



INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Farmaceutická chemie I.

2. rok studia

Proléčiva.

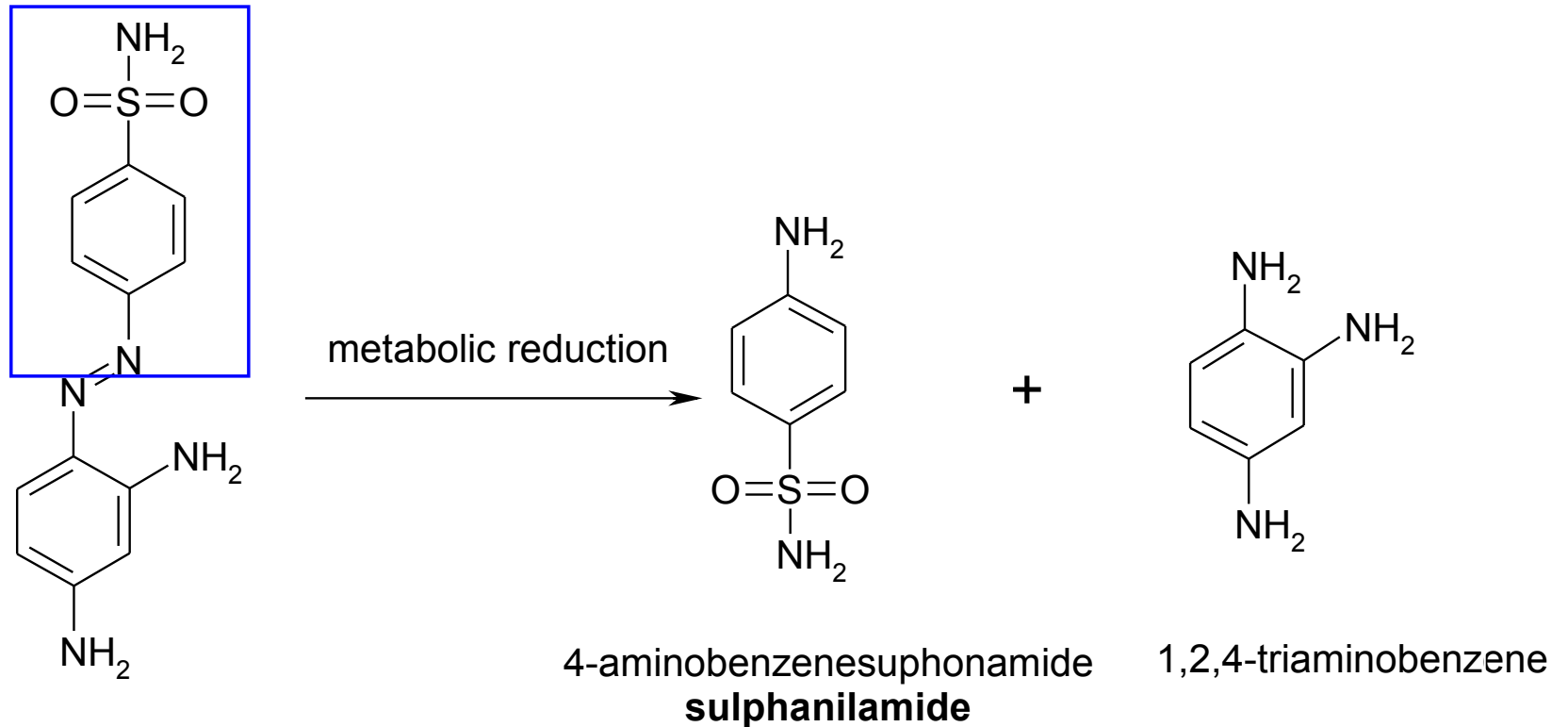
Doc. PharmDr. Oldřich Farsa, Ph.D.

Prodrugs

- inactive compounds that yield an active compound in the body
- this conversion is frequently carried out by enzyme-controlled metabolic reactions and less frequently by non-enzymatic chemical reactions within the body
- prodrugs are used as a way to:
 - increase lipid or water solubility
 - improve the taste of a drug to make it more patient compatible
 - alleviate pain when the drug is administered parenterally by injection
 - reduce toxicity
 - increase chemical stability
 - change the length of the time of duration of action
 - deliver the drug to a specific site in the body

Bioprecursor prodrugs are compounds that already contain the embryo of the active species within their structure. They rely on metabolism to produce the active compound.

Prontosil(s)



4-(2,4-diaminophenylazo)benzenesulphonamide

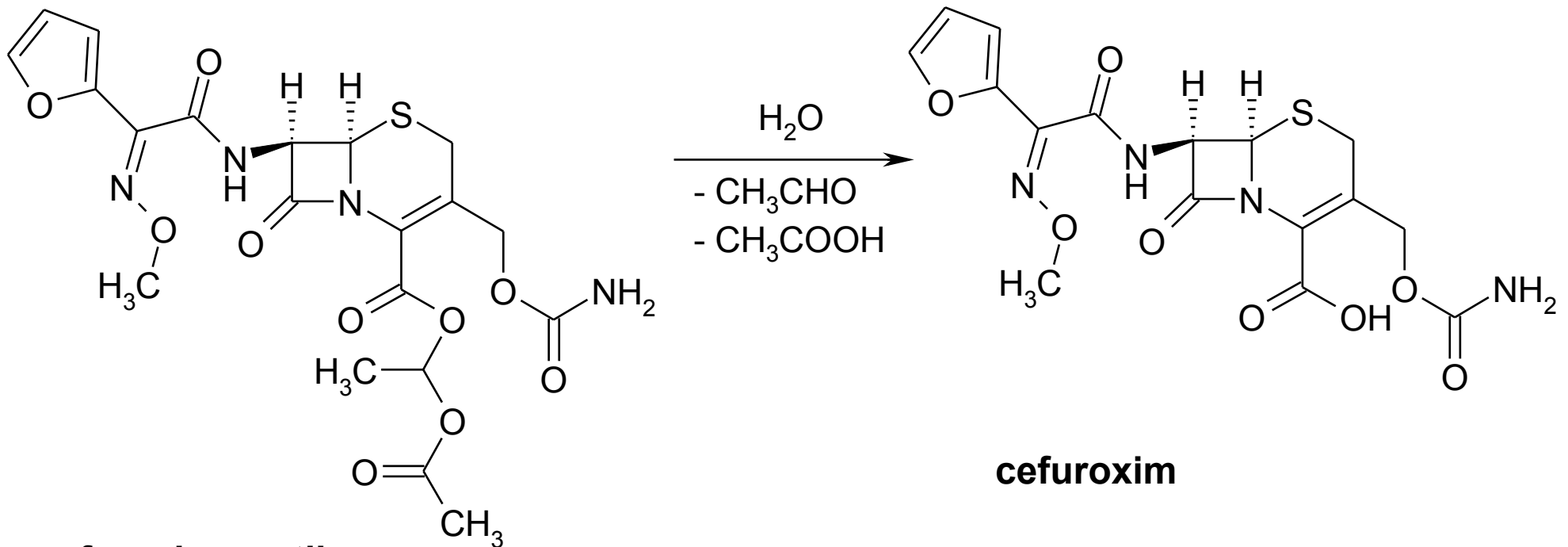
Prontosil rubrum (inactive)

- prepared 1932 by Mietsch and Klarer
- Gerhard Domagk: active against streptococci

Prontosil album
(antimicrobial)
1935 Jacques and
Thérèse Tréfoule:
sulphanilamide is the
active compound

Carrier prodrugs differ from bioprecursor prodrugs in that they are formed by combining an active drug with a carrier species to form a compound with the desired chemical and biological characteristics.

An example: cephalosporine antibiotics

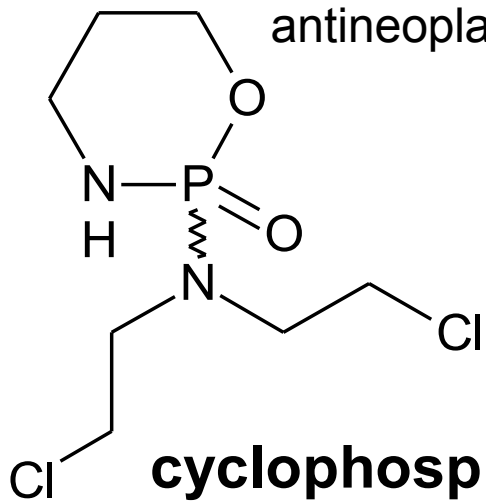


cefuroxim axetil

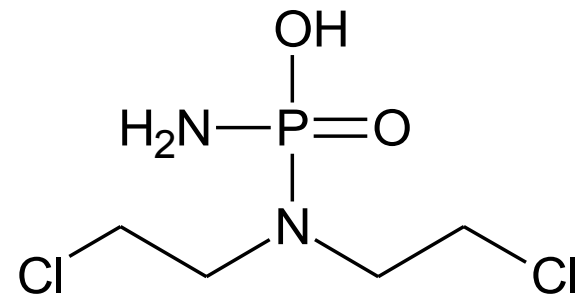
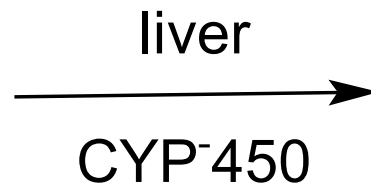
Zinnat®

• higher lipophilicity \Rightarrow improved permeation through GIT mucosa

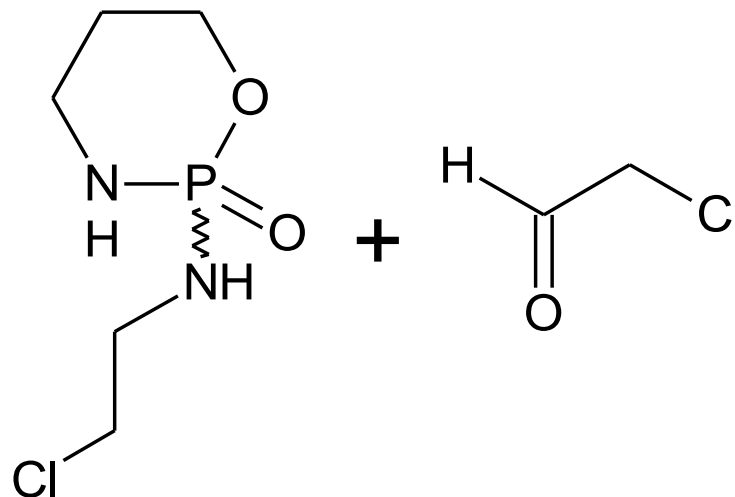
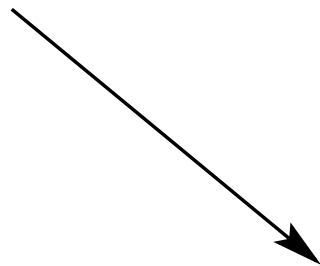
An example of a **bioprecursor prodrug** activated by oxidation:
antineoplastic **cyclophosphamide**



cyclophosphamide
(inactive)

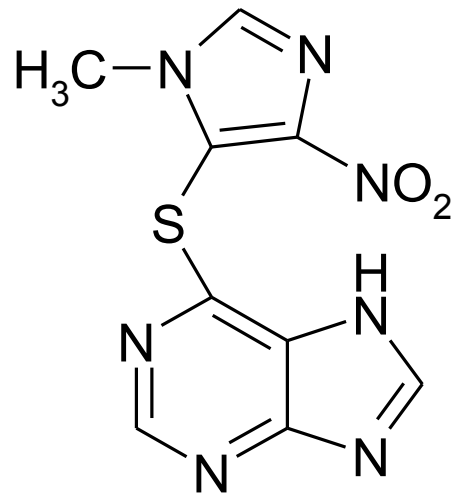


phosphoramidate mustard
(active antineoplastic)

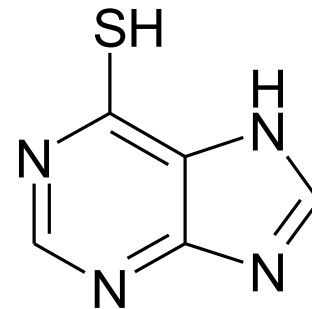


inactive
desmethylated
product

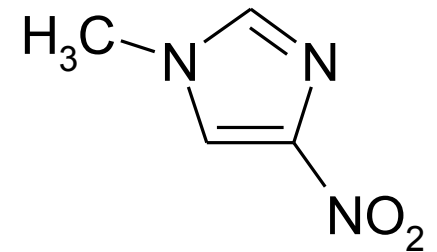
Antineoplastics: azathioprin – an example of a **bioprecursor prodrug**



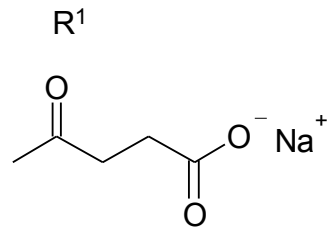
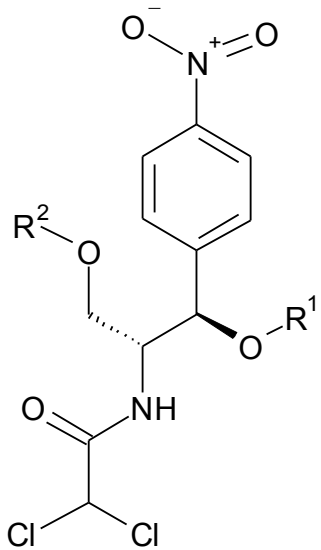
azathioprin



6-mercaptopurine



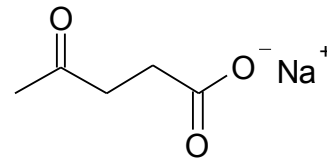
Examples of **carrier produgs**: chloramphenicol prodrugs optimized for a particular route of administration



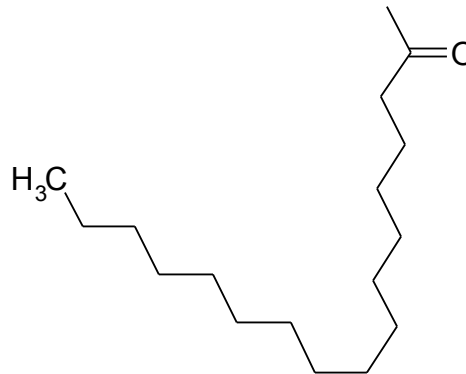
R²
H

chloramphenicol sodium succinate
Chloramphenicoli natrii succinas PhEur
Chloramphenicol® ICN plv. inj. sol.
•injection administration

H



H



chloramphenicol palmitate
Chloramphenicoli palmitas PhEur
●nearly insoluble in water, bitter taste suppressed

•esters are hydrolyzed to parent chloramphenicol by esterases