CHEM 109, Lecture 15
Medicinal Chemistry: Solubility Potential (Palleros – online)
β-Lactam Antibiotics

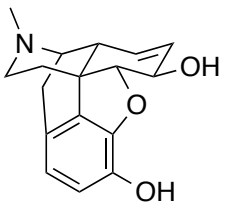
Solubility Potential

- Hydrocarbons are insoluble in water
- Adding polar functional groups increases water solubility
- The more functional groups, the more carbons the molecule can contain and still be soluble

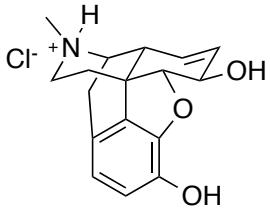
Table 1. Solubility Potential

Functional Group	Solubility Potential (in a polyfunctional molecule)
Alcohol	3-4 carbons
Phenol	3-4 carbons
Amine	3 carbons
Carboxylic acid	3 carbons
Ester	3 carbons
Amide	2-3 carbons
Ether	2 carbons
Aldehyde	2 carbons
Ketone	2 carbons
Urea	2 carbons
Charged groups (N+: ammonium salts; O^-: carboxylates, phenolates, sulfates; N^-: sulfonamides)	20-30 carbons

Calculate the solubility potential of morphine and its HCl salt.



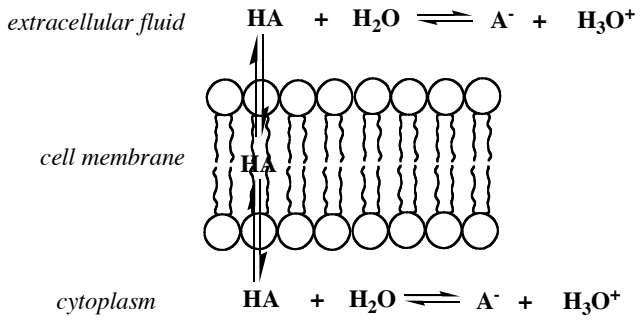
Morphine



Morphine-HCl

Effects of pKa on Solubility and Binding

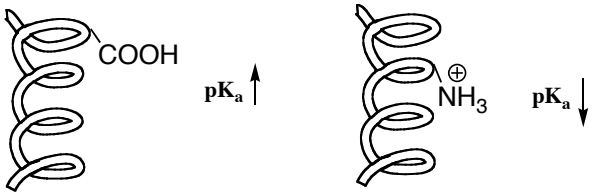
Pharmaceutical & Pharmacokinetic Phases



Pharmacodynamic Phase – binding of drug to receptor

Food for thought: how are pKa's effected if water is not the solvent??

Receptor

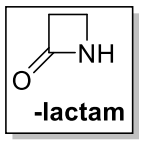


Hydrophobic pocket of peptide backbone effects pKa's
(typically we think of pKa as dissociation in water, this is different!)

Ionization states dictate whether drug can bind to receptor

Natural Products – broad class of naturally occurring substance, typically secondary metabolite (no essential metabolic function for the organism)

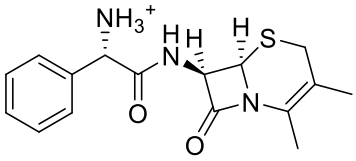
- Terpenoids (Lectures 12)
- Non-ribosomal Polypeptides (today)
- Alkaloids (Lecture 16)
- Fatty acid-derived substances & Polyketides
- Enzyme Cofactors



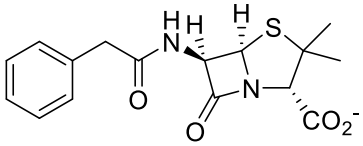
β-Lactam Antibiotics are derived from **non-ribosomal tripeptides**

But first…what's a ribosomal (normal) tripeptide look like?

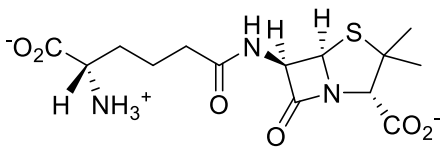
For each antibiotic below, can you draw the tripeptide from which each was derived?



Cephalexin
(a cephalosporin)

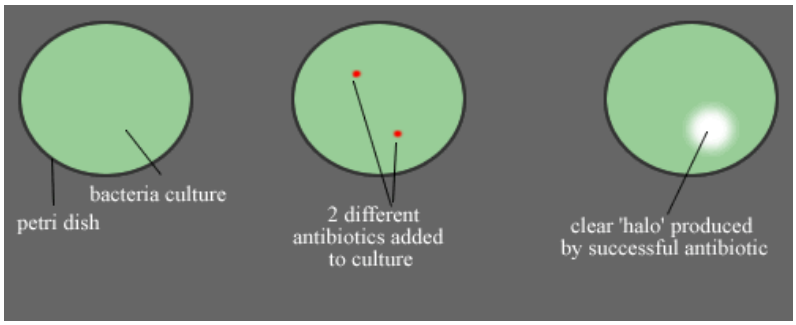


Penicillin G

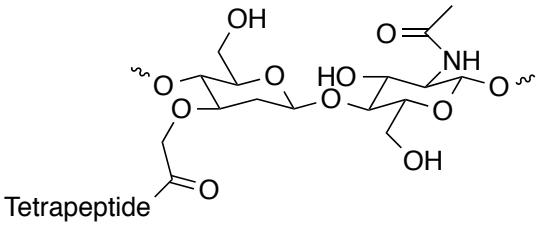


Isopenicillin N

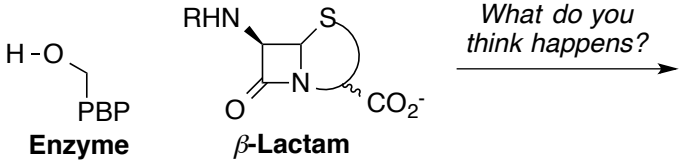
Penicillin's Mechanism of Action: Deactivation of Bacterial Transpeptidase



Bacterial cell walls surrounded by *murein,*
synthesized by *Transpeptidase* (aka *penicillin-bind protein*, PBP)



Peptidoglycan Layer
(repeating unit)



Enzyme **β-Lactam**

Next time…Morphine Day!