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# PREVAILING PERCEPTION OF NEWER ORAL ANTICOAGULANT: RIVAROXABAN

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**ABSTRACT**

Newer oral anticoagulants (NOACs) possess enhanced activity in control of cardiovascular disease. Rivaroxaban, a factor Xa inhibitor approved by FDA in 2011 is effective in nonvalvular atrial fibrillation (NVAF). The drug also possess significant pharmacokinetics features. The oral route of administration, consistent dose, improved specificity without requiring periodic checkups, patient monitoring and having more benefits. With little chance of interfering with food or other medications, rivaroxaban exhibits a quick onset of anticoagulant effect. There's no need for frequent monitoring and it can be administered at set dosages. This article provides an overview of the drug profile, synthesis, mechanism, admission route, pharmacokinetics, and medical indication of rivaroxaban, describing the pharmacodynamic profile and computational study. This study gives current insight to rivaroxaban being a safe option for physicians with advanced therapeutic choice.

**KEYWORDS:** Rivaroxaban; Atrial fibrillation; Factor Xa; Synthesis; Mechanism; Molecular docking; Spectral prediction.

## 1. INTRODUCTION

Anticoagulants are chemical compounds that limit the formation of hazardous clots and prevent or diminish blood coagulation in thrombotic disorders. The blood clots that are currently present have the potential to obstruct blood flow to the brain or heart, which can result in dangerous strokes or heart attacks.[1,2,3] Traditional anticoagulant medications are effective, but they have a number of drawbacks. They affect many coagulation components in a broad way.[4,5]

Recently developed rivaroxaban targets specific factor of coagulation. It has long been established that factor X plays a crucial role in hemostasis. Synthesis of thrombin which is formed by activated form, factor Xa, resulting in the formation of clots, and is therefore important to the blood coagulation pathway.[4,5,6,7]

As the first orally bioavailable member of a new class of potent and unique factor Xa inhibitors (oxazolidinone derivatives), rivaroxaban selectively and reversibly blocks the factor Xa active site without the need for a cofactor (like Anti-thrombin III) to be active, potentially making anticoagulation more consistent and predictable than warfarin.[6,7]

The drug received clinical approval for the purpose of preventing venous thromboembolism (VTE) in adult patients having elective hip or knee replacement surgery. It can now be used for the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), prevent recurrent DVT and PE in adult patients, and prevent stroke and systemic embolism in people with nonvalvular atrial fibrillation (AF). Additionally, the EU recently approved rivaroxaban for the secondary prevention of acute coronary syndrome (ACS).[8,9,10,11]

Atrial fibrillation (AF) and Acute coronary syndrome (ACS) are the main thromboembolic disease which contributes to morbidity and mortality worldwide. Atrial fibrillation (AF) being the most frequent cardiac arrhythmia which is responsible to 20% of stroke.[12] Drug potential affects a variety of biological processes in addition to its anticoagulant action.[13]

Basically, the FDA has approved and advised this medication for the following benefits. (Figure 1)

| Indication | Year of approval | Country |
|---|---|---|
| 1. DVT/PE prophylaxis in hip and knee surgery | 1. 2008 and 2011 | 1. Europe and USA |
| 2. Atrial fibrillation | 2. 2011 | 2. USA and Europe |
| 3. DVT/PE treatment | 3. 2012 | 3. USA and Europe |
| 4. Acute coronary syndrome | 4. 2013 | 4. Europe |
| 5. To reduce risk of VTE after 6 months of treatment of DVT/PE | 5. 2017 | 5. USA and Europe |
| 6. Stable CAD | 6. 2018 | 6. USA and Europe |
| 7. DVT/PE prophylaxis in acute medical illness | 7. 2018 | 7. USA and Europe |
| 8. PAD | 8. 2019 | 8. USA |

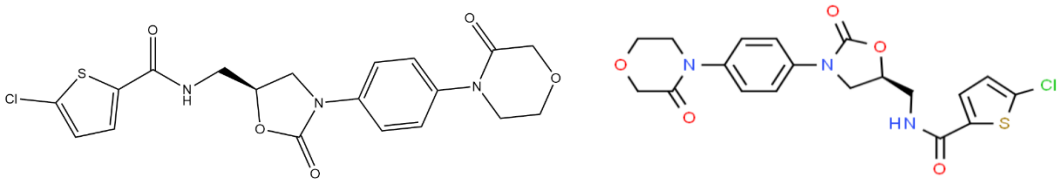
DVT/PE: deep vein thrombosis/pulmonary embolism; CAD: coronary artery disease; PAD: peripheral arterial disease.

**Fig. 1: Therapeutic benefits and year of approval of rivaroxaban.**

## 2. DRUG PROFILE

Rivaroxaban, an oral direct inhibitor of Factor Xa, targets both free and clot-bound Factor Xa as well as Factor Xa within the prothrombinase complex. It is a powerful and selective oxazolidinone analogue. Using rivaroxaban causes a quick and reversible suppression of Factor Xa activity. It binds straight to Factor Xa active site and is a small molecule.[8,9,10]

The molecular structures and brand names (manufacturers) are shown in (Figure 2,3) and computed and physio-chemical properties are listed in (Table 1,2).



(a) (b)

**Fig. 2: a) 2D structure; b) 3D structure.[14]**

**IUPAC Name:** 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl) phenyl]-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide.

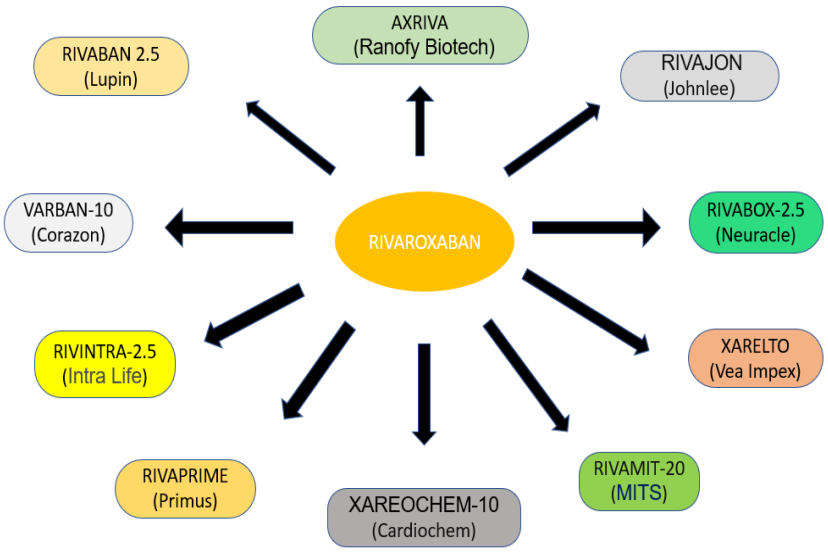



**Fig. 3: Brand names (manufacturers).**

**2.1 Synthesis:** Rivaroxaban is synthesized according to the indicated literature method (Figure 4).[2,15]

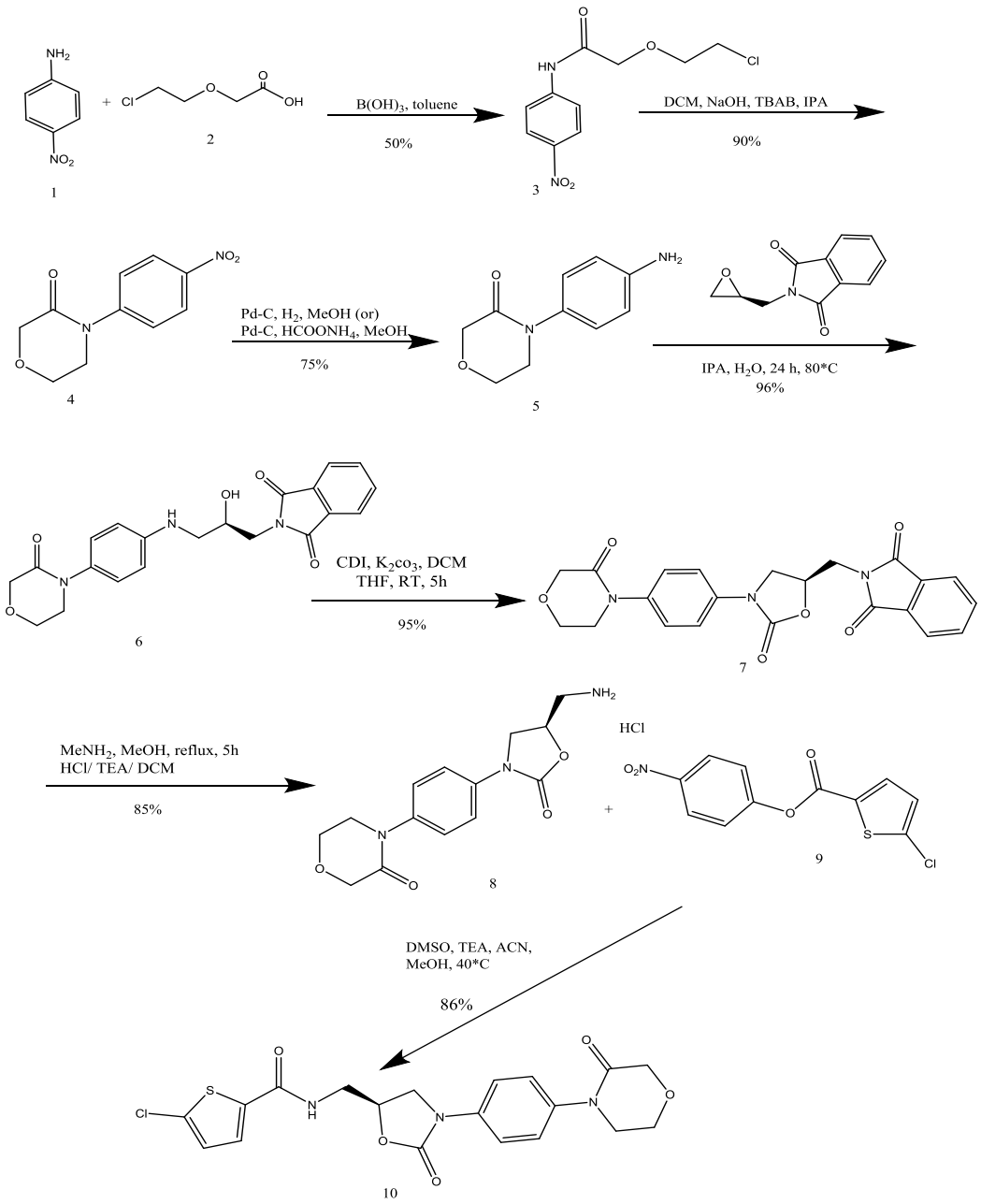



**Fig. 4: Synthetic route to rivaroxaban.**

Compounds(**1-10):**Nitro aniline **(1)**, 2- (2-chloroethoxy)acetic acid **(2)**, 2-(2- chloroethoxy)-N-(4-nitrophenyl)acetamide **(3)**, 4-(4-nitrophenyl)morpholin-3-one **(4)** 4-(4-aminophenyl)morpholin-3-one **(5),** 2-((2R)-2-Hydroxy-3-{[4-(3-oxo-4-morpholinyl)phenyl]amino}propyl)-1H-isoindole-1,3(2H)-dione **(6)**, 2-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidine-5-yl}methyl)-1H-isoindole-1,3(2H)-dione **(7)**, 4-[4-((S)-5-aminomethyl]-2-oxooxazolidine-3-yl)phenyl]morpholine-3-one **(8),** 4-Nitrophenyl 5-chlorothiophene-2-carboxylate **(9),** 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl) phenyl]-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide **(10).**

### 2.2 Mechanism of action

Novel oral anticoagulants (OACs), as opposed to conventional anticoagulant drugs like heparins and vitamin K antagonists (VKAs), are made to block particular single targets within the coagulation cascade.[9,16] In the coupling process, factor Xa sits at the intersection of the intrinsic and extrinsic routes and is in charge of converting prothrombin (Factor II) to thrombin (Factor IIa). Through both the intrinsic and extrinsic pathways of the coagulation cascade, factor X is activated to become factor Xa. The last common pathway, which is started by factor Xa, causes the prothrombinase complex to activate thrombin as shown in Figure 5.[5,16]

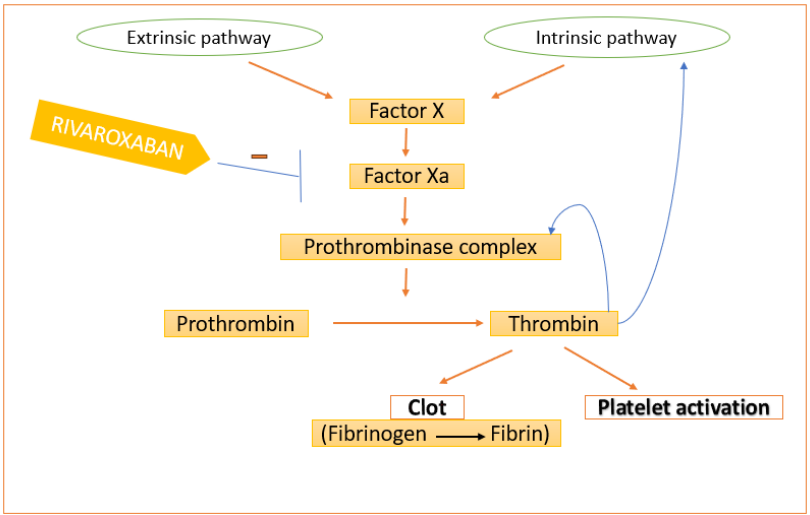



**Fig 5: Mechanism of action of rivaroxaban.**

It's significant because rivaroxaban was demonstrated to suppress Factor Xa that is free, prothrombinase-associated, and clot-associated without directly affecting platelet aggregation.

Evaluation of one molecule of factor Xa shows that it can catalyse the production of approximately 1000 molecules of thrombin and this happens because of the amplification present in the coagulation cascade. As a result, it was found that its inhibitory impact was more than 10,000 times greater than that of comparable serine proteases.[4]

### 2.3 Pharmacokinetics

**2.3.1 Absorption:** Rivaroxaban is absorbed quickly, taking 2-4 hours to reach Cmax. With a dose-dependent bioavailability, the medication is supplied as a film-coated tablet. When given in a fasting condition, the bioavailability of the 10 mg dose is predicted to be 80%–100%, whereas the 20 mg dose's bioavailability is 66%.[9,11] According to reports, rivaroxaban has a maximum plasma concentration of 30 minutes to 3 hours and a half-life of 3 to 9 hours.[7]

Tmax increases from 2.75 to 4 hours in the presence of food, resulting in a bioavailability of 90%–100%. Additionally, the Cmax and AUC increased by 41% and 28%, respectively. When rivaroxaban is released in the ascending colon or distal small intestine, its exposure is minimized.[4,11]

#### 2.3.2 Distribution

At steady state, rivaroxaban has a distribution volume of around 50 litres and is highly protein bound (92%–95%), with serum albumin being the main binding protein. The half-life of rivaroxaban's final elimination is 5–9 hours in young, healthy participants and 11–13 hours in old subjects.[11]

#### 2.3.3 Metabolism

The liver breaks down two thirds of the drug into inactive metabolites, of which half are eliminated by the kidneys, while the rest half are eliminated through the faeces. The liver uses CYP3A4, CYP345 and CYP2J2 to catalyse rivaroxaban metabolism. The kidneys eliminate the remaining third in an unaltered state.[7,9,11]

#### 2.3.4 Excretion

Thirty percent is eliminated by active renal secretion and the remaining six percent is eliminated by glomerular filtration out of the 36% of the unmodified rivaroxaban dose excreted in urine.[11]

Pharmacokinetic characteristics of Rivaroxaban is summarized in Table 3.[3,11,17]

**Table 3: Pharmacokinetic characteristics of rivaroxaban.**

| S. No. | Type | Small molecule |
|---|---|---|
| 1. | Origin | Synthetic molecule |
| 2. | FDA approval | 2011 |
| 3. | Mechanism of action | Direct Xa inhibitor |
| 4. | Route of administration | Oral |
| 5. | Absorption | Proximal small bowel + gastric |
| 6. | Bioavailability | 66% without food, 80%–100% with food. |
| 7. | Volume of distribution | 50 L |
| 8. | Onset of rivaroxaban | 2–4h |
| 9. | Biological half-life (hr) | 5–9 in adults and 11–13 in the elderly. |

| | | |
|---|---|---|
| 10. | Protein binding | 90% |
| 11. | Renal clearance | 36% |
| 12. | Removed by dialysis | No |
| 13. | P-glycoprotein transport | Yes |
| 14. | Hepatic metabolism | Oxidation occurs in Liver via CYP3A4, CYP3A5, CYP2J2 and CYP-independent mechanisms. |
| 15. | Excretion | Two-thirds excreted into urine (~36% as unchanged drug and 30% as inactive metabolism). One-third via feces (7% as unchanged drug and 21% as inactive metabolites). |
| 16. | Neutralizing agent | Andexanet alfa, prothrombin complex concentrates.(PCC) |

**2.4 Side effects:** The side effects of rivaroxaban are mention in Figure 6.

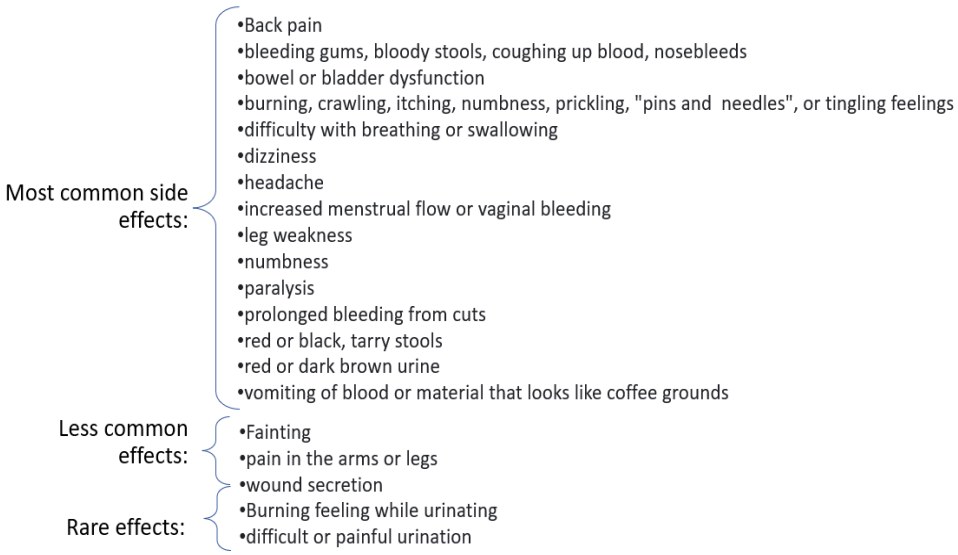



**Fig. 6: Side effects of Rivaroxaban.**

**2.5 Drug- Drug Interaction**

Strong CYP3A inhibitors in combination with P-gp reinforce exposure to rivaroxaban which may leads to risk of bleeding. The risk of thromboembolic event is increased by the combination of P-gp and powerful CYP3A inducers.[16] The Impact of Rivaroxaban Plasma Levels on Drug-Drug Interactions is summarized in Table 4.[18,19,20,21]

**Table 4: The impact of rivaroxaban plasma levels on drug-drug interactions.**

| S.No. | Drugs | Mechanism | Plasma level of Rivaroxaban |
|---|---|---|---|
| 1. | **Antiarrhythmic drugs**<br>Dronedarone | Moderate inhibitor of CYP3A4; inhibitor of P-gp | Increase the plasma level of rivaroxaban |
| 2. | **Antibiotics**<br>Clarithromycin and erythromycin<br><br>Rifampicin | Moderate inhibitor of CYP3A4 ;P-gp competition<br><br>Inducer of CYP3A4 and CYP2C9 | Increase the plasma level of rivaroxaban<br><br>Decrease the plasma level of rivaroxaban |
| 3. | **Antiviral drugs**<br>HIV protease inhibitors (e.g. ritonavir) | Inhibitor of CYP3A4; P-gp/Bcrp competition | Increase the plasma level of rivaroxaban |
| 4. | **Immunosuppressants**<br>Cyclosporin and tacrolimus | P-gp competition | Increase the plasma level of rivaroxaban |
| 5. | **Others**<br>Barbiturates (e.g. phenobarbital)<br>Carbamazepine<br>Phenytoin | Inducer of CYP3A4, CYP2J and P-gp/BCRP | Decrease the plasma level of rivaroxaban |

**Table 1: Computed Properties.**

| S.No. | Properties* | Values* |
|---|---|---|
| **1.** | Molecular Formula | $C_{19}H_{18}ClN_3O_5S$ |
| **2.** | Molecular weight | 435.9 g/mol |
| **3.** | X LogP3-AA | 2.5 |
| **4.** | Hydrogen bond donor count | 1 |
| **5.** | Hydrogen bond acceptor count | 6 |
| **6.** | Rotatable Bond count | 5 |
| **7.** | Exact Mass | 435.0655696 g/mol |
| **8.** | Monoisotopic Mass | 435.0655696 g/mol |
| **9.** | Topological polar surface area | 116 Å² |
| **10.** | Heavy atom count | 29 |
| **11.** | Formal charge | 0 |
| **12.** | Complexity | 645 |
| **13.** | Isotope atom count | 0 |
| **14.** | Defined atom stereocenter count | 1 |
| **15.** | Undefined atom stereocenter count | 0 |
| **16.** | Defined bond stereocenter count | 0 |
| **17.** | Undefined bond stereocenter count | 0 |
| **18.** | Covalently bonded unit count | 1 |
| **19.** | Compound is canonicalized | Yes |

*Properties and values obtained from PubChem.[22]

**Table 2: Physio-chemical properties.**

| S.No. | Properties* | Values* |
|---|---|---|
| 1. | Physical state | Solid |
| 2. | Color/ form | White to yellowish powder |
| 3. | Odor | Odorless |
| 4. | Melting point | 228-229°C |
| 5. | Solubility | Slightly soluble in organic solvents(e.g. acetone, polyethylene glycol 400) and is pratically insoluble in water and aqueous media |
| 6. | Vapor pressure | 0.0 ± 2.4 mmHg at 25 °C |
| 7. | Refractive Index | 1.633 |
| 8. | pKa | 13.36 ± 0.46(Predicted) |
| 9. | Collision cross section | 170.1 Å² |

*Properties and values obtained from PubChem[22] and ChemBK.[23]

### 2.6 Spectral Information

The hypothetical $^{1}H$ NMR and $^{13}C$ NMR spectrum was computed by ChemDraw Professional 16.0 (Figure 6,7).

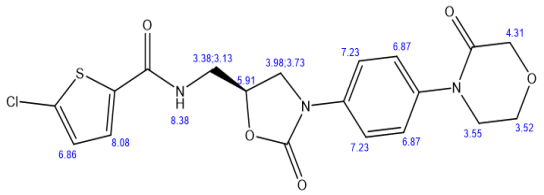



**Fig. 6: ChemNMR$^{1}$H Estimation.**

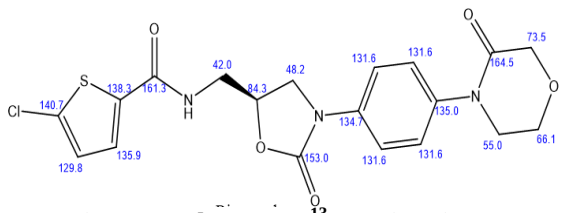



**Figure 7: ChemNMR$^{13}$C Estimation.**

## 3. METHODS OF ANALYSIS

The various reported methods for the analysis of Rivaroxaban includes:

**Spectroscopic:** It can be regarded as main of the classical tools in drug analysis. Among the various available methods for the determination of drugs, spectrophotometric technique is the commonly used one because of its simplicity, specificity and low cost.[3]

Ultraviolet spectrophotometric: Three derivative spectrophotometric techniques were presented by Sharaf et al. for the simultaneous study of Rivaroxaban in tablets and their binary combination.[24] Visible spectrophotometric: Based on the prior response, two visible spectrophotometric approaches were published for quantifying Rivaroxaban alone or in combination with other medicines. Rivaroxaban in tablets was detected spectrophotometrically either at 525 (Rivaroxaban alone) or at 510 nm (Rivaroxaban with cilostazol).[25] Spectrofluorimetric**:** The relationship

between Rivaroxaban and bovine serum albumin has only been studied using one spectrofluorimetric technique to date.[26]

**Chromatographic**

Thin layer chromatographic: The technique is perfect since it is easy to use, inexpensive, sensitive, selective, and requires small amounts of solvents to accomplish. In both pure and tablet form, RXB was quantified using numerous documented TLC spectrodensitometric methods.[27] High-performance liquid chromatographic: For the purpose of separating and quantifying the Rivaroxaban alone or in combination with other medications in pure pharmaceutical formulations and biological fluids, numerous HPLC procedures have been documented.[28] Gas chromatographic: To determine the Rivaroxaban, a gas chromatographic approach was developed.[29] Capillary electrophoretic: A stability-indicating microemulsion electrokinetic chromatographic (MEEKC) technique was used to quantify Rivaroxaban in tablets.[30]

Out of the various available method the spectroscopic has widely been used as a result of simplicity, specificity.

## 4. COMPUTATIOANAL STUDY

### 4.1 Molecular Docking

The computer technique known as "molecular docking" looks for a ligand that fits the protein's binding location both geometrically and energetically. Molecular docking is a commonly employed method for predicting the affinity and activity of a ligand or drug molecule to the binding site of target proteins. It is also frequently utilized to forecast the affinity and activity of a ligand or drug molecule. Thus, a large number of sampling algorithms have been created and are frequently utilized in molecular docking software.[31,32]

The Molecular Operating Environment 2015.10 (MOE) Windows 10 Version 22H2 for x64 was used to perform the molecular docking study in order to assess their interaction and binding modes with target receptors. The 2D structures for the synthesized molecules were created using Molecular Operating Environment 2015.10 (MOE), and those 2D structures were subsequently converted to the appropriate 3D structures. The X-ray crystal structure of 5K0H (PDB id) was retrieved from the Protein Data Bank and solved at 2.20 Å resolution. The protein was optimized by assigning H-bonds, carrying out minimization, and getting it ready using the MOE Quick Prep method. Choosing and preparing the appropriate protein, creating a grid, and preparing the ligand are the main procedures in molecular docking research, followed by its analysis. The docking score, hydrogen bonds, and pi-pi interactions produced with the enclosed amino acids were used to determine the binding affinities and proper positioning of these compounds in the receptor's active region. The ligand was saved in the.mdb format once it had been minimized. The free energy scores of the compound's binding poses were examined.

Structurally, factor Xa is a serine protease that is a member of the trypsin-like family and is involved in numerous important biological processes. The active site of human coagulation factor Xa is composed of four functional sub-pockets. The binding pockets S1 and S4 are the target pockets of Factor Xa. The essential selectivity and binding section are described by the S1 pocket, which often prefers positively charged compounds like guanidine, amine, and benzamidine. S4, the second main binding pocket, is made up of several amino acid residues. Typically, Factor Xa inhibitors bind to the active pocket in an L-shaped configuration.[33]

## RESULTS AND DISCUSSION

Molecular docking studies were used to evaluate rivaroxaban's affinity for the Factor Xa. The docking score was found to be -8.350 Kcal/mol. Figure 8 displays the 2D ligand interaction diagram for rivaroxaban. The 3D ligand interaction diagram of rivaroxaban is represented in Figure 9.

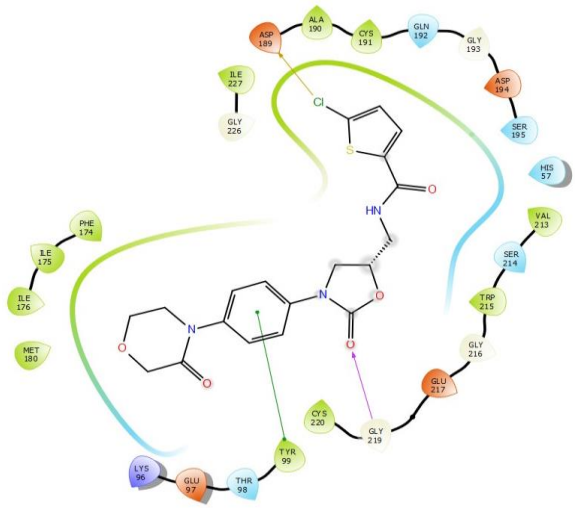



**Figure 8: 2D Ligand interaction of topiramate.**

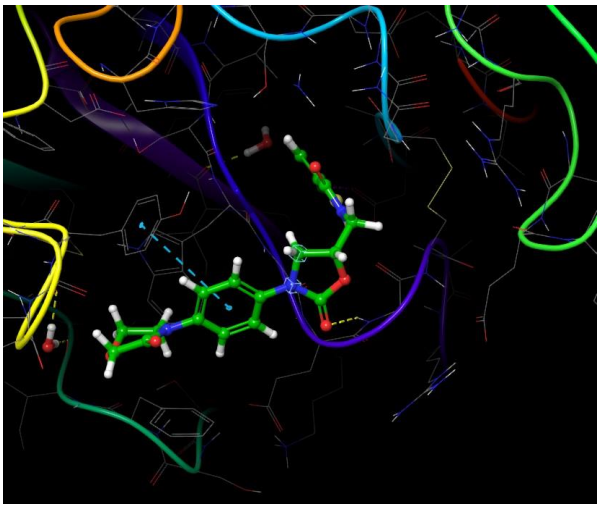


**Figure 9: 3D Ligand interaction of Rivaroxaban.**

## CONCLUSION

In the current era, the role of rivaroxaban in acute coronary disorder is continuously undergoing evaluation. The drug is globally also cost-effective and a safe option for nonvalvular atrial fibrillation. The current review will furnish vision to rivaroxaban for being a newer task force for control of atrial fibrillation.

### Future perspective

Rivaroxaban has the potency that is likely to enhance the benefit to risk profile of anticoagulant. As a result of potential of rivaroxaban, search for new oral anticoagulants have been started that are additional efficacious and favorable.

The market research report is anticipated to overabundance USD 12830 by the year 2027, which is a hike from its prevailing valuation of USD 7509 in 2022. This increase is thoughtful for a compound annual rate of increase (8.2%) between 2023-2027.[34]

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