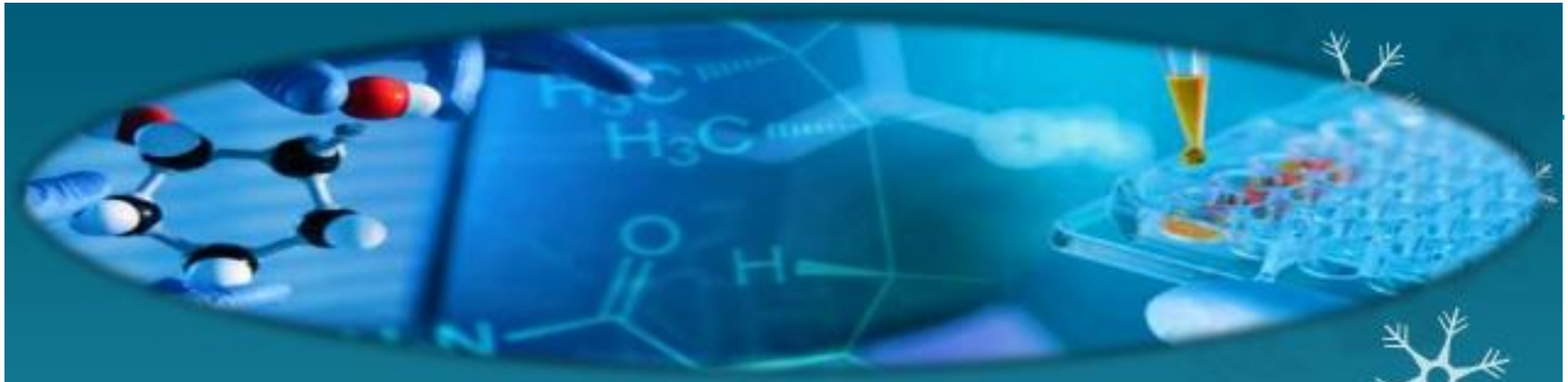


Prodrugs

Dr. Basma Al-Qadi

- The phosphates are completely ionized at physiological pH and generally hydrolyzed rapidly in vivo by phosphatase enzymes.
- Ionization of the phosphate function imparts high stability to these derivates in solution, and solutions for administration can be stored for long periods of time without hydrolysis of the phosphate.
- Such an approach has been used to produce clindamycin phosphate, which produces less pain at the injection site than clindamycin itself.
- Pain after parenteral administration is associated with local irritation caused by:

  1. Low aqueous solubility or.
  2. Highly acidic or.
  3. Highly basic solutions.

- With clindamycin phosphate, the reduction in pain is attributed to the increased water solubility of the agent.

Amines

- Derivatization of amines to give amides has not been widely used as a prodrug strategy because:

1. The high chemical stability of the amide linkage.
2. The lack of amidase enzymes necessary for hydrolysis.

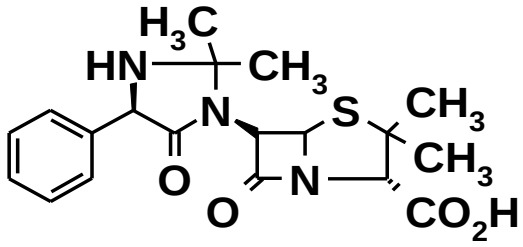
- Prodrug form of the amines:

1. There have been efforts at incorporating amines into peptide linkages in which the peptide serves to increase cellular uptake by use of an amino acid transporter. The amino acids are then cleaved by specific peptidase enzymes.
2. A more common approach has been to use Mannich bases.

Mannich bases result from the reaction of two amines with an aldehyde or ketone

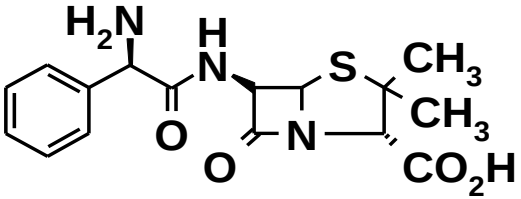
Amine derivatives as prodrugs

- Amides not used due to high stability
- **<u>Most common amine derivative used</u>** is a Mannich Base prodrug



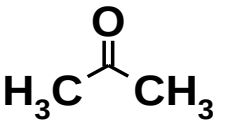
Hetacillin

Water

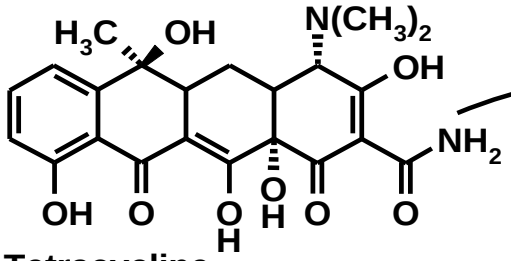


Ampicillin

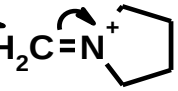
+



Acetone



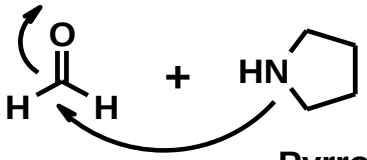
<u>Tetracycline</u>



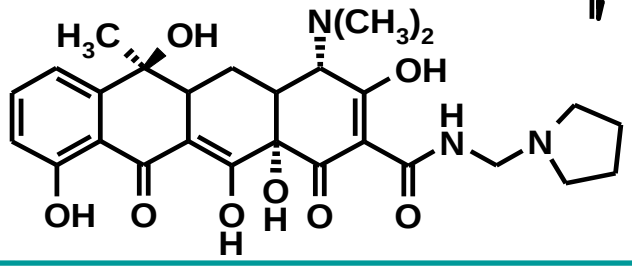
Iminium ion

-H_2O

Formaldehyde



Pyrrolidine



<u>Rolitetracycline</u> - A prodrug of tetracycline with increased water solubility

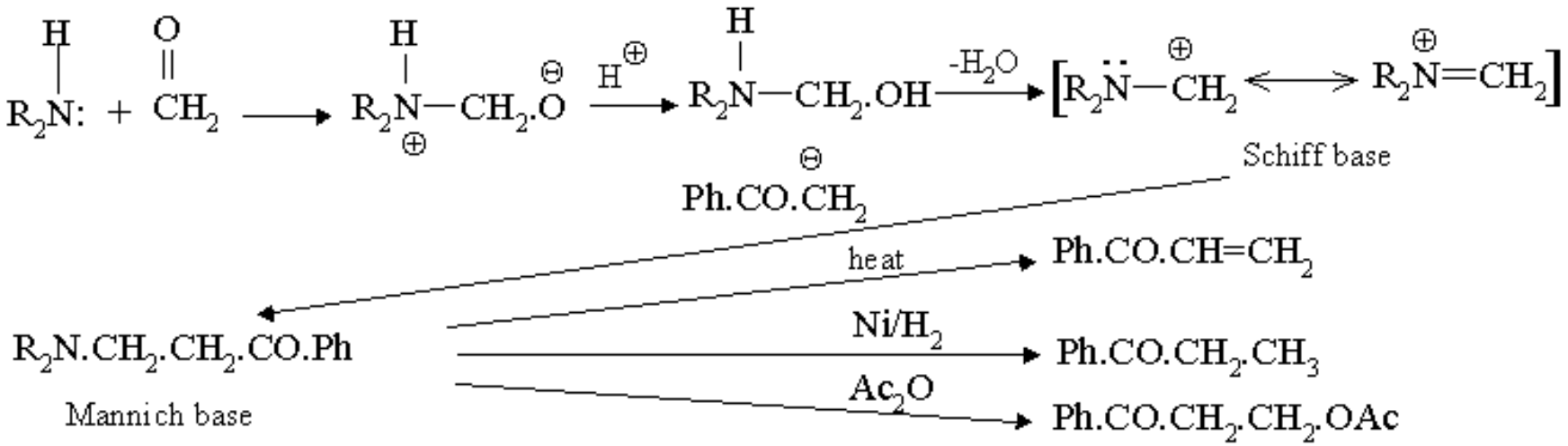
.

As seen with hetacillin, the effect of forming the Mannich base is to

1. lower the basicity of the amine and, thereby,
2. increase lipophilicity and absorption.

- When nitrogen is present in an amide linkage, it is sometimes desirable to use the amide nitrogen as one of the amines necessary to form a Mannich base.
- This approach was used with the antibiotic tetracycline—the amide nitrogen was allowed to react with formaldehyde and pyrrolidine to give the Mannich base rolitetracycline.
- In this case, addition of the basic pyrrolidine nitrogen introduces an additional ionizable functionality and increases the water solubility of the parent drug. The Mannich base hydrolyzes completely and rapidly in aqueous media to give the active tetracycline.

Mannich Base Chemistry



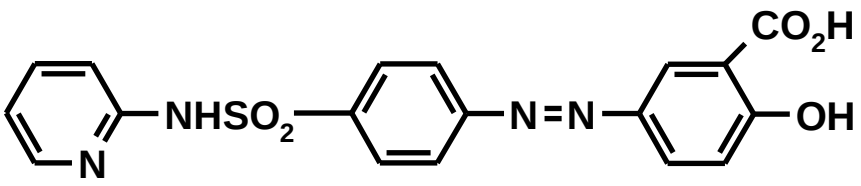
<u>Mannich Reaction</u> - This is nucleophilic addition reaction of an aldehyde and at least a secondary amine to produce what is known as a schiff base on protonation and elimination of a water molecule. The Schiff base is often stabilized by resonance. The addition of a carbanaion to the schiff base gives another base called the Mannich base. The Mannich base formed can readily eliminate the secondary amine to give the synthetic usefulness of the reaction, but when primary amines or ammonia are used the hydrogen on nitrogen atom can participate in a further reaction to give more complex products.

3- Azo linkage

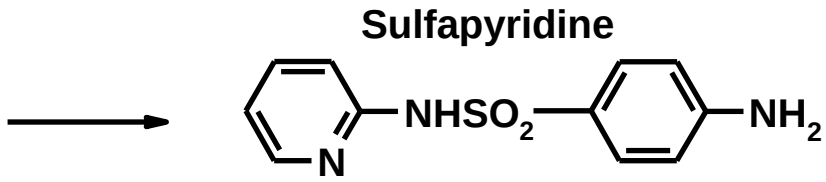
- Amines have occasionally been incorporated into an azo linkage to produce a prodrug.
- e.g. sulfasalazine, which is used in the treatment of ulcerative colitis. The azo linkage is broken in the gut by the action of azo reductases produced by microflora.
- This releases the active agent, amino salicylic acid, which has an anti-inflammatory effect on the colon, and sulfapyridine. As shown in this Scheme:

Azo Prodrugs

- Bacterial reductases → reductive cleavage
  - Release of 2 amine compounds
  - Occurs in ***colon*** → discourages small intestine systemic absorption
  - Concentrates the drug at the desired site of action

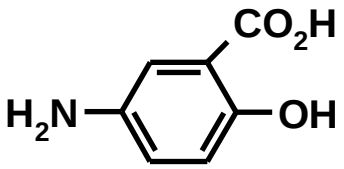


Sulfasalazine - Azulfidine® - Pharmacia & Upjohn
Sulfonamide antibiotic and antiinflammatory
Used to treat Ulcerative colitis, rheumatoid arthritis



Sulfapyridine

+



5-aminosalicylic acid

The advantage of this prodrug approach is:

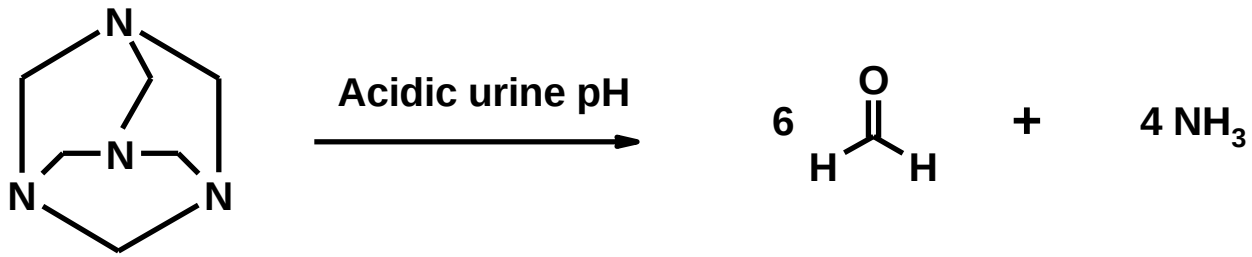
- Cleavage of the azo linkage and generation of aminosalicylic acid prior to absorption prevents the systemic absorption of the agent.
- Helps concentrate the active agent at the site of action.

Carbonyl prodrugs

- Aldehyde and ketone derivatives
- Little clinical utility with one exception Methenamine
- Under hydrolysis conditions, these functionalities are reconvened to the carbonyl compounds.

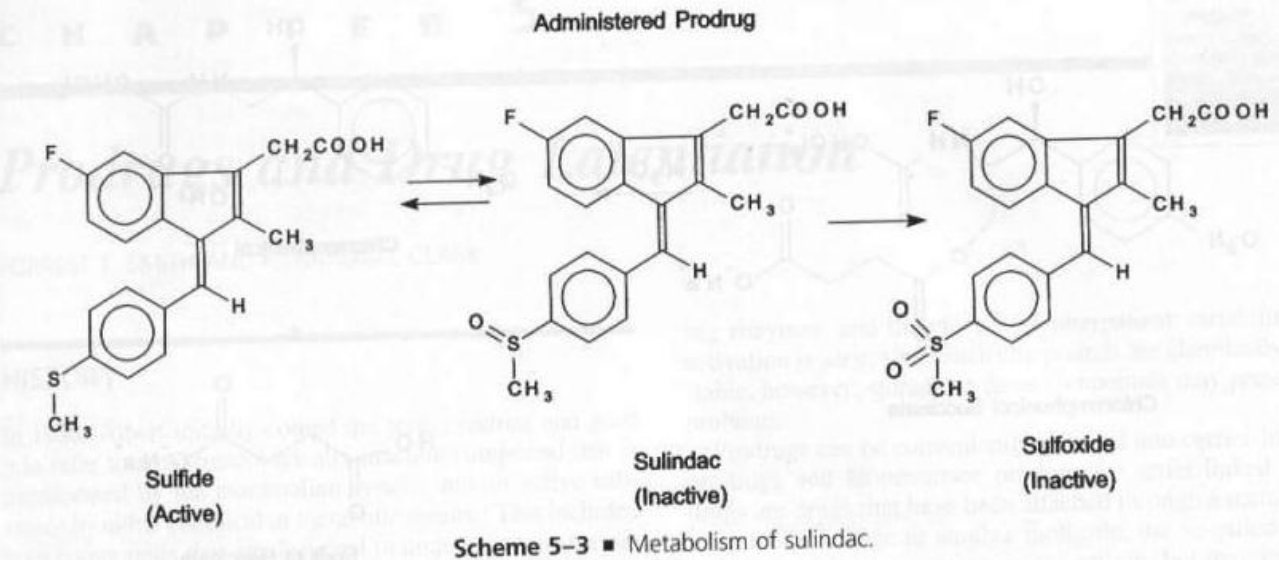
Methenamine releases formaldehyde in the urine, which acts as an antibacterial agent. The agent is administered in enteric-coated capsules to protect it from premature hydrolysis in the acidic environment of the stomach.

In the urine, where the acidic pH catalyzes the chemical hydrolysis to give formaldehyde. Use of this prodrug approach prevents the systemic release of formaldehyde and reduces toxicity.



BIOPRECURSOR PRODRUGS:

- Bioprecursor prodrugs do not contain a carrier or promoiety but rather contain a latent functionality that is metabolically or chemically transformed to the active drug molecule.
- The types of activation often involve:
- Oxidative activation, commonly seen since a number of endogenous enzymes can carry out these transformations.
- reductive activation
- phosphorylation, and
- In some cases chemical activation.
- Phosphorylation has been widely exploited in the development of antiviral agents, and many currently available agents depend on this type of activation.
- The nonsteroidal anti-inflammatory drug (NSAID) Sulindac is inactive as the sulfoxide and must be reduced metabolically to the active sulfide.



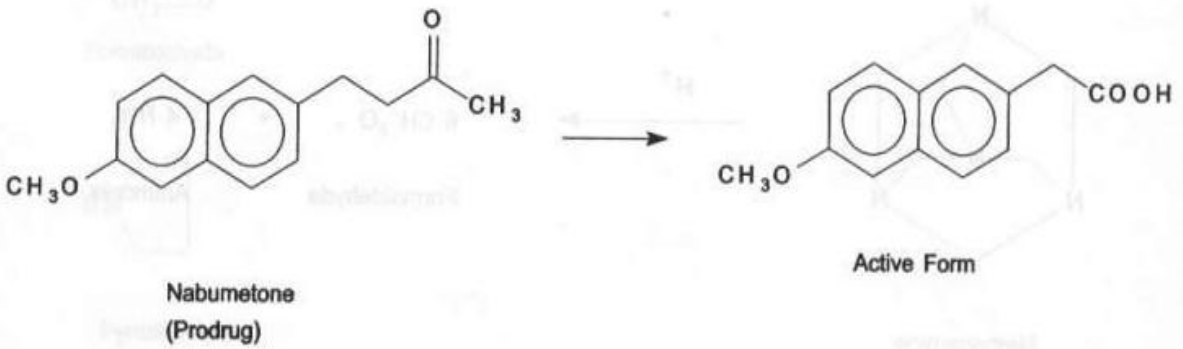
Scheme 5–3 ■ Metabolism of sulindac.

- Administration of the inactive form has the benefit of reducing the gastrointestinal (GIT) irritation associated with the sulfide.

The problems associated with bioprecursor prodrugs approach:

- Participation of alternate metabolic paths that may inactivate the compound. In this case, after absorption of sulindac, irreversible metabolic oxidation of the sulfoxide to the sulfone can also occur to give an inactive compound.
- Although seen less frequently, some prodrugs rely on chemical mechanisms for conversion of the prodrug to its active form.
- Metabolite generated after chemical hydrolysis some times toxic (it must be nontoxic and easily removed after it has performed its function).

A good example of a prodrug that requires oxidative activation is the NSAID nabumetone.



Scheme 5–18 ■ Oxidative activation of nabumetone.

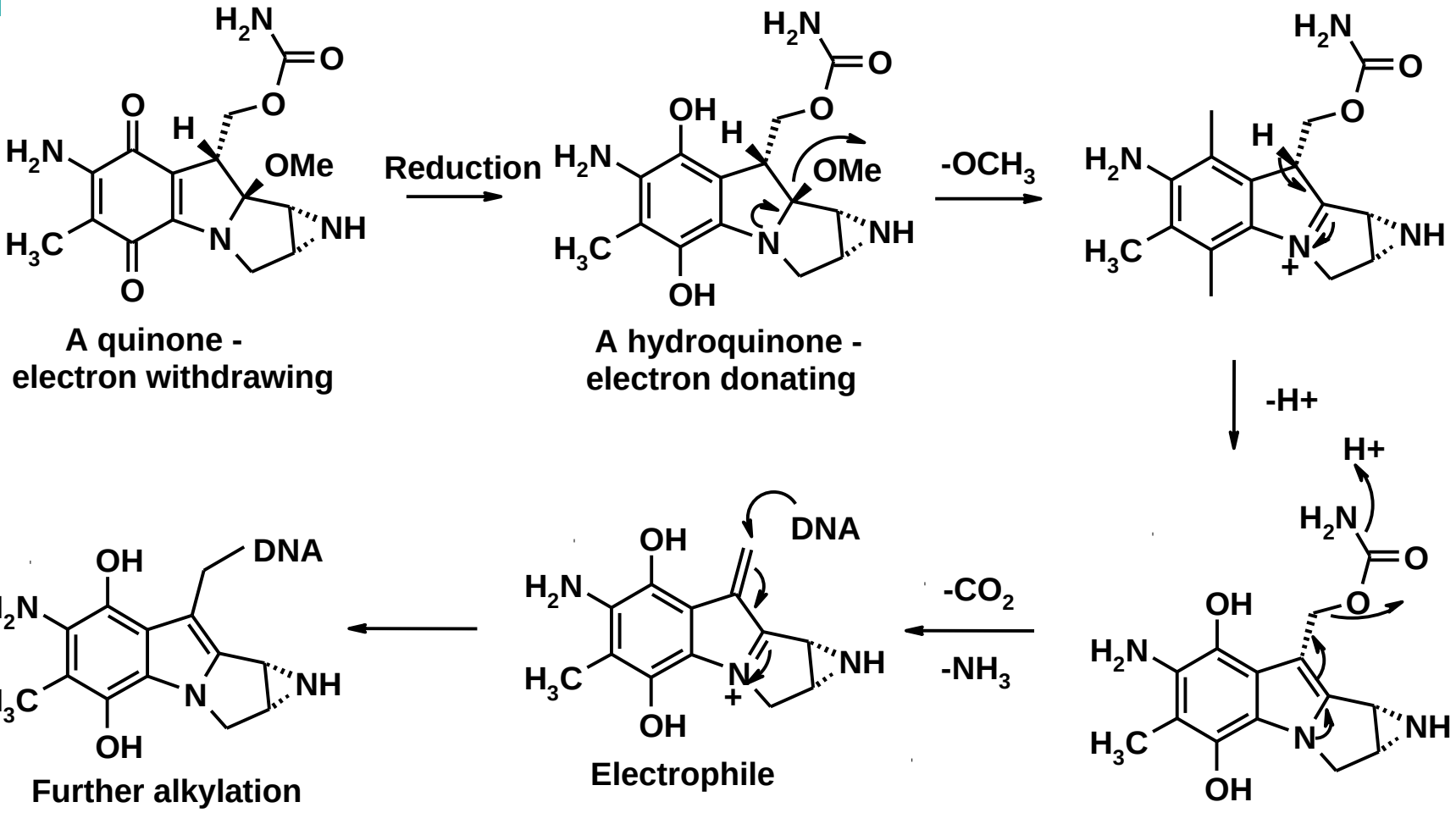
- NSAIDs produce stomach irritation. This irritation is associated in part with the presence of an acidic functionality in these agents.

- The carboxylic acid functionality commonly found in these agents is un-ionized in the highly acidic environment of the stomach. As a result, these agents are more lipophilic in nature and may pass into the cells of the gastric mucosa.
- The intracellular pH of these cells is more basic than that of the stomach lumen, and the NSAID becomes ionized. This results in backflow of H+ from the lumen into these cells, with concomitant cellular damage.
- This type of damage could be prevented if the carboxylic acid function could be eliminated from these agents: this functional group is required for activity, however. Nabumetone contains no acidic functionality and passes through the stomach without producing the irritation normally associated with this class of agents. Subsequent absorption occurs in the intestine, and metabolism in the liver produces the active compound as shown in above Scheme.

- This approach, however, did not completely eliminate the gastric irritation associated with nabumetone, since it is due only in part to a direct effect on the stomach. Inhibition of the target enzyme, cyclooxygenase, while having an anti-inflammatory effect, also results in the increased release of gastric acid, which irritates the stomach.
- Reductive activation is occasionally seen as a method of prodrug activation but, because there are fewer reducing enzymes, is generally less common than oxidative activation.
- One of the best known examples of reductive activation is for the antineoplastic agent mitomycin C. which is used in the treatment of bladder and lung cancer as shown in the following Scheme

Bioprecursor Prodrugs

Reduction example - Mitomycin C - Mutamycin® - Bristol Myers
Adenocarcinoma of the stomach and pancreas



- Mitomycin C contains a quinone functionality that undergoes reduction to give a hydroquinone. This is important because of the differential effect of the quinone and hydroquinone on the electron pair of the nitrogen.
- Whereas the quinone has an electron-withdrawing effect on this electron pair, the hydroquinone has an electron-releasing effect, which allows these electrons to participate in the expulsion of methoxide and the subsequent loss of the carbamate to generate a reactive species that can alkylate DNA.