Sulfapyridin

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Sulfapyridine (IUPAC-Name: 4-amino-N-pyridin-2-ylbenenesulfonamide) belongs to one of the first generation of sulphonamide antibiotics. It was used to treat infections like pneumonia or IgA disease.\[17]\n
**Structure:**

![Fig.1. Sulfapyridine structure](image)

Sulfapyridine is a synthetic derivate of para-aminobenzoic-sulfonamide and is constructed out of a benzene ring having an amino and a sulfonamide group.

**Properties:**

The para-position of the two side chains is important for antimicrobial activity. Through different substitution at the nitrogen of the sulfonamide arise various derivate with different solubility, protein binding, tissue distribution, and elimination rate of metabolism. Sulfapyridine forms white to yellow-white crystals, which dissolve in sugar water better than in water alone. The pH of a sulfapyridine-solution in water is neutral.\[17]\n
**Chemical data:**\[16][5]

- Molecular mass: 249,29 g/mol
- CAS-number: 144-83-2
- Melting point: 192°C
- pKa: 8,43
- LD\(_{50}\) (orally in rats): 15800 mg/kg

**History:**

Sulfapyridine was discovered in 1937 by Lionel Whitby, a british scientist. The company May & Baker Ltd. Lionel Whitby worked for, used sulfapyridine as antibiotic to cure bacterial pneumonia and reached fast fame by curing the British Prime Minister Winston Churchill. During World War II the drug was widespread, but soon after it was replaced by other sulfonamides. Some of them have been tested experimentally on concentration camp inmates.\[27]\n
**Synthesis:**

For the synthesis of sulfapyridine two synthetic routes are common, which can be selected depending on the availability of the starting chemicals. First, 2-aminopyridine must be synthesized in both variants.

![Fig.2. Synthesis of 2-aminopyridine](image)

This is done by heating pyridine with sodium amide. A nucleophilic substitution is possible, because a heteroaromatic system has a lower electron density than a homoaromatic system (Chichibabin reaction). The nucleophilic sodium-amide attacks the pyridine in ortho-position, because it is directed by the nitrogen atom. The resulting anion is hydrolyzed to obtain the reactant 2-aminopyridine for further synthesis.
In the first synthesis step the p-acetamidobenzene sulfochloride reacts with 2-aminopyridine under condensation of hydrogen chloride. The acetyl-group of the intermediate is hydrolyzed to obtain sulfapyridine.

The second pathway is close to the previous synthesis, with a condensation of hydrogen chloride. This time the reactants are p-nitrobenzene sulfonylchloride and 2-aminopyridine. In the second step, the nitro-group of the intermediate product is reduced by hydrogenation, whereby water and sulfapyridine arises.

**Effect and usage:**

Sulfonamides, also called sulfa drugs, operate antibacterial, bacteriostatic and antiparasitic against protozoa. Their antimicrobial effect is caused by their special mechanism of action, which all sulfonamides have in common: They have a similar structure such as 4-Aminobenzoic acid (PABA), which is used by the dihydropteroic acid-synthetase to form Dihydropterin acid, and can therefore work as a competitive inhibitor for this enzyme. Competitive inhibitors can, due to their similar composition, bind to the catalytic domain of the enzyme, but will not be converted to a product and therefore will block the enzyme. If Dihydropteroic-acid-synthetase gets blocked, Tetrahydrofolate acid (THF), the “active” form of Folic acid cannot be built. THF is used by the metabolism of all living organism for methyl group- or formyl group-donations. This process is especially important for the synthesis of purines, pyrimidines and amino acid metabolism. For example, the amino acids Glycine, Serine and Methionine are produced with the usage of THF. Furthermore, it has an important role in the biosynthesis of dTMP, which is produced from dUMP and has a major role in the repair of DNA. The outcome of this is, that THF is fundamental for the DNA-replication. If it is inhibited however, the replication and growth of bacteria is blocked, which does not kill them directly, but the bacteria can now be fought much easier by the immune system. Therefore, sulfonamides are also called folic acid antagonists. They are however, for mammalian cells, which include humans and animal cells, not dangerous, because folic acid is absorbed through nutrition and therefore an inhibition of the folic acid metabolism would not affect us, as we take it directly from our food and can convert it to the needed THF-form. However, it can have some serious side effects, which will be referred to in the section significance.
The usage of sulfapyridine against infections is mostly discontinued due to the huge amount of side effects. However, there are some exceptions like linear IgA dermatosis (autoimmune disease)\(^{[27]}\), Dermatitis herpetiformis Duhring (bubble-forming autoimmune dermatosis)\(^{[3]}\) and bullous pemphigoid (autoimmune disease)\(^{[2]}\), where sulfapyridine is still used. It also shows, that sulfapyridine can be taken as an unplanned alternate treatment for Pyoderma gangrenosum (autoimmune disease) and Subcorneal pustular dermatitis (rare skin condition).\(^{[7]}\) But its usage is very dependent of the patient’s reaction to Dapson, another sulfonamide, which is normally used for these diseases and more effective than sulfapyridine. If the patient shows intolerance to dapson, sulfapyridine needs to be prescribed.\(^{[15]}\) Normally sulfapyridine will be taken orally in tablet form\(^{[8]}\) and work after a period of latency of 4-6 hours.\(^{[14]}\)

In general Sulfonamides are not often used nowadays due to the development of bacterial resistance, because of their long usage. For this reason, sulfonamides are often used with other medicaments, which block the folic acid metabolism in another point, such as the Dihydrofolate reductasis-inhibitor Trimethopromin.\(^{[10]}\) Sulfonamides are often used for rodents, because they do not tolerate antibiotics.\(^{[24]}\) They are typically prescribed for infections in the urinary passage\(^{[4]}\), enderoanastomosis, infections caused by protozoen\(^{[12]}\) or for autoimmune diseases, where, as I mentioned above, sulfapyridine is still used frequently. The few nowadays used sulfonamides are Sulfamethoxazol, Silbersufladiazin and Sulfamerazin.\(^{[4]}\) In Germany only sulfadiazine is allowed to be used alone to treat acute and recurring toxoplasmosis, which is an infection, often occurring in cats.\(^{[26]}\)

**Significance:**

As mention before, sulfapyridine has serious side effects so it is no longer prescribed for treatment of infections in humans.

In many cases, patients who were given sulfapyridine suffered from damage of the liver parenchyma, stomach ache, strong icterus, vomiting, swelling of the liver and tyrosine- and leucine crystals in the urine. It can be assumed that not an overdosing, but rather individual hypersensitivity/Intolerance or hypersensitivity of organs causes the side effects mentioned.\(^{[1]}\)

As with other sulfonamides, there is a significant risk of agranulocytosis very low concentration of granulocytes (a major class of white blood cells), which is the main reason for its decline in use.

Its water solubility is very pH dependent, thus there is a risk of crystallization within the bladder or urethra, which may lead to pain or blockage.\(^{[27]}\)

**Relations:**

Sulfapyridine is part of above-mentioned sulfonamides. The para-position of the sulfonamide side chains is significant for the antibacterial effect. With a substitution on nitrogen of the sulfonamide group many sulfonamides with different solubility, protein binding, metabolism and elimination rate are formed.\(^{[30]}\) Two of the frequently-used sulfonamides are described below.

![Fig.5. Basic structure of sulfonamide](image-url)
Sulfasalazine consists of one molecule of 5-aminosalicylic acid (5-ASA, mesalamine) coupled by an azo bond to one molecule of sulfapyridine. Sulfasalazine is used for the treatment of inflammatory bowel disease, including ulcerative colitis and Crohn's disease. It is also indicated for use when treating rheumatoid arthritis and used for other types of inflammatory arthritis.

It is a prodrug, meaning that it is not active in its ingested form. It is broken down by bacterial enzyme azoreductase in the colon into its two components, 5-aminosalicylic acid, and sulfapyridine. But only 5-ASA has a therapeutic benefit. The sulfapyridine moiety is inactive and causes most of the allergic and intolerant effects of sulfasalazine. Therefore, 5-ASA and other derivatives of 5-ASA are now usually preferred and given alone (as mesalazine).

5-ASA mechanism of action on the one hand, involves the inhibition of the cyclooxygenase and lipooxygenase activity, and thus decrease of synthesis of prostaglandins, leukotrienes and free radicals, on the other hand, the suppression of the immune response in the intestinal mucosa.

Sulfamethoxazole is an antibiotic used for bacterial infections such as urinary tract infections, bronchitis, and prostatitis and is effective against both gram negative and positive bacteria such as Listeria monocytogenes and E. coli. Sulfamethoxazole is normally given in combination with Trimethoprim as an antibiotic Cotrimoxazole. Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with paraaminobenzoic acid (PABA) for binding to dihydrofolate synthetase, an intermediate of tetrahydrofolic acid (THF) synthesis, which is required for DNA synthesis.

Reference list:

[5] http://www.drugbank.ca/drugs/DB00891 (last access 02.03.2016)
[6] http://www.drugbank.ca/drugs/DB01015 (last access 02.03.2016)
[10] http://www.onmeda.de/Wirkstoffgruppe/Sulfonamide+und+Trimethoprim.html (last access 02.03.2016)