PRODRUGS OF ALCOHOLS AND PHENOLS

- Acylation or alkylation of alcohols or phenols could lead to a less polar prodrug while phosphorylation can lead to a more water soluble prodrug.

A. Aliphatic and Aromatic Esters

- Drugs containing hydroxyl groups, including alcohols and phenols can have a variety of physical/chemical properties that have advantages and disadvantages.

- Esterification of the hydroxyl group has been one of the preferred prodrug strategies to mask polar groups within a drug molecule and thereby promote membrane permeability.

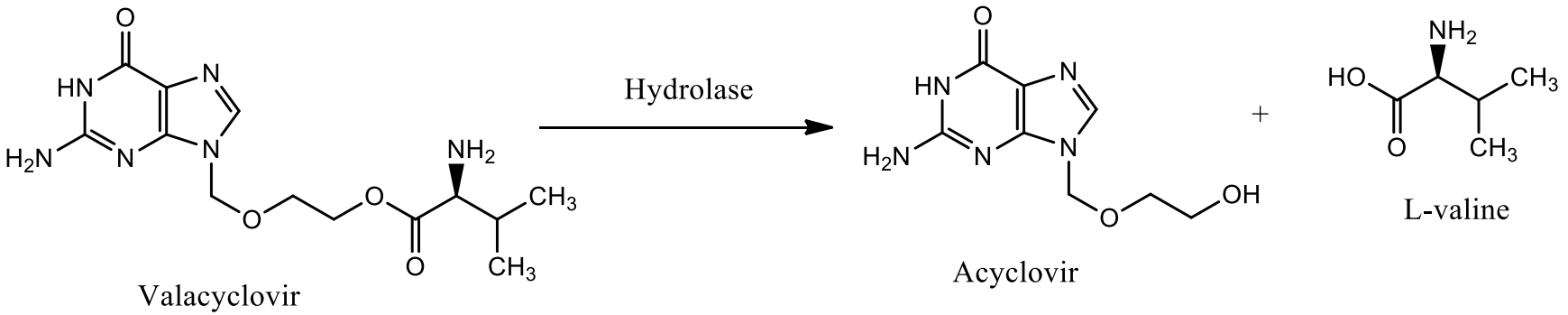
- Acyl groups that have been incorporated to form promoieties for the hydroxyl group range from lower alkyl groups to long-chain fatty acids.

- Valacyclovir is a water soluble L-valine ester prodrug of the HIV reverse transcriptase inhibitor acyclovir.

- Valacyclovir was developed to increase the oral absorption and plasma levels of acyclovir. Increased plasma concentrations of acyclovir are important to maintain antiviral activity, especially in immunocompromised patients and in the treatment of less sensitive viruses such as cytomegalovirus (CMV) and varicella zoster virus (VZV).

- Valacyclovir is rapidly absorbed and converted to acyclovir by enzymatic hydrolysis in the intestine and liver.

- It is hydrolysed by a valacyclovir hydrolase to produce acyclovir and L-valine.

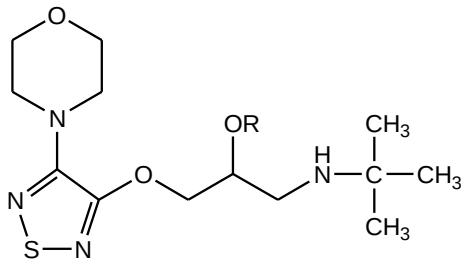


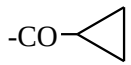
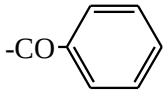
- A series of alkyl, cycloalkyl, and aryl ester prodrugs of the nonselective β-adrenergic antagonist timolol have been prepared by esterifying the hydroxyl group of timolol.

- All the prodrugs studied were more lipophilic than timolol and the most promising examples penetrated the cornea substantially better than timolol.

- The rate of ester hydrolysis of alkyl, cycloalkyl, and aryl ester-prodrug was about equal in plasma and phosphate buffer, making it difficult to design a prodrug which is stable *in vitro* but will convert quickly to an active drug *in vivo*.

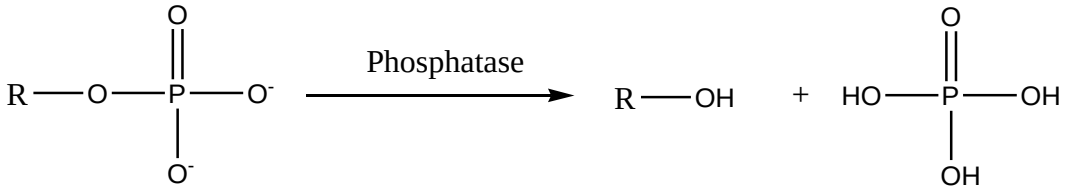
- Thus, the poor aqueous stability of the prodrugs limits their clinical usefulness although they show good biopharmaceutical properties.



R	
-H	Timolol
-COCH3	O-acetyl timolol
-CO 	O-cyclopropanoyl timolol
-CO 	O-benzoyl timolol

B. Phosphate esters

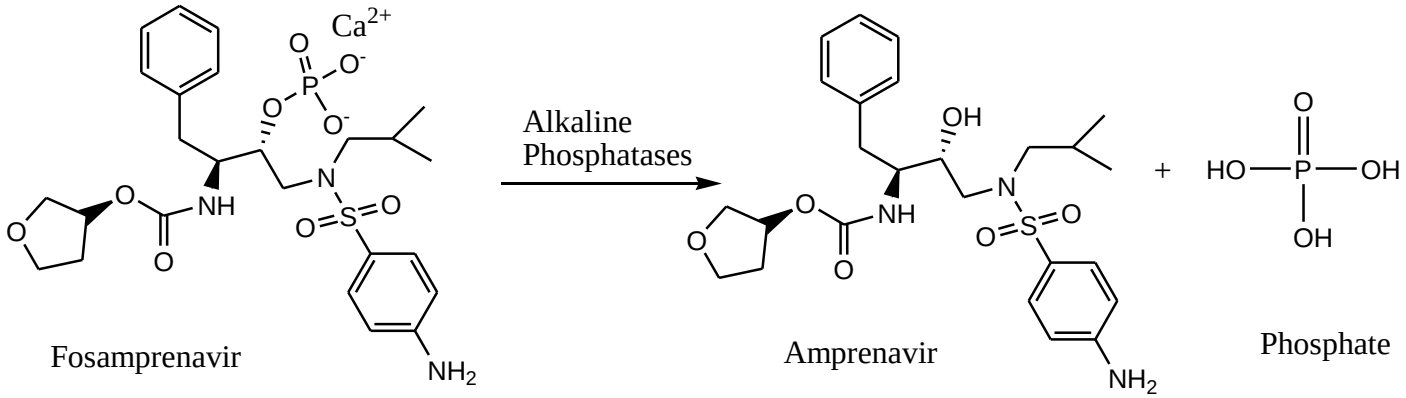
- Phosphate ester prodrugs present several advantages for formulation and development of poorly water-soluble compounds.
- They are chemically stable, need only a hydroxyl moiety, and enhance aqueus solubility to allow oral or parenteral administration.
- Phosphate ester prodrugs are readily hydrolyzed by endogenous phosphatases to release the pharmacologically active parent compounds and phosphates.
- Phosphorus is an essential mineral for normal body function and is found as phosphate in the body.
- Phosphates are extremely important in living cells. Phosphates are extensively circulated in the body and excreted in the urine and feces, and must be replaced in the diet.



- Amprenavir is a protease inhibitor with excellent antiretroviral activity and good tolerability in clinical studies, but it exhibited low water solubility.

- Fosamprenavir is a phosphate ester prodrug of amprenavir and was designed to increase water solubility and reduce the dosing burden from eight capsules to two tablets twice daily.

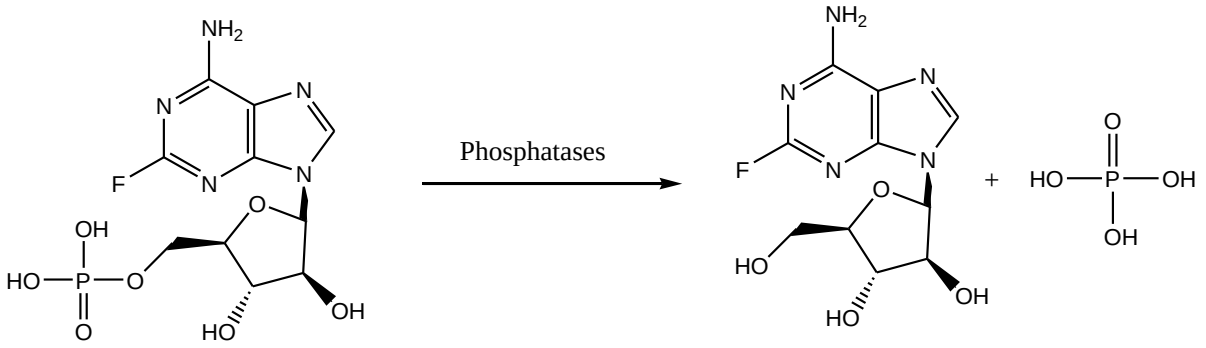
- It is rapidly and extensively hydrolyzed by alkaline phosphatase in the GI tract to yield amprenavir during absorption with minimal fosamprenavir reaching the systemic circulation.



- Fludarabine phosphate is a fluorinated nucleotide analog of the antiviral agent vidarabine, and currently used in the treatment of indolent B-cell malignancies such as follicular lymphoma and chronic lymphocytic leukemia.

- Fludarabine is also promising in combination with cytarabine for treating acute myelogenous leukemia.

- Upon administration, fludarabine is rapidly dephosphorylated to its active compound.



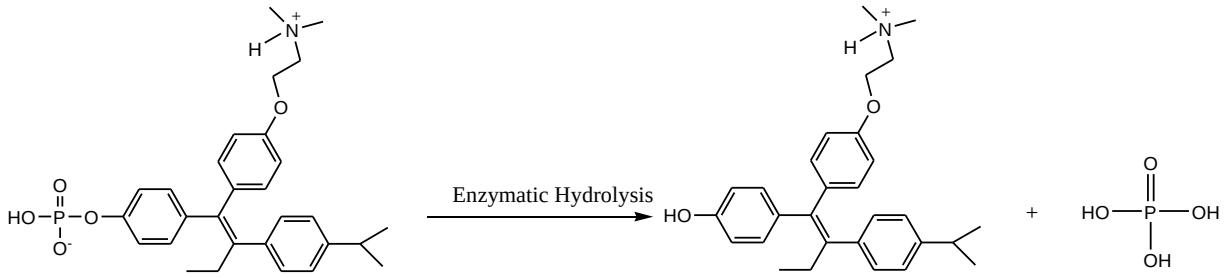
Fludarabine Phosphate Fludarabine Phosphate

- Miproxifene phosphate (TAT-59) is a triphenylethylene analog of tamoxifen.

- After oral administration, TAT-59 is immediately metabolized in the digestive tract to its active form DP-TAT-59 which has a high affinity for estrogen receptors.

- DP-TAT-59 suppresses the proliferation of human breast carcinoma cells even at concentrations lower than 1/30th of the level required for tamoxifen exhibiting this action.

- Unlike other phosphate esters, TAT-59 exhibits unusually low water solubility. The prodrug was successful because its solubility and dissolution rate were significantly higher than those of the parent drug.



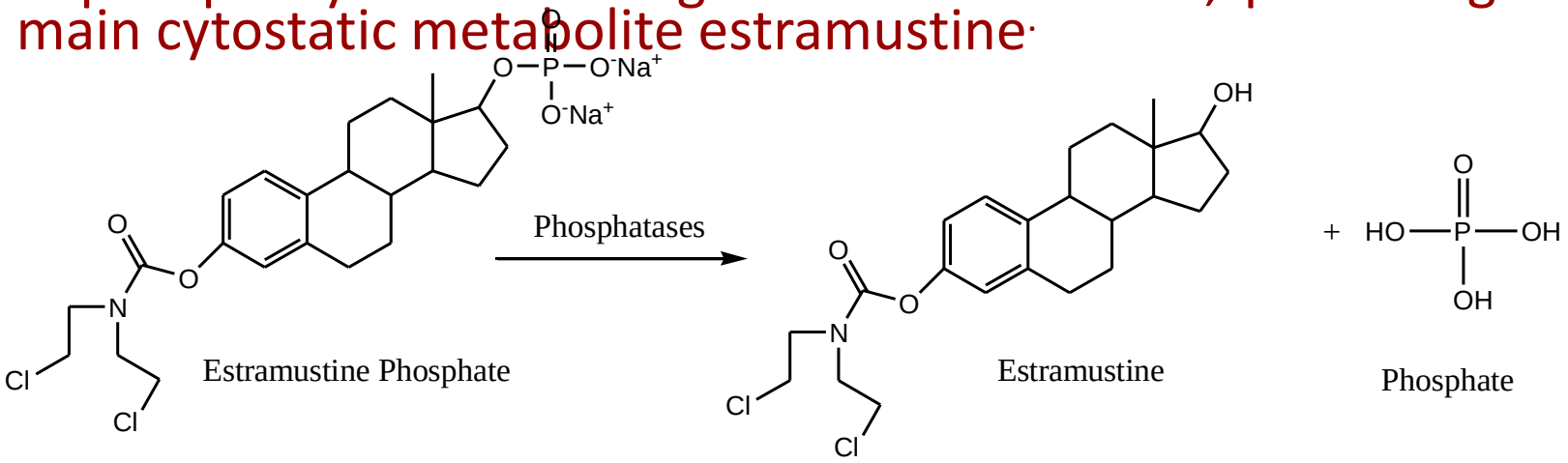
Miproxifene Phosphate (TAT-59) Miproxifene (DP-TAT-59) Phosphate

- Estramustine phosphate is a phosphate ester prodrug of the practically insoluble, non-ionizable parent drug estramustine.

- It is a cyctotoxic drug that has been used in the treatment of advanced prostatic carcinoma.

- A phosphate group was added at the 17-β position of the steroid D ring to increase the water solubility of the compound.

- Estramustine phosphate sodium is immediately dephosphorylated in the gastrointestinal tract, producing the main cytostatic metabolite estramustine.



Estramustine Phosphate

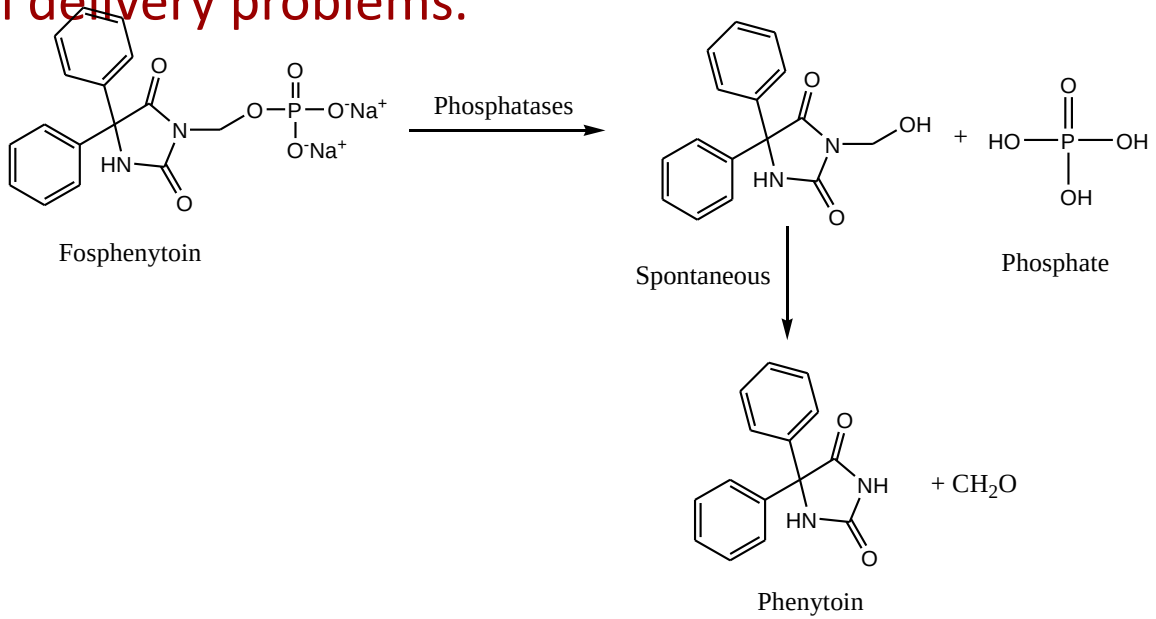
Estramustine

Phosphate

- Fosphenytoin, the disodium phosphate ester of 3-hydroxymethyl-5,5-diphenylhydantoin, is a newly developed prodrug for the parenteral administration of phenytoin which is a commonly used antiepileptic.

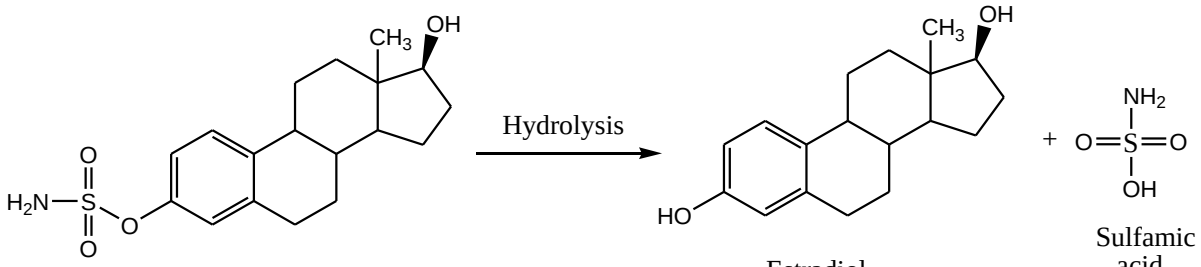
- Following either intramuscular (i.m.) injection or intravenous (i.v.) infusion, fosphenytoin is converted to phenytoin and formaldehyde by blood and tissue phosphatases with approximately 100% bioavailability.

- Fosphenytoin is an excellent example of using a prodrug to overcome parenteral delivery problems.



C. Sulfamate Esters

- Estrogens are used as oral contraceptives or hormone replacement therapy in postmenopausal women.
- Natural estrogens are extensively metabolized in the liver and this biotransformation decreases their therapeutic effects.
- Estrogen sulfamates are derivatives of steroid estrogens where the phenolic hydroxyl group is substituted with an amino sulfonyl group.
- They are new synthetic estrogens that do not undergo biotransformation in the liver and therefore may be used in much smaller doses to achieve the same therapeutic effect.
- Sulfamic acid prodrug of estradiol possesses higher systemic oral estrogenic activity and significantly reduced hepatic estrogenicity in comparison to the parent steroid.
- It undergoes systemic hydrolysis in the erythrocytes, releasing estrogen and sulfamic acid that is excreted in urine.



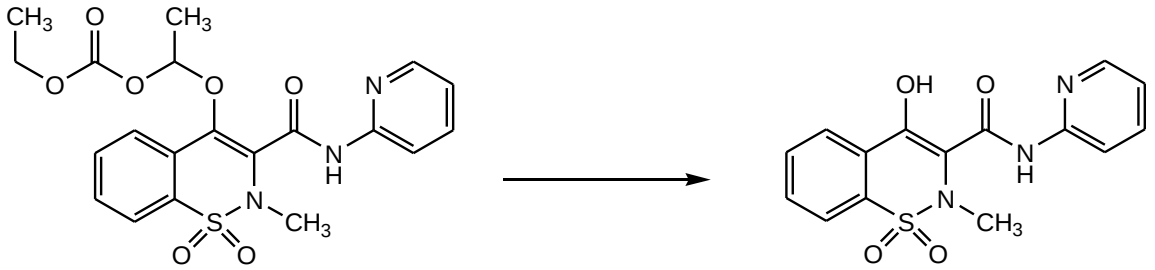
Estradiol Sulfamate

Estradiol

Sulfamic acid

D. Ether Prodrugs

- Ampiroxicam is a prodrug of one of the most potent NSAIDs, piroxicam.
- It has been developed to minimize the gastric irritation caused by piroxicam that acts by inhibiting the enzyme cyclooxygenase, a critical enzyme in prostaglandin synthesis.
- Piroxicam has low solubility in both polar and nonpolar media, and low lipophilicity. These properties result in low permeability.
- Ampiroxicam was completely converted to piroxicam after oral administration in man.
- Incorporating a moiety at the enol functionality led to elimination of the prostaglandin synthesis inhibitory activity, resulting in improved gastric tolerance.



Ampiroxicam

Piroxicam