Organic Pharmaceutical Chemistry IV
1st Semester, Year 5 (2016-2017)
Lecture 3

Organic Pharmaceutical Chemistry: Prodrugs

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This lecture is mainly based on:
Chapter 4, Prodrugs and Drug Latentiation, FORREST T. SMITH AND C. RANDALL CLARK Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, 11th ed., 2004, Lippincott Williams & Wilkins, USA.

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:

1. Oxidative activation,
2. Reductive activation,
3. Phosphorylation,
4. Chemical activation (in some cases)

Oxidation is commonly seen, since a number of endogenous enzymes can carry out these transformations.

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

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.

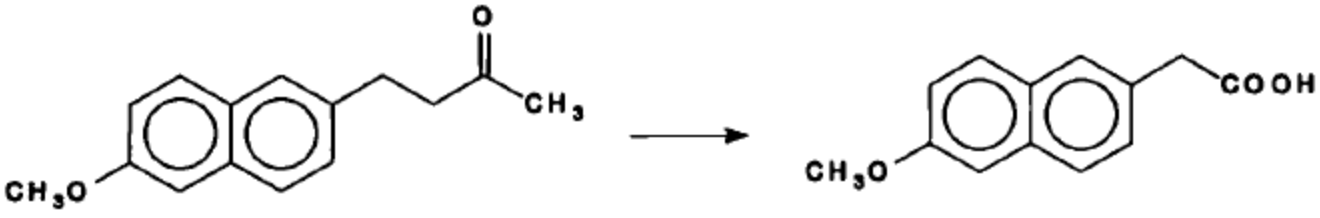
This type of damage could be prevented if the carboxylic acid function could be eliminated from these agents.

However this functional group is required for activity.

The NSAID Nabumetone (Relafen) is good example of a prodrug that requires **oxidative activation**.

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



Nabumetone (Prodrug) Active Form

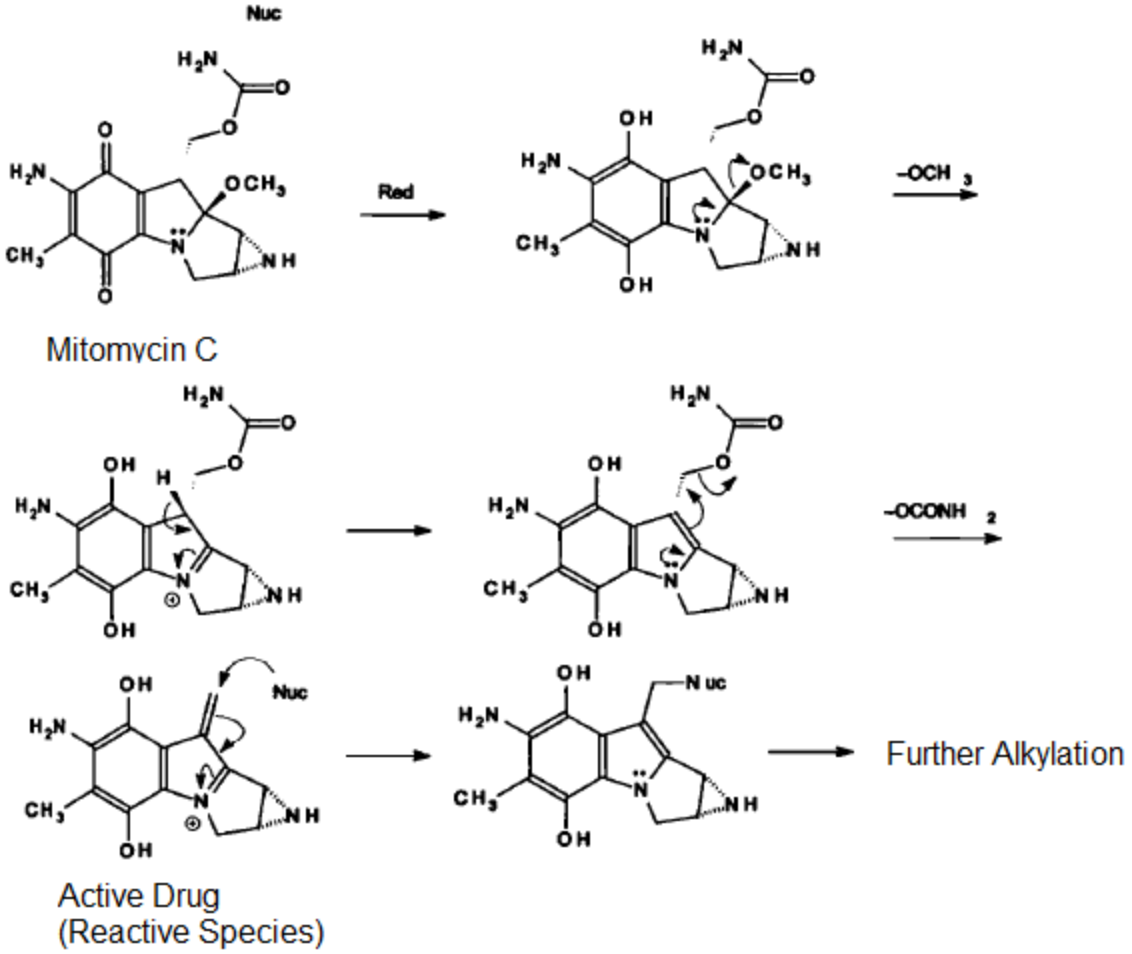
This approach, however, did not completely eliminate the gastric irritation associated with nabumetone, since it is due only in part to a direct effect on the stomach.

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.

So, while nabumetone induces less gastric irritation than other NSAIDs, this undesirable effect was not completely eliminated by a prodrug approach.

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.



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.

The cascade of events that leads to an alkylating active drug species is initiated by the reduction of the quinone functionality in mitomycin C.

The selectivity of mitomycin for hypoxic cells is minimal, however.

The selectivity is determined in part by the reduction potential of the quinone, which can be influenced by the substituents attached to the ring.

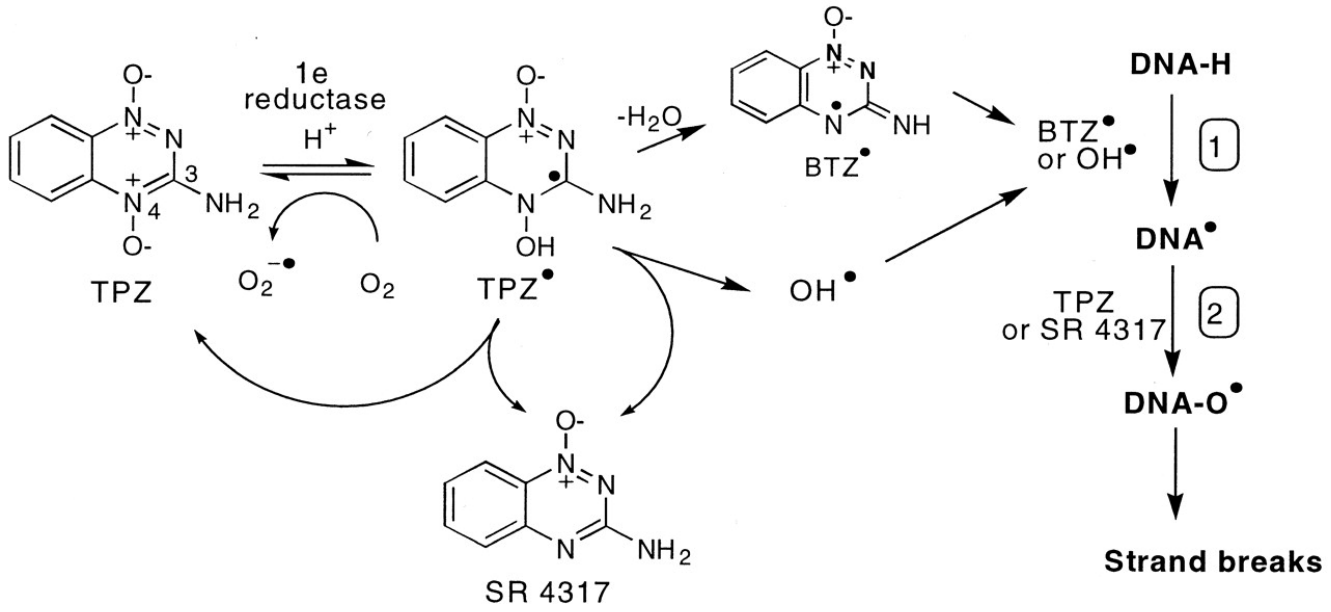
In an effort to modify the reduction potential of mitomycin C, various analogues have been prepared and tested for antineoplastic activity. It was hoped that the reduction potential could be altered so that the analogues would only be activated in hypoxic conditions, such as those found in slow-growing solid tumors that are poorly vascularized.

In these tissues with a low oxygen content it was thought that reductive metabolism might be more prevalent than in normal tissue, so the agents would be selectively activated and, therefore, selectively toxic.

Although mitomycin was the first agent used clinically to be recognized as requiring reductive activation, it is only modestly selective for hypoxic cells.

Tirapazamine is much more selective agent. It is reported to be 100 to 200 times more selective for hypoxic cells than for normal cells.

The mechanism of activation involves a one-electron reduction that is catalysed by a number of enzymes, including cytochrome P-450 and cytochrome P-450 reductase to give a radical species.

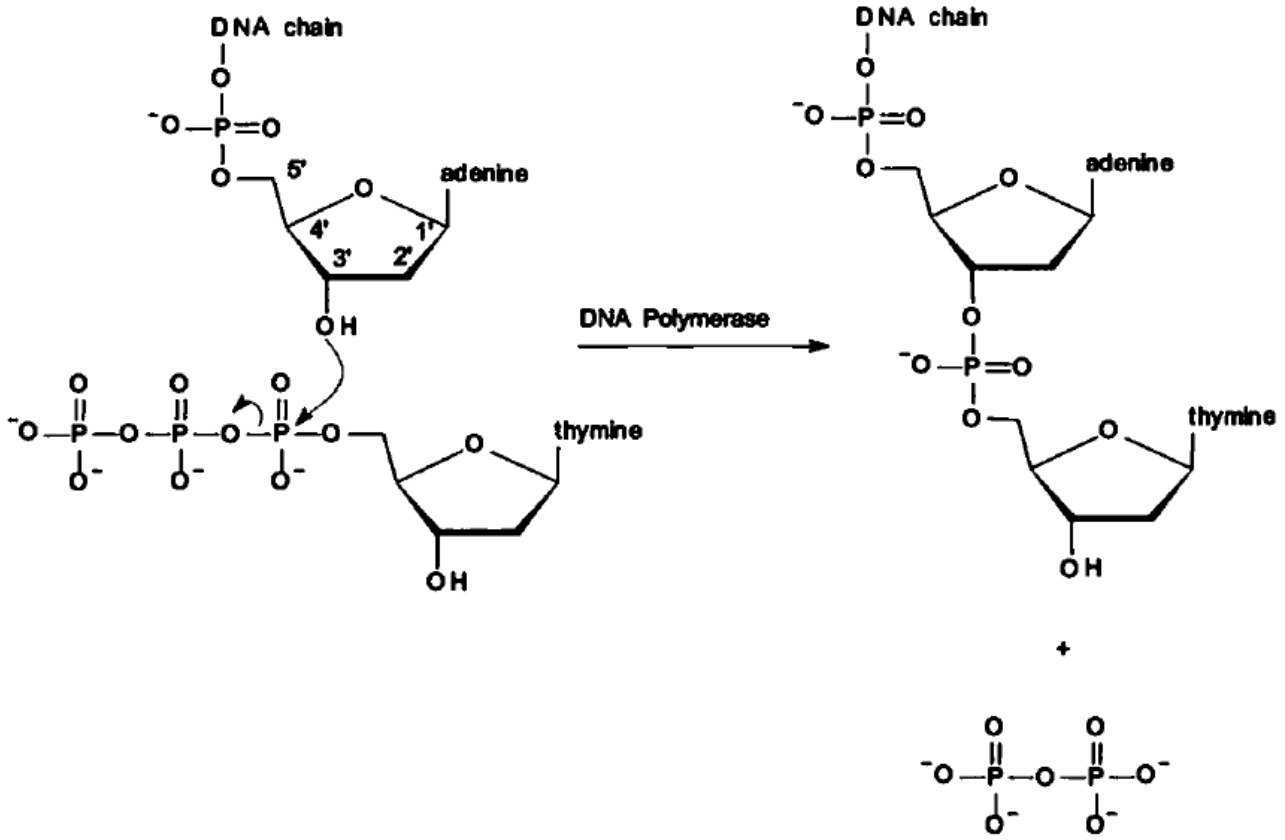


This species, which is shown as a carbon-centered radical, can initiate breaks in the DNA chain under hypoxic conditions.

Phosphorylation is a common metabolic function of the body, which is used to produce high-energy phosphodiester bonds such as those present in ATP and GTP. The body then typically uses these molecules to phosphorylate other molecules and, in the process of doing so, activates these molecules.

The type of activation achieved depends on the molecule phosphorylated, but in many cases, phosphorylation introduces a leaving group, which can be displaced by an incoming nucleophile.

This is seen, for example, in the synthesis of DNA and RNA, in which nucleotides are added to the 3' end of a growing chain of DNA or RNA



Phosphorylation is commonly required for the bioactivation of antiviral agents.

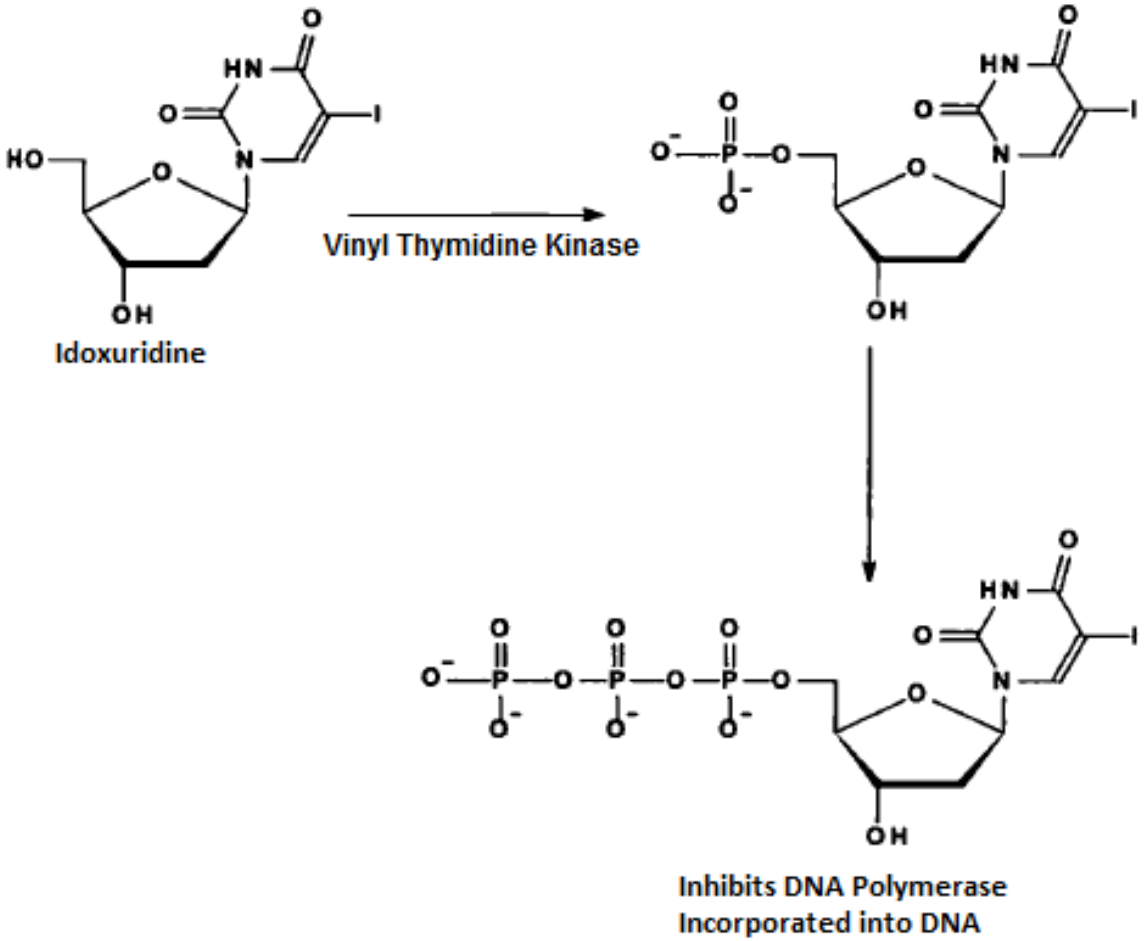
These agents are commonly nucleosides, which must be converted to the nucleotides to have activity.

Most often, antiviral agents disrupt the synthesis or function of DNA or RNA, which is generally accomplished by conversion to the triphosphate.

Since normal cells are also involved in the synthesis of DNA and RNA, compounds have been sought that would be converted to the triphosphates, the active form, in greater amounts in infected cells than in normal cells.

Therefore, nucleosides that have higher affinity for the viral kinase enzymes than the mammalian kinases are desirable and have greater selective toxicity.

This can be seen in the prodrug idoxuridine, which was the first agent to show clinical effectiveness against viruses.



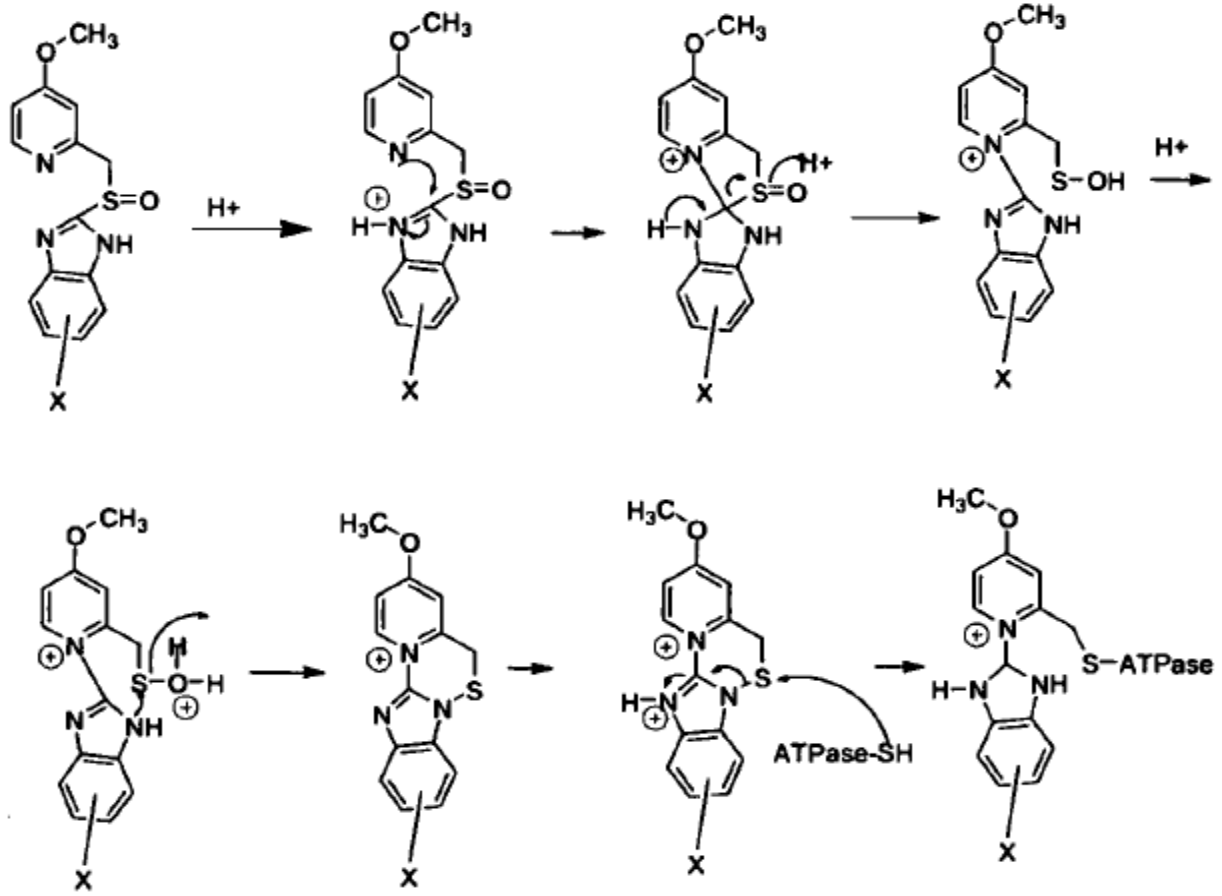
The nucleoside enters the cell, where it is phosphorylated. In virally infected cells, this phosphoiylation is accomplished preferentially by viral thymidine kinase because the idoxuridine is a better substrate for the viral enzyme than for the corresponding mammalian enzyme.

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

Once the drug has been phosphorylated to the triphosphate stage, it can inhibit DNA synthesis in a number of ways, including inhibition of viral DNA polymerase and incorporation into DNA, which results in incorrect base pairing that disrupts the ability of DNA to function as a template for DNA and RNA synthesis.

In addition to the selective toxicity mentioned, the prodrug approach offers the additional advantage of increased cell penetration. The prodrug can easily enter the cell via active transport mechanisms, whereas the active nucleotides are unable to use this process and are too polar to cross the membrane via passive diffusion.

A good example of chemical activation is seen with the proton pump inhibitors such as omeprazole. In this case, chemical activation is provided by the highly acidic environment in and around the parietal cell of the stomach



This allows protonation of nitrogen on the benzimidazole ring followed by attachment of the pyridine nitrogen. Ring opening then gives the sulfenic acid that subsequently cyclize with the loss of water. Attachment by a sulfhydryl group present on the proton pump of the parietal cell then occurs and inactivates this enzyme, preventing further release of H^+ into the GI tract, which is useful in treating gastric ulceration.