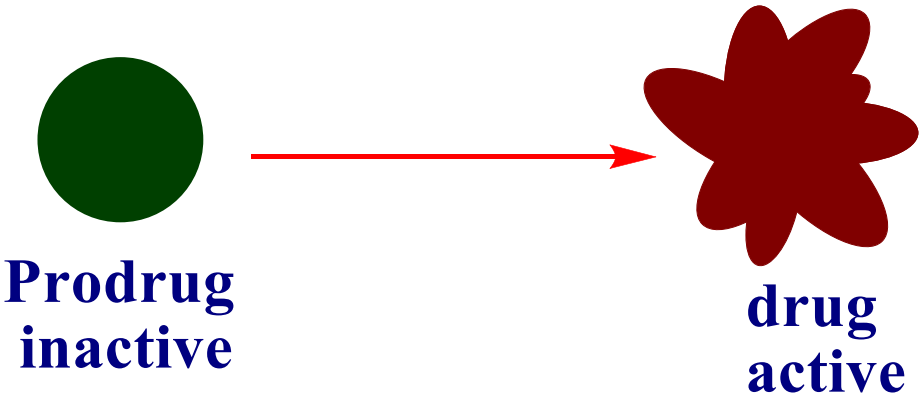
Lec 4 5th stage

Organic Pharmaceutical Chemistry IV

2018-2019

Assist prof. Dr.Rita Sabah Elias
College of Pharmacy, university of Basrah

Bioprecursur prodrugs



1- Not contain promoiety or carrier.•

2- Contain latent functionality.

3- Metabolically or chemically transformed into an active drug.

4- Types of activation includes:-

a) **Oxidation (most common method)**
b) **Reduction.**
c) **Phosphorylation.**
d) **Chemical activation in some cases.**

1) Oxidative bioactivation

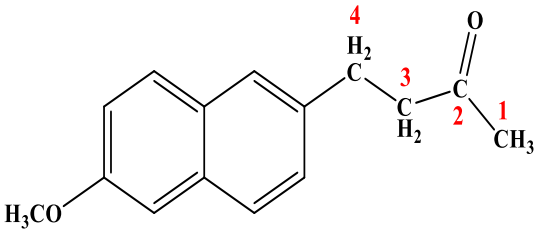
Oxidation is commonly seen because of:-

a- A number of endogenous enzymes can carry out these transformations.

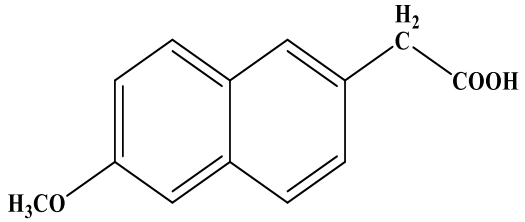
b- The abundance of oxidizing enzyme in the body made this activation a popular rout.

c- Isoenzymes of cytochrome P-450 can oxidize a wide variety of functionalities.

Example (Nabumetone)



Series of oxidative decarboxlation



Nabumetone (inactive)

Nabumetone contains no acidic functionality
And passes through the stomach without
Producing the irritation.
this ketonic form, not contain free carboxyl group, passes to stomach gastric mucosa without any irritation, After absorption is metabolized in the liver to produce the active forms

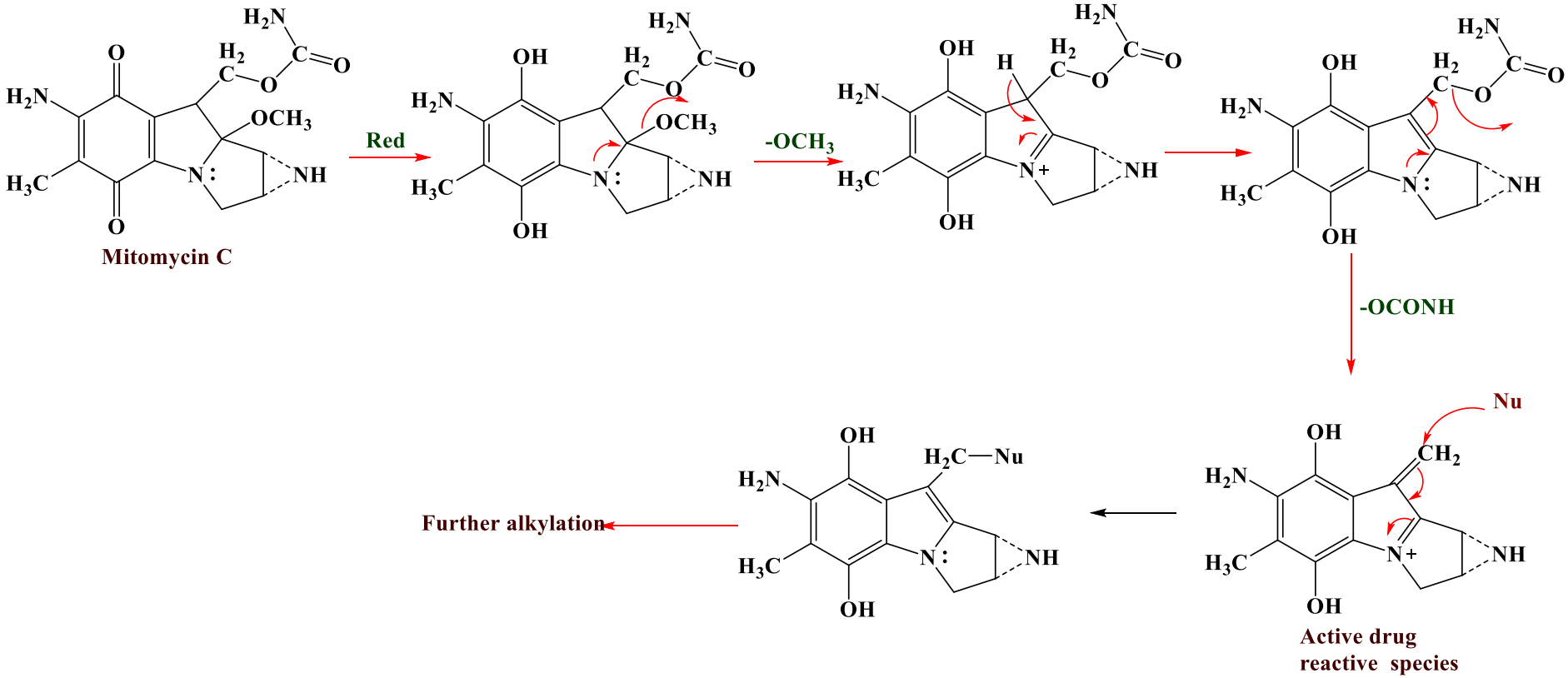
6-methoxy-2-naphthylacetic acid (active)

NSAID produce stomach irritation, this irritation come from:-
1- Inhibiting PG production by COX enzyme.
2- come from acidic functionality commonly found in these agents.

2. **Reduction bioactivation:-** This less common than oxidation bioactivation because there are few reducing enzyme.

Examples:-

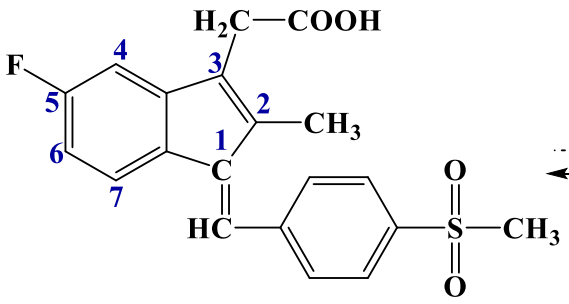
a) **Mitomycin C(antineoplastic agent use for treatment of bladder and lung cancer)**


Mitomycin C
Red
-OCH3
-OCONH
Nu
Active drug
reactive species
Further alkylation

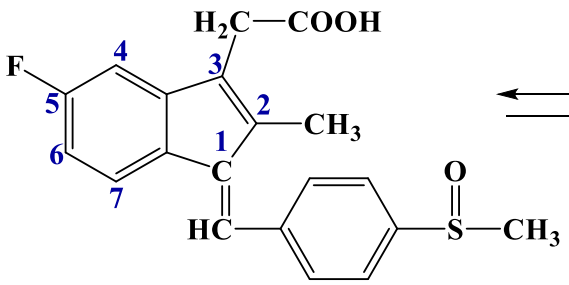
Mitomycin C contain a quinone functionality that undergo reduction to give hydroquinone. This is important because of the differential effect of the quinone and hydroquinone on the electron pair of the nitrogen. Whereas the quinone has an electron-withdrawing effect on this electron pair, the hydroquinone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

a) Sulindac(NSAID):-

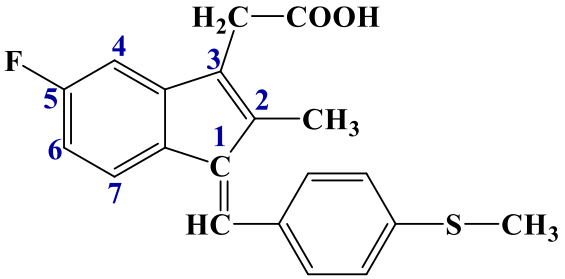
Sulindac is administered orally, absorbed in the small intestine, and subsequently reduced to the active species. Administration of the inactive form has the benefit of reducing the gastrointestinal (GI) irritation associated with the sulfide.



inactive
sulfone



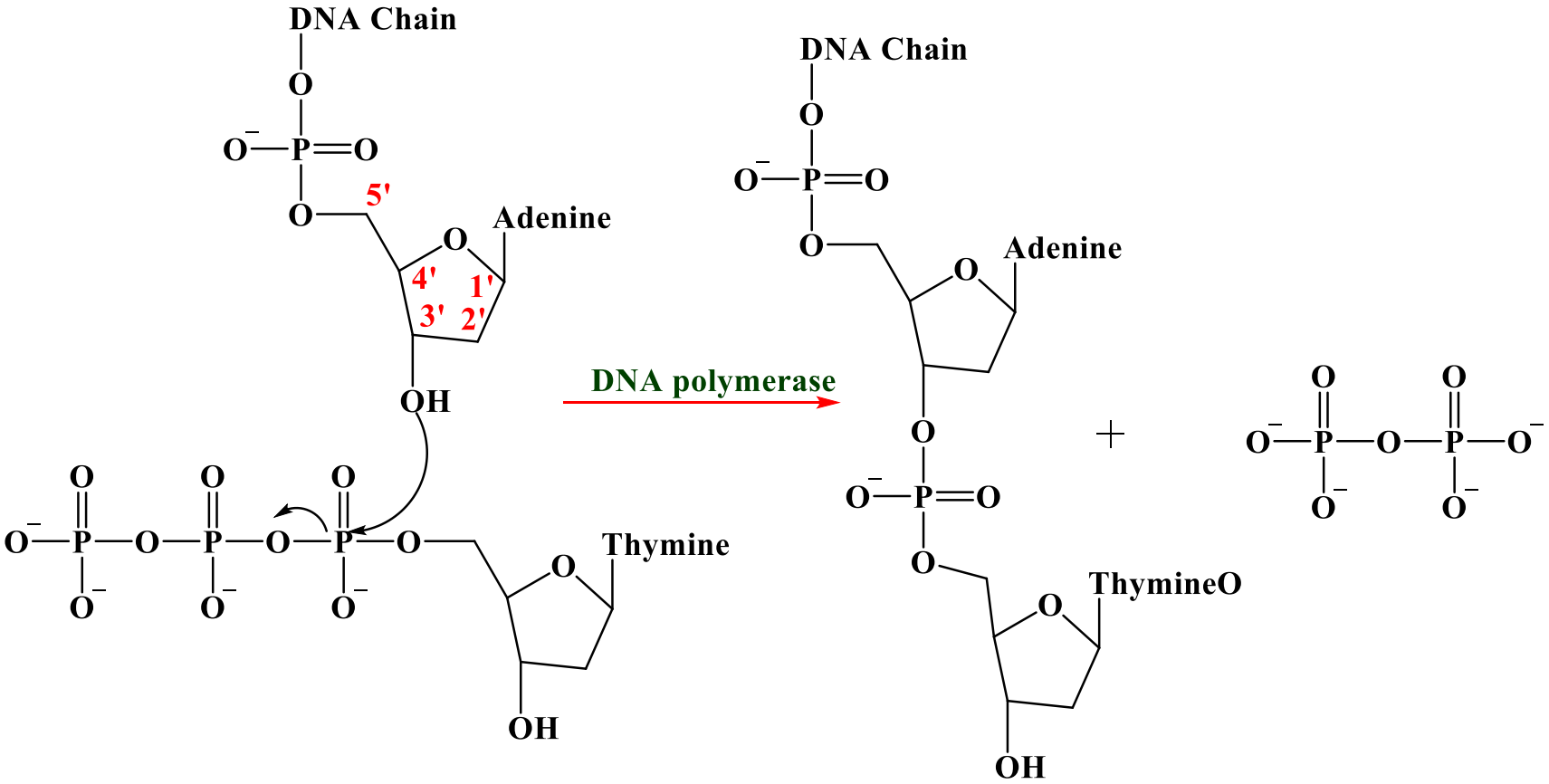
more polar and inactive sulfoxide
used as prodrug to reducing GI irritation



active (sulfide)
cause as gastric irritation so used
as sulfoxide prodrug

3- Phosphorylation reaction

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.



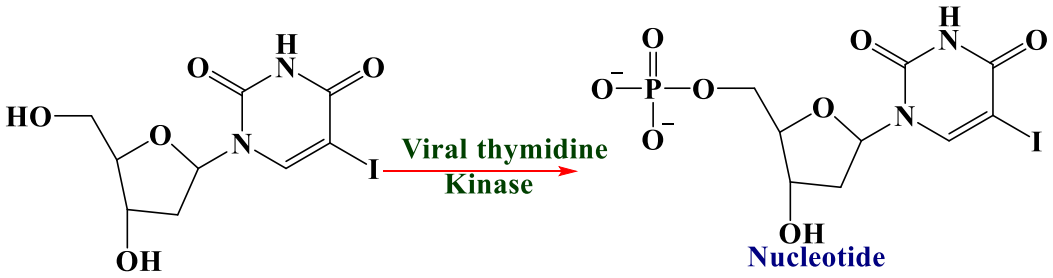
DNA Synthesis

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. This 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.

Example (Idoxuridine -antiviral agent):-

has two mechanisms of action: -

1. Inhibits DNA polymerase.
2. Incorporated into DNA affording incorrect base pairing and template activity

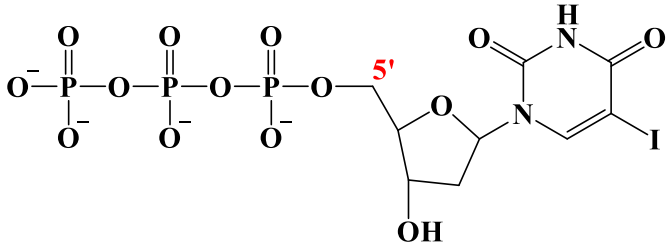


Idoxuridine

Opthalmic product for Herpes simplex keratitis
This agent act as substrate for phosphorylating enzyme found in viruses(Higher affininty for viral kinases than mammalian kinases but some toxicity) enter the cell via active transport mechanism

Nucleotide
not lipid soluble

ATP



Active antiviral agent
The phosphorylated species is incorporated into viral DNA, disrupting viral replication and thus producing the antiviral effect
It inhibit DNA synthesis in a number of ways, including
Inhibiting of viral DNA polymerase
incorporated into DNA resulting in incorrect base pairing, which disrupt the ability of DNA to function as template for DNA and RNA synthesis

The prodrug can readily penetrate the virus and the increased polarity of the phosphorylated derivative would serve to retain that active species inside the virus. The combination of increase polarity and viral retention of active phosphorylated species likely reduce any human toxicity that might be associated with this active species.

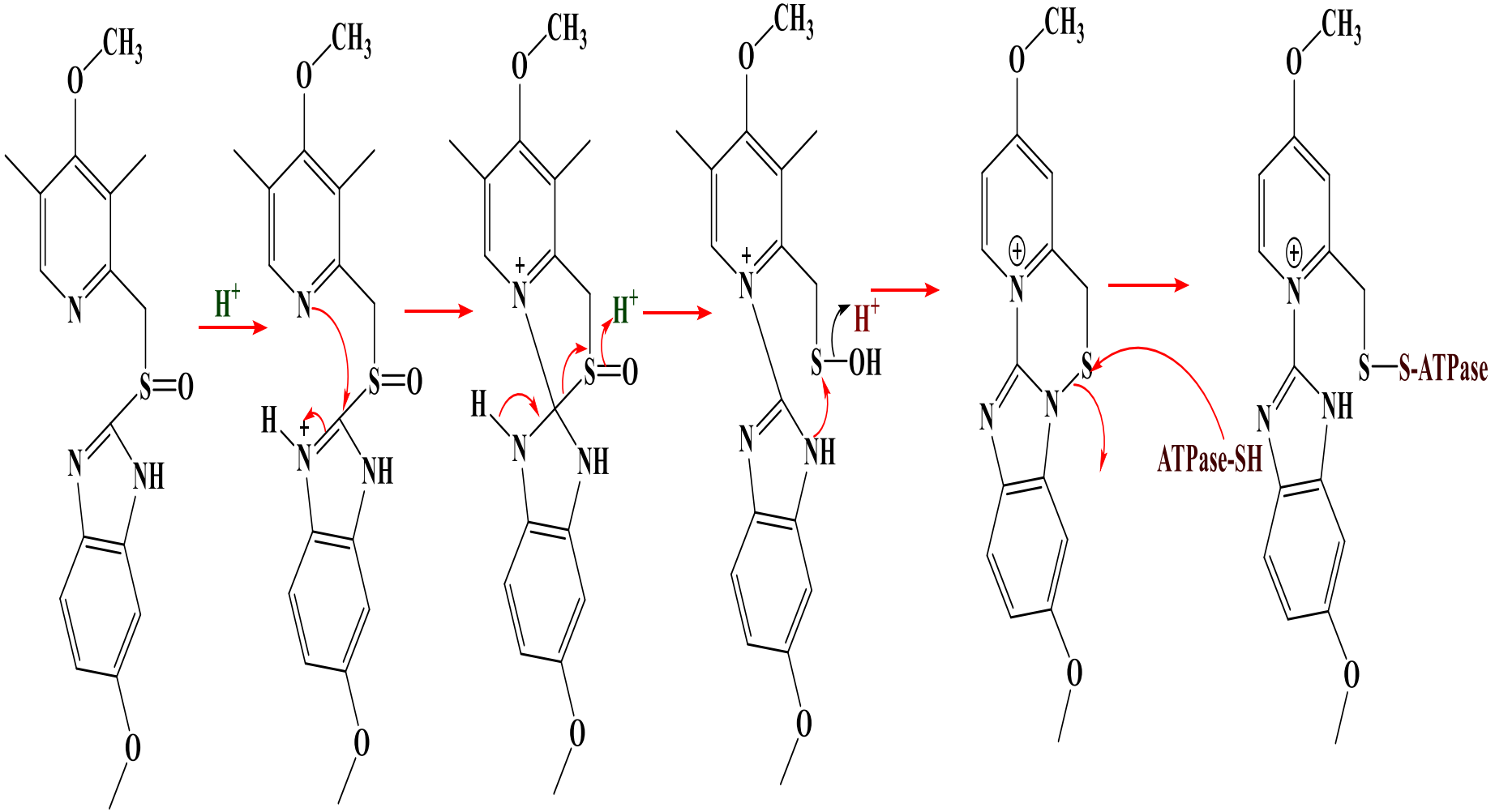
Advantage of idoxuridine

1- Greater selective toxicity.

2- Its 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.

4- Chemical activation (Omeprazole-proton pump inhibitor)

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 cyclizes 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.



Mechanism of activation of proton pump inhibitors