AL Chemistry Project (TAS)
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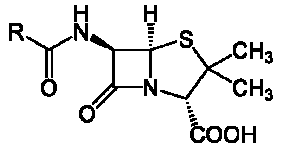
Title: drugs
Topic: Penicillin

(I) Introduction

- Many of you here only because penicillin saved your life. Penicillin which has the structure:  is a group of antibiotics derived from penicillin fungi. Antibiotics are a term by which we mean killing or stopping the growth of a disease-causing microbe. They can even work effectively at very low concentration.

- In the last half of the 20th century, penicillin itself founded a family of related molecules that have contributed significantly to a massive reduction in inflections. Penicillin kills by preventing some bacteria from forming new cell walls. One by one, the bacteria die because they cannot complete the process of division that produces two new 'daughter' bacteria from a single 'parent' bacterium. Therefore, penicillin is very useful to kill bacteria. They are still used nowadays, through many types of bacteria are now resistant.

(II) Lead compound discovery

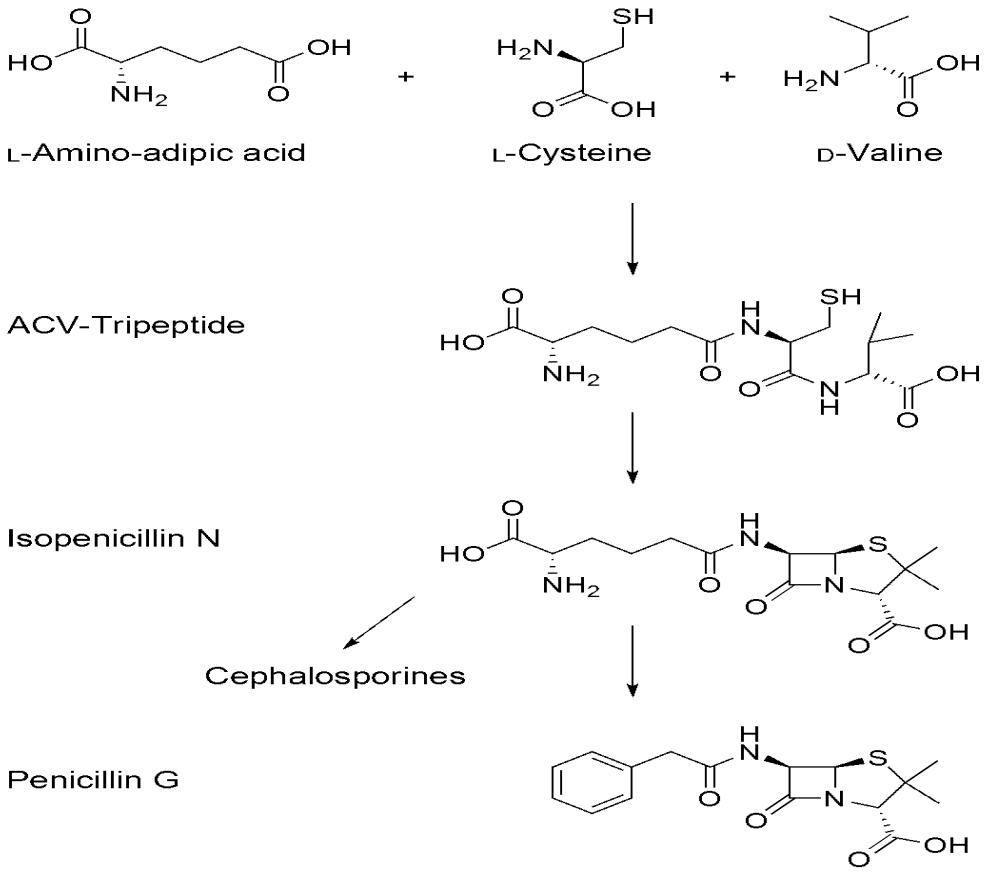
- Scottish scientist and Nobel laureate Alexander Fleming contributed to the discovery of penicillin in 1928. At that time, he was putting a pile of Petri dishes in order where he had been growing bacteria. It was not uncommon that some mold was growing on one of the dishes as he mistakenly left open. However, it was very unusual that the bacteria around the mold had been killed. He found that the mold was from the penicillin family, later known as penicillin notatum. He also concluded that the mold was releasing a substance that could inhibit the growth of bacteria. He was the first person to discover this. Notwithstanding, he was never able to purify his samples of penicillin. The work of growing,

extracting and purifying enough penicillin was done by Howard Florey, Ernst Chain and Norman Heatley later. They developed methods to do this so as to prove its value of drugs.

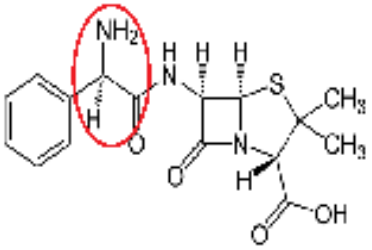
(III)Molecular modification

- There are two different categories of penicillin. **Biosynthetic penicillin** is natural penicillin that is harvested from the mold itself by fermentation.

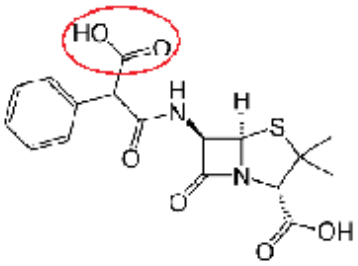
- Penicillin Biosynthesis:



- The other form of penicillin is called **semi-synthetic**. The derivatives of penicillin such as Ampicillin, Penicillin V, Carbenicillin, Oxacillin, Methicillin and so on are known as semi-synthetic. These compounds have the basic structure of penicillin, but have been **modified** chemically by removing the acyl group to leave 6-aminopenicillanic acid and then **adding acyl groups** that produce **new properties.** For example:



Ampicillin



Carbenicillin

- This modification is for the purpose that this semi-synthetic penicillin can **resist the acid in the stomach** so as to take the drugs orally. The modification also increases the degree of **resistance to penicillinase** (a penicillin-destroying enzyme produced by some bacteria) and has an extended range of **activity against some Gram-negative bacteria.**

(IV)Formulation development

- Penicillin has been developed into different types of derivatives because of the narrow range of treatable diseases. Many derivatives were developed for the sake of treating a wider range of infections.

- Benzylpenicillin, procaine benzylpenicillin, benzathine benzylpenicillin and phenoxymethylpenicillin are the four main types of drugs used nowadays. Benzylpenicillin, procaine benzylpenicillin and benzathine benzylpenicillin are given by injection, but phenoxymethylpenicillin is given orally.

- **Benzylpenicillin** may be used to treat infections of the lungs and airways, mouth and throat, skin or soft tissue, or ears, as well as other more rare infections. Benzylpenicillin is given by injection into a vein or muscle, or via a drip into a vein.

- **Procaine benzylpenicillin** is a sustained release drug that is slowly hydrolysed to benzylpenicillin after deep intramuscular injection. Its microbiological properties are the same as those of benzylpenicillin.

- **Benzathine benzylpenicillin** is slowly absorbed into the circulation, after intramuscular injection, and hydrolysed to benzylpenicillin in vivo. It is the drug-of-choice when prolonged low concentrations of benzylpenicillin are required and appropriate; allowing prolonged antibiotic action over 2–4

weeks after a single IM dose. It is marketed by Wyeth under the trade name Bicillin *L-A*.

- **Phenoxymethylpenicillin** has a similar spectrum of action to benzylpenicillin but is less active and is therefore not used for serious infections. It has the advantage that it can be taken by mouth and is more resistant to the action of gastric acids. It is available as tablets or syrup on prescription only.

(v)Safety Test and Human Trials

- Alexander Fleming decided to try to inject penicillin in rabbits and mice. With controlled experimentations, he found that cured rabbits and mice can resist bacterial infections. This definitely proves that penicillin worked as an antibiotic against serious bacterial infections.
- Human research trials began around 1940-1941. Penicillin was tried on a policeman, he had a sore on his mouth about a month previously and the infection had spread to his scalp. He'd had abscess everywhere. He was on his way towards death from the terrible infection. Heatley, Florey, Chain and the rest of the Oxford team, tried it on the dying policeman. This was one of the first tests of penicillin, each day the penicillin was extracted from the policeman's urine and used on him again. It had taken four days for him to improve.
- However, because of limited amount of penicillin, it was difficult to carry out safety tests on human.

(VI)Approval for marketing

- A new drug application must include: (1) the drug's test results, (2) manufacturing information to demonstrate the company can properly manufacture the drug (3) the company's proposed label for the drug. The label provides necessary information about the drug, including uses for which it has been shown to be effective, possible risks, and how to use it.

A. Manufacturing process

- During World War II, as the benefits of penicillin was known, the United States pushed industry into producing penicillin, recruiting more than 21 chemical companies into production.
- Yet, before 1943, it was difficult to produce enough penicillin. This was hard and expensive to accomplish. The reasons why penicillin is hard to produce are threefold:

    1. The synthesis pathway of penicillin is one of the causes. The synthesis pathway: α-ketoglutarate + AcCoA → homocitrate → L-α-aminoadipic acid →L-Lysine + β-lactam. The by-product L-Lysine inhibits the production of homocitrate, so the presence of exogenous lysine should be avoided in penicillin production.
    2. Penicillin is produced when the growth of the fungus is inhibited by stress. It is not produced during active penicillin.
    3. The carbon sources that are available are also important: Glucose inhibits penicillin production, whereas lactose does not. The pH and the levels of nitrogen, lysine, phosphate and oxygen of the batches must also be carefully controlled.

- As Fleming first foresaw, the wartime need for an antibacterial was great, it was a must to have mass production of penicillin. There were three methods to mass-produced penicillin.

    1. Creating the right environment for growth was the first step in producing enough penicillin to be used as a drug. In the United States, it was discovered the huge ‘deep fermentation’ tanks could be used if sterilized air was pumped continually through the tanks.
    2. If corn steep liquor was used, the production of penicillin increased. It was found that corn steep liquor contained concentrated nutrients that increased the yield.
    3. A moldy cantaloupe in a Peoria, Illinois, market on 1943 was found to contain the best and the highest-quality penicillin after a worldwide search.

- The discovery of the cantaloupe, the deep fermentation method and the use of corn steep liquor made mass production possible. From January to May 1943, only 400 million units of penicillin had been made, but by June 1945, over 650 billion units were produced per year. At this time, penicillin was sold in the market and was widely used.