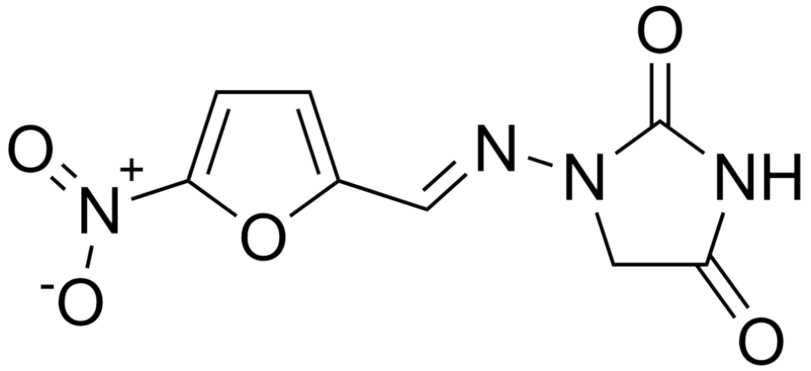
Nitrofurantoin



- For UTIs (since 1953)
- Not for systemic infections
  - Absorbed but very rapidly cleared by kidneys, 25-40% unmodified
  - Plasma half-life only ~20min; serum concentration extremely low
  - Becomes more active under acidic pH
  - Not for pyelonephritis because drug concentration in those tissues insufficient
- Active against *E. coli* (one of the most common UTI pathogens)
  - Not active against many other Gram-: *Proteus*, *Klebsiella*, *Pseudomonas*, *Enterobacter*, *Serratia*
- Active against some Gram+: *Enterococci* (including VRE; nosocomial), *Staph. aureus, Staph. saprophyticus*

Nitrofurantoin: mechanism of action

- Nitrofurantoin activated by bacterial flavoproteins, becomes reactive and damages ribosomal proteins, DNA, other macromolecules involved in metabolism, cell wall synthesis
  - Similar end effect to metronidazole, but no cross-resistance
  - Not particularly susceptible to resistance developing, trasferable resistance rarely observed
- Bactericidal at concentrations reached in urine

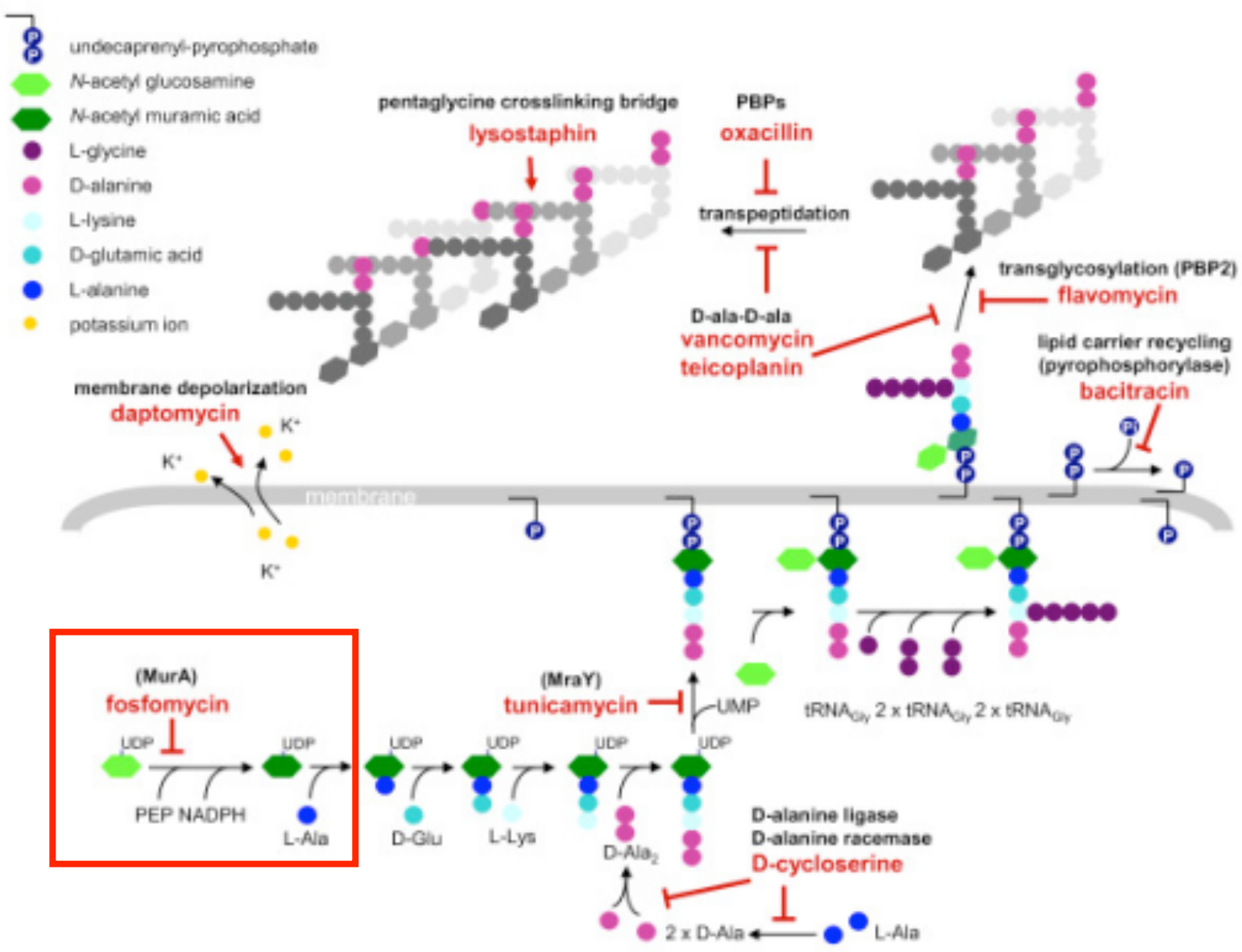
Nitrofurantoin: adverse effects

- GI effects (dose related): nausea, vomiting
- Rare but serious adverse effects (<<1%)
  - Peripheral neuropathy
  - Hepatotoxicity
  - Pulmonary toxicity, fibrosis with long-term use: lung disease
  - Affects glutathione reductase activity: in Glucose-6-Phosphate Dehydrogenase (G6PD) deficient patients (cannot regulate glutathione levels), risk of hemolytic anemia
- Contraindicated in pregnancy (>38 weeks gestation) and neonates due risk of hemolytic anemia resulting from neonates' immature blood cells
- Renally cleared, so contraindicated in renal insufficiency
- Carcinogenicity observed in small animals, mutagenic in bacteria; but the clinical significance not known

Nitrofurantoin forms

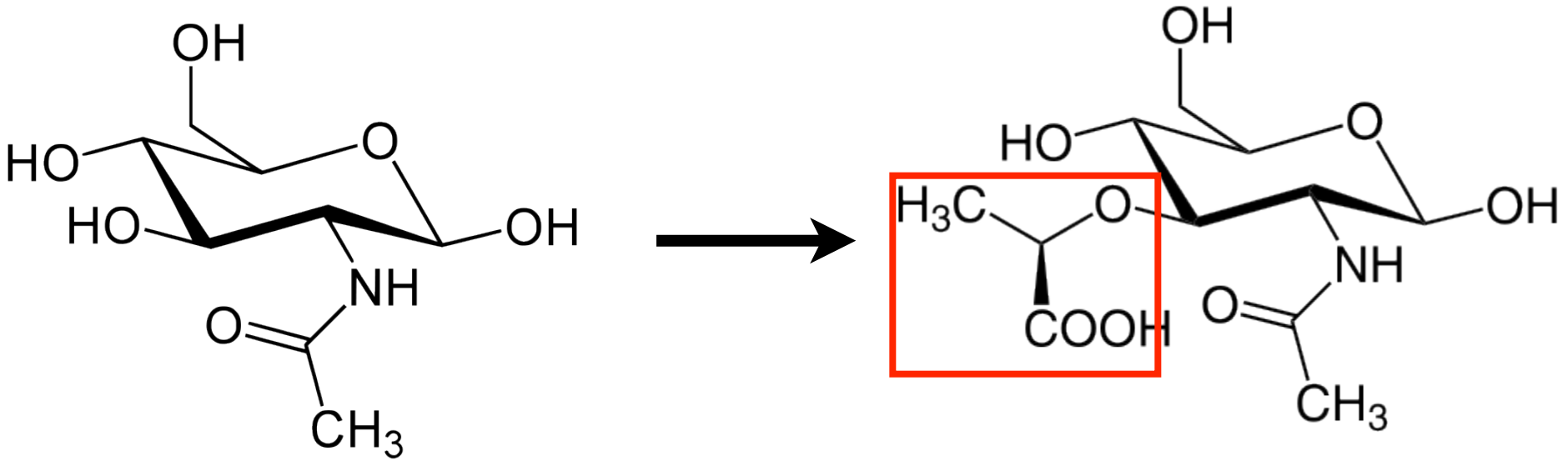
- Taken with food increases absorption
- Microcrystalline: Furadantin ®
- Macrocrystalline: Macrobid ®, Macrodantin ®
    - Absorbed more slowly, so less GI distress

Fosfomycin: another UTI drug



- Fosfomycin competes PEP from MurA and prevents it from initiating peptidoglycan synthesis: prevents formation of N-acetylmuramic acid

Fosfomycin: another UTI drug

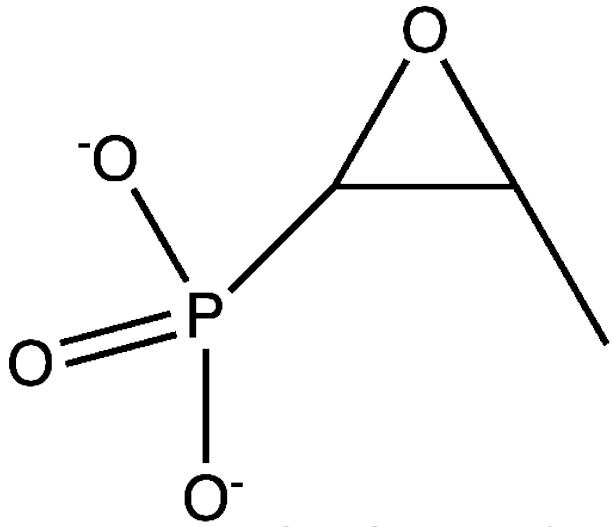


N-acetylglucosamine

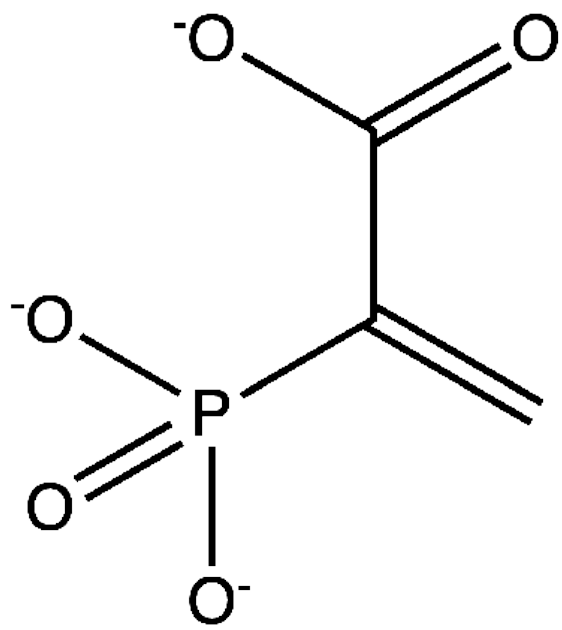
N-acetylmuramic acid

- MurA enzyme (a.k.a. UDP-N-acetylglucosamine enolpyruvyl transferase) normally would generate N-acetylmuramic acid from N-acetylglucosamine by adding enolpyruvate

Fosfomycin: another UTI drug



fosfomycin



phosphoenol pyruvate

- Fosfomycin mimics PEP, which would normally be ligated to UDP-N-acetylglucosamine by MurA (a.k.a. UDP-N-acetylglucosamine enolpyruvyl transferase)

Fosfomycin

- Monurol ®
- Uncomplicated UTI
- Broad activity against Gram+ and Gram-
  - Some *Enterobacteriaceae: E. coli, Proteus, Citrobacter*
    - Including some ESBL-producing *E. coli*
  - *Enterococci*: *E. faecalis*
- Bactericidal
- Single 3gm dose.
- Excreted to urine (and some to feces)
- Relatively low frequency of adverse reactions
- Resistance emerges readily: transporter protein needed for fosfomycin uptake mutates so drug doesn't get taken up