Alddehyde or ketone Mannich bases result from the reaction of two amines with an
A more common approach has been to use Mannich bases.
cleaved by specific peptidase enzymes.
use of an amino acid transporter. The amino acids are then
peptide in which the peptidase serves to increase cellular uptake by
have been efforts at incorporating amines into peptide

Prodruq form of the amines:
The lack of amidease enzymes necessary for hydrolysis.
The high chemical stability of the amide linkage.
as a prodruq strategy because:
Derivatization of amines to give amides has not been widely used

Amines
Water solubility

Tetraacycline - A product of

Pyrorilrine

Formaldehyde

Ampicillin

Acetone

Water

Most common amine derivative used is a Mannich base prodrg

Amine derivatives as products

Amides not used due to high stability
Tetacyclline completely and rapidly in aqueous media to give the active component and readily in aqueous media to give the active.


In this case, addition of the basic pyrrolidine nitrogen introduces pyrrolidine to give the Mannich base rolletacyclline.

This approach was used with the antibiotic tetacyclline—the necessary to form a Mannich base.

Desirable to use the amide nitrogen as one of the amines. When nitrogen is present in an amide linkage, it is sometimes

increase lipophilicity and absorption.

lower the basicity of the amine and, thereby,

As seen with hetacillin, the effect of forming the Mannich base is to
can participate in a further reaction to give more complex products. But when primary amines or ammonia are used the hydrogen on nitrogen atom eliminate the secondary amine to give the synthetic usefulness of the reaction, another base called the Mannich base. The Mannich base formed can readily stabilized by resonance. The addition of a carbanion to the Schiff base gives the Schiff base is often at least a secondary amine to produce what is known as a Schiff base on Mannich Reaction. This is nucleophilic addition reaction of an aldehyde and an R₂N⁺CH₂CO₂⁻.\[ \text{Ph.CO.CH₂CH₂OCH₂CO₂⁻} \]

R₂N⁺CH₂CO₂⁻ + Ph.CO.CH₂CH₂$\text{OCH₂CO₂⁻}$ → \[ R₂N⁺CH₂CH₂$\text{OCH₂CO₂⁻}$ \]

Mannich Base Chemistry
Shown in this scheme:

- Effect on the colon, and sulfapyridine. As salicylic acid, which has an anti-inflammatory action.
- This releases the active agent, amino salicylate.
- Azo reductases produced by microflora.
- Linkage is broken in the gut by the action of the azo reductase of ulcerative colitis. The azo linkage is converted to produce a drug.
- Amine linkage has occasionally been incorporated.

3. Azo Linkage
5-aminoosalicylic acid

\[
\text{5-aminosalicylic acid}
\]

Used to treat ulcerative colitis, rheumatoid arthritis, sulfonamide antibiotic and antiinflammatory.

Sulfasalazine - Azulfidine® - Pharmacia & Upjohn

Concentrates the drug at the desired site of action.

Colon occurs in colon.

Release of 2 amine compounds.

Bacterial reduction reductive cleavage.

Azo Products
Helps concentrate the active agent at the site.

- Prevents the systemic absorption of the
  aminoacetylcylcic acid prior to absorption

Cleavage of the azo linkage and generation

- The advantage of this prodrug approach is:
Compounds. Functionalities are resonance to the carbonyl.

Under hydrolysis conditions, these oxygen, nitrogen, or sulfur.

Aromatic heteroatoms, such as attached to two heteroatoms, such as converted to an sp³ hybridized carbon which the sp² hybridized carbonyl carbon is converted to an sp³ hybridized carbon.

These have generally involved derivatives in Methenamine.

Little clinical utility with one exception.

Aldehyde and ketone derivatives.

Carbonyl Prodrugs.
Methylenamine releases formaldehyde in the urine, which

In the urine, where the acidic pH catalyzes the chemical

hydrolsis in the acidic environment of the stomach.

Entero-coated capsules to protect it from premature

approach prevents the systemic release of formaldehyde.

Hydrolsis to give formaldehyde. Use of this product

and reduces toxicity.

\[
\begin{array}{c}
\text{Acidic urine pH} \\
\downarrow \\
\text{Hydrolsis}
\end{array}
\]

\[
\text{formaldehyde}
\]
active sulhide.

inactive as the sulfoxide and must be reduced metabolically to the
The nonsteroidal anti-inflammatory drug (NSAID) Sulindac is

type of activation.

antiviral agents, and many currently available agents depend on this
Phosphorylation has been widely exploited in the development of

In some cases chemical activation.

and

phosphorylation, and

reductive activation

enzymes can carry out these transformations.
Oxidative activation, commonly seen since a number of endogenous

The types of activation often involve:

transformed to the active drug molecule.
Rather contain a latent functionally that is metabolically or chemically

Bioprecursor prodrugs do not contain a carrier or promoter but
With the sulfide:
Reducing the gastrointestinal (GI) irritation associated with the inactivation of the inactive form has the benefit of

Scheme 5-3: Metabolism of sulfide

Administrated Producing

Administered: (inactive) Sulfide
after it has performed its function.

Metabolite formed after chemical hydrolysis some
its active form.

Although seen less frequently, some products rely on
inactive compounds.

although sulfoxide to the sulphone can also occur to give an
of sulindac, irreversible metabolic oxidation of the
inactivate the compound. In this case, after absorption
Participation of alternate metabolic pathways that may

approach:

The problems associated with bioprecursor products
Activation is the NSAID's formation from its prodrug, which requires oxidative activation.
produces the active compound as shown in above scheme. Absorption occurs in the intestine, and metabolism in the liver. Subsequent irritation normally associated with this class of agents. Furthermore, benzene containing no acidic functionality and passes through the stomach without producing the is required for activity. However, naproxenone contains no acidic function could be eliminated from these agents: this functional group. This type of damage could be prevented if the carboxylic acid

- The lumen into these cells, with concomitant cellular damage. The lumens, and the NSAID becomes ionized. This results in backflow of H+ from intracellular pH of these cells is more basic than that of the stomach. Mucosa.

- Agents are more lipophilic in nature and may pass into the cells of the ionized in the highly acidic environment of the stomach. As a result, these

- The carboxylic acid functionality commonly bound in these agents is un-
shown in the following scheme used in the treatment of bladder and lung cancer as is for the antineoplastic agent mitomycin C, which is one of the best known examples of reductive activation.

One of the best known enzymes is generally less common than oxidative enzymes, is generally less common than oxidative producing activation but because there are fewer reducing Reductive activation is occasionally seen as a method of stomach.

Increased release of gastotic acid, which irritates the having an anti-inflammatory effect, also results in the inhibition of the target enzyme, cyclooxygenase, while due only in part to a direct effect on the stomach, gastric irritation associated with nabumetone, since it is this approach, however, did not completely eliminate the
Bioprecursor Prodrugs

Adenocarcinoma of the Stomach and Pancreas

Example Mutamycin C - Mitomycin C - Bristol Myers

Further alkylation

Electrophilic

Electron donating

A hydroquinone

A quinone

Reduction
that can alkylate DNA.

alkylate the carbamoyl to generate a reactive species

expulsion of methoxide and the subsequent loss

which allows these electrons to participate in the

"withdrawing effect on this electron pair, the

Whereas the quinone has an electron-

differential effect of the quinone and

Mitomycin C contains a quinone functionality
Cells

A much more selective agent, trimipramine, is reported to be 100 times more selective for hypoxic cells than for normal activated and, therefore, selectively toxic. It was thought that the metabolism might be more prevalent than in normal tissues, so the agents would be selectively poorly vascularrized. In these tissues, with a low oxygen content it was thought that reduction metabolism might be more prevalent antineoplastic activity in slow-growing solid tumors that are antineoplastic activity.

In an effort to modify the reduction potential of mitomycin C, various analogues have been prepared and tested for substitutions attached to the ring.

The selectivity of mitomycin for hypoxic cells is minimal, however, the selectivity is determined in part by the reduction potential of the guanine, which can be influenced by the guanine.

Mitomycin C.

The cascade of events that leads to an alkylating active drug is initiated by the reduction of the guanine functionality in species

Important notes:
Chain breaks.

Aerobic conditions, hydroxide radical is formed, which can initiate DNA chain breaks in the DNA chain. Under hypoxic conditions, the following scheme:

Cytochrome P-450 reductase to give a radical species as shown in the catalyzed by a number of enzymes, including cytochrome P-450 and the mechanism of activation involves a one-electron reduction that is
Following scheme:

A growing chain of DNA or RNA as shown in the RNA, in which nucleotides are added to the 3' end of the RNA, for example, in the synthesis of DNA and can be displaced by an incoming nucleophile. This is seen, for example, in the synthesis of DNA and RNA, in which the incoming nucleophile introduces a leaving group, which displaces the growing chain.

Phosphorylation introduces these molecules. By doing so, it activates these molecules, in the process phosphorylating other molecules, and in the process body then typically uses these molecules to bond such as those present in ATP and GTP. The is used to produce high-energy phosphodiester bonds, which is a common metabolic function of the body, which
Scheme 5-21: DNA Synthesis

DNA Polymerase

DNA chain

Adenine

Thymine

DNA chain

Adenine

Thymine
The following scheme:

This can be seen in the product idoxuridine, which was the first
to show clinical effectiveness against viruses as shown in

have greater selective toxicity.

Therefore, nucleosides that have higher affinity for the viral
cells than in normal cells.

Since normal cells are also involved in the synthesis of DNA and

which is generally accomplished by conversion to the

antiviral agents disrupt the synthesis or function of DNA or RNA,

must be converted to the nucleotides to have activity. Most often,
antiviral agents. These agents are commonly nucleosides, which

Phosphorylation is commonly required for the bioactivation of
(Note: Thymine contains CH3 instead of I)

Two mechanisms of action: 1. Inhibits DNA polymerase. 2. Incorporates into DNA attracting incorrect base pairing and template activity.

Knase but some toxicity
Higher affinity for viral Kinase
Viral Thymidine
Phosphorylation Example
Bioactive Drugs

Iodouridine - Herplex
Allergan - Iridis soluble
Iodouridine - Iridis soluble

Higher affinity for viral Kinase
Higher than mammalian Kinase
Virial Thymidine
Not lipid soluble
ATP
and RNA synthesis.
that disrupts the ability of DNA to function as a template for DNA
Incorporation into DNA, which results in incorrect base pairing
Inhibition of viral DNA polymerase.

Inhibiting:

Stage, it can inhibit DNA synthesis in a number of ways.
Once the drug has been phosphorylated to the triphosphate

cells.

Selectivity is rather low, and there is significant toxicity to normal
intact cells and achieves some selective toxicity, although this
Therefore, the drug is activated to a greater extent in the virally

Corresponding mammalian enzyme.

is a better substrate for the viral enzyme than for the
preferentially by viral thymidine kinase, because the idoxuridine
In virally infected cells, this phosphorylation is accomplished
The nucleoside enters the cell, where it is phosphorylated.
passive diffusion and are too polar to cross the membrane via nucleotides are unable to use this process mechanisms, whereas the active easily enter the cell via active transport increased cell penetration. The prodrg can achieve some selective toxicity.

Advantages of the prodrg idoxuridine