Linezolid

Ipek Celik, Egzon Cermjani, Lucas Eckert, Malte Erbe

1. General Information and discovery
2. Structure
3. Synthesis
4. Mechanism of action
5. Use
6. Source
1. General information and discovery

Linezolid is an antibiotic and belongs to the family of oxazolidinone. Linezolid is active against most Gram-positive bacteria. In 1987, Du Pont scientist presented a new class of antibiotics, the oxazolidinoes. Linezolid was originally planned for plants and agriculture, but the demand was high for new efficient antibiotics at this time and the effect against human pathogen bacteria was discovered. So in the following years Pharmacia & Upjohn has developed Linezolid and on 26.09.2001 it was published under the name of Zyvoxid. Today Linezolid is one of the most effective and safe medicines in the world.

Image 1)
Structure of Linezolid

The molecular formular of Linezolid is $\text{C}_{16}\text{H}_{20}\text{FN}_3\text{O}_4$ and its molecular weight is 337.346 g/mol. Linezolid is a protein synthesis inhibitor, which affects the power of a bacteria to produce protein. It is used for pneumonia, infections of the skin and infections that are resistant to other antibiotics.

---

1 https://en.wikipedia.org/wiki/Linezolid
2. Structure

The activity of Linezolid depends, same as every other antibiotic, on its structure. The antibiotic effect of oxazolidinone, the essential core of Linezolid, was discovered 1978 during the search for plant protecting agents against bacterial and fungal diseases. Modification of early oxazolidinones lead to more active and safer antibiotics lead to the development of Linezolid.\textsuperscript{23}

![Image 2)
Structure of Linezolid
blue: required for good activity
orange: improves activity and pharmacokinetic properties](image)

The oxazolidinone in Linezolid has two substituents, a phenyl group with two more substituents at position 3 and a methyl group in S-configuration (the R-configuration has no antibiotic properties) at position 5. This methyl group has an acetamid substituent, which is used in all so far developed oxazolidinones due to its high activity compared to other substituents.

At the 3' position of the methyl group is a fluorine atom, it increases the antibacterial activity. At position 5' is a morpholine ring, connected by its nitrogen atom. The nitrogen atom acts as electron donator, the group increases the solubility in water and improves the pharmacokinetic properties by increasing the duration of adequate concentration in the bloodstream.\textsuperscript{1}

\textsuperscript{2} https://books.google.de/books?id=av5SHPiHVcsC&lpg=PA273&ots=Ppk8WOSoBC&dq=S-6123%20%20EI%20DuPont%20Nemours%20%20Co%20&hl=de&pg=PP1#v=onepage&q&f=false

\textsuperscript{3} https://edoc.ub.uni-muenchen.de/9894/1/Hartung_Rainer.pdf

\textsuperscript{1} https://en.wikipedia.org/wiki/Linezolid
3. **Synthesis**

Linezolid is a completely synthetic drug, which doesn't occur in the nature. There are more synthesis routes to Linezolid, but the original method is from Upjohn and Brickner. A drawback of the route is the length and the high cost, because of expensive reagents, such as palladium on charcoal.

The starting compounds are morpholine and 3,4-difluoronitrobenzene. The reaction starts with a nucleophilic aromatic substitution of the 4-fluoro group by morpholine, followed by palladium-catalysed reduction.
of the aromatic nitro group to give the corresponding aromatic amine. The next step is to produce carbamate by using benzylchloroformate, which is deprotonated by lithium tertiary-butoxide. Then it will react with glycidyl butyrate to a five-membered oxazolidinone ring, because the intermediat is not isolated, but spontaneously cyclises. The new intermediat reacts with 3-nitrophenylsulfonyl chloride to a sulfonate ester. The last step is a nucleophilic substitution with ammonia, followed by acetylation and Linezolid is created.\textsuperscript{12}

### 4. Mechanism of action

Linezolid is MRSA (methicillin-resistant Staphylococcus aureus) effective. The mode of action is basically different to other antibiotics. Linezolid appears to work on the first step of protein synthesis, initiation, unlike most other protein synthesis inhibitors, which inhibit elongation. Linezolid binds to the 50S subunit of the ribosome and inhibits the building of a functional initiation complex, which is an essential component of the bacterial translation process and so the translation of mRNA is stopped. This is the different between other well-known protein synthesis inhibitors, such as macrolide, which inhibit the peptid extension.\textsuperscript{3}

Linezolid operates only bacteriostatic, like the most of the other antibiotics.

---

\textsuperscript{1} https://books.google.de/books?id=g5CCAXpBwtIC&pg=PA245&lpg=PA245&dq=linezolid+synthese+brickner&source=bl&ots=eFmo4DY8bm&sig=zOpGhxrc4coDhxXMizmpz7ToW6c&hl=de&sa=X&ved=0ahUKEwje5IeBueHUAhVJa1AKHcuACpIQ6AEINTAC#v=onepage&q=linezolid%20synthese%20brickner&f=false

\textsuperscript{2} https://edoc.ub.uni-muenchen.de/9894/1/Hartung_Rainer.pdf

\textsuperscript{3} https://en.wikipedia.org/wiki/Linezolid
5. Use

Linezolid is the only MRSA-effective antibiotic, which is used either by injection into a vain or in mouth. When given for short periods, linezolid is a relatively safe antibiotic. It can be used in people of all ages and in people with liver disease or poor kidney function.¹ Common side effects of short-time use are headache, diarrhea, rash and nausea. If linezolid is used for a longer time, it may cause sometimes irreversible nerve damage including optic nerve damage. Linezolid is also a weak MAOI (monoamine oxidase inhibitor) and so other MAOIs, large amounts of tyramine-rich foods, (such as pork, aged cheeses, alcoholic beverages, or smoked and pickled foods) can interact with linezolid.

¹https://en.wikipedia.org/wiki/Linezolid
The main use of linezolid is the treatment of severe infections caused by Gram-positive bacteria that are resistant to other antibiotics, such as Enterococcus faecium and Enterococcus faecalis, Staphylococcus aureus and more other; it should not be used against bacteria that are sensitive to drugs with a narrower spectrum of activity, such as penicillins and cephalosporins. The most Gram-negative bacteria, like Pseudomonas and the Enterobacteriaceae, are resistant against Linezolid.\textsuperscript{12}
6. Sources

Alle Quellen wurden zuletzt am 28.06.17 um 14Uhr aufgerufen

Image:
https://en.wikipedia.org/wiki/Linezolid
Image 3): http://worlddrugtracker.blogspot.de/2015/04/linezolid.html
Image 4):

Text:
https://en.wikipedia.org/wiki/Linezolid
https://www.drugbank.ca/drugs/DB00601
http://www.biologie-seite.de/Biologie/Linezolid
https://edoc.ub.uni-muenchen.de/9894/1/Hartung_Rainer.pdf
https://books.google.de/books?id=g5CCAXpBwtIC&pg=PA245&lpg=PA245&dq=linezolid+synthese+brickner&source=bl&ots=eFmo4DY8bm&sig=zOpGhxrc4coDhxXMiZmpzT0W6c&hl=de&sa=X&ved=0ahUKEwje5IeBueHUAhVJaIwKHXcAcAc#v=onepage&q=linezolid%20synthese%20brickner&f=false
https://www.drugs.com/zyvox.html