

SMART Teams 2015-2016 Research and Design

Saint Dominic Middle School SMART Team

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Modeling the Catalytic Domain of Activated Factor X Coagulation Protein Bound to Apixaban

PDB: 2P16

Primary Citation: Donald J. Pinto, Michael J. Orwat, Stephanie Koch, Karen A. Rossi, Richard S. Alexander, Angela Smallwood, Pancras C. Wong, Alan R. Rendina, Joseph M. Luetzgen, Robert M. Knabb, Kan He, Baomin Xin, Ruth R. Wexler, and Patrick Y. S. Lam. (2007) Discovery of 1-(4-Methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (Apixaban, BMS-562247), a Highly Potent, Selective, Efficacious, and Orally Bioavailable Inhibitor of Blood Coagulation Factor Xa. *J.Med.Chem.* 50: 5339-5356

Format: Alpha carbon backbone

RP: Zcorp with plaster

Description: An estimated 900,000 people a year develop venous blood clots in the United States and 60,000 to 100,000 die as a result. Anticoagulants are used to prevent and treat thrombosis. New oral anticoagulants (NOAC's), like apixaban (Eliquis) are designed to specifically inhibit blood clotting Factor X. Made in the liver, Factor X acts at the end of both the intrinsic and extrinsic blood clotting cascade. With the help of Factor V, calcium ions, and phospholipids, Factor X cleaves prothrombin, to make thrombin. Thrombin in turn activates fibrinogen, which then forms a mesh of fibrin strands to complete clot formation. Using 3D printing technology, the St. Dominic SMART (Student Modeling a Research Topic) Team modeled the catalytic domain of activated Factor X to investigate how apixaban blocks the active site. The catalytic triad (His57, Asp102, and Ser195) is necessary for Factor X to cleave prothrombin by hydrolysis of a peptide bond, but does not interact directly with apixaban. Trp215, Phe174, and Tyr99 surround the phenylactam group of apixaban, while Gln192 interacts with its pyrazole ring. Gly216 and Glu146 interact with a scaffold carboxamide and the carboxamide group of apixaban, respectively. Asp189 and Tyr228 are important in positioning the natural substrate. NOAC's are superior to traditional anticoagulants because older anticoagulants, such as warfarin, had a need for constant blood tests to ensure patients were getting the correct dosage. However, apixaban like other NOAC's, has no reversal agent in case of emergency. A better understanding of Factor X's structure could help scientists develop a life-saving antidote.



Specific Model Information:

- The heavy chain (A) backbone is colored white.
- The light chain (L) backbone is colored silver.
- Beta sheets in the heavy chain are colored khaki and tan in light chain.
- Alpha helices are pink in heavy chain and light coral in light chain.
- Hydrogen bonds are pale turquoise in heavy chain and turquoise in light chain.
- Disulfide bonds are sea green in both chains with cysteines colored cpk.
- The disulfide bond connecting the heavy and light chain is darkolivegreen with cysteine sulfurs colored goldenrod.
- Struts are colored old lace.
- The light chain amino terminus (lys87) is colored steelblue and the heavy chain amino terminus (Ile16) is colored dodgerblue.
- The light chain carboxy terminus (glu138) is colored maroon and the heavy chain carboxy terminus (Thr244) is colored red.

Active Site

- Active site amino acids are displayed in ball and stick and colored cpk.
- The catalytic triad sidechains are: His57, Asp102, and Ser195.
- The phenylactam portion of apixaban is positioned in a pocket bounded by: Trp215, Phe174, and Tyr99.
- The N-2 nitrogen atom of the apixaban pyrazole ring interacts with backbone of Gln192.
- Magnet #1 connects the carbonyl oxygen of the scaffold carboxamide with the backbone the peptide bond nitrogen of Gly216.
- Magnet #2 connects an N-H of the apixaban carboxamide group to the backbone carbonyl oxygen of glu146.
- The p-methoxyphenyl group of apixaban does not appear to interact with a specific amino acid in the active site.
- Asp189 and Tyr228 are active site amino acids important in position Factor X's natural substrate, prothrombin.
Inhibitor
- Apixaban is colored in a lighter version of cpk so it is easier to see in the active site with carbon colored silver, oxygen light pink, and nitrogen light blue.

Disulfide Bonds

- Heavy chain disulfide bonds are seagreen with the cysteines displayed in ball and stick and colored cpk.
 - Cys191-Cys220
 - Cys168-Cys182
 - Cys42-Cys58
 - Cys22-Cys27
 - Cys100-Cys89
- The disulfide bond connecting the heavy chain and light chain is colored dark olive green with the sulfurs of the cysteines colored goldenrod.
 - Cys122H-132L
- Light chain disulfide Bonds are seagreen with the cysteines colored cpk
 - Cys111-Cys124
 - Cys89-Cys100
 - Cys109-Cys96

Ligands

- The calcium ion and the amino acids Asp70 and Glu77 that coordinate it are ball and stick and colored cpk.

<http://cbm.msos.edu/smartTeams/index.php>

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