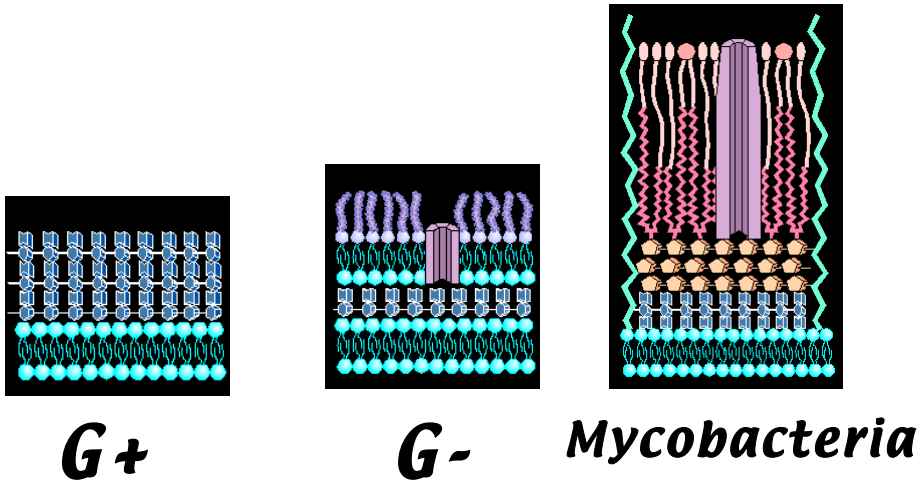
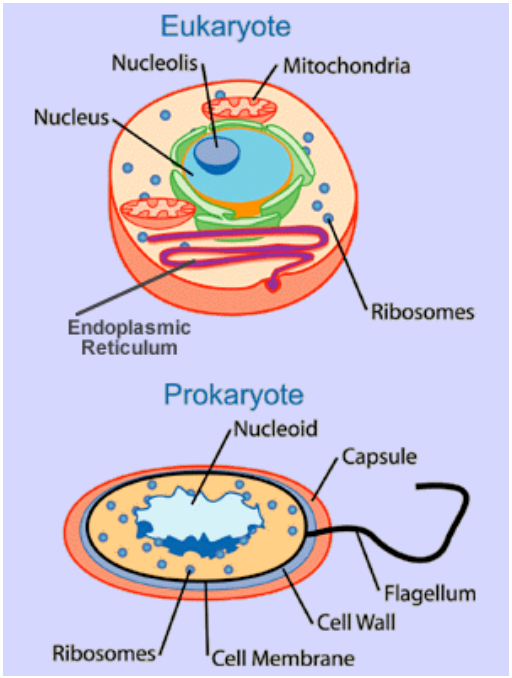
Chemotherapeutic Agents / Antibiotics, chapter 38-43

- **Antibacterial compounds (procaryotes)-Antimycobacterials** **chapt 41**
- Antiparasitic agents (eucarytotes) chapt. 39
- Antifungal compounds (eucarytotes) chapt. 40
- Antiviral compounds
- Anticancer compounds





Pathogenic mycobacteria:

M. tuberculosis **(tuberculosis)**
M. Leprae **(Leprosy)**
M. Avium **(Opportunistic infection in AIDS patients)**
M. bovis **(mainly cattle infect, infected milk USA)**

TUBERCULOSIS (TB)

High lipid / wax content in cell wall (mycolic acid)
Slow growing organisms
Aerobe bacteria
Resistant to chemicals and drying
Easily killed by heat

Until ca. 1950; 50 % of all infected died

Infection by inhalation of the bacteria

Pulmonary TB most common

May also attack other organs including CNS

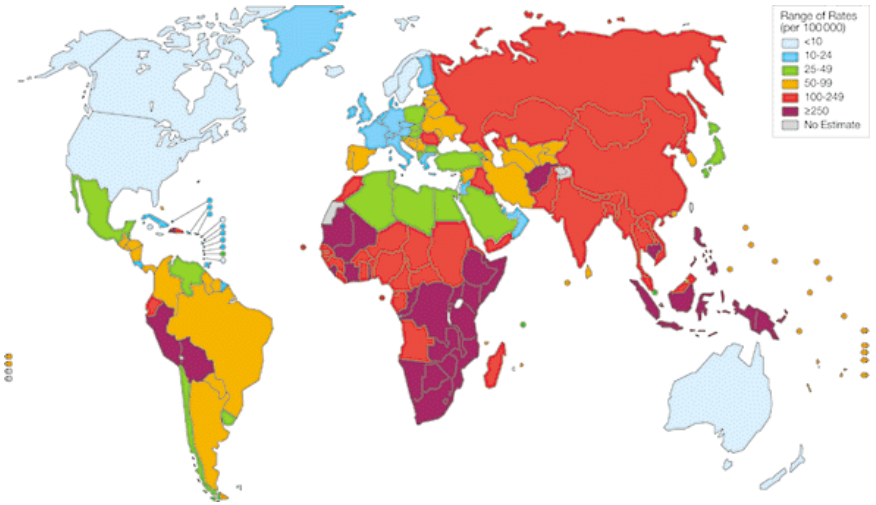
30 million people will die from TB the next 10 years

8 million new cases each year

ca. 1/3 of the world population are infected (incl. dormant infections)

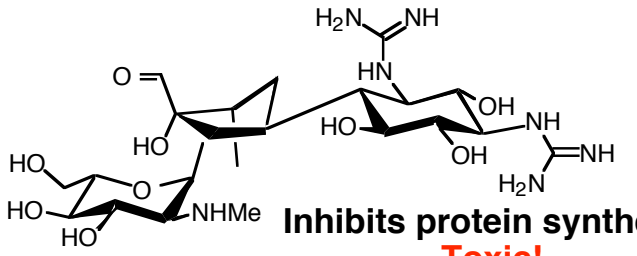
ca. 95% of the cases in developing countries

no new drugs on the marked for the last 25 - 30 years



WHO (1993): TB a "global emergency"

First effective drug: Streptomycin 1946
(see aminoglycosides chapt. 38)



Inhibits protein synthesis
Toxic!

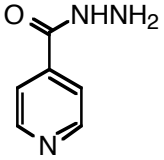
Treatment
•Long time ≥6 mnds
•Combination of drugs } **Different stages of bacterial growth**

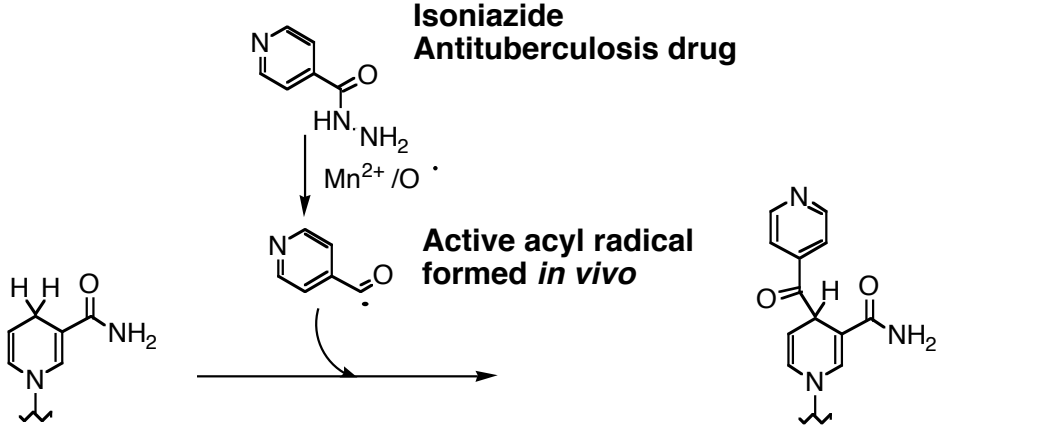
DOT: Directly observed therapy

First-line drugs

Isoniazid

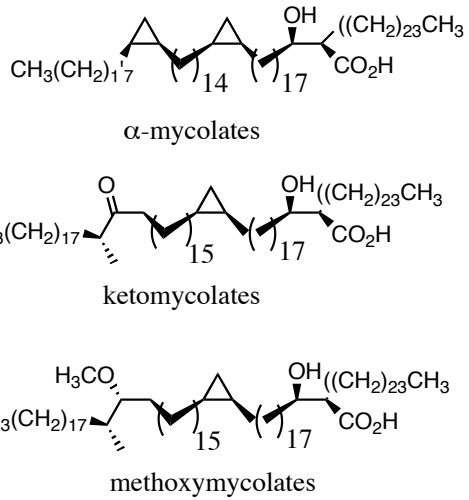
Isoniazid®



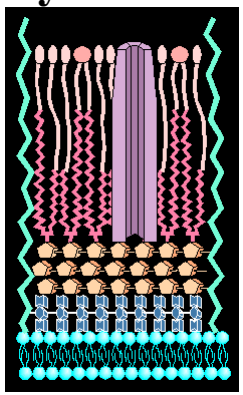


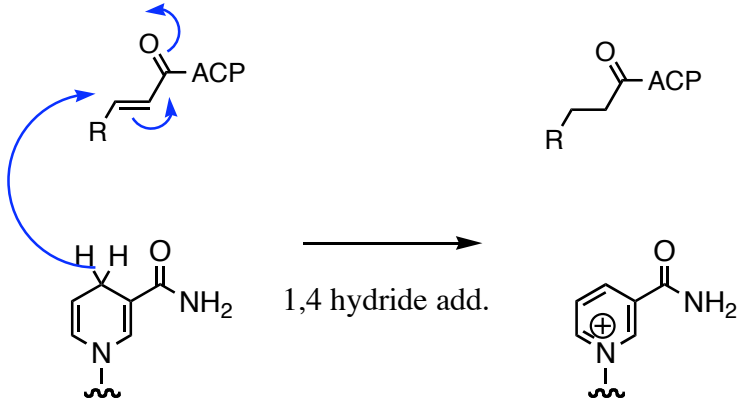
Long Chain ACP-Enoyl
Fatty Acid Reductase (inhA)

APC: Acyl carrier protein)



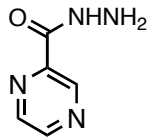
Mycolic acid

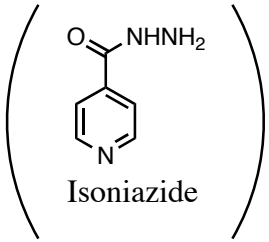




First-line drugs

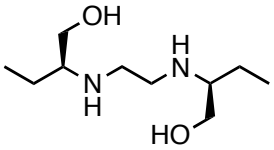
Pyrazinamide

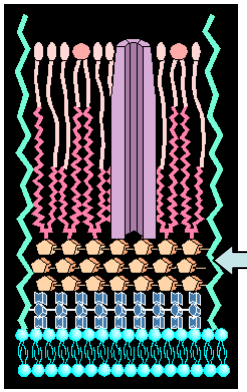




Mechanism not known

Ethambutol

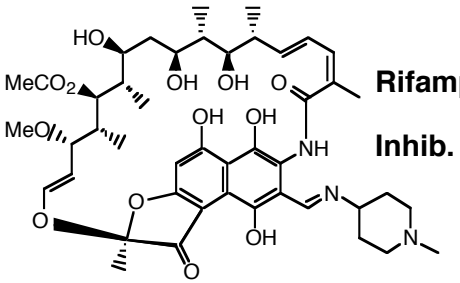




Mechanism not fully known
Synth of cell wall comp.:
Inhib. arabinocyl transferase?
Arabinose,
Arabinomannan
and Lipoarabinomannan

Rifampicin

Rimactan®



Rifampicin

Inhib. RNA-synth.

Broad spectrum antibiotic

From *Streptomyces* sp

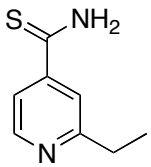
Inhib bacterial RNA polymerase

(π–π intract. naphtalene rings aromatic AA?)

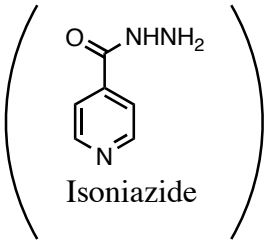
(Induce CYP2C; increased metabol. of certain anti AIDS drugs)

Second-line drugs

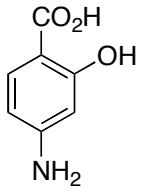
Ethionamide



Mech. ca. as Isoniazide



p-Aminosalicylic acid

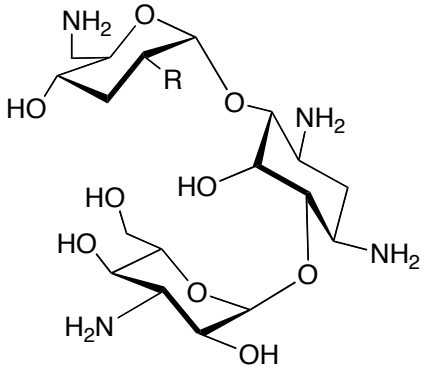


c.f. PABA antimetabolite

Folic acid synth (≈antibact. sulfa)

Kanamycin

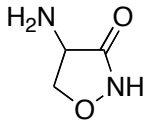
(aminoglycoside antibiotics)



R=OH: Kanamycin A
R=NH_2: Kanamycin B

Cycloserine

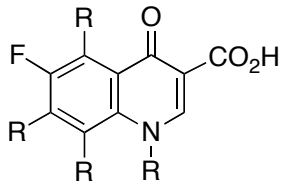
Isolated *Spreptomyces* sp



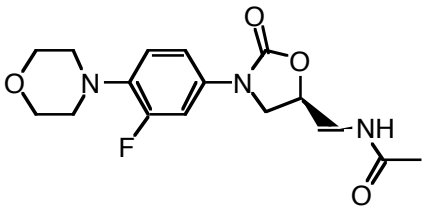
Inhib. alanine racemase and alanine ligase; Inhib. peptidoglycan synth

Others

Quinolones

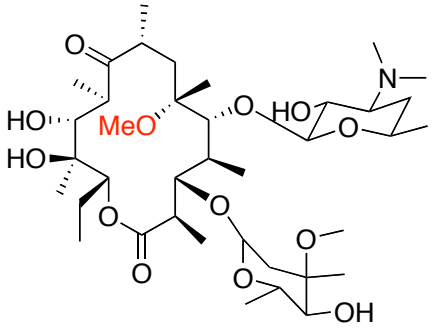


Oxazolidinones



Treatment of MAC infections (*M. avium*) AIDS etc

Clarithromycin
(Macrolide)



Other macrolides

Ethambutol

Quinolones

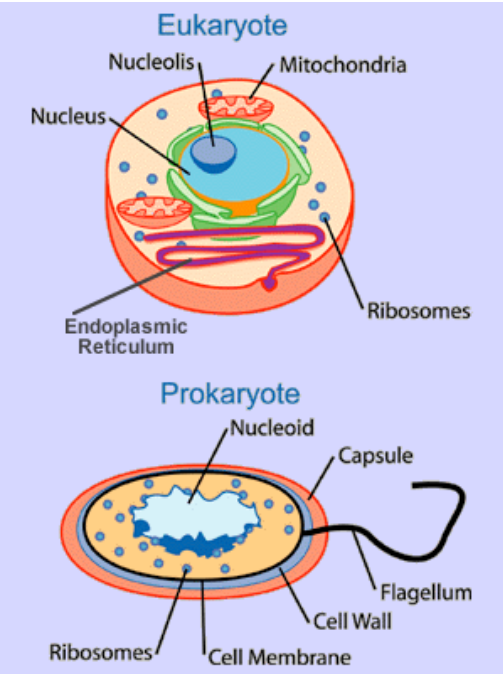
Rifabutin (Rifamycin)

Chemotherapeutic Agents / Antibiotics, chapter 38-43

- Antibacterial compounds (procaryotes)
- **Antiparasitic agents (eucarytotes) - Chapt 39**
- Antifungal compounds (eucarytotes)
- Antiviral compounds
- Anticancer compounds

Protozoa
Helmints (worms)
Insects (Scabies, lice etc.)

(Fungi chapt. 40)



Protozoa

Eucaryotes, unicellular (may exist in colonies)

Protozoa and algae (protocista)

Complex replication (sexual and asexual)

Patogenic P. most common tropical area

3. world diseases

Many diseases can be prevented by clean drinking water

Certain protozal diseases spread by insects

Ex. patogenic protozoa

polluted drinking water
Bergen 2004, Oslo 2007 ⇒

- *Trichomonas vaginalis*: Gelital infections
- *Giardia lamblia*: Diarea

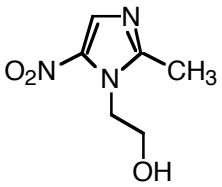
cats and pregnants ⇒

- *Toxoplasma gondii*: Toksoplasmosis
- *Trypanozomas sp*: Sleeping sickness
- *Entamoeba histolytica*: Dysentery
- *Plasmodium sp*: Malaria
- *Pneumocystis carinii*: Oportunistic, AIDS

Treatment of diseases caused by amebia, giardia, trichomonas

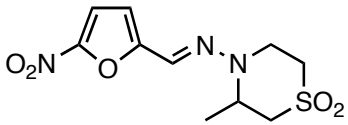
Metronidazol

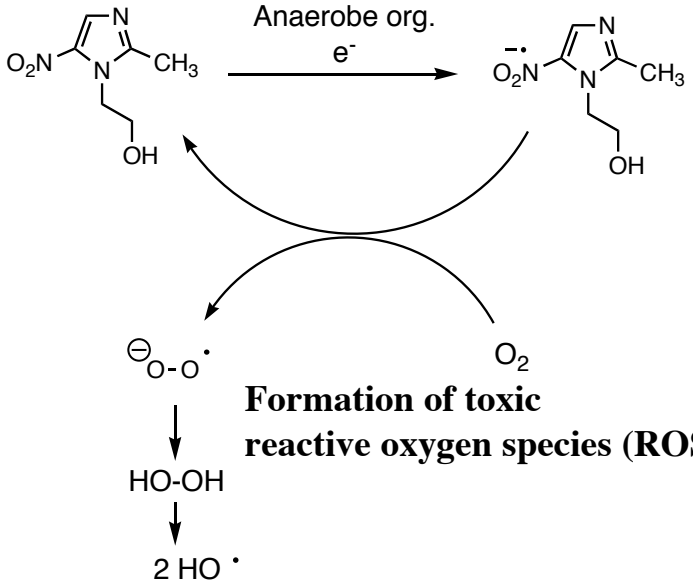
Flagyl®, Metronidazol®



Also effective against anaerobic bacteria
Probably pro-drug -reductive activation
(mech. not fully understood)

Related comp.
treatment of
African sleeping sickness





Formation of toxic
reactive oxygen species (ROS)

Anti - Malaria drugs

***Plasmodium* sp.**
Vektor: *Anopheles* moskito.
Complex life cyclus.

Mal aria = bad air

40% of world population at risk
300 mil acute illnessess pr year
ca 1 mill deaths pr year
Malaria kills a child every 30 sec.
90% in incidents sub-sahara Africa

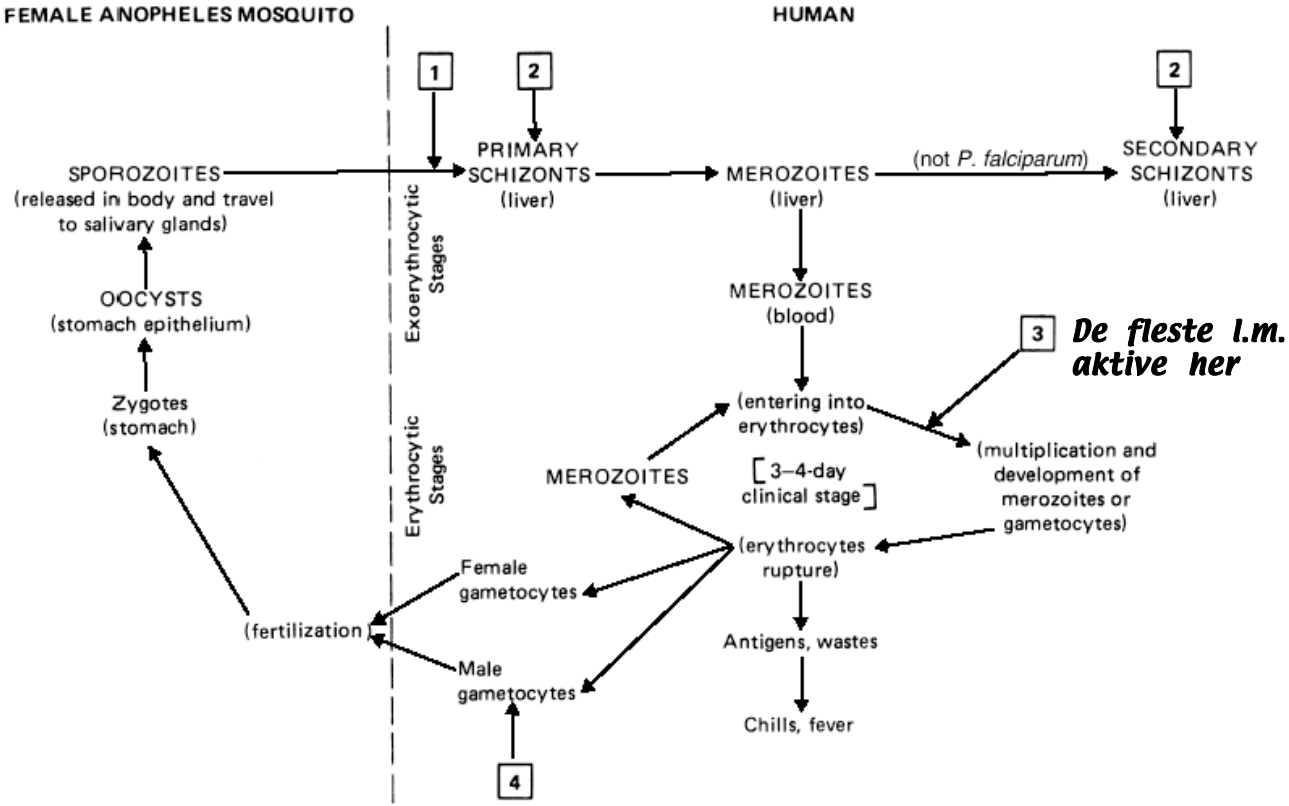


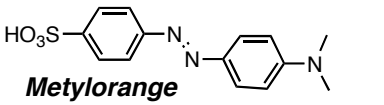
Figure 9–1 ■ Stages of the parasite that causes malaria after injection into its victim. See discussion in the text. ? indicates site of antimalarial drug action in humans.

Historic drugs

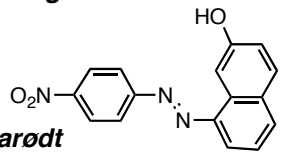
-Azodyes and salvarsan (1. synthetic effective drug)

-Quinine fra Cinchona (Kinabark)

Azo dyes
Bayer etc
Late 1800-century, ex.

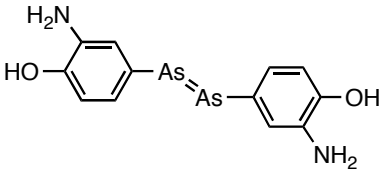


Metylorange



Pararødt

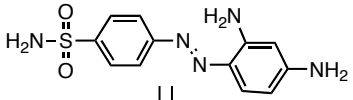
Salvarsan
1. antisyphilis drug 1912



Screening of dyes as antibacterials

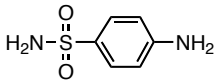
⇓

1932: ***Prontocil*** active against Streptoccocces infection
no activity on bacterial cultures



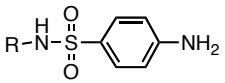
⇓

1935: Prontocil metabilized (azoreductase) to ***Sulfanilamid*** *in vivo*

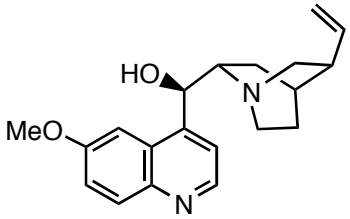

(rel. toxisk)

⇓

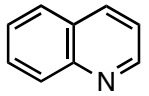
Modern sulfa drugsr



R: Aryl or hetroaryl



Quinine



Quinoline

⇓

MOdern antimalarials

Cinchona pubescens (Kinatre) from South America

Quinolines

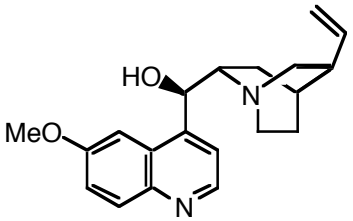
Mechanism

(DNA Intercalation)

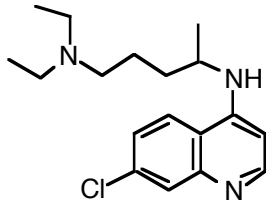
Ferriprotoporphyrin IX: **Binds to FPIX (metabolite from hemoglobine); tox. form of FPIX, proteinbound FPIX less tox.)**

Weak base Hypothesis: **Increase pH in parasite**

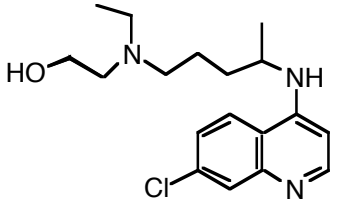
Quinine
Kinin®



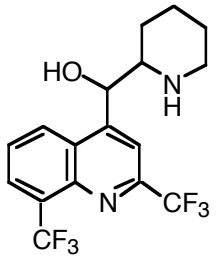
Klorokin
Klorokinfosfat®



Hydroksyklorokin
Plaquenil®



Meflokin
Lariam®

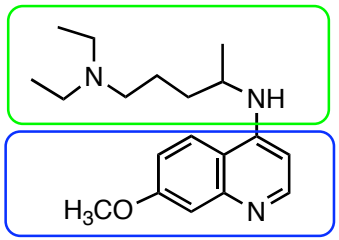


Also klorokin resistant *P. palsifarum*

More active, less tox (comp Quinine)
Resistance!

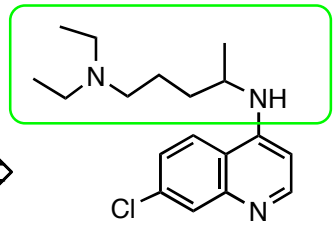
Dye ⟹

Quinine ⟹



Pamakin, 1926

⟹



klorokin

Biguanides

Proguanil (= Chloroguanide)

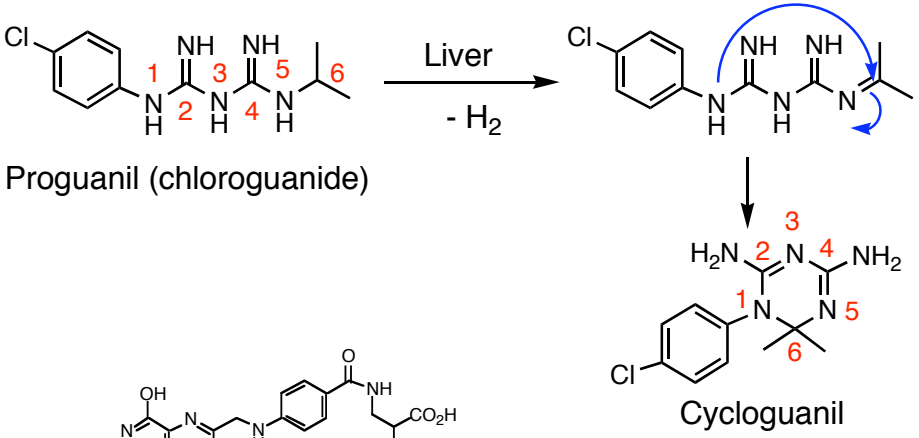
Paludrine®

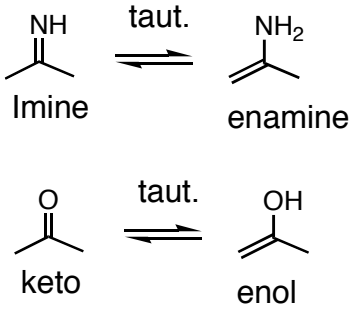
Malarone® + atovakvon

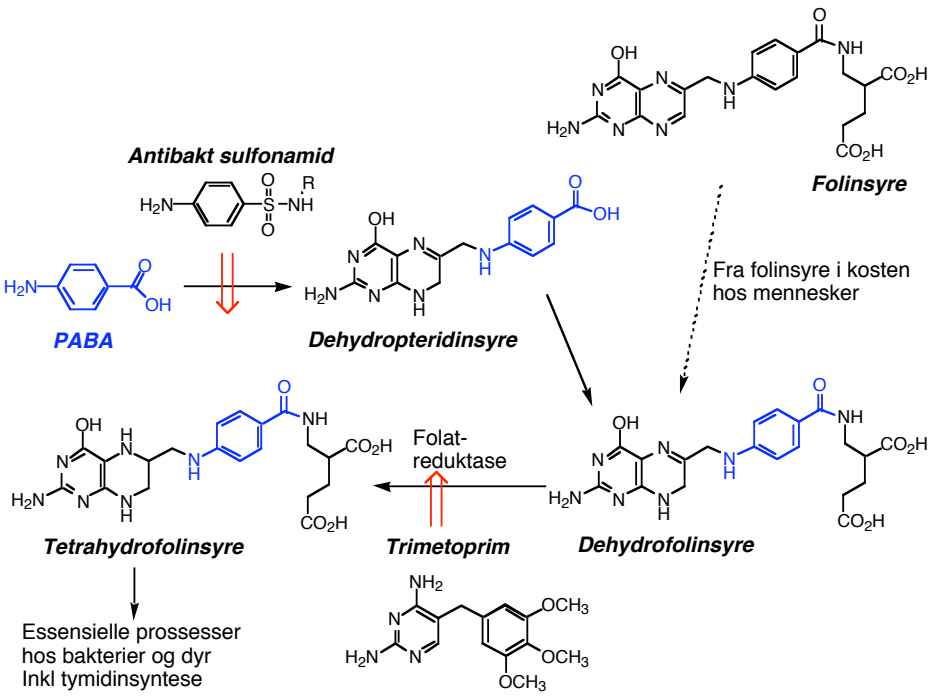
Pro-drug

Inhib. protozoan folate reduktase

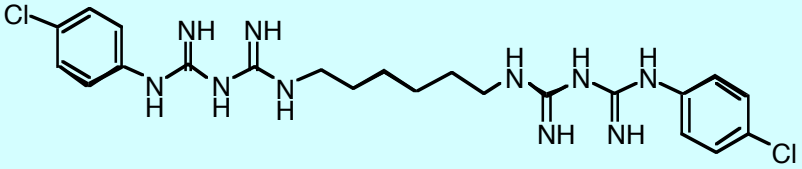
(c.f. Trimetoprim)



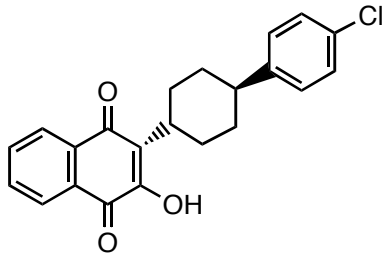




Other biguanides
Klorhexidine cleaning of wounds

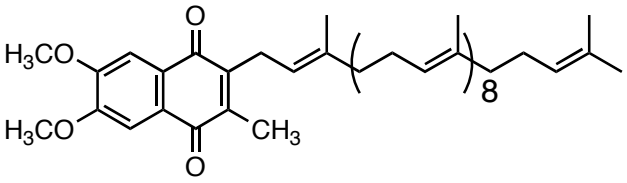


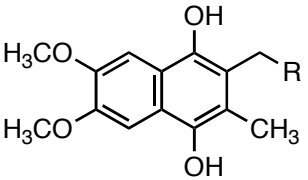
Others



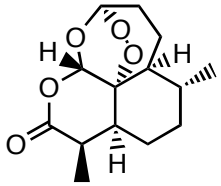
Atovakvon

Malarone® + proguanil.
Also other parasites (P. carinii)
Ubiquinone antimetabolite?

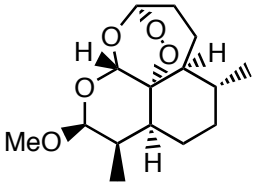




Ubiquinone, Q10, Cenzyme Q
electron carrier
cellular respiration



Artemisin
from *Artemisia annua*
Chinesee trad. med.



Artemeter

Semisynth. analog
Improved solubil.

Artemeter **og** *Lumefandrin*

Riamet®

Mech. involves radicals

No cross resist.

Synth. analogs, active field

Drugs for Helmint infections

Eukaryotes – Invertebrates.

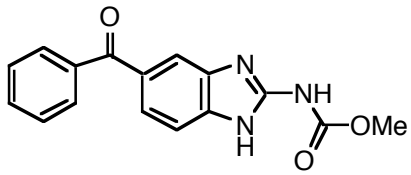
Tropical diseases!

Animal parasites; ex *Trichinella spiralis* (trikiner).

Benzimidazoles
Many active analogs known
Binds to tubulin - prevents formation of microtubules
inhib. mitosis (c.f. certain anticancer drugs)
May also inhib. fumarate reductase

Mebendazol

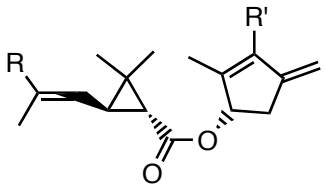
Vermox®

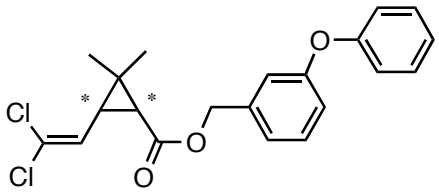


Drugs against Ectoparasites (insects)

Lice, scabies etc

Pyretrines
Insecticides from *Crysantemum* sp



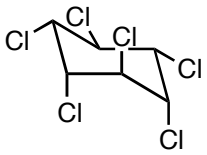


Permetrin

Nix®

Synth. analog, more stabile
Mixt. of 4 stereoisomers

Chlorinated pesticides:
Lindane
Block GABA CNS neurtransmittor
(Also neurotox. effects on humans)



Irreversible Inhibitors
Acetylcholine esterase

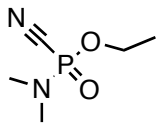
Not drugs, nerve gasses, insecticides etc.

Malation

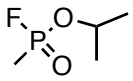
Prioderm® lice

Gen structur mustard gasses

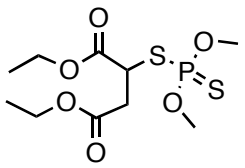
L: Leaving group
R1: alkoksy
R2: alkyl, alkoksy, amino



Tabun

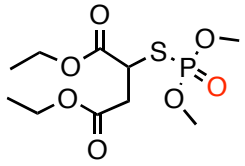


Sarin



Malation

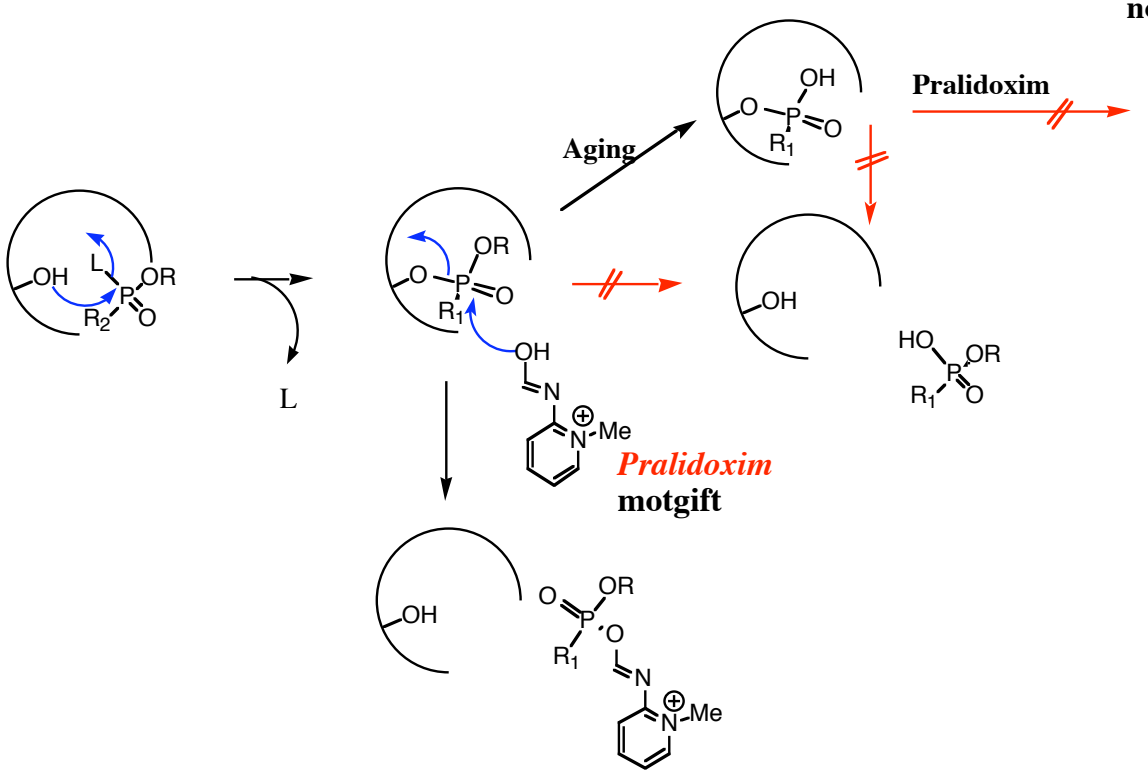
only insects



Malaoxon

not tox.

Act as mustard gasses

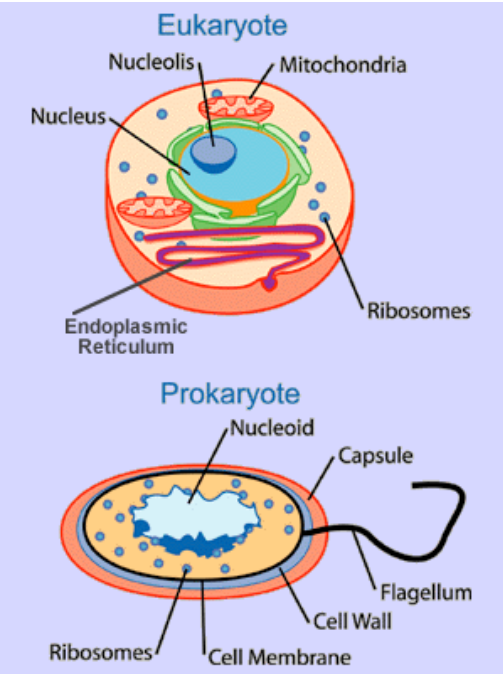


Chemotherapeutic Agents / Antibiotics, chapter 38-43

- Antibacterial compounds (procaryotes)
- Antiparasitic agents (eucarytotes) -
- **Antifungal compounds (eucarytotes) - Chapt 40**
- Antiviral compounds
- Anticancer compounds

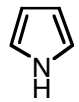
Fungicides / Fungistatics / Antimycotics

Chemotherapeutics / Antibiotics

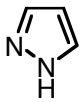


Synthetic Antifungals

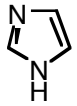
Azoles



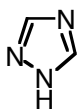
Azol / Pyrrol



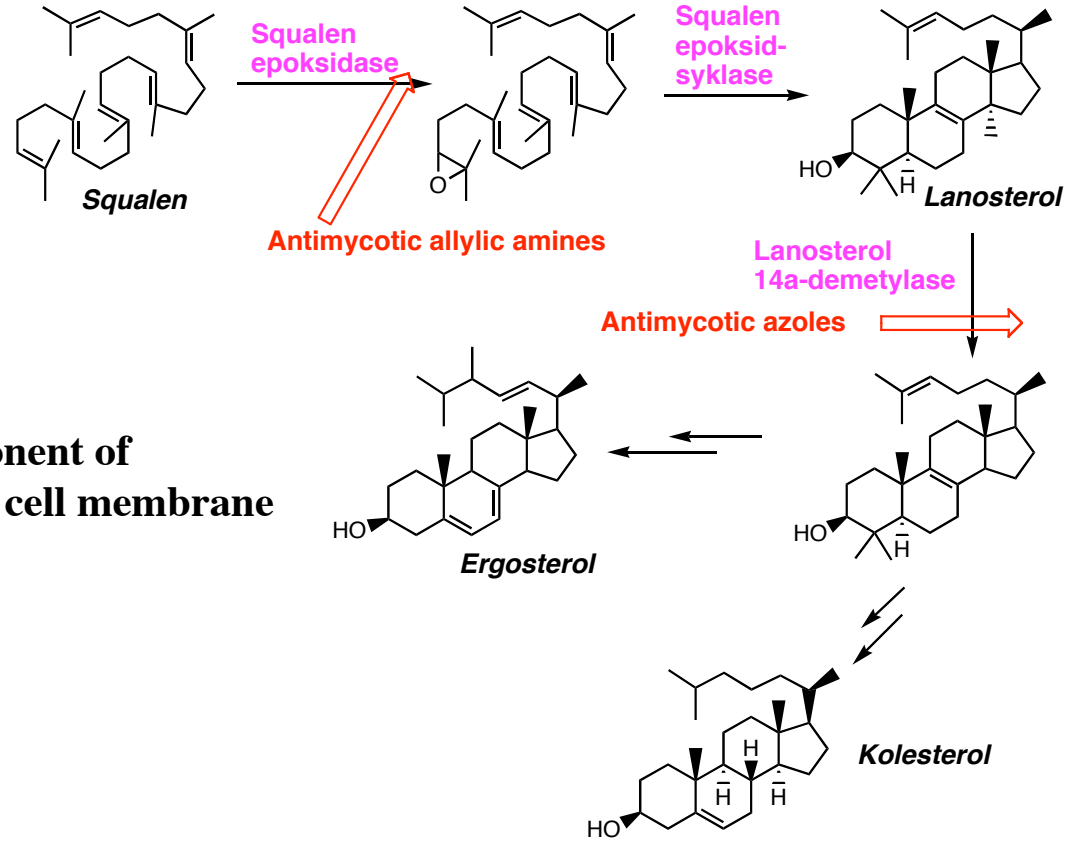
1,2-Diazol



1,3-Diazol / Imidazol

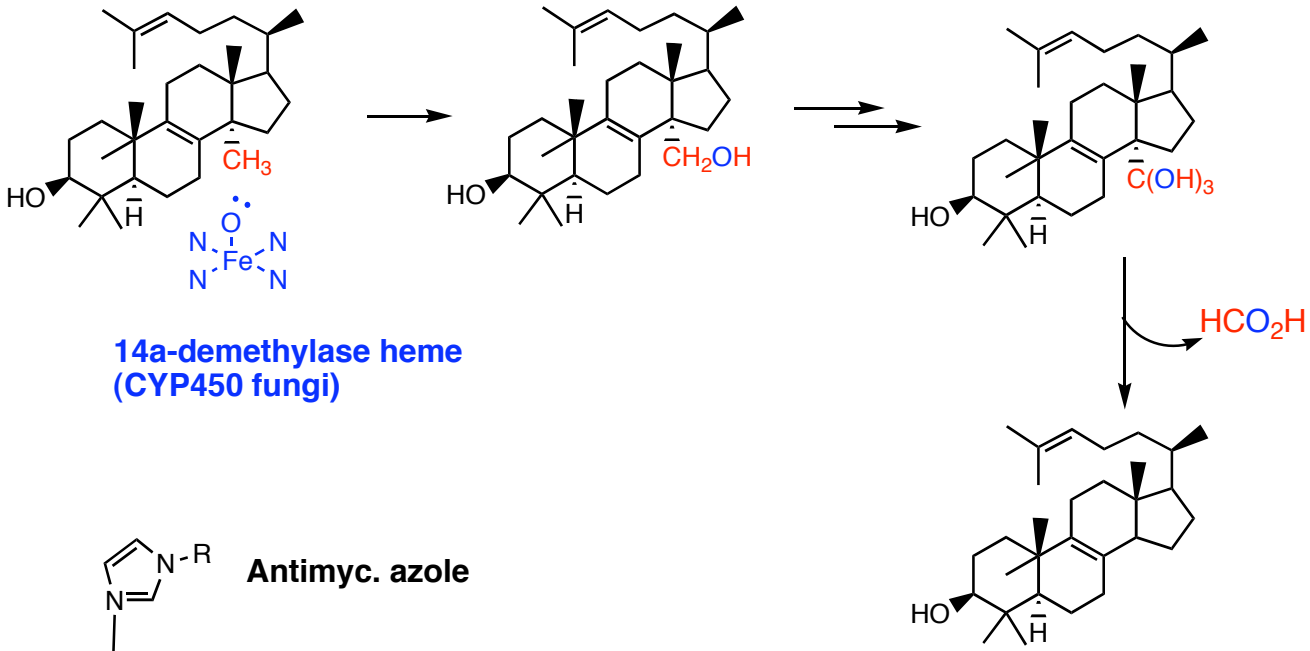


1,2,4-Triazol



Component of fungus cell membrane

Lanosterol



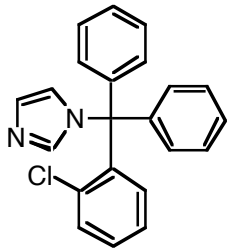
14a-demethylase heme
(CYP450 fungi)

Antimyc. azole

***Klotrimazol*:**

Canesten®, Klotrimazol® utvortes

Canesten®, vaginal behandlig



***Ekonazol*:**

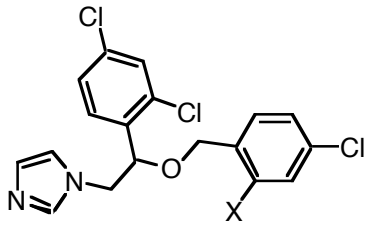
Pevaryl®, utvortes

Pevaryl®, vaginal behandlig

***Miconazol*:**

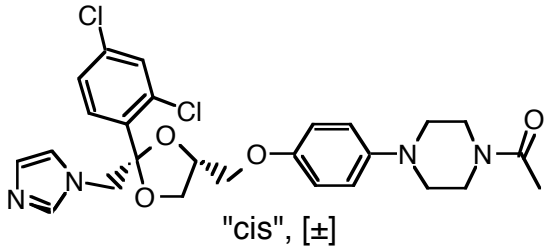
Daktar®, utvortes

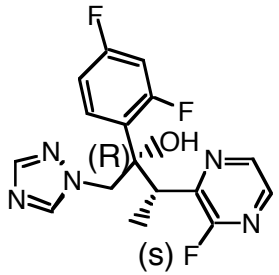
Daktar®, vaginal behandlig



X=H: Ekonazol
X=Cl: Mikonazol

***Ketokonazol*:**



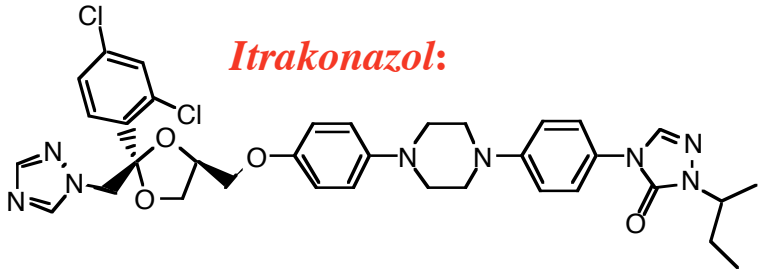


Vorikonazol

Flukonazol

(Racemate)

***Itrakonazol*:**



SAR:

-Weakly basic azole ring, imidazol / 1,2,4-triazol

(less tox. humans), pKa 6.5-6.8

-2 or 3 other aromatic rings

-Cl (or F) on at least one aromatic ring

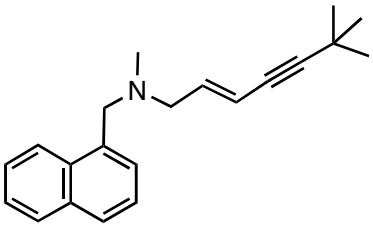
(F i flukonazol)

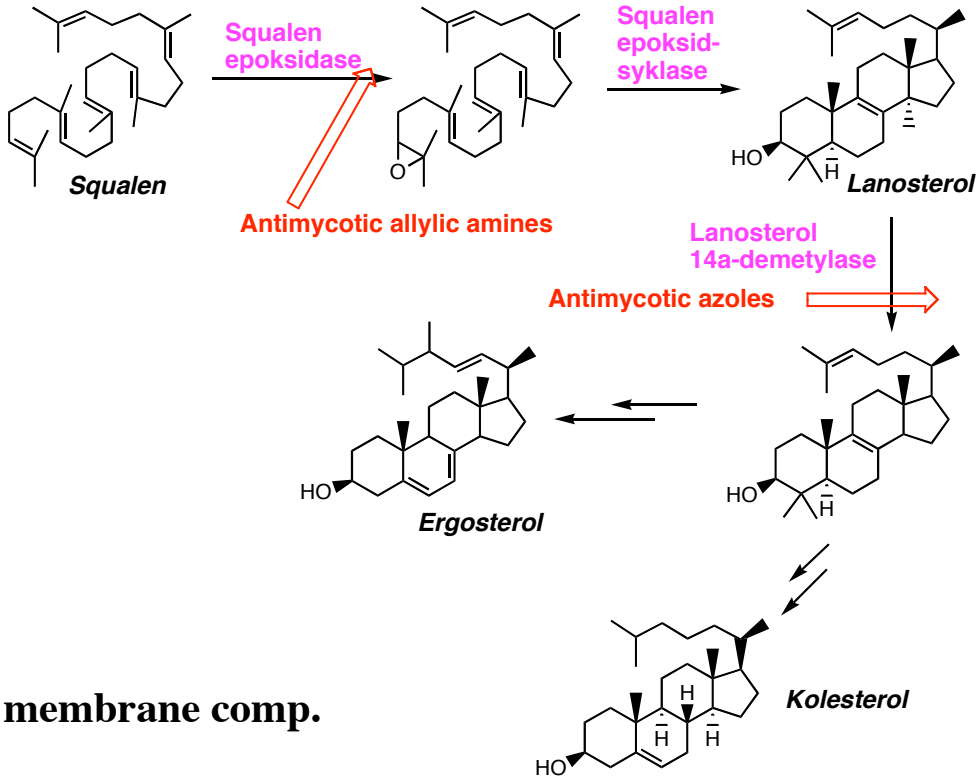
-Lipophilic structures (as lanosterol)

Allylic amines

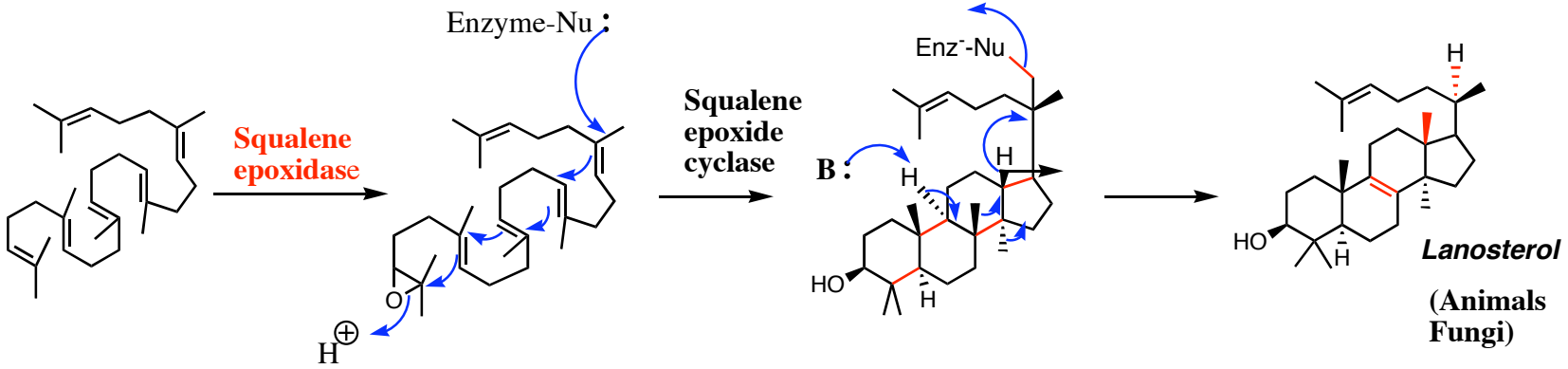
Terbinafin

Lamicil®



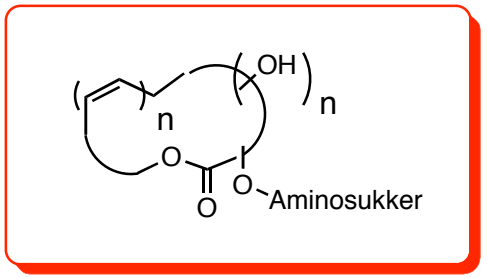


Prevents formation of ergosterol, cell membrane comp.
Accumulation of toxic squalene



Antimycotic Antibiotics

Polyenes



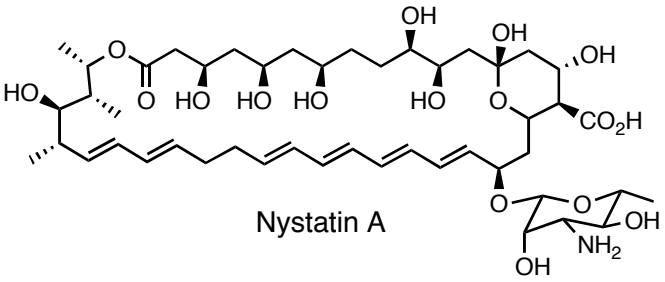
Proad spectrum. Some effect on certain protozoa.

Isolated, *Streptomyces* sp.

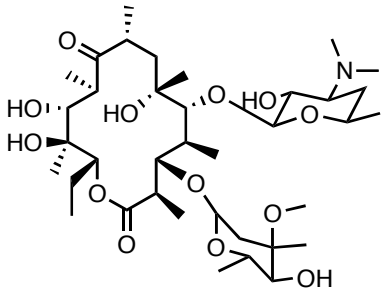
Binds to sterols in fungal cell membrane; cell leaks K^+, small org. molecules

SAR:

- **Macrolaktone [26 or 38-ring, Larger than macrolides (erytromycin etc)]**
- **Polyene (Macrolides not polyenes)**
- **Several OH-groups**
- **amino sugar, mycosamine**
- **Low water sol.**



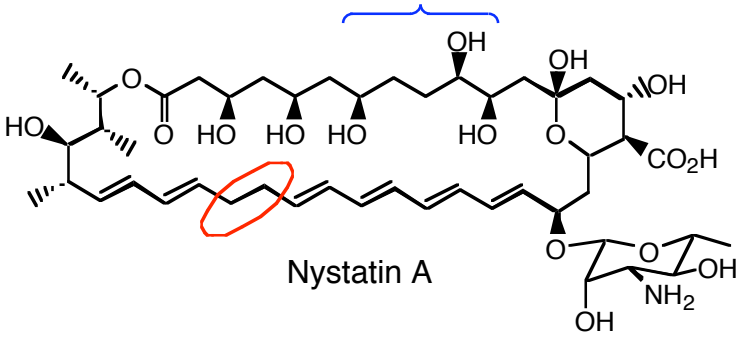
Nystatin A



Erytromycin

Nystatin A

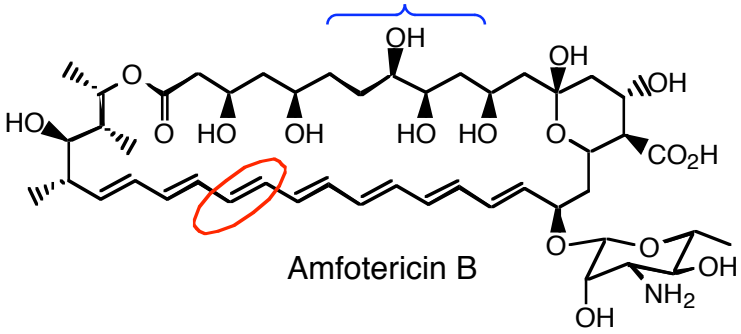
toxic, low oral avail;
Local treatment, mouth, GI tract



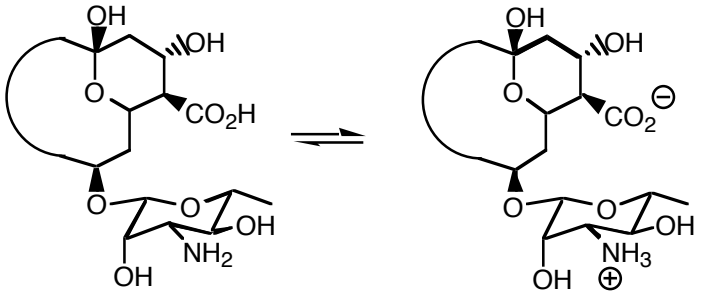
Amfotericin B

Systhemic infect (infusion)

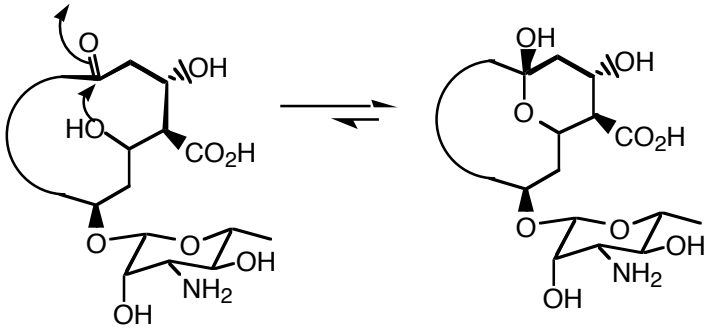
Somewhat less tox.



Amfotær struktur



Hemiacetal



Peptides

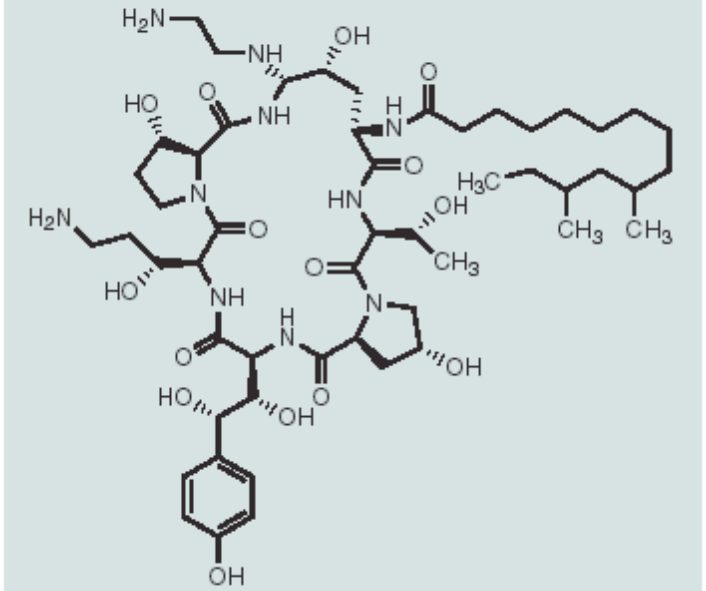
Caspofungin

<u>Serious</u> systhemic infect.

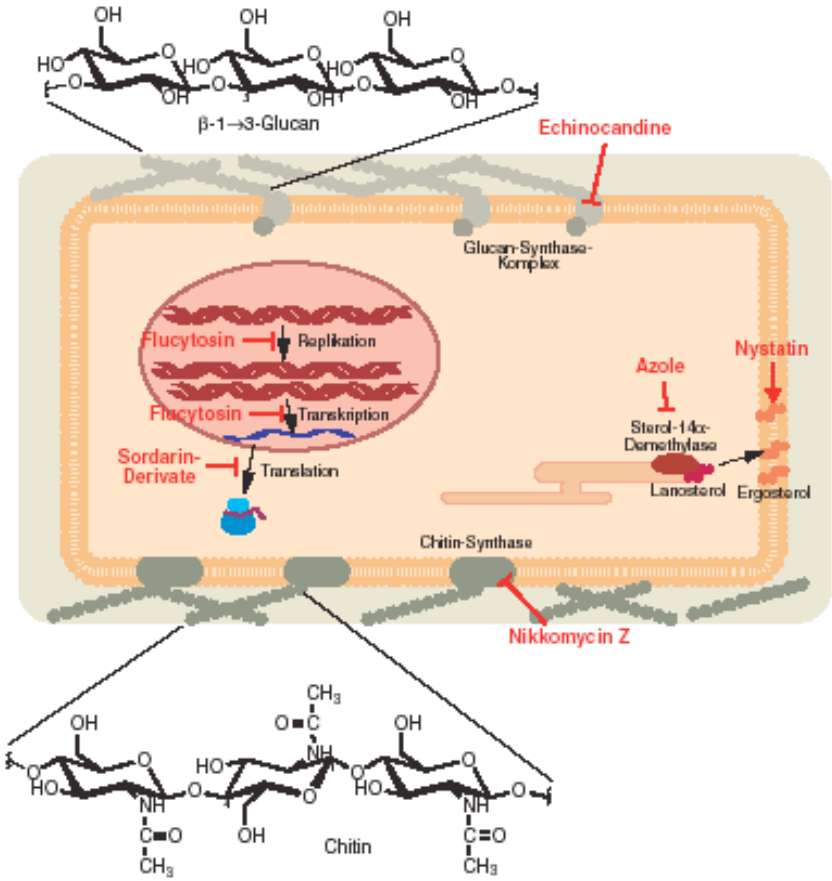
Semisynth. from prod. of fermentation (*Glarea lozoyensis)*

Inhib. synth of β-1,3-D-glucan; cell wall comp. certain fungi

ABB. 2 | CASPOFUNGIN



Few good inhib. of fungi cell wall comp. compared to antibacterials



Alte und neue Zielstrukturen von Antimykotika: Neben DNA-Replikation, Transkription und Translation sind die Pilz-spezifischen Zellmembran- und Zellwandsynthese Ziel der Wirkstoffe.