ANTITUBERCULOSIS DRUGS

Prof. Zeynep Ateş-Alagöz

Ankara University Faculty of Pharmacy

Department of Pharmaceutical Chemistry

Tuberculosis

- a chronic granulomatous disease
- In developing countries it is a major health problem
- ≈ 30% of world population is infected with Myc. Tuberculosis infection
- In India > 2 million people develop active disease every year & half million die.
- Typical growth characteristics
- Peculiar cell wall structure (waxy appearance) due to mycolic acid.
- Resistance to infection emerges quickly.

Mycobacterium tuberculosis

It is an infection difficult to treat

Mycobacterium Infections

Common infection sites

- Lung (primary site)
- Brain
- Bone
- Liver
- Kidney
- Intestines
- Lymph nodes

- **Aerobic bacillus**
- **Passed from infected:**
  - Humans
  - Cows (bovine) and birds (avian)
    - Much less common

Tuberculosis - Pathophysiology

- **M. tuberculosis** – gram-positive, acid-fast bacillus

- **Spread from person to person via airborne droplets**
  - Coughing, sneezing, speaking – disperse organism and can be inhaled
  - Not highly infectious – requires close, frequent, and prolonged exposure
  - ***Cannot be spread by hands, books, glasses, dishes, or other fomites***

Tuberculosis – Diagnostic Studies

- **Tuberculin Skin Testing** -- + reaction 2-12 weeks after the initial infection
  - **PPD** – Purified protein derivative – used to detect delayed hypersensitivity response
    - Two-step testing – health care workers
    - 5mm > induration – Immunosuppressed patients
    - 10 mm> "at risk" populations & health care workers
    - 15 mm> Low risk people
  - **Chest X-ray** -- used in conjunction with skin testing
    - Multinodular lymph node involvement with cavitation in the upper lobes of the lungs
    - Calcification – within several years after infection
  - **Bacteriologic Studies** –
    - Sputum, gastric washings –early morning specimens for acid-fast bacillus -- three consecutive cultures on different days
    - CSF or pus from an abscess

Antitubercular Agents

- Now there is emergence of multidrug resistant (MDR) TB . More than 0.4 million cases globally.

History

- First successful drug for treating TB was **PAS (Para- aminosalicylic acid)** developed by **Lehman in 1943**.
- Dramatic success came when **Waksman & Schutz** discovered Streptomycin which has made remarkable progress.
- Followed by **Thiacetazone** by **Domagk** in 1946
- In 1952 **Isoniazid** came into being
- **Pyrazinamide** by **Kushner & colleagues** in 1952 & later on **Rifampicin** in 1957

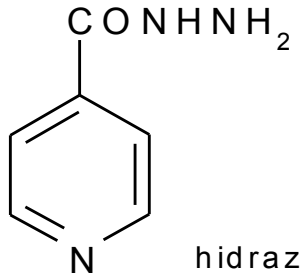
by **S. Margalith** has totally changed the strategy in the chemotherapy.

- **Ethambutol** came in 1961 by **Lederle -laboratories**
- Fluoroquinolones, newer macrolides & congener of Rifampicin →Rifabutin are recent addition in antimycobacterial drugs

Antitubercular Agents

First line drugs:

Isoniazid (Isonicotinic acid hydrazide, INAH):



4-piridinkarboksilik asit hidrazit

isonikotinik asit hidrazit

hidrazit 2 veya 3. konumda ⟹ etki düşer

diğer karbonil trv. ⟹ etki kaybolur

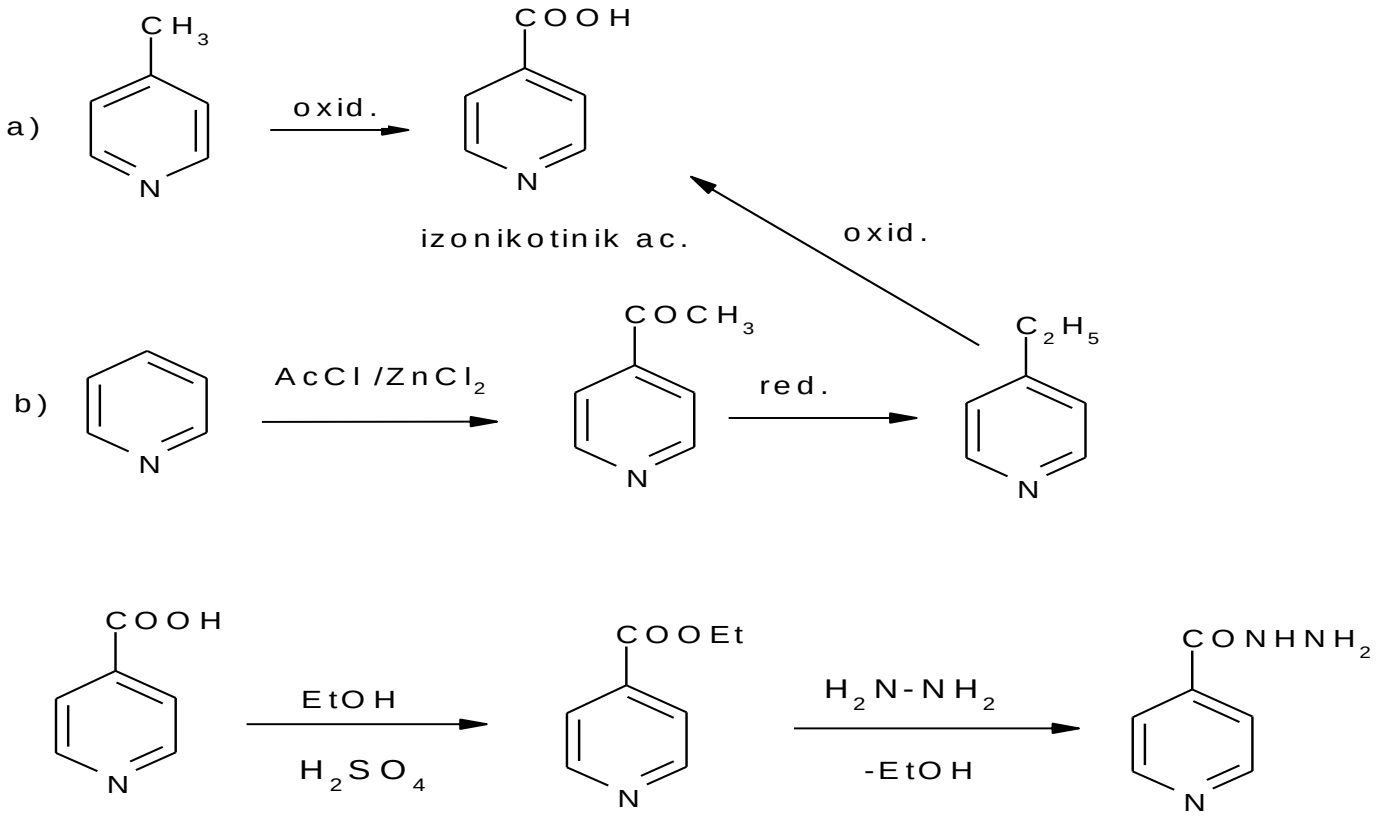
Essential component of all anti TB regimen (except intolerance or resistance)

-Interferes with mycolic acid synthesis (unique to mycobacterial cell wall)

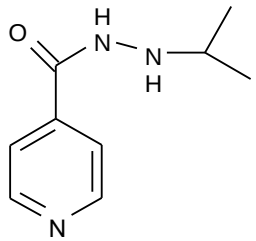
-It is tuberculocidal , **kills fast multiplying organism** & inhibit slow acting organism

-Acts both on intracellular (present in macrophages) & extracellular bacilli

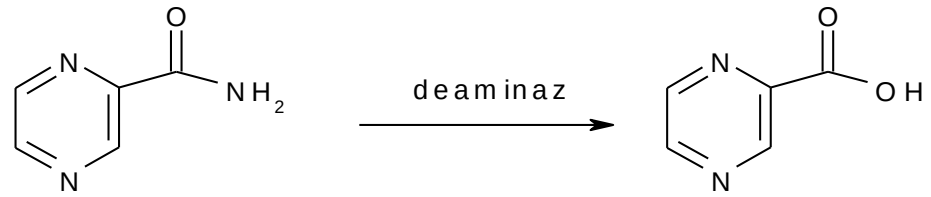
-It is the cheapest agent


a)
CH3
oxid.
COOH
N
izonikotinik ac.
oxid.
b)
AcCl /ZnCl2
COCH3
red.
C2H5
N
COOH
EtOH
H2SO4
COOEt
H2N-NH2
-EtOH
CONHNH2

İPRONİAZİD


O
H
N
N
H
N

Pyrazinamide

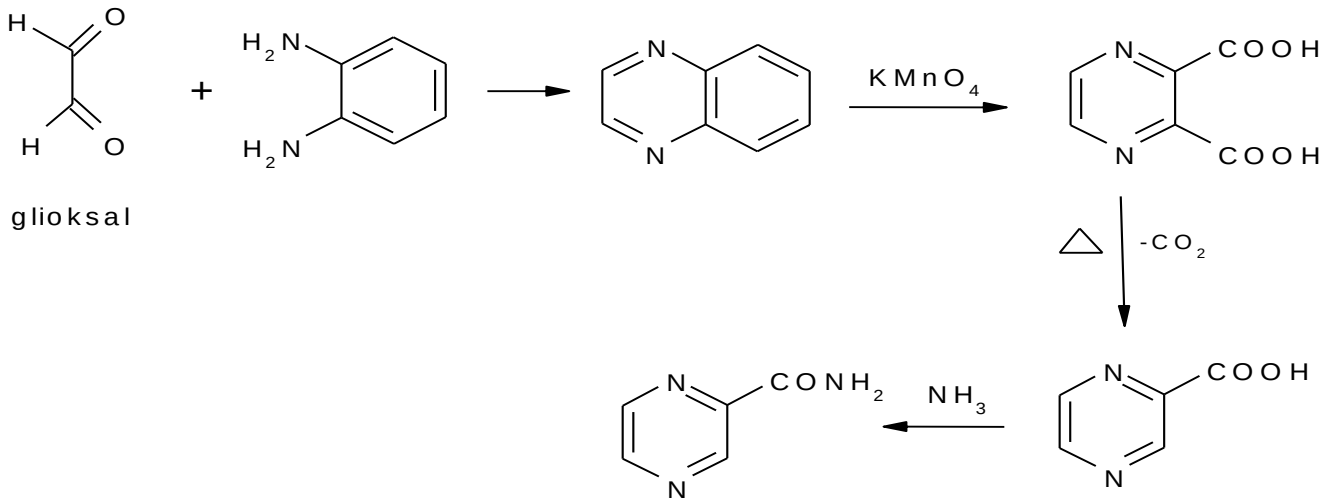


pirazinkarboksamid

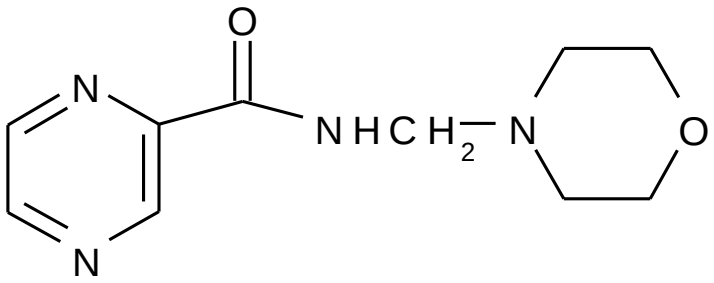
pirazinoik ac.
(aktif metabolit)

bactericidal
hepatotoxic,
Anorexia

Interferes with mycobacterial fatty acid synthesis



MORPHAZINAMIDE (Morphozide)



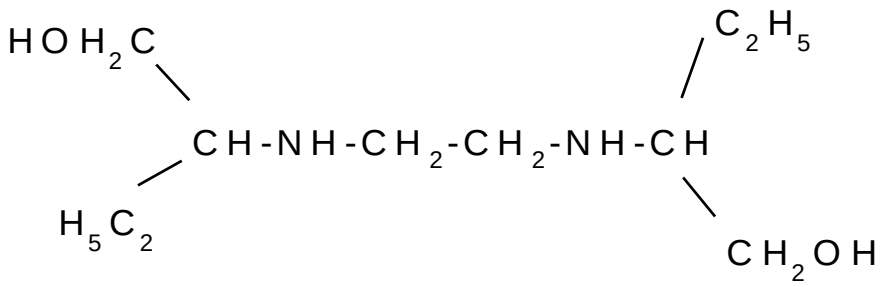
aminometilasyon ile e.e.

Turning Pyrazineamide to show effect.

Side effects less

tuberculocides

Ethambutol

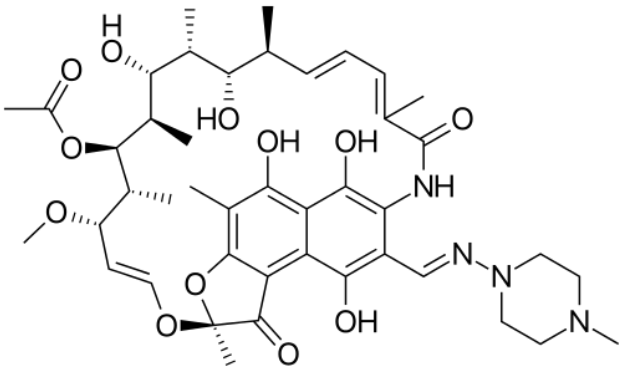


(d) N,N'-bis(1-hidroksimetil-1-propil)etilendiamin

(d) 2,2'-(etilendiamino)-dibutan-1-ol

- Inhibits arabinosyl transferases involved in cell wall biosynthesis
- Bacteriostatic to *M.tuberculosis*
- Resistance develops rapidly if used alone

Rifampicin



-Semisynthetic derivative of Rifamycin B from **Streptomyces mediterranei**

-Inhibits bacterial DNA-dependent RNA polymerase

-bactericidal

-Gram positive and negative

-kill intracellular organism

-Resistance – chemical modification of DNA-dependent RNA polymerase

Streptomycin

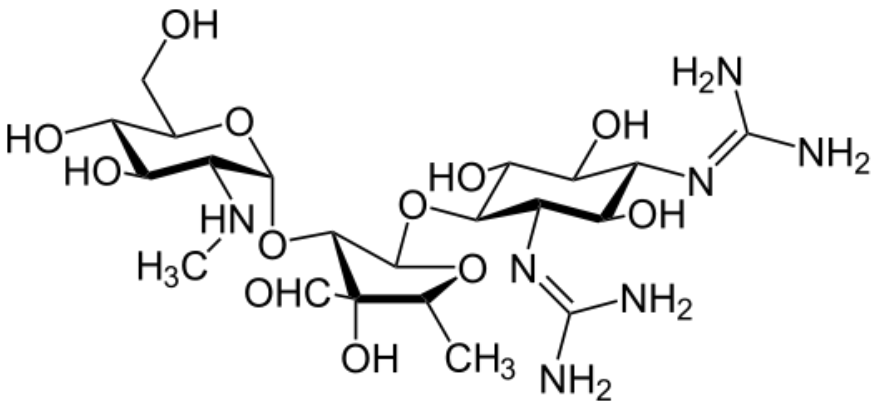
-Aminoglycoside - Inhibits protein synthesis

-Bactericidal

-Poorly absorbed from GIT - given IM.

-CSF penetration: poor

-Renal elimination



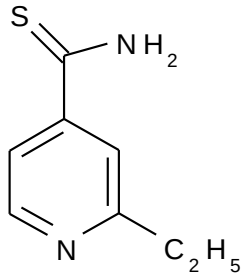
Adverse effects

Ototoxicity, vestibular toxicity, nephrotoxicity

Uses
very ill patients
Multi- drug resistance
Not responding to treatment

Second line drugs:

Ethionamide :



2-etil-tiyo-isonikotinamid
2-etil-4-piridin karbotiyoamid
2-etil-isonikotinil-tiyoamid

-Tuberculostatic , having moderate efficacy

-Inhibits dehydrogenases enzymes .... inhibits peptide synthesis.

-The effect is up to 10% of isoniazid, more toxic

-Behaves like pyridoxine antagonist ... peripheral neurite (pyridoxine) teratogenic

-Resistance develop readily & some cross resistance to TZN

-Absorbed orally ,distributed all over including CSF

PROTİYONAMİDE

-At high concentration ... bactericide

- CSF penetration: enough

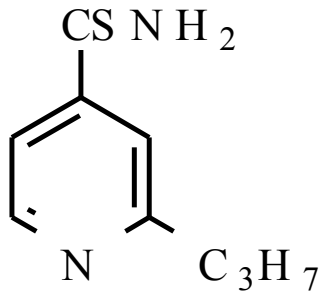
-Oral abs.fast

-Some metabolites are also effective

-Also used in Lepra

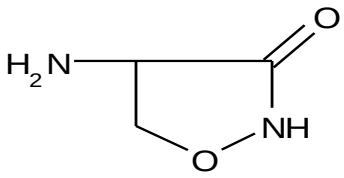
-pyridoxine

-combined



2-Propyl-4-piridinkarbotiyoamit

Cycloserine



D (+) 4-amino-3-isoxazolidinone

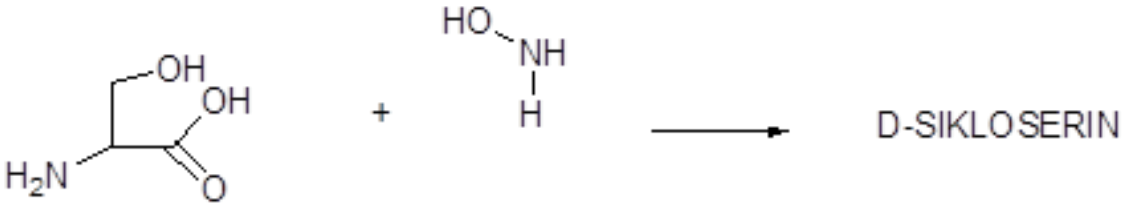
- Obtained from S. archidacces

-↓ Bacterial cell wall synthesis

-Tuberculostatic & ↓ other G -ve organisms

(E. coli , Chlamydia)

-Resistance develop slowly , no cross resist.



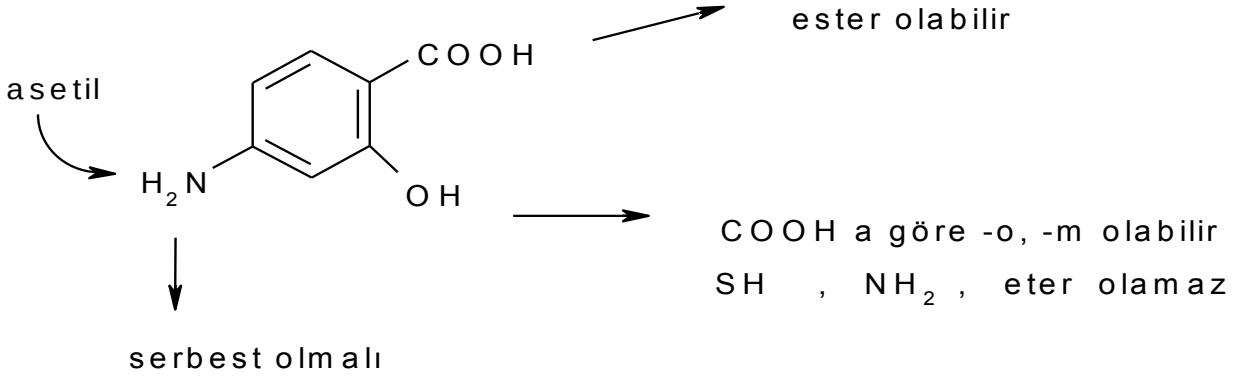
Broad spectrum antibiotic

Reaches the CSF well

Causes CNS side effects

Use in drug resistant TB

PAS – Paraaminosalicylic acid:



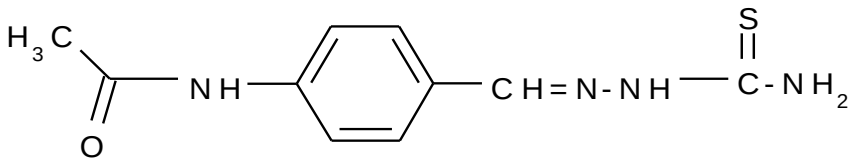
-Related to sulfonamides chemically as well as in mech. of action.

-Tuberculostatic , not add to therapeutic value , only delay resistance

-Interfere with absorption of Rifampicin

S/E - Acceptability is poor due to frequent anorexia , nausea & epigastric pain

Thiazethazone (Citazone)



p-asetil amino benzaldehit tiyosemikarbazon

-Oral use.

-Also use in Lepra.

-There is no cross resistance with isoniazid ..... the mechanisms of action are different (not completely known)

-Combined with isoniazid + streptomycin

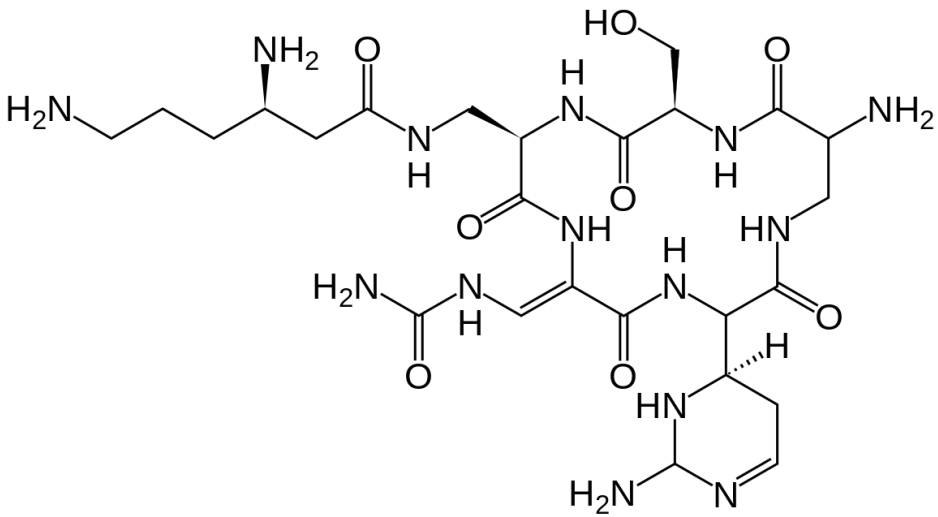
Anemia
leukopenia
HIV enf. should not be used. Skin reactions can be seen.

Capreomycin

Capreomycin is a peptide antibiotic from the group of aminoglycosides

It is another alternative when resistance develops in first class compounds.

Obtained from Streptomyces



DRUGS USED IN LEPRA TREATMENT

Mycobacterium leprae (Hansen basil, Gram-positive)

Infection ability is low
Slowly developing
deformations
mutilation

In mild leprosy reactions ..... aspirin,

prednisone, thalidomide, clofazimine use in some cases

The WHO recommendation is the use of Dapson + clofazimine + rifampin for 2 years

DRUGS USED IN LEPRA TREATMENT

Primer Drugs

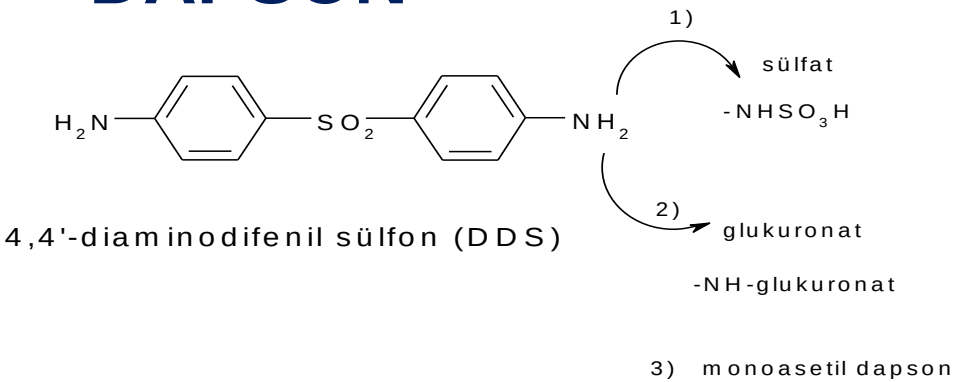
- Dapson
- Rifampicin
- Clofazimine
- Ethionamide or Protionamid

Secondary Drugs

- Tiasetazone
- Tiambutazon
- Long acting sulfonamides
- Aminoglycosides

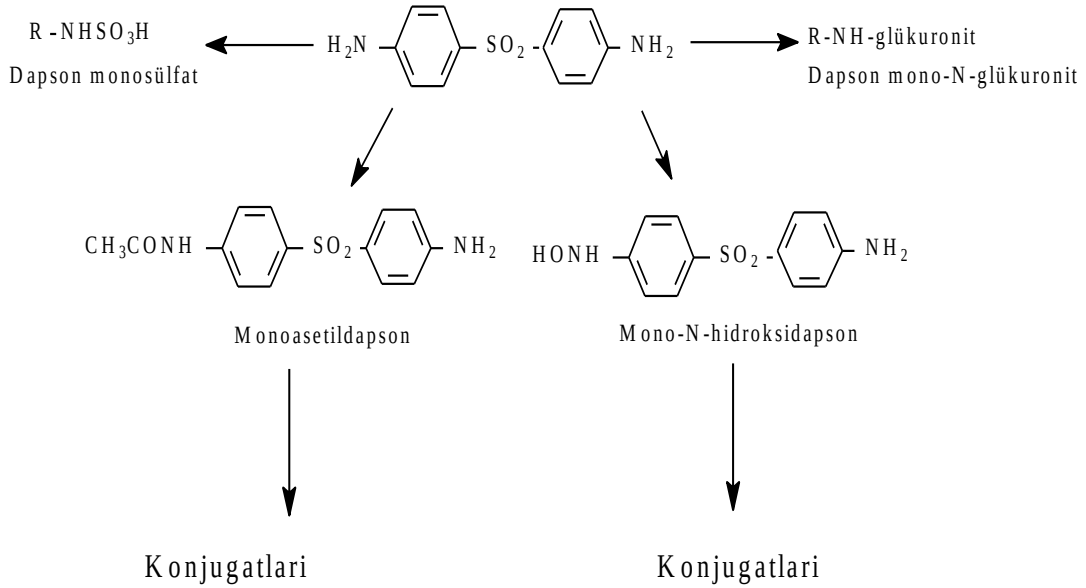
1- Sulphones

DAPSON



4,4'-diaminodifenil sülfon (DDS)

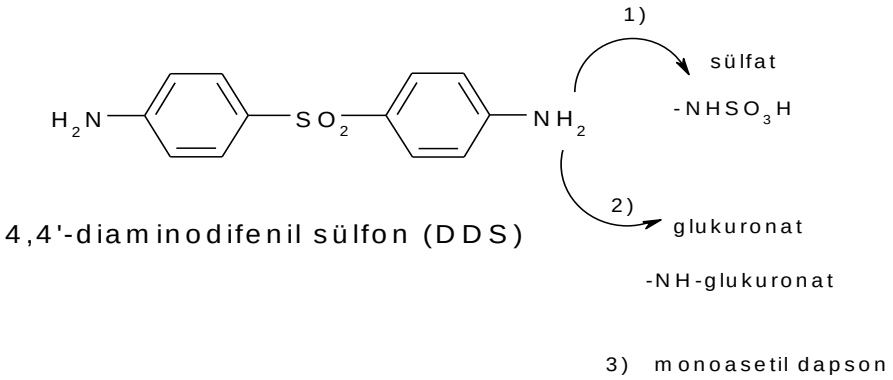
Approximately 70-80% of the dose is discarded as N-glucuronide or N-sulphate conjugates.



bacteriostatic
bactericide in high doses
Used safely in pregnancy, cheap

ASEDAPSON
Prodrug ..... diacetyl derivative
Prophylaxis + treatment

Structure-Activity Relations:



4,4'-diaminodifenil sülfon (DDS)

-Linked hydroxyl, amine, chlorine, methoxy and methyl groups to ring make it inactive.

-Replacement of one of the amine groups with hydroxyl, nitro, or hydroxylamino groups reduces activity.

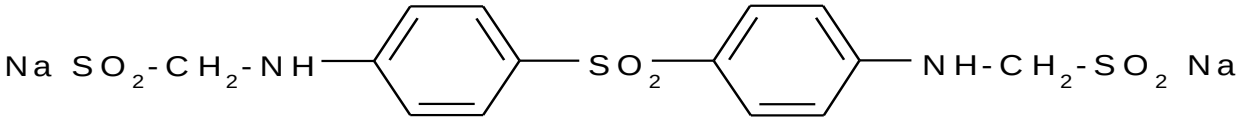
-When both amine groups are replaced by hydroxyl groups, inactive compounds form.

-Reduction of the sulphone group to sulfoxide or conversion to thioether destroys the activity.

-As with sulfoxone sodium, aldehyde-bisulfite complexes of amine groups are the active compounds.

Because they turn into daps with in vivo breakdown.

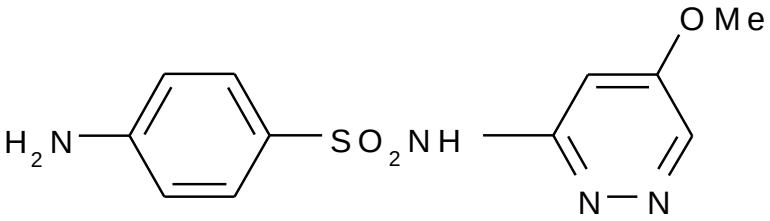
SULFOXONE SODIUM



Disodyum [sülfonil bis (4-fenilamino)]dimetan sülfinat

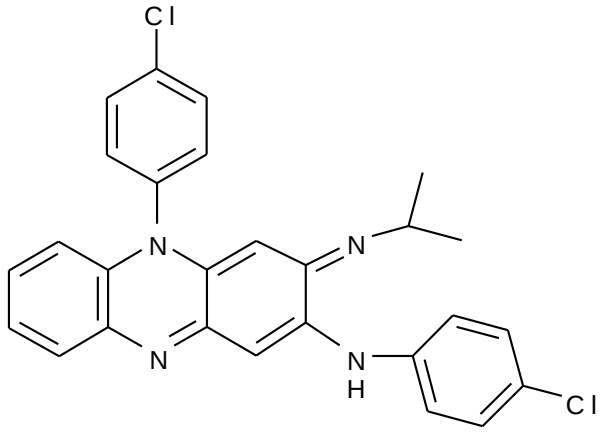
Absorption variable

SULFAMATEOXY PYRIDAZINE



2-Other Drugs

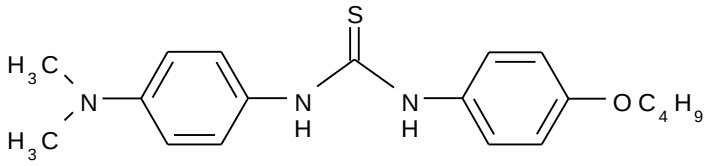
CLOFAZİMİNE



N,5-Bis(4-klorofenil)-3,5-dihidro-3-[(1-metiletil)imino]-2-fenazinamin

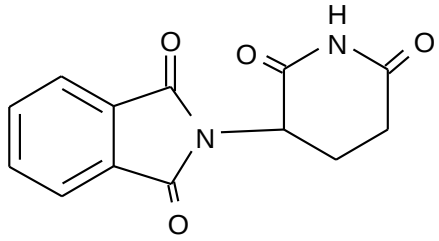
-The isozyme shows an equivalent potency to isoniazide
-The only drug that does not develop resistance
-Cross resistance does not develop
-70-95% unchanged with feces
-bacteriostatic
-red coloration in conjuctiva and mucous membranes

THYAMBUTOSINAL



1-(4-dimetilaminofenil)-3-(4-butoksifenil)-2-tiyoüre

THALIDOMITE



3-ftalimido glutarimid

Resistance develops in 2-3 years ..... dose is increased.

Hypnotic, Antiemetic, Antineoplastic
Antilepra

Rifampin

The body secretions are reddish

bactericidal

ethionamide
Protiyonamid
the Tiyasetazo
isoniazid

Priority Order For Antimicrobial Therapy:

Initial treatment (for 2-3 months)

isoniazid
rifampicin
Etambutol or Streptomyces.,
pyrazinamide

Stabilization treatment (for 4-7 months)

isoniazid
Rifampicin (if pregnancy Etambutol)

Classic Combinations for Lepra

*Isoniazid + Procyanamide + Dapson (8-12 months treatment duration)

* Dapson + Clofazimin (4-6 months duration of treatment)

* Dapson + Clofazimine + Rifampin (Rifampin every two days)

* Clofazimine + Rifampin (2-3 months duration of treatment)

* Dapson + Isoniazid + Thioacetazone (Sekonder combination)

NEW TREATMENT COMBINATIONS

Combinations made with the following drugs are the most common of the new generation drugs.

- Minocycline
- Ofloxacin, moxifloxacin, sparfloxacin ..... bactericide
- Clarithromycin
- Rifapenetin, rifabutin
- Rifampicin

- Cefoxitin
- Sefoliprin i.v. and because it is expensive, it is not widely used in practice

Rifampicin: 600 mg + ofloxacin: 400 mg + Minocycline: 100 mg
RIFAM + ofloxacin + clofazimine + minocycline 1 week
Rifapenetin + Moxifloxacin + Minocycline

In our country, the multi-drug treatment protocol recommended by the world health organization is applied (1983).

According to this regulation, Lepra is a disease that must be recognized and declared by health personnel at all levels in our country.

Lepra is treated free of charge in our country.

WHO aims to launch multidrug therapy:

- Increase treatment effectiveness
- Reduce the duration and frequency of treatment
- Prevent the development of resistan bacilli
- Removing resistant strains from the center
- reduce side effects most
- Reduce costs