Prodrugs for Improving Parenteral Delivery

- When a drug cannot be taken orally or when immediate action of drug is required, parenteral drug dosing is the desired route of administration.

- Most phosphate esters used in parenteral formulations are soluble prodrugs of poorly water-soluble parent drugs.

- Phosphate esters are ionizable and have considerably higher aques solubility than the parent compounds, and they are rapidly hydrolyzed by phosphatases yielding the parent drugs.

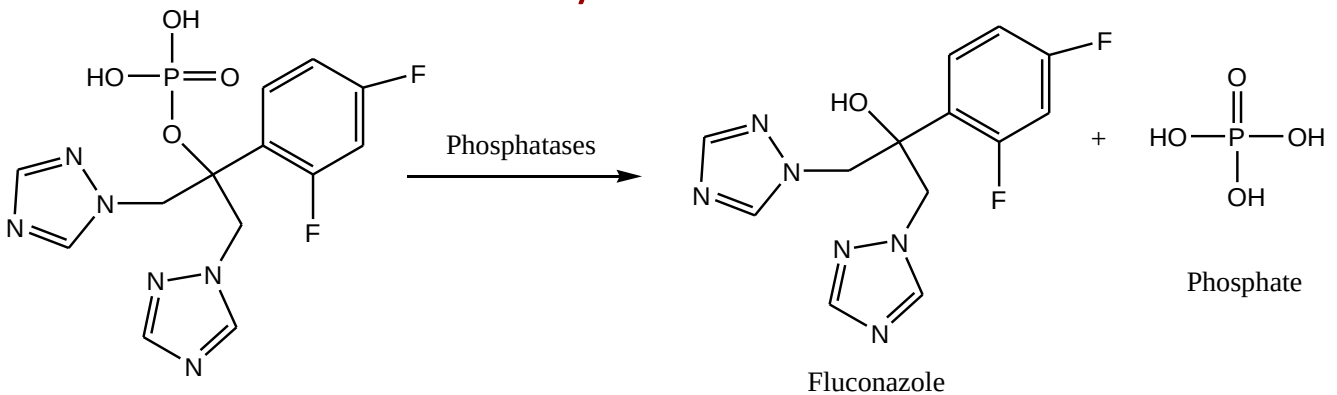
- Fluconazole is a broad-spectrum antifungal drug marketed in both oral and intravenous formulations.

- Fluconazole`s intravenous (IV) formulation has to be administered at up to a 400-mL dose volume.

- Fosfluconazole is a phosphate prodrug of fluconazole, which is being developed to reduce the volume of fluid required to administer fluconazole by the IV route.

- It is more soluble than fluconazole, allowing the delivery of fluconazole in a smaller volume.

- Fosfluconazole is rapidly converted to fluconazole and phosphate group which is essential for normal body function[49].



Fosfluconazole

Fluconazole

Phosphate

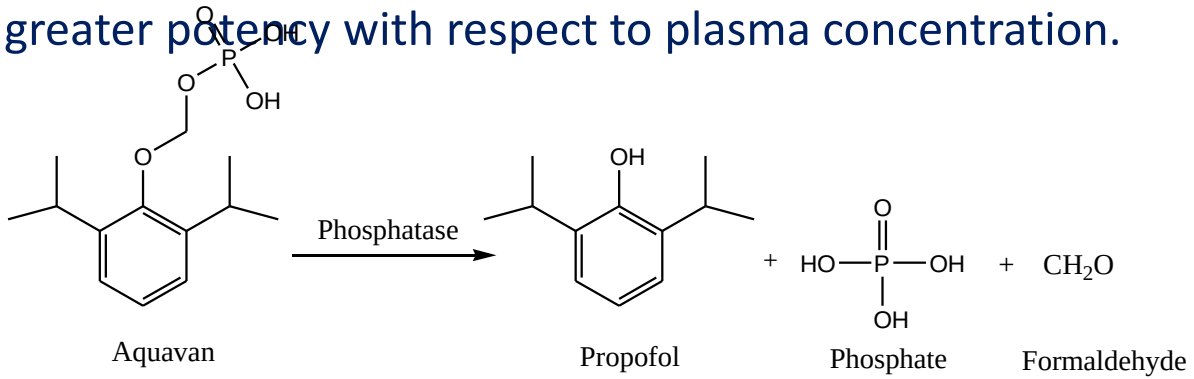
- Propofol is a potent intravenous sedative–hypnotic agent and is widely used for general anesthesia and sedation.

- It has very slight solubility in water and, thus, is formulated as an oil-in-water emulsion.

- Lipid emulsion formulation of propofol has some disadvantages such as lipid intake, risk of infection, and aggravated pain on injection. This formulation can lead to hyperlipidemia when used long-term to maintain an ICU patient in a coma.

- Aquavan is a water-soluble phosphonooxymethyl ester prodrug of propofol and is intended to eliminate the disadvantages associated with the current lipid-emulsion formulation of propofol.

- Aquavan undergoes hydrolysis to give propofol, and show a longer half-life, an increased volume of distribution, a delayed onset, a sustained duration of action, and an apparent greater potency with respect to plasma concentration.

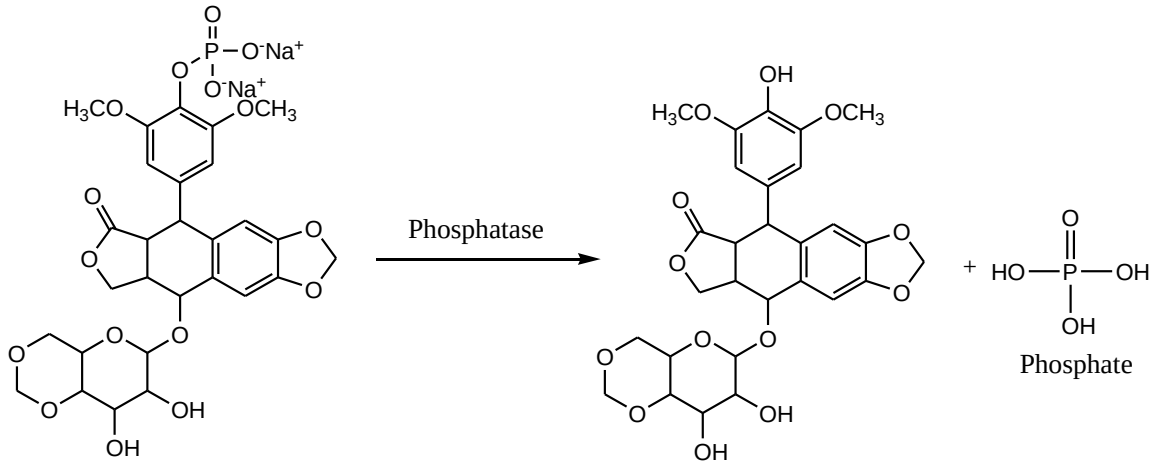


- Etoposide is an important chemotherapeutic agent in the treatment of cancer.

- The clinical use of etoposide is adversely affected by its very poor water solubility and is formulated in polysorbate-80, polyethylene glycol, and alcohol. Even with this formulation, etoposide must be diluted to avoid precipitation.

- This may cause fluid overload problems in patients receiving high doses of this agent and requires prolonged nursing supervision, higher expenses, and patient inconvenience and discomfort.

- In addition, hypersensitivity and hypotensive reactions have been reported. Etoposide phosphate, a water soluble prodrug of etoposide, has several potential advantages including easier and more rapid administration, avoidance of large fluid loads, and elimination of hypersensitivity reactions and other problems related to the solubilizer.

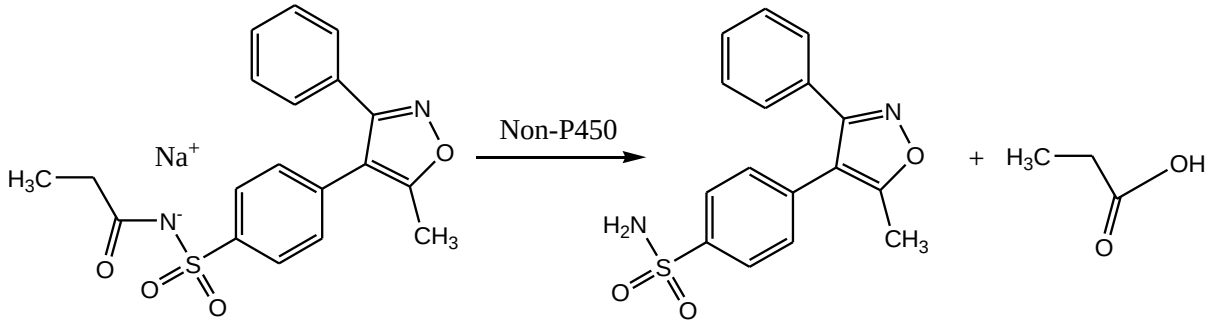


- Valdecoxib is a new COX-2-selective inhibitor, and it is approved for the treatment of rheumatoid arthritis, osteoarthritis, and primary dysmenorrhea. Clinical studies have found valdecoxib to have superior anti-inflammatory, analgesic, and antipyretic activity.

- To develop a COX-2 inhibitor for parenteral administration, a water-soluble prodrug of valdecoxib was synthesized by acylation of the sulfonamide group to give parecoxib sodium.

- It had improved solubility necessary for parenteral application and showed excellent efficacy and a rapid onset of action comparable with the most potent analgesic ketorolac.

- It hydrolyzes *in vivo* by enzymatic hydrolysis to pharmacologically active valdecoxib.



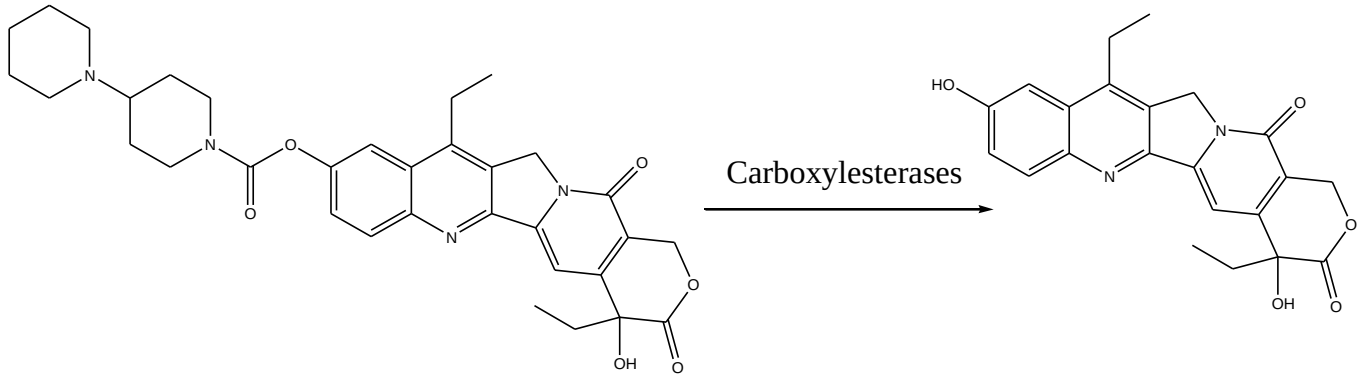
Parecoxib Valdecoxib Propionic acid

- The anticancer drug CPT-11 (irinotecan), is a prodrug that is activated by esterases to yield SN-38, a potent topoisomerase I poison.

- Irinotecan is a semisynthetic water-soluble camptothecin produced in an attempt to reduce the toxicity and improve the therapeutic efficacy of the drug.

- Irinotecan shows encouraging activity in the treatment of several types of tumours such as nonsmall cell lung cancer, colorectal adenocarcinoma, and cancer of the cervix.

- SN-38 has been shown to be 100-1000 times more potent than CPT-11 in *in vitro* and *in vivo* tests of cytotoxicity.



CPT-11 (Irinotecan)

SN-38