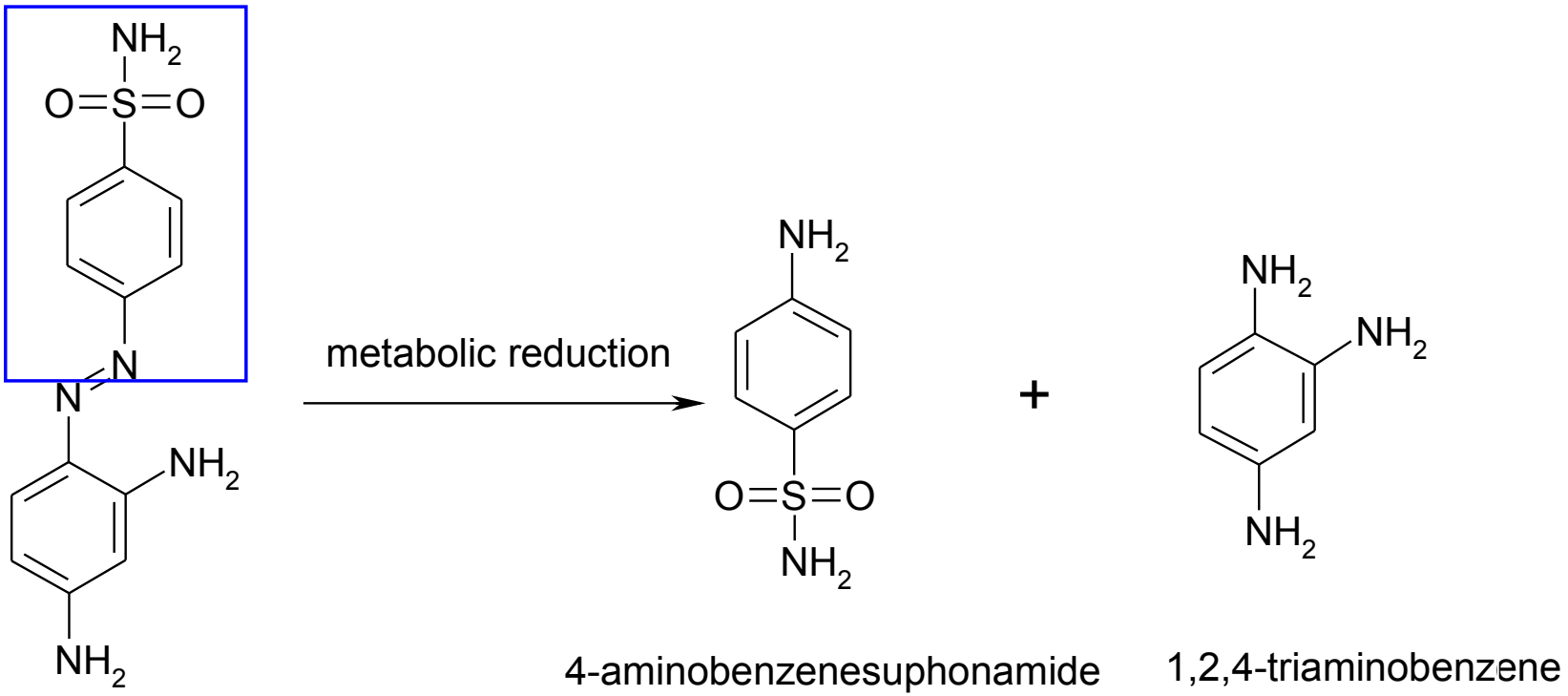
Prodrugs

Prodrugs

- inactive compounds that yield an active compound in the body
- this conversion is frequently carried out by enzyme-controlled methabolic 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 srtucture. They rely on metabolism to produce the active compound.

Prontosil(s)



4-(2,4-diaminophenylazo)benzenesulphonamide

4-aminobenzenesuphonamide
sulphanilamide

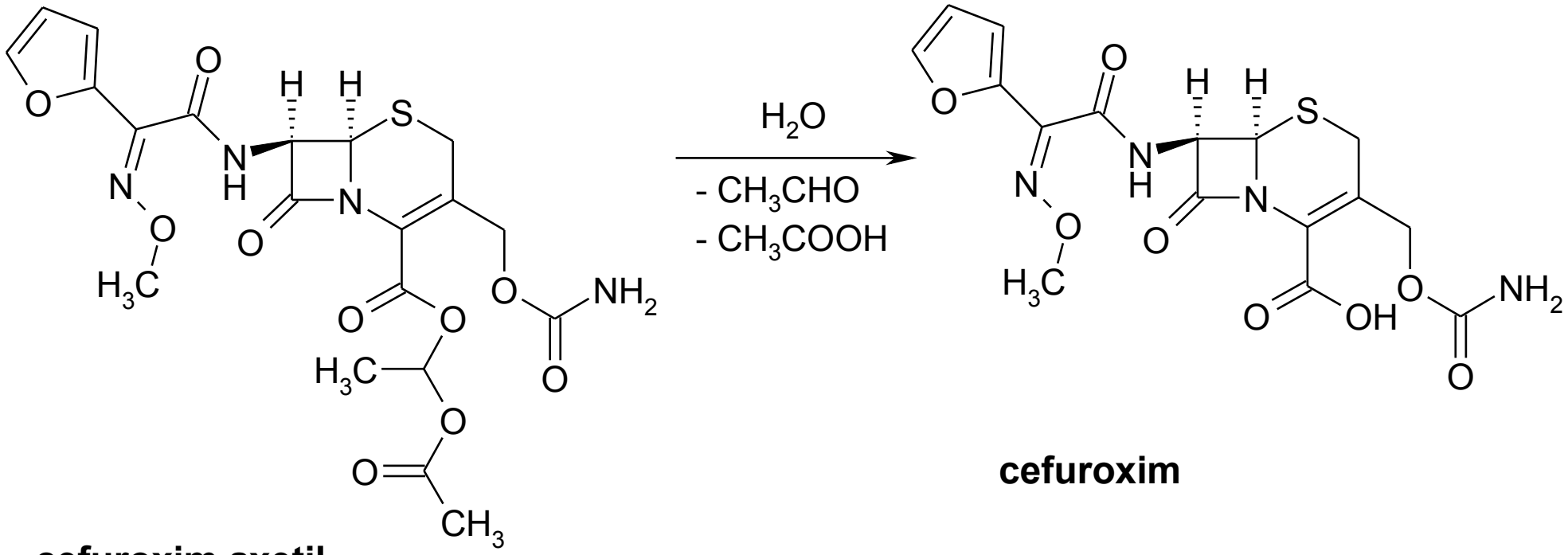
1,2,4-triaminobenzene

Prontosil rubrum (inactive)
- prepared 1932 by Mietsch and Klarer
- Gerhard Domagk: active against streptococci

Prontosil album (antimicrobial)
1935 Jacques and Therése 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.

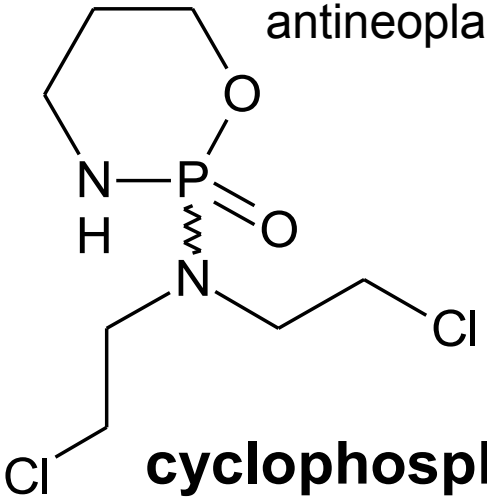
An example: cefalosporine antibiotics



cefuroxim axetil
Zinnat ®
•higher lipohilicity ⇒ improved permeation through GIT mucosa

cefuroxim

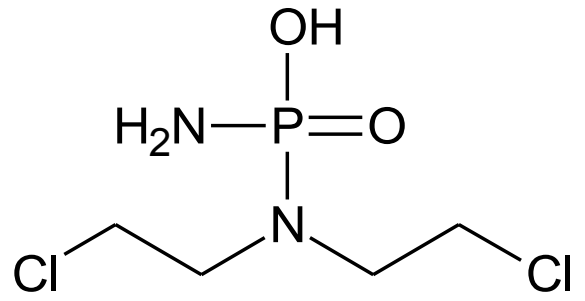
An example of a bioprecursor prodrug activated by oxidation:
antineoplastic **cyclophosphamide**



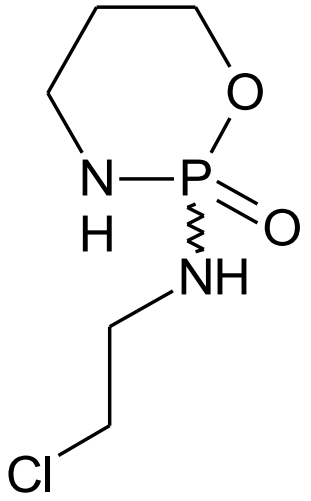
cyclophosphamide
(inactive)

liver

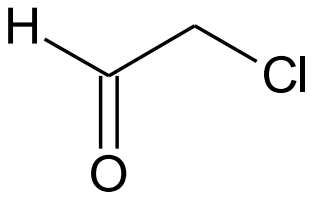
$CYP^{-}450$



phosphoramide mustard
(active antineoplastic)

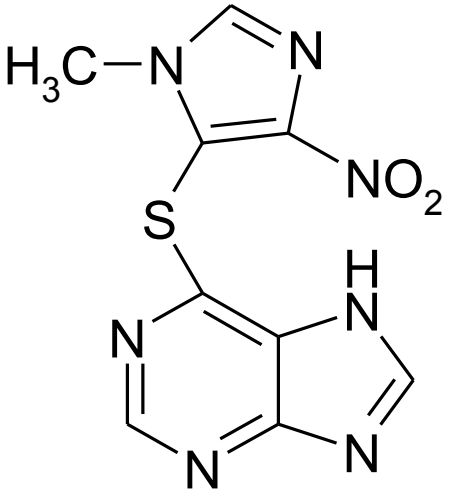


+



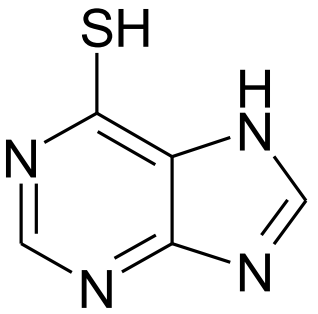
inactive
desmethylated
product

Antineoplastics: azathioprin – an example of a bioprecursor prodrug



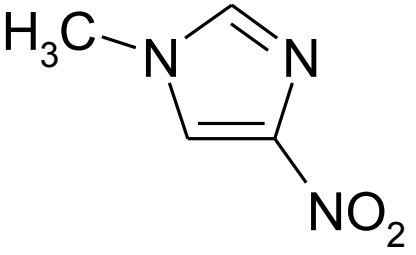
azathioprin

metabolism

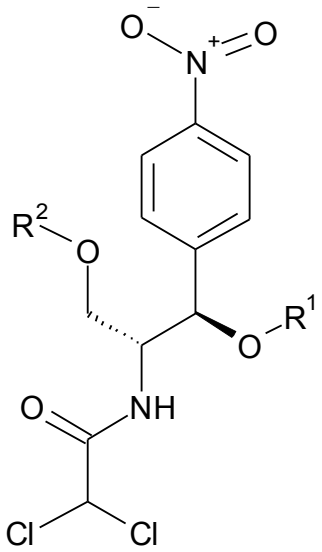


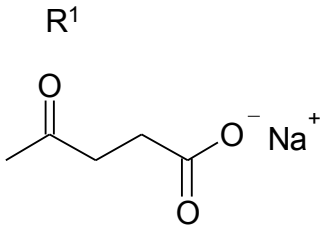
6-mercaptopurine

+



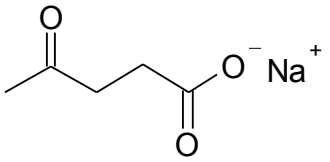
Examples of carrier produgs: chloramphenicol prodrugs optimized for a particular route of administration





H

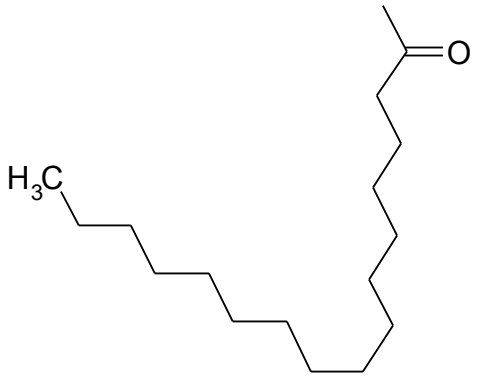
nebo



H

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

H



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

•esters are hydrolyzed to parent chloramphenicol by esterases