Apixaban

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IUPAC: 1-(4-Methoxyphenyl)-7-oxo-6-\([4-(2-oxopiperidin-1-yl)phenyl]\)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridin-3-carbamid
**Usage:**
The molecule Apixaban is the active ingredient in a drug, called Eliquis®, which is used as an inhibitor for blood clotting (more specifically for the factor Xa in the coagulation cascade) in order to prevent thrombotic diseases such as embolisms or strokes. The drug itself, first introduced to the market in 2011, is available as a pill and therefore designed for oral taking. This drug is an anticoagulant and direct inhibitor of Factor Xa, which is an important part of the blood coagulation system. It is mainly used for prophylaxis of venous thromboembolism (VTE) by adults after hip or knee replacement surgery. Furthermore it is also used to reduce the risk of strokes and systematic embolism by adult patients with not valvular atrial fibrillation (NVAF). Additionally Eliquis® is used for medical treatment and prophylaxis of deep vein thrombosis (DVT) or pulmonary embolism (PE)\(^1\)+\(^2\). A great benefit from this drug is the oral medication\(^1\).

**Blood clotting:**
The in general used therme of blood thinner is in some way irritating, because the substances doesn’t change the viscosity off the blood they are just reducing the coagulation. Blood clotting is a biochemical process that leads to the step by step production of Fibrin. Fibrin closes wounds and prevents blood loss in case of an injury. In course of the process enzymatical factors are catalyzing biochemical reactions that produce new factors, which, again, catalyze follow- up-reactions, to the next factors until Fibrin is produced (coagulation cascade). Blood clotting can occur in two possible ways: the intrinsic and the extrinsic pathway. While the extrinsic path is triggered by trauma, such as a cut on the skin, and produces Fibrin to close the wound, the intrinsic path sometimes occurs unintentionally. The blood clots inside the blood vessels because inorganic surfaces stick to the lining of the vessels and bind the factors needed for the coagulation. This may cause fibrin production and thereby calcify the vessel. If the blood is unable to flow through the vessel an embolism or a stroke may occur, depending on which vessel has been calcified.

Figure 1:
In the picture, both, extrinsic and intrinsic pathways are outlined. The central factor which is essential of both pathways is factor Xa. By reversibly inhibiting this factor with a high selectivity, the Apixaban Molecule indirectly blocks both pathways of blood clotting. This may as well have negative side effects if the drug user gets wounded.

**Negative side effects:**
As mentioned before a relatively high risk of taking Eliquis® is that it influences extrinsic blood clotting as well. Especially patients that have recently been operated or suffer from cerebral hemorrhage are advised not to take Eliquis®. Other side effects which are most frequently occurring during the intake of Eliquis® are anemia, tiredness, bleeding and nausea.

**Synthesis:**

Step 1: Substitution of the hydroxyl group via SNi in Benzene.

\[
\text{COCl}_2, \text{Benzene} \quad \xrightarrow{\text{Br}} \quad \text{Cl}
\]

"7-Bromohept-1-en-3-one (19), prepared from 5-bromopentanoic acid via the acid chloride and reaction with trimethyl(vinyl)silane, \(^{[40]}\) was reacted with \(\alpha\)-(alkylideneamino)nitrile 1d in the presence of DBU.\(^{[5]+[6]}\)

Step 2: Reduction of the nitro group with Zinc and formic acid in methanol\(^{[5]+[7]+[8]}\).

Step 3: Addition of the 5-bromovaleryl chloride molecule to the 4-Iodo- Aniline and synthesis of the "bicyclic pyrazolo-dihydropyridinone scaffold".\(^{[5]+[9]}\)
Step 4: Combination of the “bicyclic pyrazolo-dihydropyridinone scaffold” with morpholine leads to a morpholine-enamine which is the first major compound (Compound A) for the Apixaban synthesis.\(^5\)+\(^9\)

\[
\text{PCl}_5, \text{CHCl}_3 \xrightarrow{\Delta H} \text{N} \text{N} \text{O O I N H O} + \text{I} \text{N} \text{I O} \xrightarrow{\text{PCl}_5, \text{CHCl}_3} \text{N} \text{N} \text{O O I N H O}
\]

Step 5: “Preparation of (Z)-Ethyl 2-Chloro-2-(2-(4-methoxyphenyl)-hydrazono)acetate”, the second major component of Apixaban (Compound B) via a diazotized intermediate.\(^5\)+\(^10\)

\[
\text{NH}_2 \xrightarrow{1. \text{HCl, } \text{H}_2\text{O (5 °C)}} \text{N} \text{N} \text{O O} \xrightarrow{2. \text{Add NaNO}_2(aq) (-5 °C)}} \xrightarrow{1. \text{Stir at 0 °C}} \text{N} \text{N} \text{O O} \xrightarrow{2. \text{Gradually add } \text{C}_7\text{H}_7\text{ClO}_2, \text{C}_2\text{H}_5\text{OH, H}_2\text{O, NaC}_2\text{H}_5\text{COOH slow} \text{ly raise temperature to room temperature, stir}} \xrightarrow{\text{H}_3\text{C O O}} \text{N} \text{N} \text{O O} \xrightarrow{\text{N} \text{N} \text{O O}} \xrightarrow{\text{H}_3\text{C O}} \text{N} \text{N} \text{O O} \xrightarrow{\text{N} \text{N} \text{O O}}
\]

Step 6: 3+2 addition of Component A and Component B leads to the next intermediate.\(^5\)+\(^10\)

\[
\text{O O} \xrightarrow{1. \text{Toluene, } N(C_2H_3)_3} \text{O O} \xrightarrow{2. \text{quench with } H_2O, \text{extract with ethyl acetate}} \text{H}_3\text{C O O} \xrightarrow{\text{N} \text{N} \text{O O}} \xrightarrow{\text{H}_3\text{C O}} \text{N} \text{N} \text{O O} \xrightarrow{\text{N} \text{N} \text{O O}} \xrightarrow{\text{H}_3\text{C O}}
\]
Step 7: Under Ullmann conditions δ-valerolactam is added to the molecule by using a cross reaction.\(^5\)+\(^10\)+\(^11\)

(Cross reactions):
In the synthesis of Apixaban a cross reaction, called Ulmann coupling, is used. This type of reaction is also very popular in Catalysis and usually occurs in three steps and is depicted in the scheme afterwards:

The first step consists of the addition of a Molecule to the catalyst where the part of the molecule that shall be linked in course of the reaction (R) is reduced because the catalyst splits up the bond between (R) and the component (X) that shall not be linked in the reaction. The catalyst itself is oxidized (oxidative addition).

Step two, or metathesis, consists of the part of a molecule (R’Y) that shall be linked to (R), named (R’) switches positions with component (X) at the catalysts central atom. Also (X) is linked to (Y) which is also not needed in the product.

In the final step (R) and (R’) are linked to the product (RR’) the reaction aimed for. They also are separated from the catalyst in this step. The catalyst is reduced into its initial oxidation state (reductive elimination).\(^5\)+\(^10\)
**Similar drugs:**

At this chapter of pharmaceuticals are many different types of medicines, which have sometimes similar effectiveness as Apixaban, but also such that have totally different. Pharmaceuticals that are in the district of anticoagulants are for example Hirudin, vitamin k antagonists, and Heparine, but also as noval oral anticoagulants called pharmaceuticals, like Apixaban, Dabigatran and Rivaroxaban.\(^\text{12}\)

A further possibility to reduce the coagulation of blood, and so reduce the risk of apoplexy, is to use antiplatelet drug, which are mostly used in the arteria circulation, because the anticoagulants have less effect. Pharmaceuticals of this class work by inhibiting reversible or irreversible the process involved in platelet activation and so prevent the thrombocyte by doing its work. There are many different pharmaceuticals that work on this principle.\(^\text{13}\) For example Aspirin or Triflusal but also many other drugs.\(^\text{14}\)
Apixaban is, like already said, a pharmaceutical of the novel oral anticoagulants (NOACs), which are also called directly acting oral anticoagulants (DOACs). They are inhibitors of the factors Xa and IIa and are the newest form of anticoagulants. One Type of ila-inhibitor is Dabigatranetexilat, which is in its function really similar to Apixaban. But this anticoagulants is filtered by the waterworks, for which reason patients with renal failure cannot take this medicine.

Xa- Inhibitors like Apixaban is Rivaroxaban, which is mostly used by hip joint or knee joint surgeries, to prevent strokes. This pharmaceutical is produced by the Bayer AG and was published in 2008. Apixaban is a pharmaceutical by Pfizer and Bristol- Myers Squibb and was developed and published in 2011. The scope of application if both pharmaceuticals are really close, so they arrange a competition on the pharmaceutical market.
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