Journal of Bioanalysis & Biomedicine

Sen, J Bioanal Biomed 2015, 7:1
DOI: 10.4172/1948-593X.1000e127

Editorial Open Access

Xabans as Direct Factor X_a Inhibitors

Dhrubo Jyoti Sen*

Department of Pharmaceutical Chemistry, Shri Sarvajanik Pharmacy College, Gujarat Technological University, Gujarat, India

Abstract

Direct factor X_a inhibitors are being used clinically. Clinical trials have shown promise for these compounds as substitutes for the currently administered vitamin K antagonists or low molecular weight heparin. Those trials demonstrated efficacy and safety against warfarin for stroke prevention in atrial fibrillation and against low-molecular-weight heparin for treatment and secondary prevention of venous thromboembolism or for initial treatment and prevention of venous thromboembolism in patients undergoing hip or knee replacement. Advantages of orally administered direct X_a inhibitors lie in the fact that they have a rapid onset and offset of action which reduces need for "bridging" with a parenteral anticoagulant, that they don't require frequent monitoring or re-dosing whilst having few strong drug interactions and no food interactions, leading to greater convenience by patients and doctors and that they have a lower risk of intra cranial bleeding in trials. Disadvantages compared to warfarin include the currently limited prospective experience, concerns regarding patient adherence without laboratory monitoring, uncertainty about dosing in some patient populations (eg, renal dysfunction, marked extremes of body weight), their contraindication in severe renal impairment, their lack of specific antidotes and assays to measure drug levels in case of severe bleeding, their potential to overuse in low risk atrial fibrillation people, their short half live affecting efficacy and their higher drug acquisition costs. Direct factor X_a inhibitors ('xabans') are a class of anticoagulant drugs which act directly upon Factor X in the coagulation cascade, without using antithrombin as a mediator.

Keywords: Stuart-Prower factor; Endopeptidase; Anticoagulant; Xabans

Factor X, also known by the eponym Stuart–Prower factor or as prothrombinase, thrombokinase or thromboplastin, is an enzyme (EC 3.4.21.6) of the coagulation cascade. It is a serine endopeptidase (protease group S1). The first crystal structure of human factor X_a was deposited in May 1993. Till now, 191 crystal structures of factor X_a with various inhibitors have been deposited in the protein data bank. The active site of factor X_a is divided into four sub pockets as S1, S2, S3 and S4 [1] (Figures 1-3).

The S1 sub pocket determines the major component of selectivity and binding. The S2 sub-pocket is small, shallow and not well defined. It merges with the S4 sub pocket. The S3 sub-pocket is located on the rim of the S1 pocket and is quite exposed to solvent. The S4 sub-pocket has three ligand binding domains: the "hydrophobic box", the "cationic hole" and the water site. Factor X_a inhibitors generally bind in an L-shaped conformation, where one group of the ligand occupies the anionic S1 pocket lined by residues Asp189, Ser195, and Tyr228 and another group of the ligand occupies the aromatic S4 pocket lined by residues Tyr99, Phe174, and Trp215. Typically, a fairly rigid linker group bridges these two interaction sites [2].

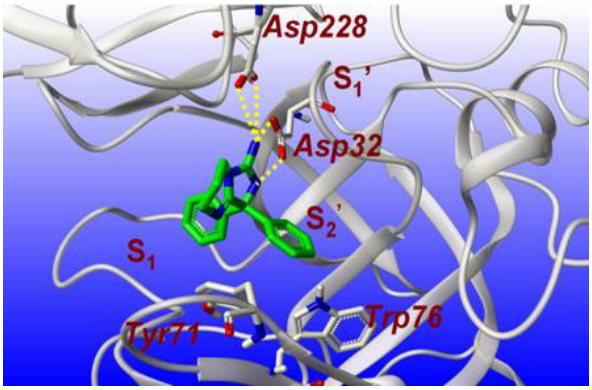

Figure 1: Stuart-Prower factor.

Rivaroxaban (BAY 59-7939) is an oral anticoagulant invented and manufactured by Bayer. It is the first available orally active direct factor X_a inhibitor. Rivaroxaban is well absorbed from the gut and maximum inhibition of factor X_a occurs four hours after a dose. The effects last approximately 8–12 hours, but factor X_a activity does not return to normal within 24 hours so once-daily dosing is possible. Rivaroxaban ((S)-5-chloro-N-{[2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl]oxazolidin-5-yl]methyl}thiophene-2-carboxamide) is an oxazolidinone derivative optimized for inhibiting both free Factor X_a and Factor X_a bound in the prothrombinase complex. It is a highly selective direct Factor X_a inhibitor with oral bioavailability and rapid onset of action. Inhibition of Factor X_a interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi [3].

Rivaroxaban does not inhibit thrombin (activated Factor II), and no effects on platelets have been demonstrated. Rivaroxaban has predictable pharmacokinetics across a wide spectrum of patients (age, gender, weight, race) and has a flat dose response across an eightfold dose range (5–40 mg) [3]. Rivaroxaban bears a striking structural similarity to the antibiotic linezolid ((S)-N-({3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide): both drugs share the same oxazolidinone-derived core structure. Accordingly, rivaroxaban was studied for any possible antimicrobial effects and for the possibility

***Corresponding author:** Dhrubo Jyoti Sen, Department of Pharmaceutical Chemistry, Shri Sarvajanik Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana-384001, Gujarat, India, Tel: +91-2762-247711; E-mail: dhrubosen69@yahoo.com

Received January 28, 2015; **Accepted** January 31, 2015; **Published** February 02, 2015

Citation: Sen DJ (2015) Xabans as Direct Factor X_a Inhibitors. J Bioanal Biomed 7: e127. doi:10.4172/1948-593X.1000e127

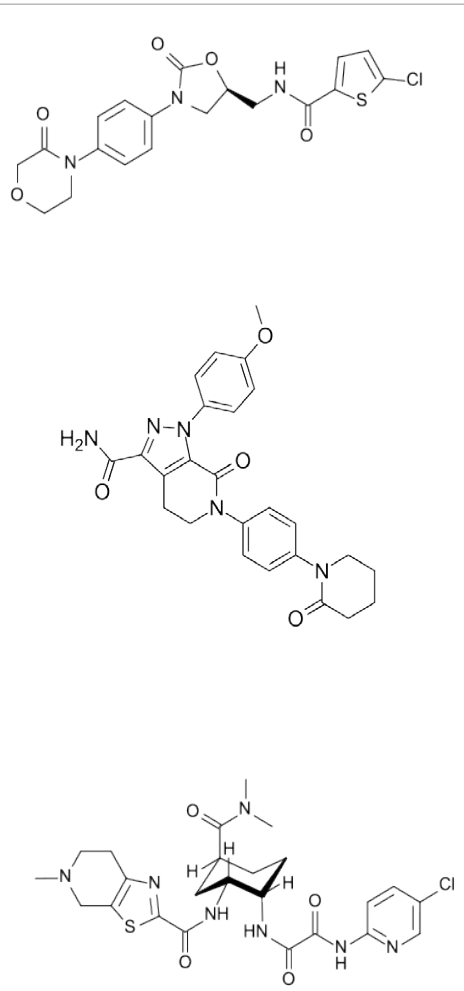

Figure 2: Structures of Apixaban, Rivaroxaban, Edoxaban.

of mitochondrial toxicity, which is a known complication of long-term linezolid use [4].

Apixaban (BMS-562247-01) is an anticoagulant for the treatment of venous thromboembolic events. It is a direct factor X_a inhibitor. Apixaban (1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl) phenyl]-4,5-dihydropyrazolo[5,4-c]pyridine-3-carboxamide) has been available in Europe since May 2012. In the United States, it is undergoing phase III trials for the prevention of venous thromboembolism. It is being developed in a joint venture by Pfizer and Bristol-Myers Squibb. Apixaban is a highly selective; orally bioavailable and reversible direct inhibitor of free and clot-bound factor X_a. Factor X_a catalyzes the conversion of prothrombin to thrombin, the final enzyme in the coagulation cascade that is responsible for fibrin clot formation. Apixaban has no direct effect on platelet aggregation, but by inhibiting factor X_a, it indirectly decreases platelet formation induced by thrombin [5].

Edoxaban (DU-176b) is an anticoagulant drug which acts as a direct factor X_a inhibitor. Edoxaban (N'-(5-chloropyridin-2-yl)-N-[(1S,2R,4S)-4-(dimethylcarbamoyl)-2-[(5-methyl-6,7-dihydro-4H-[1,3]thiazolo[5,4-c]pyridine-2-carbonyl)amino]cyclohexyl] oxamide) is being developed by Daiichi Sankyo. It was approved in July for the prevention of stroke and non–central-nervous-system systemic embolism. Several Phase II clinical trials have been conducted, for example for thromboprophylaxis after total hip replacement (phase III early results compare well to enoxaparin and for stroke prevention in patients with atrial fibrillation (phase III has completed enrollment [6]. A large phase III trial (ENGAGE AF-TIMI) showed that edoxaban was non inferior to warfarin in preventing recurrent venous thromboembolic events with fewer episodes of major bleeding. This paper follows similar recent major trials showing similar results for the other new factor X_a inhibitors, rivaroxaban and apixaban [7].

Betrixaban (PRT-054,021) is an anticoagulant drug which acts as a direct factor X_a inhibitor. It is potent, orally active and highly selective for factor X_a, being selected from a group of similar compounds for its low hERG affinity. Betrixaban (N-(5-chloropyridin-2-yl)-2-([4-(N,N-dimethylcarbamimidoyl)benzoyl]amino)-5-methoxybenzamide) has undergone human clinical trials for prevention of embolism after knee surgery and prevention of stroke following atrial fibrillation, with promising results. Joint development with Portola was discontinued in 2011 by Merck [7].

Darexaban (YM150) is a direct inhibitor of factor X_a created by Astellas Pharma. It is an experimental drug that acts as an anticoagulant and antithrombotic to prevent venous thromboembolism after a major orthopaedic surgery, stroke in patients with atrial fibrillation and possibly ischemic events in acute coronary syndrome. It is used in form

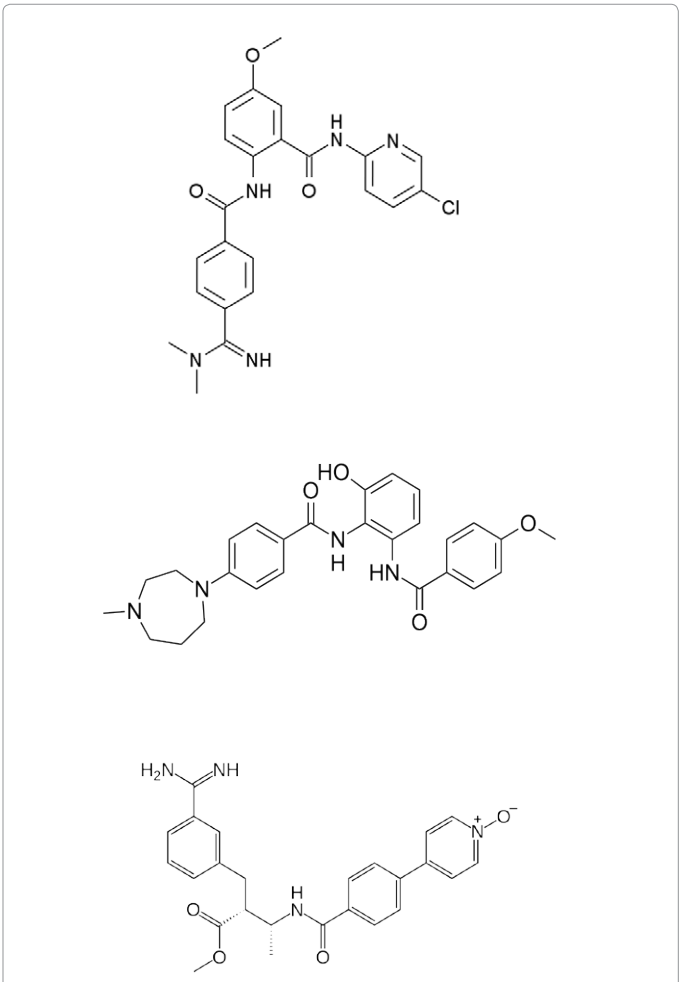

Figure 3: Srtuctures of Betrixaban, Darexaban, Otamixaban.

of the maleate [8]. Factor X_a (FX_a) is an essential blood coagulation factor that is responsible for the initiation of the coagulation cascade. FX_a cleaves prothrombin to its active form thrombin, which then acts to convert soluble fibrinogen to insoluble fibrin and to activate platelets. Stabilization of the platelet aggregation by fibrin mesh ultimately leads to clot formation. Darexaban (N-(3-Hydroxy-2-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}phenyl)-4-methoxybenzamide) and darexaban glucuronide selectively and competitively inhibit FXa, suppressing prothrombin activity at the sites of blood clot (thrombus) formation. This leads to a decrease in blood clot formation in a dose dependent manner. Reducing blood clot formation will decrease blood flow blockages, thus possibly lowering the risk of myocardial infarction, unstable angina, venous thrombosis, and ischemic stroke. Atrial fibrillation is an abnormal heart rhythm that causes a reduction in the cardiac output and blood flow to the brain. It also promotes the formation of blood clots in the atria. Atrial fibrillation is associated with an increased risk of embolic stroke due to the increased risk of blood clot development. Oral anticoagulant drugs such as Darexaban decrease the incidence and severity of stroke in patients with atrial fibrillation by preventing the formation of blood clots [9].

Otamixaban (INN: Methyl (2R,3R)-2-{3-[amino(imino)methyl] benzyl}-3-{[4-(1-oxidopyridin-4-yl)benzoyl]amino}butanoate) is an experimental injectable anticoagulant direct factor X_a inhibitor that was investigated for the treatment for acute coronary syndrome. In 2013, Sanofi announced that it had ended development of the drug candidate after poor performance in a Phase III clinical trial [10].

Conclusion

The oral direct factor X_a inhibitors include rivaroxaban and apixaban that recently have been evaluated comprehensively in multiple randomized clinical trials. Based on the efficacy and safety data from these trials, these novel anticoagulants are disseminating throughout clinical practice for thromboprophylaxis in major lower-extremity joint replacement, acute medical illness, atrial fibrillation and acute coronary syndromes. The advantages of the xabans over vitamin K antagonists include no requirement for routine anticoagulation monitoring as well as a fast and reliable onset of action. The first preoperative limitation of the xabans is the lack of a routine coagulation test for monitoring their anticoagulant effect in scenarios, such as the timing of surgical procedures, the reversal of xaban-related bleeding and the conduct of regional anesthesia. A second preoperative limitation is the lack of fully validated clinical reversal agents although prothrombin complex concentrate, recombinant factor VIIa and factor X concentrate are options for xaban reversal in life-threatening bleeding scenarios. Given their clinical efficacy and advantages, further xabans are in clinical development, with edoxaban already in phase III clinical trials. Although the xabans have ushered in a new paradigm for clinical anticoagulation, further clinical trials are indicated to refine their clinical indications even further, such as anticoagulation for patients with mechanical heart valves.

References

1. Broze GJ, Warren LA, Novotny WF, Higuchi DA, Girard JJ, et al. (1988) The lipoprotein-associated coagulation inhibitor that inhibits the factor VII-tissue factor complex also inhibits factor Xa: insight into its possible mechanism of action. Blood 71: 335-343.
2. Siegal DM, Cuker A (2013) Reversal of novel oral anticoagulants in patients with major bleeding. Journal of Thrombosis and Thrombolysis 35: 391-398.
3. Abdulsattar Y, Bhambri R, Nogid A (2009) Rivaroxaban (xarelto) for the prevention of thromboembolic disease: an inside look at the oral direct factor xa inhibitor. P & T: a peer-reviewed journal for formulary management 34: 238-244.
4. Eriksson BI, Borris LC, Dahl OE, Sylvia H, Menno VH, et al. (2006) A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. Circulation 114: 2374–2381.
5. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, et al. (2010) Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Engl J Med 363: 2487-2498.
6. Raskob G, Cohen AT, Eriksson BI, Puskas D, Shi M, et al. (2010) Oral direct factor Xa inhibition with edoxaban for thromboprophylaxis after elective total hip replacement. Thrombosis and Haemostasis 104: 642-649.
7. Weitz JI, Connolly SJ, Patel I, Salazar D, Rohatagi S, et al. (2010) Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. Thromb. Haemost. 104: 633-641.
8. Turpie AG, Bauer KA, Davidson BL, Fisher WD, Gent M, et al. (2009) A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement (EXPERT). Thrombosis and Haemostasis 101: 68-76.
9. Steg PG, Mehta SR, Jukema JW, Lip GY, Gibson CM, et al. (2011) RUBY-1: A randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome. European Heart Journal 32: 2541-2554.
10. Guertin KR, Choi YM (2007) The discovery of the Factor Xa inhibitor otamixaban: from lead identification to clinical development. Curr Med Chem 14: 2471-2481.