**Historic influence:**

In 1949 the three Australian scientists Price, Drummond and Lahey first described the structure and synthesis of 3-carboxy-substituted quinolones. However, they did not test for biological activity. In 1950 the antibacterial activity was discovered on a side product 2 of the synthesis of Chloroquin 1 (malaria medicine) at Sterling Drug Inc.. This discovery led to further research.

From February 1957 to March 1960 the British company Imperial Chemical Industries (ICI) filed and published a patent about antibacterial quinolones 3. From January 1961 to July 1962 Sterling Drug Inc. filed and published a patent about antibacterial 1,8-naphthyridones 4.

1957 - 1960: patenting of antibacterial active quinolones (Imperial Chemical Industries ICI, GB)
1961 - 1962: patenting of antibacterial active naphthyridones (George Y. Lesher, Sterling Drug Inc., USA) [1]

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<th>antibiotic agent</th>
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It could be considered, that Sterling wanted to bypass the ICI patent by replacing the quinolone core with 1,8-naphthyridone 4, so their research would still be profitable. Of course it also could have been a result of their research, but it is unknown where this idea had come from. Both have the carboxy group and substituents at the righter N and the left ring in common. The main difference is the Nitrogen in the left ring of the 1,8-naphthyridone 4 by Sterling. In 1963
to 1964 the first clinical tests and launch of Nalidixic acid took place in the USA. Today Nalidixic acid has mostly been replaced by its fluoroquinolone derivates (compare 3) due to better effectiveness and bacterial resistances.

Relation to derivates:
The quinolones are a family of synthetic broad-spectrum antibacterial drugs. The active structure, of the fluoroquinolone class is based upon the quinoline ring system. The addition of the fluorine atom at C6 distinguishes the successive-generation fluoroquinolones from the first-generation of quinolones.

nonfluorinated drugs: Nalidixic acid, Pipemidic acid etc.
fluoroquinolones: Ciprofloxacin 5, Norfloxacin 6, Moxifloxacin 7, Levofloxacin 8 etc.

Since the introduction of Nalidixic acid, more than 10,000 analogs have been synthesized, but only a handful have found their way into clinical practice.

Synthesis:
At first EMME (ethoxy methylene malonic diethyl ester) reacts via a nucleophile substitution with 2-amino-6-methylpyridine to the intermediate of (1). Ethanole is being split off during this reaction.

Then the 1,8-Diazanaphthalene structure is built via a Claisen condensation with natrium hydride in (2).
The next step is a alkaline hydrolysis with natriumhydroxide in a mixture of water and ethanole. After preparation with water the acid group is formed in (3).

In the last step (4) the nitrogen at position 1 is added with ethane via the first step of a Hofmann elimination.

An alternative synthesis begins with the same first two steps. But in this case step (3) and (4) are swapped. The other solvent is dimethylformamide and natriumcarbonate.

**Antibacterial effect:**

The quinolones, such as Nalidixic Acid, prevent the topoisomerase II enzyme Gyrase from unwinding and duplicating bacterial DNA, which leads straightaway to the cellular necrosis. By inhibition of the Gyrase activity the bacterial cell is not able to form a supercoiled structure and the cell collapses. During the Gyrase is working on the bacterial DNA the quinolones intercalate between the bases of the desoxyribose phosphate backbone and shapes a DNA-Gyrase inhibition complex 9. A cooperative effect is measurable in form of a sigmoid curve shape (comparable to oxygen binding haemoglobin). Against the expectation of an additive π-interaction-stacking the effect can be explained by assuming a superposition of three interacting stabilizations, where the stacking effect is just part of it.
1. The first effect locates the quinolones with hydrogen bonds between the nucleobases of a double-stranded DNA. It is necessary that the quinolone molecules are correctly positioned for two further interactions that affect the antibiotics themselves. This explains the importance of an electron-withdrawing group at position 3 and 4 as well.

2. The reason why most of the used drugs contain alkyl-substituted groups such as piperazine is given by the hydrophobic interactions. The big groups pointing to the area inside a DNA strand and push the water molecules away. A resulting maximum of entropy is one reason for a strong bond within the DNA-Gyrase inhibition complex. \[8\][10]

![Diagram](image)

3. The π-interaction stacking between the bicyclo mesomeric system of the quinolones is possibly the strongest one. According to that the binding complex is converted into a three-dimensional phenomenon.