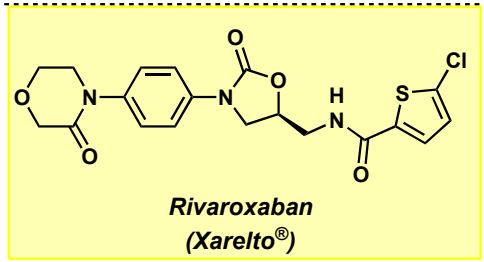
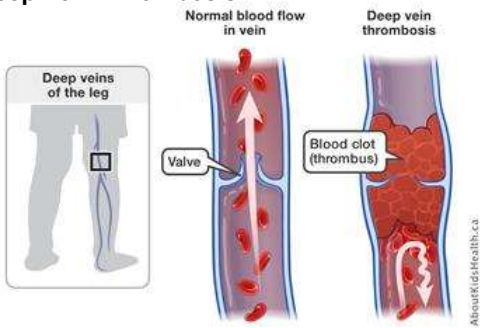
DOTW: Rivaroxaban (Xarelto®)



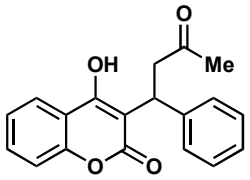
Rivaroxaban (Xarelto®)

Anti-coagulent for thromboembolic diseases
Developed by Bayer

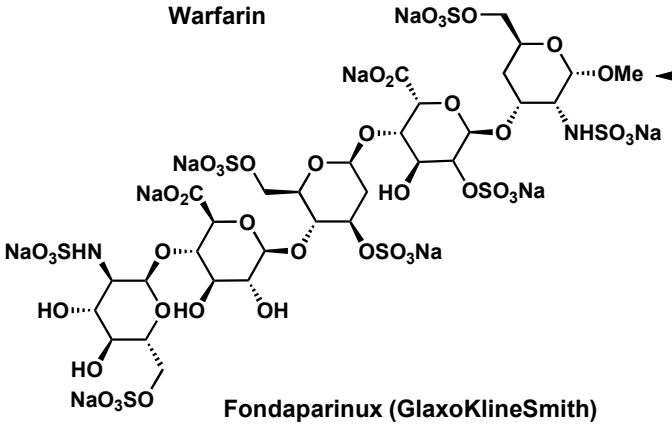
Deep Vein Thrombosis



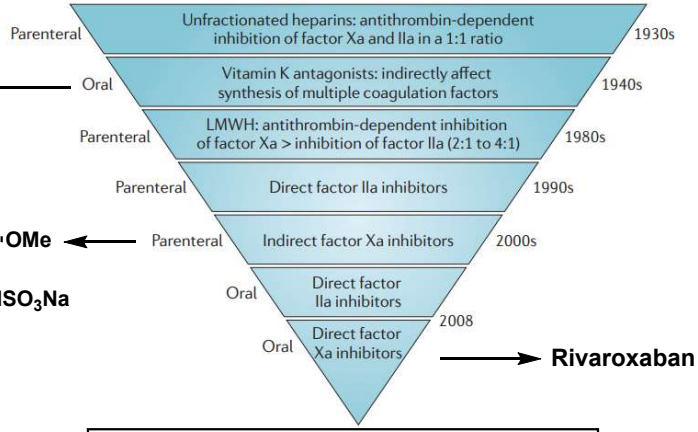
Development of Anti-Coagulants



Warfarin



Fondaparinux (GlaxoKlineSmith)



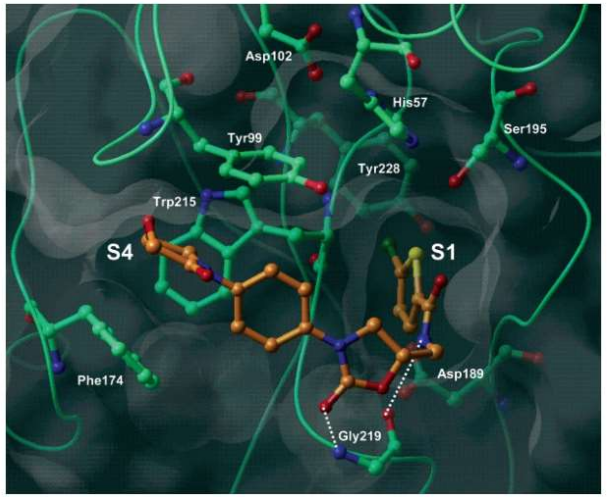
For a comparison of direct factor Xa inhibitors, see *Clin. Pharmacokinet.* **2012**, *48*, 1-22.

Nat. Chem. Rev. **2011**, *10*, 61-75.

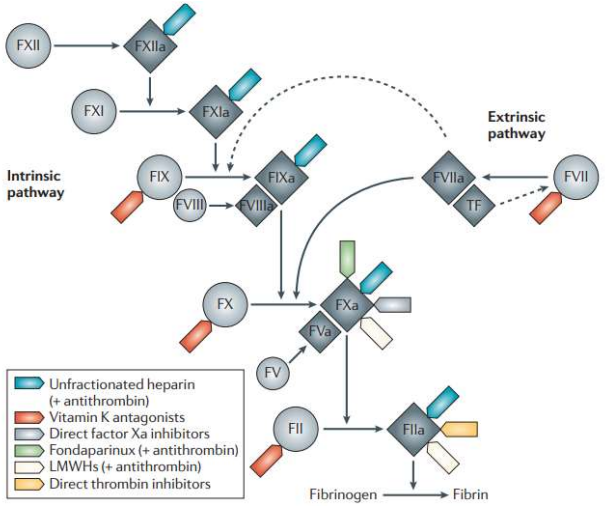
Binding Site and Mechanism of Action

Binding Site:
- Gly219 and Asp189 H-Bond to Rivaroxaban
- Oxazolidione establishes L-Shape-conformer
- Drug is guided into S4 and S1
- Morpholinone is sandwiched in hydrophobic pocket
- Chloro substituent interacts with Tyr 228

Mechanism of Action:
- Rivaroxaban binds to FXa (prothombinase complex)
- Inhibits formation of thrombin
- Fibrin complex cannot form
- Does not directly interact with platelets
- Inhibits coagulation cascade



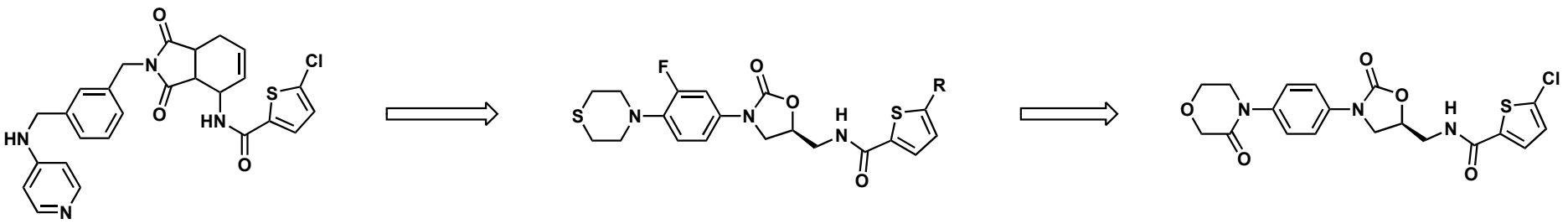
J. Med. Chem. **2005**, *48*, 5900-5908.



Nat. Chem. Rev. **2011**, *10*, 61-75.

DOTW: Rivaroxaban (Xarelto®)

Optimization of Lead and SAR



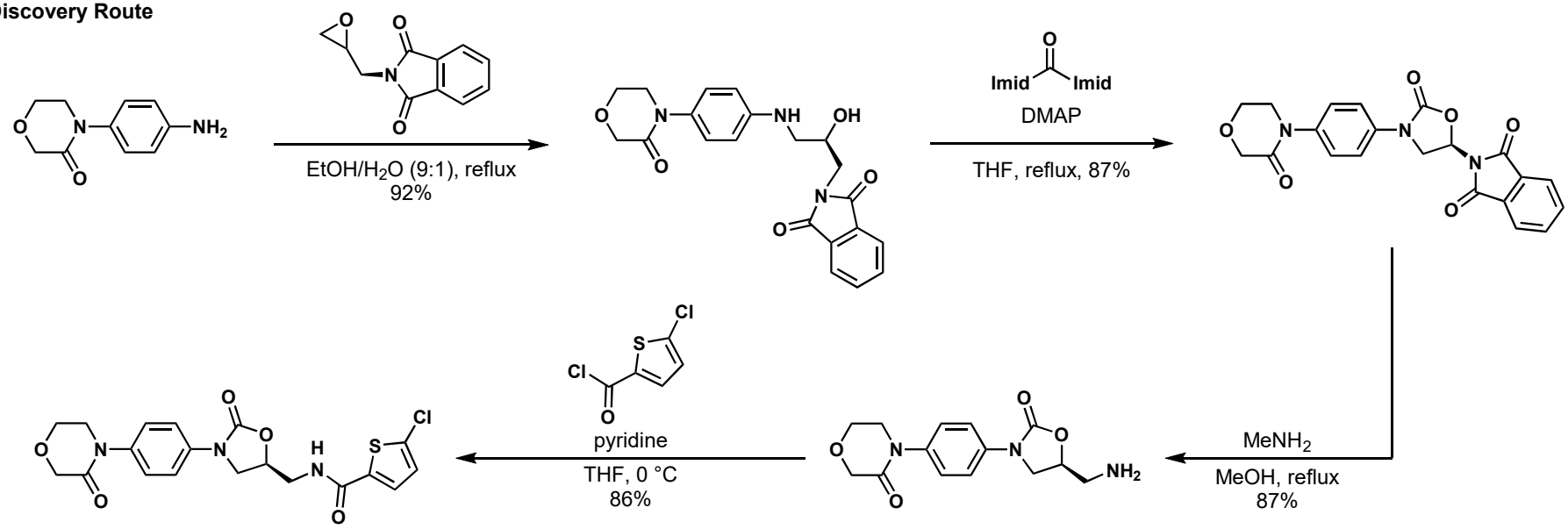
- IC_{50}: 8 nM
- Low bioavailability
- Chloro substituent is important

- R = H; IC_{50}: 20 μM
- R = Cl; IC_{50}: 90 nM
- Significant increase in IC_{50} with (R)-Configuration

- IC_{50}: 0.4 nM
- Morpholinone gives lower IC_{50}
- Substituents on aryl ring increase IC_{50}
- Substituents on amide increase IC_{50}

J. Med. Chem. **2005**, *48*, 5900-5908.

Discovery Route



Rivaroxaban (Xarelto®)

J. Med. Chem. **2005**, *48*, 5900-5908.