammatory processes, as well as the relevant FDA-approved inhibitors as anticoagulant and anti-inflammatory drugs and others in clinical trials in the last two decades. This review is based on research from PubMed database,

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Research gate, Google scholar, Science direct, company websites, and FDA website.

Serine protease: Catalytic activity and specificity

The specificity of cleavage of a given protease is determined by how a protein or peptide substrate interacts with the protease residues at the active site. Substrate amino acid chains occupy enzyme sub-sites in the groove, where amide bond hydrolysis takes place[15]. From each side of the cleavage site, the subsites are numbered S1–Sn to the N-terminus and toward S1′–Sn′ to the C-terminus of the substrate **(Fig. 1).** P1–Pn and P1′–Pn′ are the numbers for the corresponding residues on the substrate.

Based on their affinity for cleaved residues (P1) serine proteases can be classed as trypsin, chymotrypsin, or elastase analogs[16]. The scale and function of the residue involved in the enzyme's catalytic pocket directs this precision.

Trypsin or trypsin-like analogs cleave after lysine or arginine residue. Tyrosine, phenylalanine, and leucine are examples of big hydrophobic residues that can be adopted by the chymotrypsin-like S1 pocket due to its hydrophobicity and width[17&18]. On the other hand, tiny hydrophobic residues like alanine and valine can be incorporated into the elastase-like S1 pocket[19]. The identification of the whole peptide portion can be necessary for some protease activities. For instance, enterokinase's S1–S5 subsites need to engage with an Asp–Asp–Asp–Lys sequence to function properly[20].

The catalytic triad (Asp His Ser) defines the catalytic location (Figure 2) and has the ability to increase the nucleophilicity of serine residues[21].

The Ser195 hydroxyl group serves as a nucleophile throughout the peptide cleavage, His57 acts as a general base/acid catalyst, and Asp102 helps His57 adopt the correct orientation. The carbonyl group of the substrate peptide bond (scissile bond) is initially attacked by the OH group of Ser195, while His57 boosts Ser nucleophilicity by acting as a base (step 1). As a result, a tetrahedral intermediate is created (step 2). The oxyanion hole generated by the interaction of the NH groups of Gly193 and Ser195 with the oxyanion intermediate stabilizes the negatively charged tetrahedral intermediate (Oxyanion). The tetrahedral intermediate collapses, an acyl-enzyme intermediate forms, and an amine product is released in the subsequent step, when His57 adds a proton to the amine of the tetrahedral intermediate (step 3). A second tetrahedral intermediate is then formed when a water molecule interacts with the acyl-enzyme complex (step 4), and it is stabilized by the oxyanion hole (step 5). The tetrahedral intermediate finally collapses due to general acid catalysis by His57, producing the free acid product and regenerating Ser195 (step 6) **(Fig. 2).**

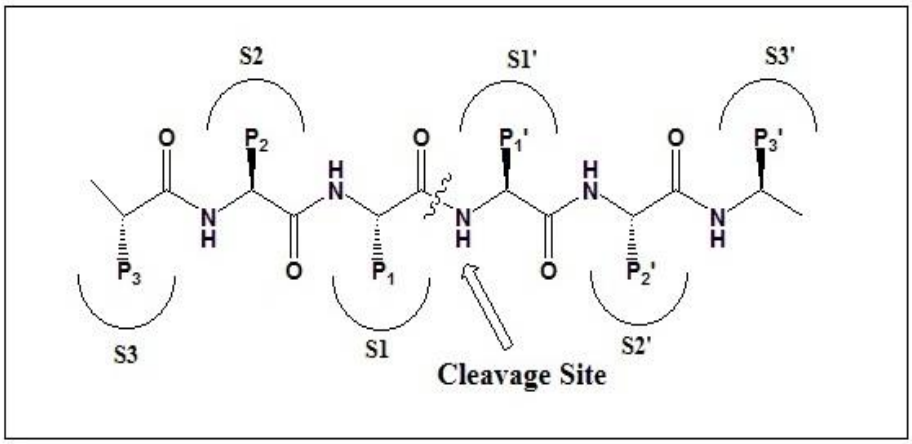


Fig. 1: Interaction of peptide substrate residues (P)with protease subsites (S). The amino acid residue of a substrate is designated using the nomenclature P1-Pn, P1′-Pn′. The binding sites on the protease are referred to as the equivalent S1-Sn and S1′-Sn′ subsites.

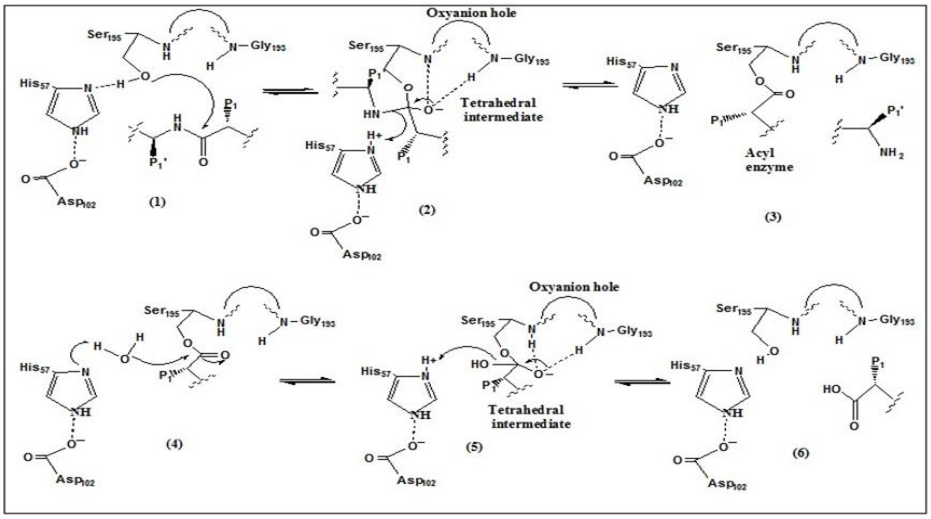


Fig. 2: A description of the trypsin-like serine protease's catalytic mechanism.

Serine protease inhibitors

Inhibition of serine protease is achieved through macromolecular endogenous proteins or low molecular weight synthetic compounds. Endogenous serine protease inhibitors (Serpins) are classified as non-drugs under the Lipnisiki's criterion because of their large molecular weight However, they are a great source for learning about the requirements for substrate binding and giving advice on how to produce more drug-like substrate-based synthetic compounds. Two methods are used in the development of serine protease inhibitors. The first issue is substrate-based drug design, where the scissile amide bond is replaced with a transition state isostere to transform the substrate into a peptidomimetic inhibitor, and the second one is screening compound libraries followed by modifications to improve pharmacological and pharmacokinetic properties[22–25].

Substrate based inhibitor

In order to achieve great selectivity towards the target protease, peptidic targeting sequences are used to build a powerful and specific synthetic inhibitor. The peptidic part functions as a protease recognition motif where the side chains optimally fill their corresponding binding pockets and the scissile amide is then replaced by a non-scissile isostere to replace the transition state intermediate. Different isosteres for serine protease known as serine traps have electrophilic carbonyl group **(Fig. 3).** The serine hydroxyl of serine protease attacks the electrophilic carbonyls to produce either a covalent reversible hemiacetal bond or covalent irreversible acyl- or alkyl- bonds[26-28].

On the other hand, the introduction of a serine trap in a molecule make it more susceptible to metabolism and chemical instability. It may lead also to lack of selectivity since it can react with a range of nucleophiles in the human body like glutathione. Another inherent issue of serine trap containing molecules is the slow binding kinetic in physiological condition[29].

Non-covalent serine protease inhibitor

Non-covalent inhibitors targeting serine protease will not interact covalently with serine hydroxyl moiety in active site. Inhibitory effect is achieved through conformational changes or steric blockade of active site or formation of hydrogen bonding. On the other hand, it is characterized by higher selectivity and lower reactivity in terms of chemical and metabolism characters than covalent inhibitors. Binding kinetics of non-covalent inhibitors are characterized by a rapid binding behavior, which is critical in some cases like thrombin inhibitors. Non-covalent serine protease inhibitors include serpins, hirudin, and trifluoro(organo)borate derivatives[30-32]. The different interaction mechanisms of serine protease inhibitors (Covalent and non-covalent) are illustrated in **Fig. 4**.

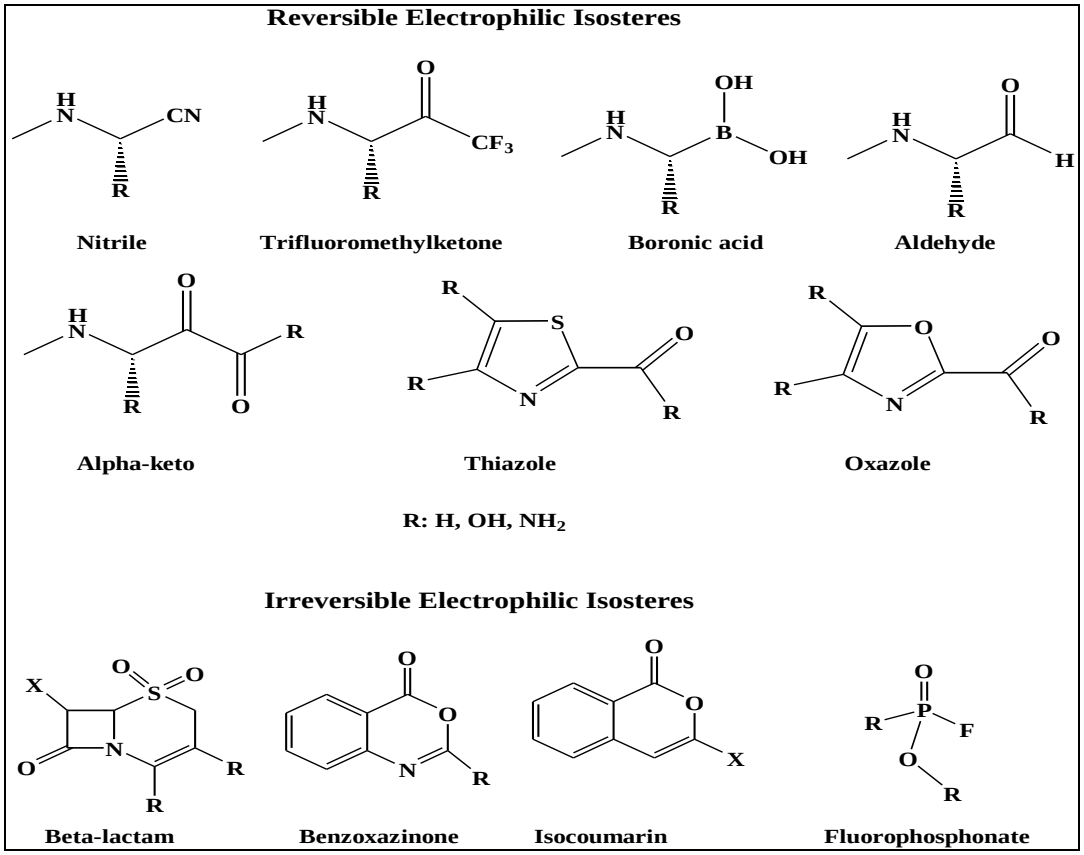


Fig. 3: Serine traps. Reversible and irreversible electrophilic isosteres.

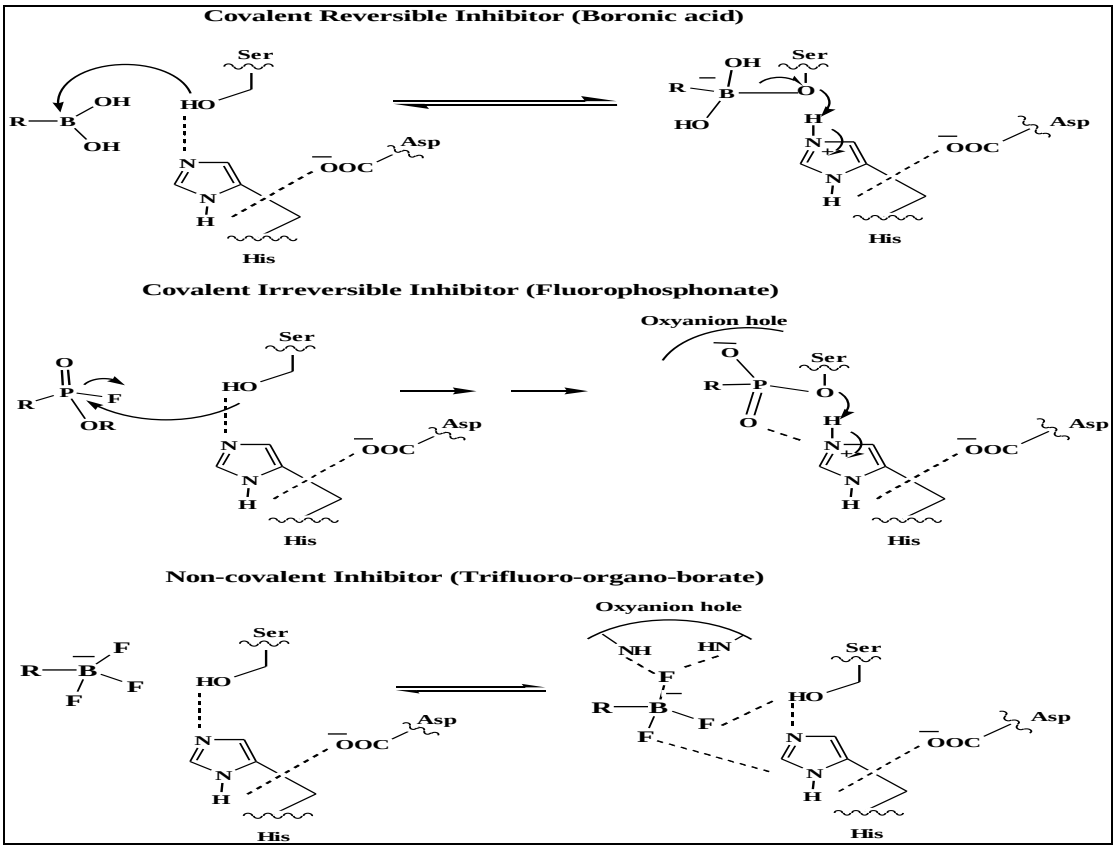


Fig. 4: Serine protease active site inhibition by different mechanisms.

The development of serine protease inhibitors still faces two major challenges increasing the selectivity and specificity of inhibitors and optimizing the pharmacokinetic characteristics. Protease inhibitors must have a high degree of specificity since off-target effects can result in serious disorders. A nonspecific matrix metalloprotease designed as anticancer drug can have procancer effect since matrix metalloprotease are involved in physiological as well as pathological pathways[33].

The next sections will discuss the development of serine protease inhibitors targeting thrombin, FXa, NHE, and DPP4 for treatment of thrombosis and inflammatory conditions, and diabetes mellitus.

Thrombin (Factor IIa)

The principal trypsin-like serine protease involved in the blood coagulation cascade is thrombin. It is produced from inactive prothrombin by proteolytic activity of factor Xa. By promoting platelets, converting fibrinogen to fibrin, and facilitating clot stabilization, thrombin plays a crucial part in the onset and progression of thrombotic[34].

The active form of thrombin (α-thrombin) consists of a light chain of 36-amino acids (A chain) and a peptidase domain of 259-amino acids (B chain) covalently connected by a disulfide bond. Thrombin has three subsites: S1, S2 and S3 in the active site. The specificity pocket S1 is characterized by Asp-189 at the bottom, which has a negative charge in physiological pH and is responsible for interaction with basic side chain. The difference in S1 sites between thrombin and other trypsin is the residue 190 which is an alanine in thrombin whereas it is a serine in other trypsin like proteases. S2 pocket is hydrophobic that can accommodate more substantial aliphatic residues, like valine and proline. Pocket S3 is smooth, with solvent exposure. Along with the active site, thrombin also has exosites that bind fibrinogen and heparin, and is made up of a number of basic arginine and lysine side chains[35&36].

Thrombin inhibitor

Several drugs of indirect thrombin inhibitors like unfractionated heparins, low molecular weight heparins, and vitamin K antagonists were widely been utilized in treating various thromboembolic and cardiovascular and diseases. This group of drugs had several disadvantages like parenteral application of heparin, bleeding risk, requirement of dose monitoring, interactions of vit. K antagonist with food and several drugs, and critical side effects like heparin-induced thrombocytopenia (HIT), and osteoporosis. Accordingly, there was an urgent need to develop new thrombin inhibitors[36].

Hirudins are non-covalent, bivalent peptide inhibitors of thrombin. The C-terminus of hirudins binds to the fibrinogen-binding exosite and wraps the active site of thrombin with its N-terminus to form a 1:1 complex with thrombin. Thrombin-hirudin complex does not involve interaction with S1 subsite. Hirudins as peptide is applied parenterally and still have bleeding risk [37].

There was still a need for direct thrombin inhibitors (DTIs), which are non-peptide small compounds that reversibly inhibit both free and clot-bound thrombin. DTIs may be advantageous since they do not require monitoring, have a wide therapeutic index, and can be administered orally. DTIs are argatroban, ximelgatran, and dabigatran etexilate (Table 1). Usually DTIs have a P1 group which fills S1 pocket. To obtain a significant inhibitory effect the P1 group should be a strongly basic group like guanidine (argatroban), alkylamine, amidine, benzamidine (dabigatran), or 4-aminopyridine[38].

Table 1: Serine proteases and their corresponding inhibitors.

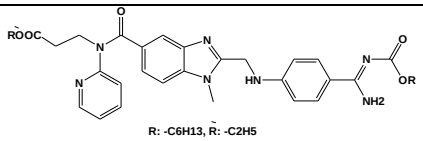
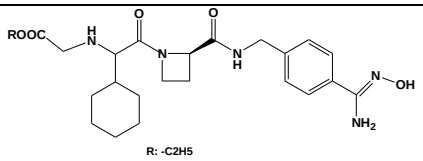
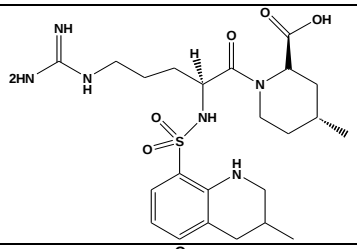
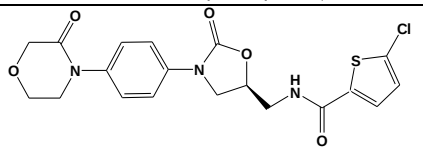
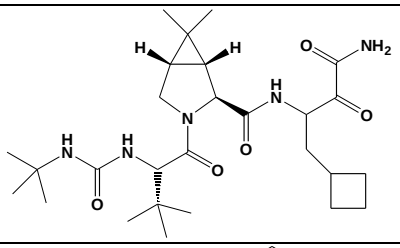
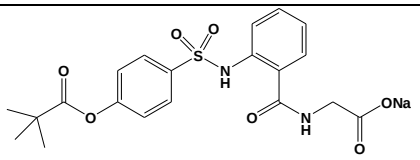
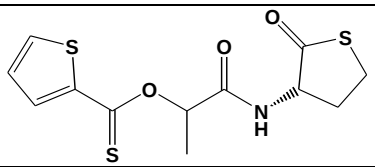
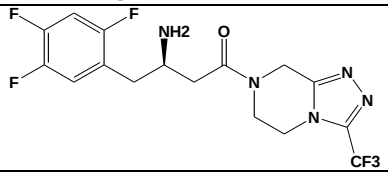
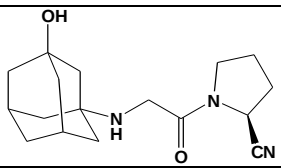
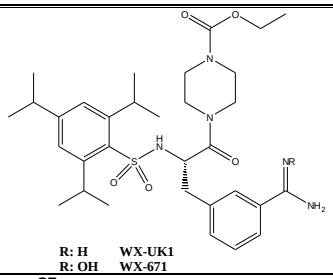
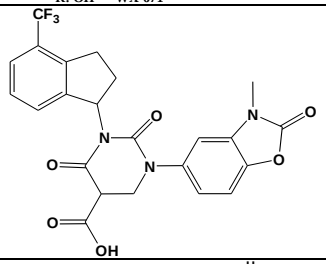
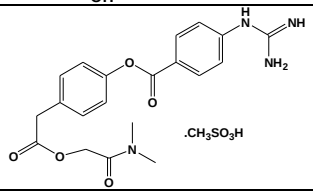
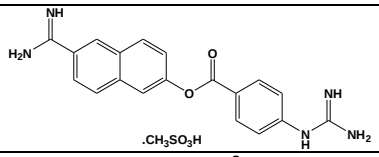
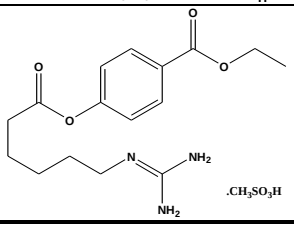
Target	Inhibitor	Chemical structure	Indication /Status
FIIa	Dabigatran etexilate		Thrombosis *Noehringer Ingelheim*, Launched 2008.
	Ximelgatran		*Thrombosis Exanta, Launched and withdrawn in 2004.*
	Argatroban		*Thrombosis Mitsubishi Pharma*, Launched 2000.
FXa	*Rivaroxaban*		*Thrombosis Bayer*, Launched 2008.
Hepatitis C NS3 protease	*Boceprevir*		*Hepatitis C infection Schering-Plough Research Institute*, Launched 2001.
Human Neutrophil Elastase (HNE)	Sivelestat		*Pulmonary disease Ono Pharmaceutical Co*, Launched 2001.
	Midesteine (MR 889)		*Chronic obstructive pulmonary diseases Medea Research*, Discontinuation.
DPP-4	*Sitagliptin*		*Diabetes mellitus Merck*, Launched 2006.
	Vildagliptin (LAF-237)		*Diabetes mellitus Novartis*, Launched 2008.

Table 1: Continued.

Urokinase type-plasminogen activator	*WX-UK1 WX-671*		*Metastasis, pancreas tumor, solid tumor Wilex AG* Clinical trial phase 2.
	Fulacimstat (BAY-1142524)		Acute myocardial infraction *Bayer Healthcare Clinical trial phase 3.*
Chymase	Camostat mesylate (FOY-305)		*Esophagitis, pancreatitis Ono Pharmaceutical Co Ltd, Launched in Japan.*
Troponin I	SERP-1 (VT-111)	Not available	*Acute coronary symptoms, antirehumatic, organ transplantation University of Alberta, Phase II 2010.*
Multiple serine protease	Nafamostat mesylate (FUT-175)		Inflammatory conditions *Torii Pharmaceutical* Launched in Japan.
	Gabexate mesylate		*Pancreatitis, regional anticoagulant Ono Pharmaceutical Co Ltd, Launched in Japan*

Argatroban –first noncovalent direct and reversible thrombin inhibitor approved by FDA in 2000 for prophylaxis and treatment of thrombosis – was developed by the Mitsubishi/Kobe University group starting with a simple arginine derivative (TAME: N-alpha-tosylarginine methyl ester). Argatroban developing approach based on replacement of ester with a hydrolytically stable amide, optimization of the amide substituent and sulfonyl substituent, and incorporation of carboxylic group to reduce toxicity of arginine **(Fig.5**). A similar approach was followed by Sturzebecher et al. to produce NAPAP (N-alpha-(2-naphthyl-sulphonyl-glycyl)-DL-p-amidinophenylalanyl-piperidine). The basic arginine residue was replaced by 4-amidinophenylalanine. NAPAP did not progressed into clinical trials[32]. Regarding argatroban interaction the guanidine residue builds ionic interaction with aspartic acid in the S1 pocket, and the piperidine ring binds in the S2 pocket **(Fig. 5).** Argatroban is administered parenterally due to the ionizable guanidine moiety, which prevents absorption from the gastrointestinal tract[13,39].

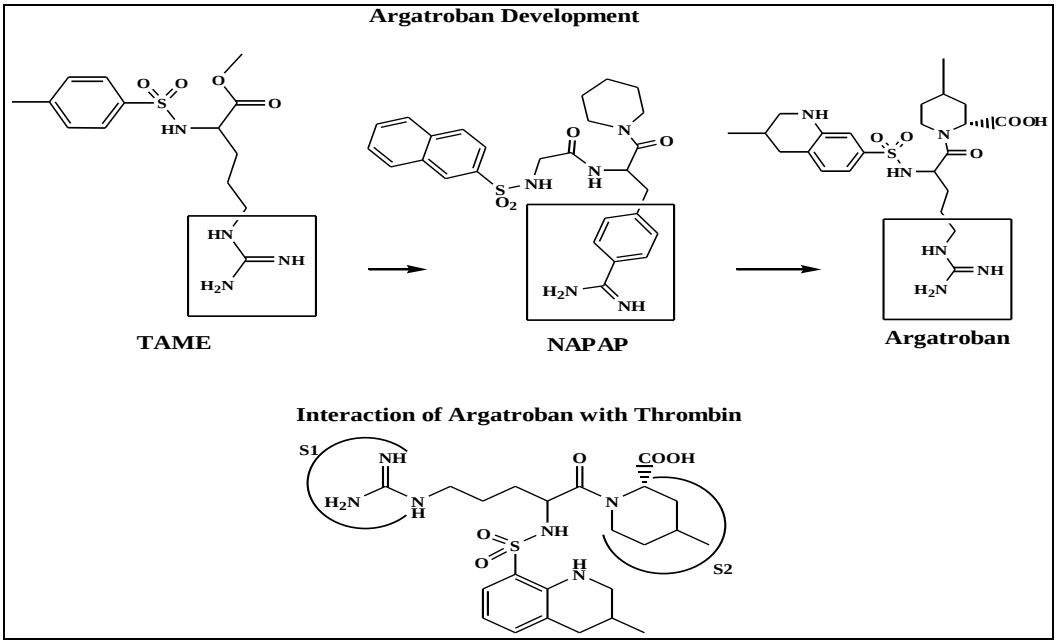


Fig. 5: Development of thrombin direct inhibitors originate from TAME and interaction of argatroban with thrombin subsites. TAME: N-alpha- tosylarginine methyl ester, NAPAP: N-alpha-(2-naphthyl-sulphonyl-glycyl)-DL-p-amidinophenyl-alanyl-piperidine. Elements surrounded with a square represent the basic P1 groups; guanidine and benzamidine.

Improving oral bioavailability can be accomplished by reducing basicity of P1 residue or a prodrug strategy. During development of serine protease (trypsin-like) inhibitor, it was established that total elimination of basic P1 was associated with retention of the inhibitory effect like rivaroxaban (It will be discussed in next section). Thus, the hypothesis that, a positively charged P1 residue is necessary for high affinity binding cannot be overcome can be contested[40].

The enhancement of oral bioavailability through prodrug issue was applied in production of ximelgatran and dabigatran etexilate. Both are prodrugs of melagatran and dabigatran, in which the basicity of amidine moiety was reduced by transforming into amidoxime group. Lipophilicity of prodrugs was increased through esterification of carboxylic group. The amidoxime is metabolized in the liver back to the amidine, hence activating the prodrug and the ester bond is hydrolyzed. Ximelagatran was the first oral DTI, which was discontinued due to hepatotoxicity[14]. Dabigatran etexilate is administered orally once daily. Since being approved in 2008 dabigatran etexilate is indicated for the prevention of venous thromboembolism[14,41].

Factor Xa

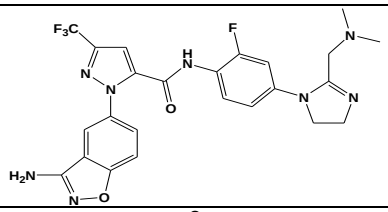
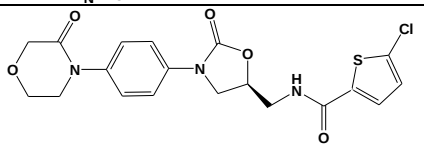
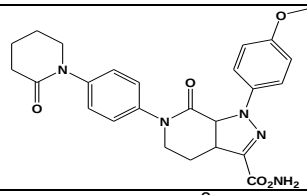
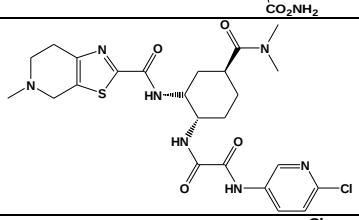
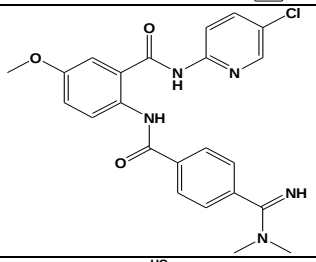
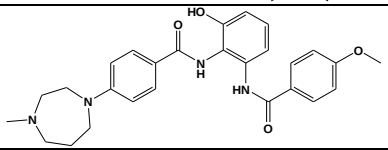
It is a trypsin like serine protease, which emerged as attractive target for developing novel inhibitors indicated in thrombosis. It was suggested that inhibition of FXa could produce anticoagulants with reduced bleeding risks[42].

FXa interacts with a substrate through the four subsites S1-S4. The S1 pocket is characterized by hydrophobicity and the existence of a deep anionic cleft due to the side chains of Tyr228, Ser195, and Asp189. S4 subsite has three ligand-connecting domains: a cationic pocket created by Glu97 and Lys96; a hydrophobic pocket defined by Tyr99, Trp215, and Phe174, and a water pocket. S2 subsite is poorly defined, has a slightly deep pocket, and is merged with the S4 subsite. Finally, the S3 pocket, which is at the edge of the S1 subsite region, is exposed to the solvent[35,43].

Factor Xa inhibitor

To achieve FXa inhibitory effect with high affinity and selectivity S1 and S4 pockets should be primarily targeted[44&45]. Several drugs were developed as direct reversible FXa inhibitor are given in Table 2[13&14].

Table2: Direct FXa inhibitors and clinical indications.

Inhibitor	Status	Chemical structure	Indication
Razaxaban	*Bristol Myers Squibb* Discontinue in phase II, 2004.		Venous thrombosis
Rivaroxaban	*Bayer Schering Pharma AG* Approved 2008		Atrial fibrillation, treatment and prophylaxis of venous thrombo-embolism, chronic coronary artery disease.
Apixaban	*Bristol-Myers Squibb Co* Approved 2012.		Treatment and prophylaxis of venous thrombo-embolism
Edoxaban	*Daiichi Sankyo* Approved 2015		Atrial fibrillation, treatment of venous thrombo-embolism.
Betrixaban	*Portola Pharmaceuticals* Approved 2017		Prevention of venous thrombosis in acute hospitalized adults
Darexaban	*Astellas Pharma* Discontinue in phase II, 2011		Venous thrombosis.

The binding sites S1 and S4 of FXa are present in the "L" configuration. Natural substances have polar, charged components at ends of the "L" bind the target selectively. Instead, synthetic inhibitors have aromatic rings with different moieties attached. The interaction of inhibitors with S1 and S4 pocket maintain the binding efficiency while increasing bioavailability. Several of the direct oral factor FXa inhibitors rely on hydrophobic and hydrogen-bonding interactions with the target rather than polar ionic interactions.

The interaction of rivaroxaban with FXa is shown in **Fig. 6**. The oxazolidone ring builds hydrogen bonds with Gly219, which give rivaroxaban its bent L-shape. Oxazolidone core structure direct morpholinone and benzenic rings into S4 site and chlorothiophene into the deep S1 site. The interaction of chlorine atom of chlorothiophene with aromatic ring of Tyr228 in S1 is essential for the high affinity to FXa without a positively charged moiety. Morpholinone ring is responsible for the high potency and has hydrophobic interactions with Phe174 and Tyr99 residues of S4[46&47].

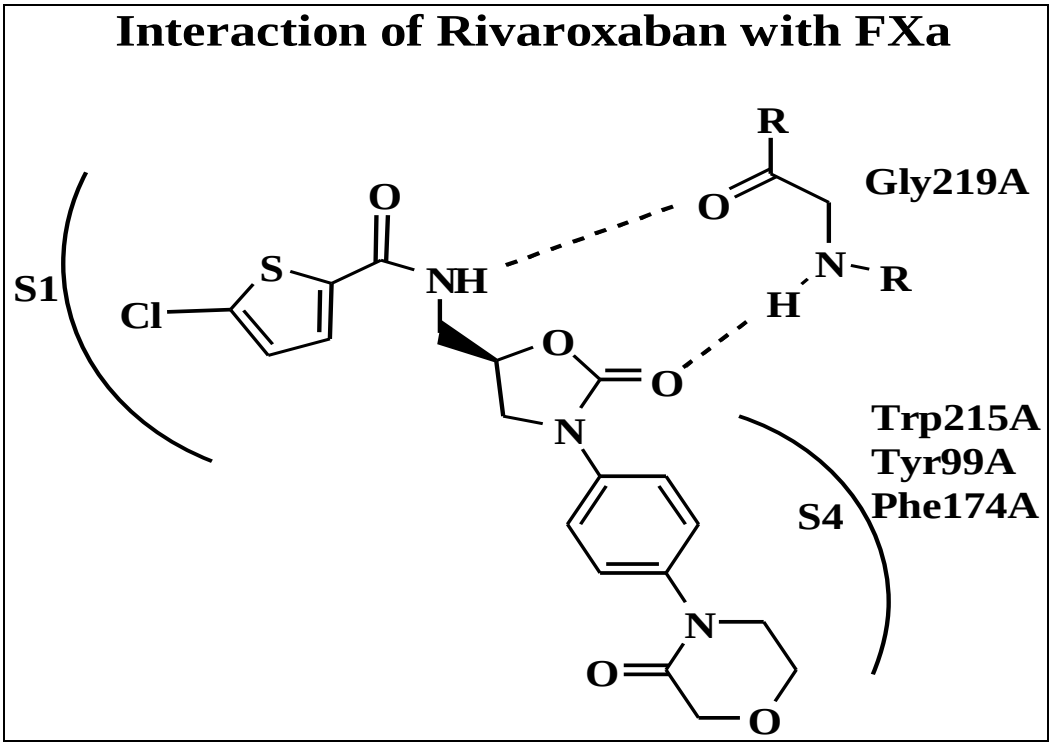


Fig. 6: Interaction of Rivaroxaban with FXa. L-Configuration directed by oxazolidone ring.

Human neutrophil elastase (HNE)

Human neutrophil elastase is a serine protease that is secreted along with other proteolytic enzymes e.g. proteinase 3 and cathepsin G from neutrophils into extracellular matrix. It is responsible for the degradation of extracellular proteins such as collagen, elastin, and fibronectin, which support the tissues physically. On the other side, HNE enhances the immune response and inhibits the inflammatory cytokines. Natural serine protease inhibitors, such as α1-antitrypsin, elafin, and secretory leukocyte protease inhibitor, inactivate HNE under physiological conditions. Imbalances between NHE and its inhibitors have been implicated significantly in a number of human disorders like pulmonary fibrosis, respiratory distress syndrome, chronic obstructive pulmonary disease, pulmonary emphysema, chronic kidney disease, rheumatoid arthritis, chronic skin ulceration, and breast cancer[48&49].

Consequently, HNE is a useful target for research and development in the pharmaceutical industry[50].

HNE inhibitor

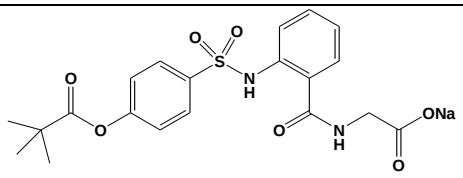
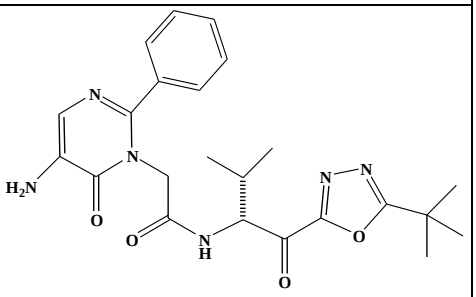
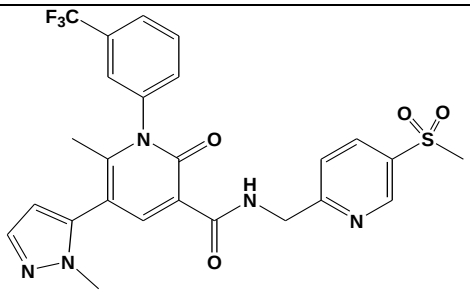
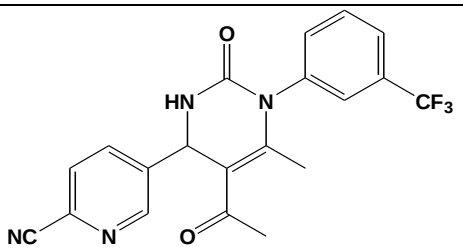
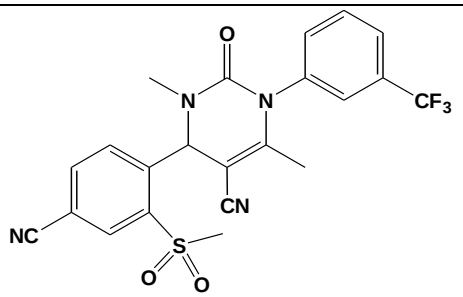
There are five classes of NE inhibitors that are available for use in clinical practice[51-55]. Only two medicines are presently on the market: the purified peptide α1-antitrypsin (FDA approved), and the small molecule sivelestat[13]. Reported HNE inhibitors are given in Table 3[13&14].

Sivelestat is a suicide inhibitor of HNE. It attacks Ser195 in active site of HNE and builds a covalent bond **(Fig. 7).** Other interactions are hydrogen bonds and hydrophobic interactions in S1 subsite. Hydrogen bonds are formed between sivelestat and Ser195, and Gly193. Ser195 is acylated and sivelestat is transformed and the metabolite is released[56].

Freselestat attacks covalently Ser195 and uses hydrogen bonds to stabilize the connection to HNE. As a result, a transition state analogue is formed. The inhibitory effect of ONO-6818 is specific and reversible[57].

The third and fourth generations of HNE inhibitors interact in similar manner with HNE. The third-generation inhibitors bind the S1 subsite, which causes a conformational change in HNE and triggers deepening of S2 subsite. This allows further exceptional interactions with NHE. The interaction with S2 subsite produces very potent and more selective HNE inhibitory effect[53,58].

Table 3: Human neutrophil elastase inhibitors and clinical indication.

Type	Inhibitor/status	Structure	Indication
1st generation	AAT (α1-antitrypsin) *Alpha Therapeutic Crop*, Launched 2003.	Biological	Acute respiratory distress syndrome, hereditary emphysema.
2nd generation	Sivelestat (ONO-5046), *Ono Pharmaceutical* Marketed in Japan and Korea, 2002.		Chronic obstructive pulmonary disease, α1-Antitrypsin deficiency, Acute respiratory distress syndrome
	Freselestat (ONO-6818) Ono Pharmaceutical Discontinued in phase I.		
3rd generation	Alvestat (AZD9668) *Astra Zeneca*, Under clinical trial phase II.		Acute respiratory distress syndrome, Chronic obstructive pulmonary disease, Acute lung injury
4th generation	BAY-678 *Bayer Health Care AG*, Under clinical trial phase II.		*Lung emphysema, Acute lung injury*
5th generation	BAY 85-8501 *Bayer Health Care AG*, Under clinical trial phase II.		*Anti-inflammatory in pulmonary disease.*

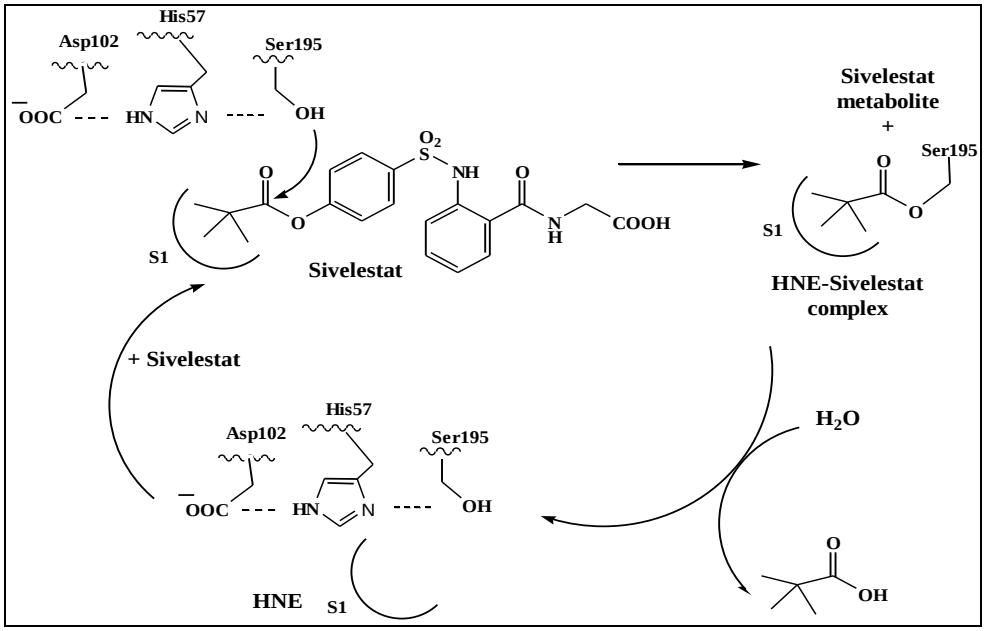


Fig. 7: Inhibitory mechanism of human neutrophil elastase (HNE) by sivelestat.

The fourth and fifth generation inhibitors are closely linked. The fifth generation of inhibitors are based on pharmacophore of the fourth generation, but they are characterized by an extra substituent, which stabilizes the structure in the most appropriate conformation for binding the protease. This rigidification is achieved by preventing the rotation around pyrimidinone-cyanophenyl axis[59].

Dipeptidyl peptidase-4

DPP-4 is a transmembrane glycoprotein that is mostly present in the renal, pancreas, liver, spleen, and thymus. Circulatory DPP4 was also detected as a soluble form. DPP 4 catalyzes selectively the cleavage of dipeptides XAA-Ala and XAA-Pro from the N-terminus of proteins, (XAA are other amino acids). This inactivates the gastrointestinal incretin hormones. Incretins like glucagon-like peptide-1 (GLP1) and gastric inhibitory peptide (GIP) increase insulin secretion in response to glucose level. Suppression of DPP-4 is expected to be a drug candidate to treat type 2 diabetes mellitus[60&61].

The extracellular part of DPP4 comprises a ß-propeller domain and a catalytic domain. The first one helps inhibitor binding and second one contains catalytic triad Ser630 - Asp708 - His740. The active site is enclosed inside both domains. The S1 subsite is hydrophobic and showed selectivity to proline. It is made up by side chains of Tyr631, Val656, Trp662, Tyr666 and Val711[62]. DPP-4 is characterized by the existence of different binding sites such as S1, S2, S1′, S2′ and S2 extensive subsites[63&64].

DPP4 inhibitor

Inhibition of DPP4 has a main challenge regarding selectivity since there are nine enzymes of DPP. DPP-8 and DPP-9 showed similarity in structure and selectivity to DPP-4. Side effects were reported when nonselective DPP-4 inhibitor was applied in rats due to DPP-8/-9 inhibition [64]. Therefore, the development of DPP-4 inhibitor as antidiabetic needs high selectivity. Dipeptide structure Phe-Pro was the basis to design DPP-4 inhibitors[65].

Currently, many antidiabetic targeting DPP-4 were launched across many countries. The diversity of DPP 4 inhibitor chemical structures are due to the broad cavity of DPP-4 and the ability to interact with several binding sites. According to interaction with binding sites DPP 4 inhibitors were classified into three classes (Table 4)[13&14]. Saxagliptin, sitagliptin, linagliptin, and alogliptin are officially approved by FDA[66-74].

Table 4: DPP 4 inhibitors classified according to binding domain.

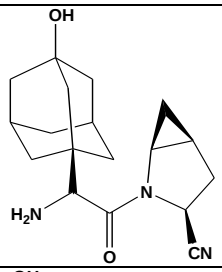
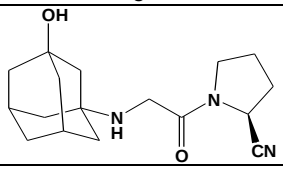
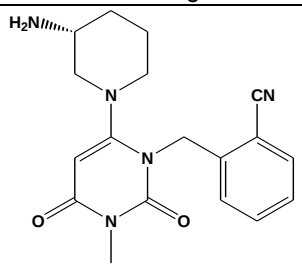
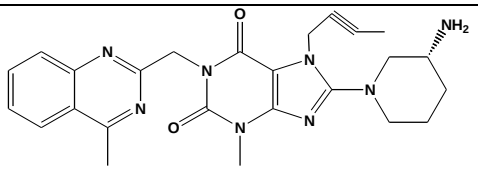
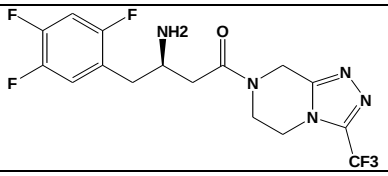
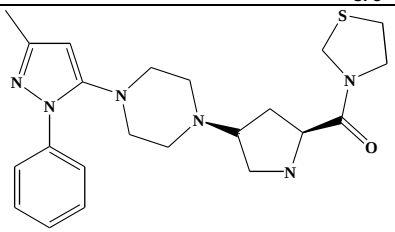
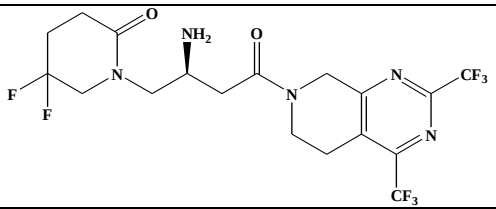
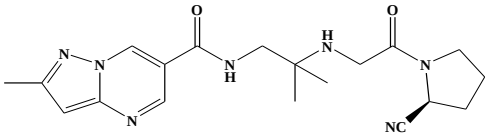
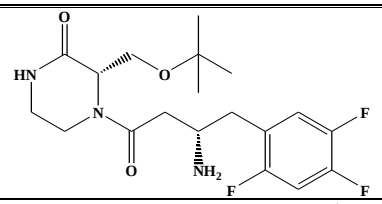
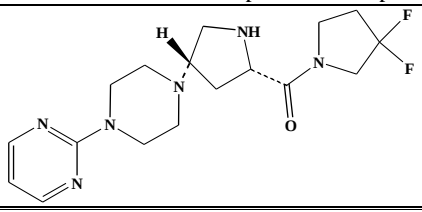
Class	Inhibitor	Chemical structure	Status
Class 1	Saxagliptin		*Astrazeneca and Bristol Meyers Squibb'* launched 2009.
	Vildagliptin		*Novartis,* Launched 2008.
Class 2	Alogliptin		*Takeda,* Launched 2010.
	Linagliptin		*Boehringer Ingelheim,* Launched 2011.
Class 3	Sitagliptin		*Merck,* Launched 2006.
	Teneligliptin		*Mitsubishi Tanabe pharma,* 2012.
	Gemigliptin		*LG Life Sciences,* Approved in south Korea, 2012.
	Anagliptin		*Sanwa Kagaku Kenkyusho and Kowa,* Launched in Japan, 2012.

Table 4: Continued.

	Evogliptin		*Dong-A ST*, Launched in South Korea and Russia, 2015.
	Gosogliptin		*Pfizer*, *SatRx*, Launched in Russia, 2016

Class 1: Interaction with S1 and S2 subsites, Class 2: Interaction with S1, S2 subsites, and S1′ and/or S2′ subsites, Class 3: Interaction with S1, S2, and S2 extensive subsites of DPP 4.

The interaction of inhibitors with the DPP-4 S2-extensive subsite ensures a high sensitivity towards DPP4, since other peptidases such as DPP8, DPP9, and fibroblast stimulation protein lack this subsite[70].

DPP-4 inhibitors characterized collectively by the building of salt bridges with Glu-residues in the S2 subsite[74]. Teneligliptin's unique structure, which is distinguished by a J-shape and an anchor-lock region, demonstrates its potent inhibitory effect[70].

The DPP4 inhibitors are also classified into substrate like inhibitor and non-substrate like inhibitor. Substrate like inhibitors resemble the cleavage dipeptidyl product (Proline mimic). They have an electrophilic group (nitrile) attached to pyrolidine. In this case a cyanopyrolidine ring fills the S1 pocket and hydrophobic interactions build with Tyr666. Ser 630 of the catalytic triad attaches nitrile and a covalent bond is formed. An imidate species is produced as a result **(Fig. 8).** Imidate hydrolyzed slowly, thus the inhibition is pseudo-irreversible. This is the case of saxagliptin and vildagliptin[75].

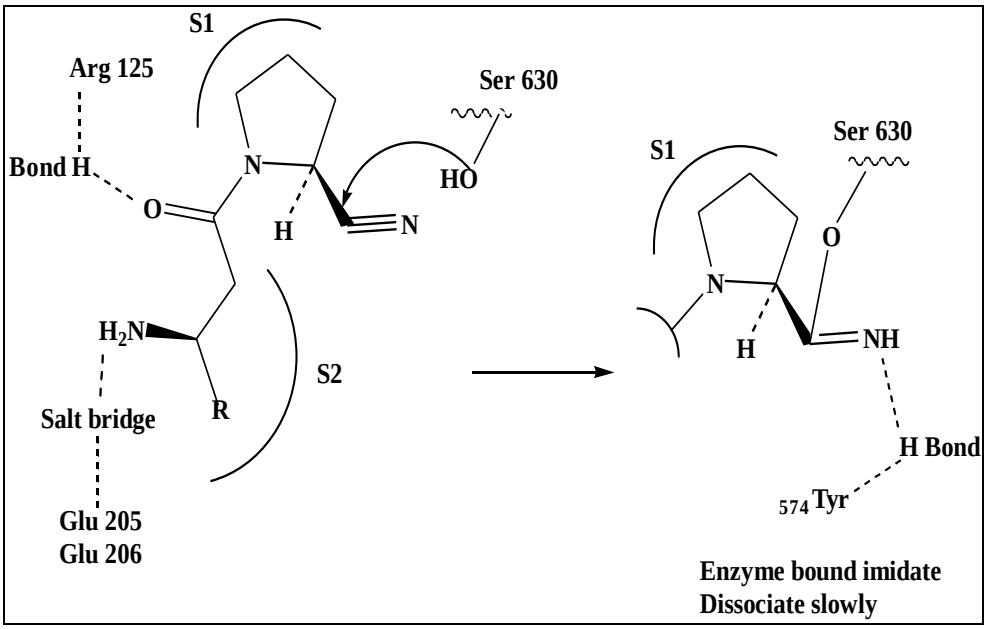


Fig. 8: DPP-4 inhibitory mechanism of cyanopyrolidine derivative (Saxagliptin and vildagliptin). A covalent bond is formed between Ser630, and enzyme bound imidate is produced. Imidate is stabilized through H bond with Tyr574. The carbonyl group and amine group in side chains interact with S2 pocket.

Non-substrate like inhibitors do not resemble the substrate specificity and show reverse binding in the active site of DPP-4 when compared to proline mimics. This category is characterized by diverse chemical scaffolds. Despite the chemical diversity X Ray analyses showed that, all inhibitors of DPP-4 bind in the active site and having additional interactions with active site amino acid residues. Sitagliptin is a non-substrate like inhibitor of DPP-4. The P1 site could accommodate the trifluorophenyl moiety. This was supported by the X-ray test, which revealed the amide carbonyl reverse binding orientation to its alpha amino acid scaffolds that contain peptidomimetic inhibitors. The S2 pocket is occupied by the amino amide moiety. A salt bridge and hydrogen bonding interactions are formed by the primary amine group with Glu205 and Glu206, and Tyr662, respectively. Tyr547 residue forms hydrogen bonding interaction with the carbonyl group via water molecules. The S2 extended pocket is filled by triazolopiperazine ring and heaps against Phe357. The trifluoromethyl group has hydrogen bonding interactions with Arg358 and Ser209 side chains, which enhances also the selectivity[76-78].

Serine protease and future studies:

Serine protease inhibition is still a valuable and attractive target for researcher and pharmaceutical companies. After the recent outbreak of COVID-19 from Wuhan city of China caused by SARS-CoV-2, the serine protease (TMPRSS2 - responsible for viral entry) was a potential target. Known serine protease inhibitors e.g. camostat were tested for COVID-19 patients. These findings encouraged many research groups to investigate potential candidates among which the natural phytochemicals had significant interest. In the next years it is expected to have a significant number of serine protease inhibitors[80-87].

Conclusion

Numerous disease states, such as cancer, inflammatory disorders, pulmonary disorders, viral infections, blood clotting, and Alzheimer's disease, are linked to serine proteases. As a result, inhibition of serine proteases was an attractive therapeutic target to produce new pharmaceuticals. The specificity of the target enzyme is thoroughly researched before an inhibitor is developed, then the potency and pharmacokinetic profile are optimized.. Few inhibitors were approved despite the great efforts made. Many candidates are still in clinical trial. Significant number of serine protease inhibitors is anticipated in the upcoming years.

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مراجعة الادبيات المتعلقة بمثبطات انزيم السيرين بروتياز من حيث التطوير والاستخدامات

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انزيمات البروتياز هي انزيمات هاضمة تعمل على تحليل الروابط الببتيدية . السيرين بروتياز وهو الاسم المشتق من الحمض الاميني السيرين الذي يقع في الجزء النشط منه والمسؤول عن تحليل الروابط الببتيدية يمثل تقريبا ثلث انزيمات البروتياز مجتمعة. تلعب هذه الانزيمات دورا هاما في عمليات الهضم، اضافة الي دورها في عمليات اخري مثل الالتهاب، تخثر الدم، نقل الاشارات، الاستجابة المناعية، وموت الخلايا. لهذا السبب تعتبر هذه الانزيمات هدفا هاما لتصميم وتطوير أدوية تستهدفها وتؤثر عليها لأغراض علاجية.

يهدف هذا المقال لعرض السيرين بروتياز من حيث الية العمل لتحفيز تحلل الروابط الببتيدية، والهيئة الكيميائية لها، وعرضا لتطويرالمثبطات.

سيتم مناقشة مثبطات السيرين بروتياز الخاصة بكل من thrombin, FXa, human neutrophil elastase (HNE), DPP4 المستخدمة في المجالات الطبية واخري ما زالت قيد التطوير في العقدين المنصرمين.