MOXIFLOXACIN

Archive entry

Content:

1. Basic information about Moxifloxacin
2. History of quinolone-drugs
3. Structure of Moxifloxacin
4. 3D-structure of Moxifloxacin
5. Synthesis of Moxifloxacin
6. Biological function
   6.1 Function of gyrase inhibitors
   6.2 Application
7. Sources

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1. Basic information about Moxifloxacin

Moxifloxacin is an antibacterial agent, which belongs to the group of fluoroquinolones. The physical properties are summarized in table 1.1. It was developed by the Bayer AG\[^{[11]}\] in the nineties of the past century and authorized in 1999 \[^{[5,6]}\] in the US and is e.g. marketed under the name Avalox. It is able to act against a wide range of bacteria: gram-negative as well as gram-positive and some atypical types of bacteria. Its structure is given by figure 1.1 and will be discussed in chapter 2. Because of its strong side effects it will be only used to treat infections, if other antibacterial agents will not work on the disease. For example it is used for intraabdominal infections, meningitis or tuberculosis.

Moxifloxacin works as an inhibitor of the enzyme DNA-Gyrase, which is necessary for a process called supercoiling. Due to the inhibition the replication of the bacteria will be harmed and the cell finally will die (mechanism will be the topic of chapter 4).

Fig. 1.1: structure of Moxifloxacin \[^{[1]}\]

Properties

According to IUPAC the exact systematic name of the molecule is:

1-Cyclopropyl-7-\{(1S,6S)-2,8-diazabicyclo[4.3.0]nonan-8-yl\}-6-fluoro-8-methoxy-4-oxoquinoline-3-carboxylic acid

Table 1.1: physical properties of Moxifloxacin \[^{[5]}\]

<table>
<thead>
<tr>
<th>Name</th>
<th>Moxifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>(\text{C}<em>{21}\text{H}</em>{24}\text{FN}<em>{3}\text{O}</em>{4})</td>
</tr>
<tr>
<td>CAS-number</td>
<td>151096-09-2</td>
</tr>
<tr>
<td>(M\ [\text{g/mol}])</td>
<td>401,43</td>
</tr>
<tr>
<td>(T_m [\text{°C}])</td>
<td>203-208°C</td>
</tr>
<tr>
<td>colour</td>
<td>yellow (monochloride)</td>
</tr>
</tbody>
</table>
2. History of quinolone-drugs

The first hint, that quinoline carbolic acids can be used as antibacterial agent were found in 1954. The development of Nalidixin acid by Lesher in 1962 as agent against gram-negative bacteria was another milestone in the history on quinolone-drugs. The first generation of quinolones like Nalidixin acid, Oxolin acid or Cinoxacin have cyclic amine-substituents in the 7-position and are able to fight gram-negative bacteria but only have a low rate of resorption by the body and bacteria can easily generate resistance.

The second generation of quinolones is characterized by a fluorine-substituent in position 6 and a piperazine-substituent in position 7. These enable them to act against some gram-positive bacteria as well. Examples for second generation quinolones are Ciprofloxacin, Ofloxacin or Levofloxacin.

The Grohe-method constitutes a huge improvement for the research on the quinolones by making it possible to introduce the cyclopropyl-ring into the molecules.

Since than the research concentrates on finding new substituents in position 7 to expand the range of effected bacteria, especially in terms of gram-positive bacteria. Moxifloxacin, which can be classified as a third generation quinolone is characterized by a higher activity against gram-positive bacteria, also in a higher state of dilution and a longer half-life period.
3. Structure of Moxifloxacin

The Moxifloxacin molecule is made up of a quinolone frame, which carries five relevant substituents beside a carbonyl group:

As a member of the class of fluoroquinolones the fluourine-substituent at position 6 plays a main role in the function of the agent: it increases the lipophilic properties and leads to a higher ability of transport in the body.

This leads to a higher effectivity and antibacterial activity in comparison to the fluoroquinolones of earlier generations. The methoxy-group in position 8 decreases the toxicity of the molecule and is responsible for the antibacterial function as well: the molecule has an effect on anaerobic bacteria and atypic germs. In combination with the previous two substituents the carboxylic acid group in position 3 is necessary for the antibacterial function of Moxifloxacin. The cyclopropyl-group in position 1 supports the formation of the enzyme-DNA complex. The nitrogen-base in position 7 ((15,6S)-2,8-diazabicyclo[4.3.0]nonan-8-yl) simplifies the bonding on the target enzyme gyrase. Further it has effects on the half-life period of the drug (12 hours) in the body and it improves the excretion through the kidneys.
4. 3D-Structure

3D-structure of Moxifloxacin (simulated with avogadro)

Fig. 4.1: Showing location of single and double bonds

Fig. 4.2: Stick model of the molecule
5. Synthesis of Moxifloxacin

There are two methods to synthesize the quinolone frame of Moxifloxacin: the Grohe-method (Fig. 3.1) and the use of the Gould-Jacobs reaction (Fig. 3.2). Figure 3.1 also includes the following steps. In comparison the product of the Gould-Jacobs reaction still lacks of some substituents, which have to be introduced in further steps. These reactions will lead to molecule 1.104. From this point on the synthesis accords to the Grohe-method.

The bicyclic molecule 1.104 is made by an intramolecular nucleophilic substitution, which is supported by a catalyst. In the following step the nitrogen-base 1.105 will react under a nucleophilic aromatic substitution to receive Moxifloxacin. This reaction can be executed in a one-pot reaction to achieve a higher yield.[1]

Molecule 1.105 ((S,S)-2,8-diazabicyclo[4.3.0]nonane), which is required in the last step of the synthesis, can be formed by undergoing two nucleophilic substitutions of N-tosylamine and 2,3-bis-chloromethylpyridine and a consecutive hydration with palladium on elemental carbon as catalyst (Figure 3.3).

Fig. 5.1: Grohe-method [10]
Fig. 5.2: Gould-Jacobs reaction\textsuperscript{[1]}

Fig. 5.3: Synthesis of ((S,S)-2,8-diazabicyc\[4.3.0\]nonane\textsuperscript{[1]}}
6. Biological function

6.1 Function of gyrase inhibitors

Gyrase inhibitors take influence on the function of the DNA-gyrase. This enzyme is responsible for the supercoiling of prokaryotic DNA. When gyrase is inactivated the DNA will lose its compact structure which finally will destroy the cell. This mechanism as well as the consequences of the disfunction of supercoiling are used in antibiotica, for example Moxifloxacin: DNA gyrase (topoisomerase II) and topoisomerase IV are required for DNA synthesis [7]. The relaxation of the DNA is a main pre-condition for the replication and the translation [4].

In detail the quinolones will insert between the base-pairs of the DNA and will fix it in the open position. This will lead to a various number of enzymatic reactions. Among those the SOS-signal will lead to the death of the cell.

![Action of a gyrase](image)

Fig. 6.1: function of gyrase [8]
As already mentioned Moxifloxacin belongs to the group of quinolones, in detail it is a fluoroquinolone. Besides the quinolones other gyrase inhibitors are quinolones, naphthyridines and pyridopyrimidines.

The following figures show the core of the respective inhibitors:

![Fig. 6.2: Nalixidic acid](image)

![Fig. 6.3: Cinnoline](image)

The common element is a heterocyclic aromatic ring, which contains at least one nitrogen-atom in position one, a carboxic acid group in position three a carbonyl group in position four.

Depending on the amount of antibiotic agent, there are two main ways how they can work:

Low doses will inhibit the growth of bacteria. This function is called bacteriostatic, while higher concentrations result in the destruction of the cell by mechanic strain, as mentioned earlier. This is referred to as bactericide.

Besides the mentioned volitional effects of the agents, there are several adverse effects that can occur by ingesting the gyrase inhibitors. In many cases vomiting, diarrhea or nausea can be observed. Moreover fluoroquinolones are able to influence the growth of cartilage.
6.2 Application

Moxifloxacin is a very strong and effective antibiotic agent which is only prescribed, if the patient has been since a real long time already and his or her condition becomes worse. So it only will be used, if conventional agent’s didn’t work. Further the ingestion can be oral or intravenous in form of tablets, juices, capsules, syringes and infusions. Moxifloxacin has different effectiveness levels towards different types of bacteria, but it helps against gram-negative bacteria as well as gram-positive bacteria.

Moxifloxacin is often prescribed at following diseases:
- bronchitis
- pneumonia
- diabetic foot
- inflammations of paranasal sinus

Table 6.1: Effectiveness level of different bacteria of Moxifloxacin

<table>
<thead>
<tr>
<th>Effectiveness level</th>
<th>Good</th>
<th>Very good</th>
<th>Excellent</th>
<th>Not effective (Pseudomonas gap)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>- chlamydia (gram-negative)</td>
<td>- hemophilic influenza (gram-negative)</td>
<td>- pneumococci (gram-positive)</td>
<td>- pseudomonas aeruginosa (gram-negative)</td>
</tr>
<tr>
<td></td>
<td>- mycoplasma (gram-positive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- legionella (gram-negative)</td>
<td>- moraxella catarrhalis (gram negative)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- other atypical bacteria</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If the patient has an intolerance against gyrase inhibitors like Moxifloxacin, it should not be prescribed. Furthermore children are not allowed to consume Moxifloxacin because of possible cartilage damages. Breastfeeding mothers and mothers-to-be also are not allowed to take Moxifloxacin, because it accumulates in mother’s milk. Exactly like people with hepatic disorder, damaged mineral balance, diseases of heart like cardiac dysrhythmia.

Moxifloxacin is definitively the last antibiotic agent, doctors will prescribe, for the use-risk assessment is highly against Moxifloxacin. As effective as Moxifloxacin is, it has many harmful side effects.
Differences between gram-positive and gram-negative bacteria:

<table>
<thead>
<tr>
<th>Gram-positive</th>
<th>Gram-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>- artificial color complexes are not washed out by alcohol =&gt; color dark blue</td>
<td>- artificial colors complexes are washed out by alcohol =&gt; colorless until fuchsine is added =&gt; red, orange-red</td>
</tr>
<tr>
<td>- multilayered diaphragm circa 50% of the cell</td>
<td>- slim, monolayer diaphragm circa 10% of the cell</td>
</tr>
<tr>
<td>- cell wall has 20% - 40% lipoteichoic acid</td>
<td>- no teichoic acid</td>
</tr>
<tr>
<td>- potassium iodide solution gathers between the interstitial</td>
<td>- second lipid membrane on top of each other</td>
</tr>
</tbody>
</table>

Fig. 6.4: structure of gram-positive and gram-negative bacteria[^1]
7. Sources