Topic: Antitubercular agents.

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ANTITUBERCULAR AGENTS

Objectives:

By the end of the chapter you will be able to know

- About Tuberculosis as a deadly disease
- About the drugs (antitubercular agents) used to treat tuberculosis and their classification.
- Mechanism of action of antitubercular agents.
- Synthesis, drug structure and structure activity relationship of some antitubercular agents.

Tuberculosis (TB) is a chronic infectious disease caused by various strains of *Mycobacterium* especially *Mycobacterium tuberculosis* which is an acid fast aerobic bacillus. It is transmitted via the respiratory route. It mainly affects the lungs but can spread through blood stream and lymphatic system to the brain, bones, eyes and skin.

CLASSIFICATION

i) First line agents.

An effective bacterial agent, with an acceptable degree of toxicity.

Isoniazid, Ethambutol, Rifampicin, Streptomycin, Pyrazinamide, Rifabutin.

ii) Second line agents.

For microbial resistance or patient related factors.

Ethionamide, Aminosalicylic acid, Cycloserine, Amikacin, Capreomycin.

MECHANISM OF ACTION OF ANTITUBERCULAR AGENTS.

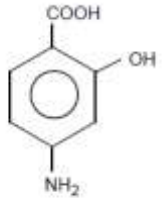
Mycobacterium tuberculosis an acid-fast, nonmotile, nonsporulating, weakly gram positive rod. An important characteristic is the high lipid (60% dry weight) content of the cell wall.

Mycoloic acid is a major component that is characteristic of Mycobacteria. Some drugs act by interfering with mycolic acid synthesis.

Slow growth, ability to survive within phagocytes, and resistance to chemical disinfectants are important factors to consider.

Body defenses are crucial for resistance. TB incidence is increasing as diseases and life styles harmful to body defense systems increase. Cellular immunity is crucial for control of TB.

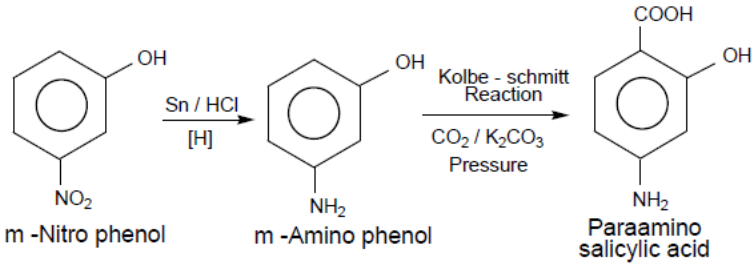
PAS (Para amino salicylic acid)



4 - Amino - 2- hydroxy benzoic acid.

Aminosalicylic acid was introduced to clinical use in 1944. It was the second antibiotic found to be effective in the treatment of tuberculosis, after streptomycin. PAS formed part of the standard treatment for tuberculosis prior to the introduction of rifampicin and pyrazinamide.

Synthesis



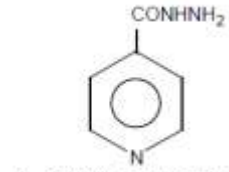
m -Nitro phenol m -Amino phenol Paraamino salicylic acid

STRUCTURE ACTIVITY RELATIONSHIP

- The amino and the carboxyl group must be free and para to each other
- The hydrozyl group may be present in ortho or meta position to carboxyl group, but optimum activity is observed with ortho group.

USE: It is used in the treatment of tuberculosis. PAS is a bacteriostatic agent, so it only arrest but does not eradicate the *tubercle bacilli*. Therefore PAS is always used in combination with one or two other antitubercular drugs.

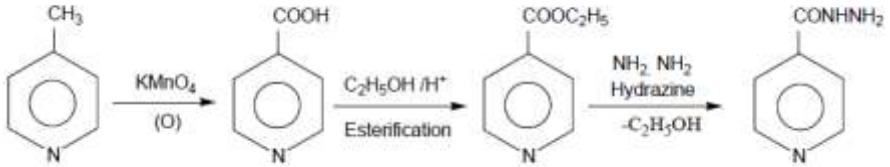
INH (ISONIAZID)



4 - Pyridinecarboxylic acid hydrazide

Isoniazid, also known as **isonicotinylhydrazide** (**INH**), is an antibiotic used for the treatment of tuberculosis. For active tuberculosis it is often used together with rifampicin, pyrazinamide, and either streptomycin or ethambutol. For latent tuberculosis it is often used by itself. It may also be used for atypical types of mycobacteria, such as *M. avium*, *M. kansasii*, and *M. xenopi*. It is usually taken by mouth but may be used by injection into muscle.

SYNTHESIS OF INH



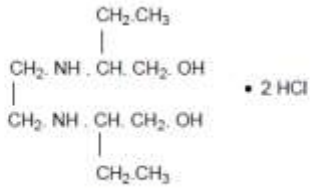
γ- Picoline Isonicotinic acid Ethylisonicotinate Isoniazid

STRUCTURE ACTIVITY RELATIONSHIP

- Derivatives of nicotinaldehyde, isonicotanaldehyde and substituted isonicotinic acid hydrazide are screened for antitubercular activity. Isoniazid hydrazones were found to possess antitubercular activity but are unstable in GIT releasing INH.
- Substitution of hydrazine portion of INH with alkyl or aralkyl substituents resulted in a number of active and inactive derivatives.
- Substitution of N_2 position resulted in active compounds (R_1 and /or R_2=Alkyl; R_3=H)
- Substitution of N_1 hydrogen with alkyl groups resulted in inactive compounds(R_1 and R_2=H, R_3=alkyl.)

USE: Primary drug for treatment of *Mycobacterium tuberculosis*. It is most potent and selective of the known tuberculostatic antibacterial agent and it is regarded as the most effective agents in the therapy of tuberculosis.

Ethambutol Hydrochloride (Mycoback, Mycobutol, Mycobutol)

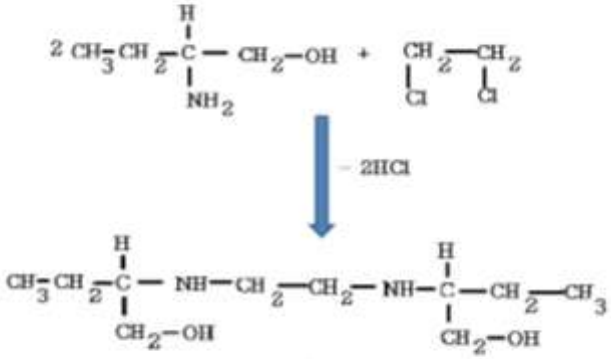


(+) 2,2' - (1,2 - Ethanediyl diamino) bis -1- butanol dihydrochloride

Ethambutol (**EMB**, **E**) is a medication primarily used to treat tuberculosis. It is usually given in combination with other tuberculosis medications, such as isoniazid, rifampicin and pyrazinamide. It may also be used to treat *Mycobacterium avium complex*, and *Mycobacterium kansasii*.

Ethambutol is 200 to 500 fold more active than (-) enatiomer.

Chemical Synthesis



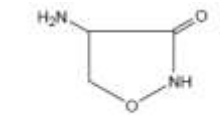
2-amino butanol reacts with 1, 2 dichloro ethane to produce ethambutol

STRUCTURE ACTIVITY RELATIONSHIP

- Though many analogues of Ethambutol have been prepared, none of them is observed to be superior than ethambutol. Any changes such as replacement or substitution in its structure resulted in loss of biological activity.

USE: It is a tuberculostatic drug that is effective against tubercle bacilli resistant to Isoniazid or Streptomycin.

Cycloserine (Cyclokox, Cyclorine, Seromycin)



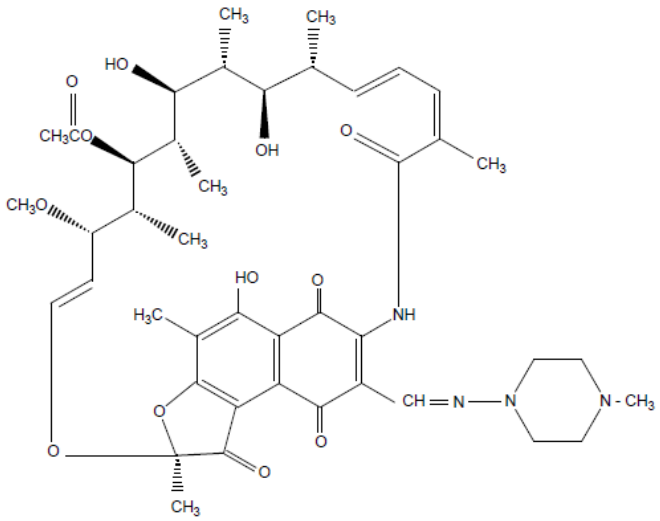
4 - Amino -3- isoxazolidinone

It is an antibiotic, isolated from *Streptomyces* species. The compound slowly dimerizes on standing or in solution.

Use: It is useful in the therapy of tuberculosis resistant to other drugs. It is always combined with other anti- tubercular drug.

Rifampicin (Rifampin) (LS Rif, Rimpacin)

It inhibits bacterial DNA- dependent RNA polymerase (DDRP) and blocks the chain formation of RNA synthesis. It has been suggested that the aromatic naphthalene ring (π- π) bonds to the DDRP



3 - [[(4- Methyl - 1 - piperazinyl) imino] methyl] - rifamycin

Use: A broad spectrum antibiotic effective against most of the Gram positive bacteria and variably active against Gram negative organisms. Both *Mycobacterium tuberculosis* and *Mycobacterium leprae* are very susceptible to this drug. Its clinical use is mainly in the treatment of tuberculosis. It is not recommended in the treatment of HIV- infected patients, since it decreases the effectiveness of protease inhibitors.

MULTI DRUG RESISTANT TUBERCULOSIS

The bacteria that cause tuberculosis (TB) can develop resistance to the antimicrobial drugs used to cure the disease. Multidrug-resistant TB (MDR-TB) is TB that does not respond to at least isoniazid and rifampicin, the 2 most powerful anti-TB drugs.

The 2 reasons why multidrug resistance continues to emerge and spread are mismanagement of TB treatment and person-to-person transmission. Most people with TB are cured by a strictly followed, 6-month drug regimen that is provided to patients with support and supervision. Inappropriate or incorrect use of antimicrobial drugs, or use of ineffective formulations of drugs (such as use of single drugs, poor quality medicines or bad storage conditions), and premature treatment interruption can cause drug resistance, which can then be transmitted, especially in crowded settings such as prisons and hospitals.

In some countries, it is becoming increasingly difficult to treat MDR-TB. Treatment options are limited and expensive, recommended medicines are not always available, and patients experience many adverse effects from the drugs. In some cases even more severe drug-resistant TB may develop. Extensively drug-resistant TB, XDR-TB, is a form of multidrug-resistant TB with additional resistance to more anti-TB drugs that therefore responds to even fewer available medicines. It has been reported in 117 countries worldwide.

Drug resistance can be detected using special laboratory tests which test the bacteria for sensitivity to the drugs or detect resistance patterns. These tests can be molecular in type (such as Xpert MTB/RIF) or else culture-based. Molecular techniques can provide results within hours and have been successfully implemented even in low resource settings.

New WHO recommendations aim to speed up detection and improve treatment outcomes for MDR-TB through use of a novel rapid diagnostic test and a shorter, cheaper treatment regimen. At less than US$ 1000 per patient, the new treatment regimen can be completed in 9–12 months. Not only is it less expensive than current regimens, but it is also expected to improve outcomes and potentially decrease deaths due to better adherence to treatment and reduced loss to follow-up.

Solutions to control drug-resistant TB are to:

- cure the TB patient the first time around

- provide access to diagnosis
- ensure adequate infection control in facilities where patients are treated
- ensure the appropriate use of recommended second-line drugs.

In 2016, an estimated 490 000 people worldwide developed MDR-TB, and an additional 110 000 people with rifampicin-resistant TB were also newly eligible for MDR-TB treatment. The countries with the largest numbers of MDR/RR-TB cases (47% of the global total) were China, India and the Russian Federation. It is estimated that about 6.2% of these cases were XDR-TB.

CURRENT RESEARCH IN TUBERCULOSIS

Bedaquiline, sold under the brand name Sirturo, is a medication used to treat active tuberculosis. It is specifically used to treat multi-drug-resistant tuberculosis (MDR-TB) when other treatment cannot be used. It should be used along with at least three other medications for tuberculosis