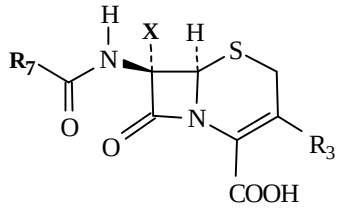
CEPHALOSPORIN STRUCTURE-ACTIVITY RELATIONSHIP SUMMARY

The following pages contain a summary of the more general structure-activity relationships observed for the cephalosporins. These three pages do not contain all of the information you are required to know, but should focus your thinking on the general relationships between structure and properties involving reactivity, formulation, spectrum of activity, PBP affinity, beta-lactamase resistance, oral activity, stbaility, metabolism, plasma protein binding, adverse reactions, etc.



Beta-Lactam Ring:

- Required for PBP reactivity and antibacterial activity
- Reactivity reduced compared to the penicillins (2 reasons)
- Compare mechanism of action, resistance, pharmacodynamics, etc to penicillins

2-Carboxyl Group:

- Acidic: Salt formation, product formulation
- Prodrug formation
- Elimination profile: Renal

X-Substituent:

- Cephalosporins and cephamycins
- Determines, in part, resistance to beta-lactamase inactivation

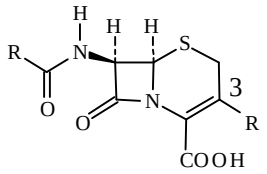
3- Substituent (R_3): **SEE PAGE 2 FOR SAR SUMMARY**

- Chemical/acid stability/instability
- Metabolic stability/instability
- Minimal impact on antibacterial activity
- Protein binding and half-life: Heterocycles
- Adverse Reaction and Drug Interaction
- Some role in cephalosporin classification (generation)

7-Substituent (R_7): **SEE PAGE 3 FOR SAR SUMMARY**

- Incorporated by semisynthesis: Variable structures
- Impact on spectrum of activity (beta-lactamases, PBP affinity, etc.)
- Significant role in activity and classification by generation

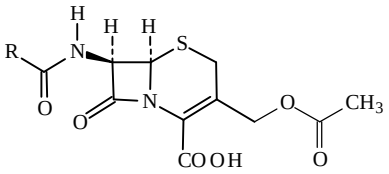
CEPHALOSPORIN STRUCTURE-ACTIVITY RELATIONSHIPS: THE 3-POSITION



R = H, CH_3, Cl, CH_2OCH_3, CH=CHR'

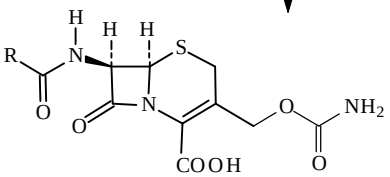
Cephalosporins/cephamycins with acid stable and metabolically stable 3-substituents:

- Minimal effective on spectrum of activity
- May impart oral activity
- Metabolically stable and low ppb: Short $t_{1/2}$



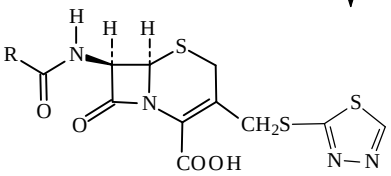
Cephalosporanic Acids: Acid unstable and metabolically unstable 3-substituent:

- Minimal effective on spectrum of activity
- Not orally active: H+ and metabolism
- Metabolically unstable and low ppb: Short $t_{1/2}$



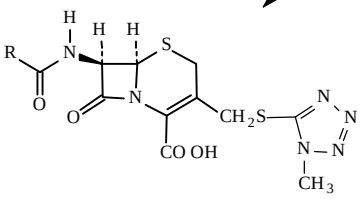
3-Carbamoylcephalosporins: Acid unstable but somewhat metabolically stable (>cephalosporanic acids):

- Minimal effective on spectrum of activity
- Not orally active: H+ instability
- Metabolically stabilized, but low ppb: Short $t_{1/2}$

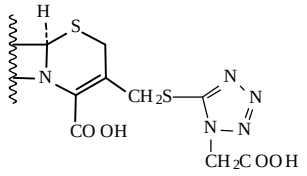


3-Thiothiadiazole: Acid unstable but metabolically stable:

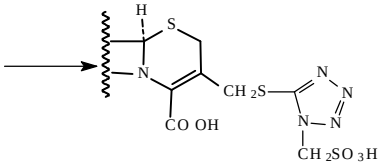
- Minimal effective on spectrum of activity
- Not orally active: H+ instability
- Metabolically stabilized
- Increased ppb (vs compds above) — Longer $t_{1/2}$



N-Methylthiotetrazole (NMTT):

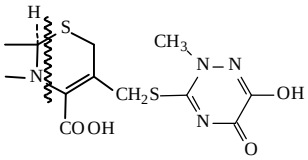


N-Methylthiotetrazole-1-acetic acid:



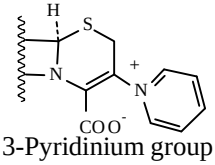
N-Methylthiotetrazole-1-methansulfonic acid:

- NMTT group has minimal effect on spectrum of activity
- All are metabolically stable
- All are acid unstable : Not orally active
- %ppb and half-life increases with NMTT side chain acidity
- Disulfiram and hematologic adverse reactions?

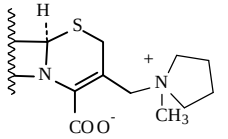


3-Thiotriazine ring system:

- Metabolically stable but acid unstable
- High ppb: Longer $t_{1/2}$
- Shift toward hepatic clearance
- Pseudocholelithiasis



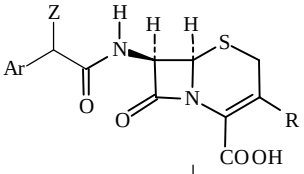
3-Pyridinium group



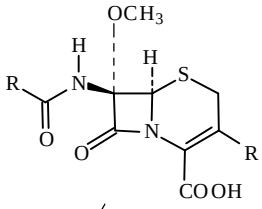
3-Pyrrolidinium Grou

-Acid and some metab. stable
- Permanent ion: Decr absorption
- Antipeusodmonal activity
- Low ppb

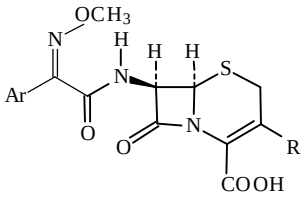
CEPHALOSPORIN STRUCTURE-ACTIVITY RELATIONSHIPS: THE 7-POSITION



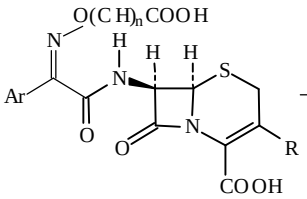
Z = NH_2 or OH, OCHO: (1st and 2nd generation)
- Minimal resistance to beta-lactamases
- More acid stable than Z = H
- G (+) activity; Minimal to Low G(-) Activity



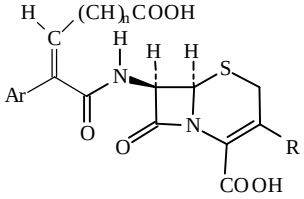
Cephamycins:
- Stability to some beta-lactamases
- May induce beta-lactamase
- Incr G(-) nd decr G(+) activity



Methoxyimine

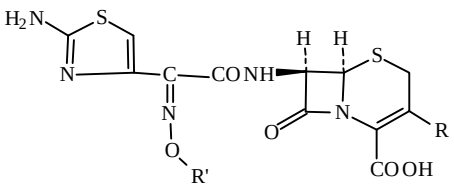


N-alkoxyacid-imine



Alkene-acid

- Stereochemistry: syn for activity
- Acid stability/oral activity dependent on imine/alkene structure
- Good beta-lactamase stability
- Induce beta-lactamases
- Incr G(-) activity
- Decr G(+) activity



Aminothiadiazole alkoximines:

- Good beta-lactamase stability
- Good PBP binding except G(+)
- Generally more CDAD