Pro-Drugs

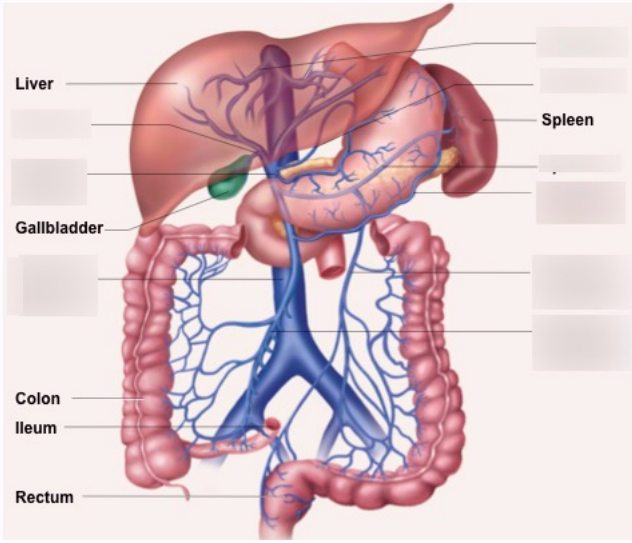
Permeability and Drug Metabolism, Kinetics

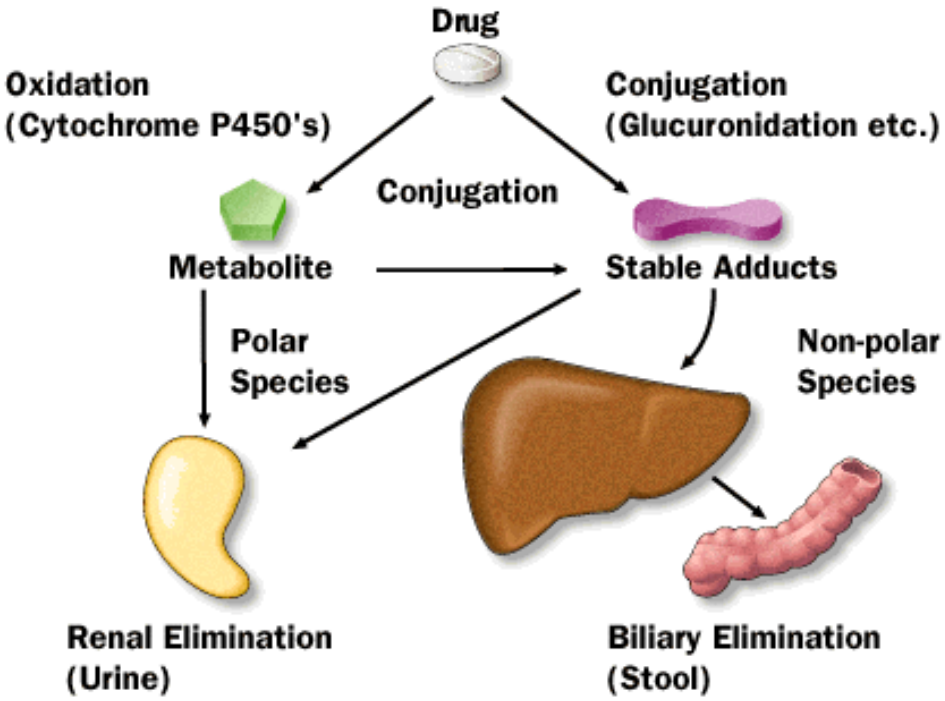
Nucleoside Analogs, CNS

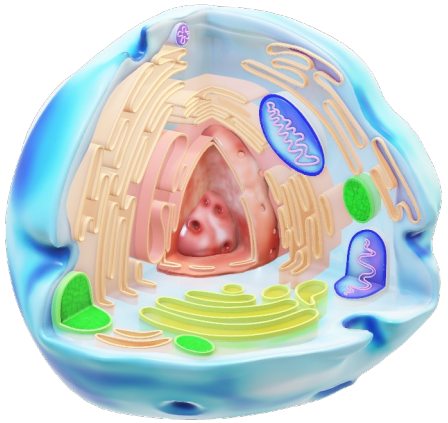
Paxlovid: Nirmatrelvir + **Ritonavir**

Drug transformations

- Formulation: active ingredient (precursor), salts, excipients, main ingredient gets dissolved
- Permeation : neutral form of a drug gets absorbed from GI, may be pH dependent. Result: drug in plasma
- Metabolism: Hepatic portal vein brings the drug from the gut to liver by **hepatic portal vein system** (1st pass metabolism, 2nd pass), further transformation in cells
- The remaining ingredient, metabolites reach blood plasma

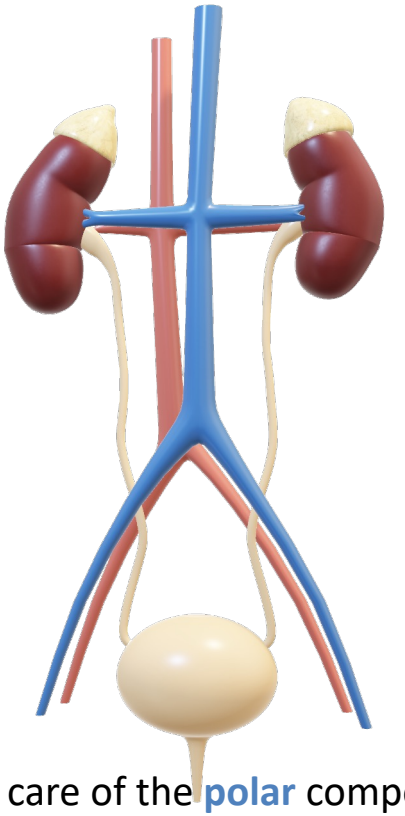




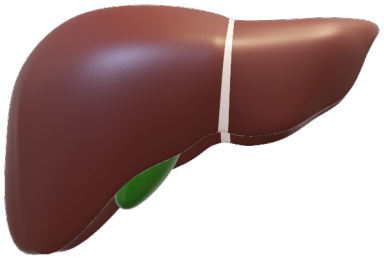


Sorting xenobiotics by lipophilicity

- Polar and charged molecules – *renal clearance* (fast).
  *Probenecid (OAT inh.) increases excretion of uric acid but blocks renal excretion of and other drugs.
- BBB blocks passive permeation of the polar and charged compounds to CNS
- Hydrophobic compounds are (mostly) converted into polar ones by *metabolism*. Cyp450s modify hydrophobic compounds to more polar forms.



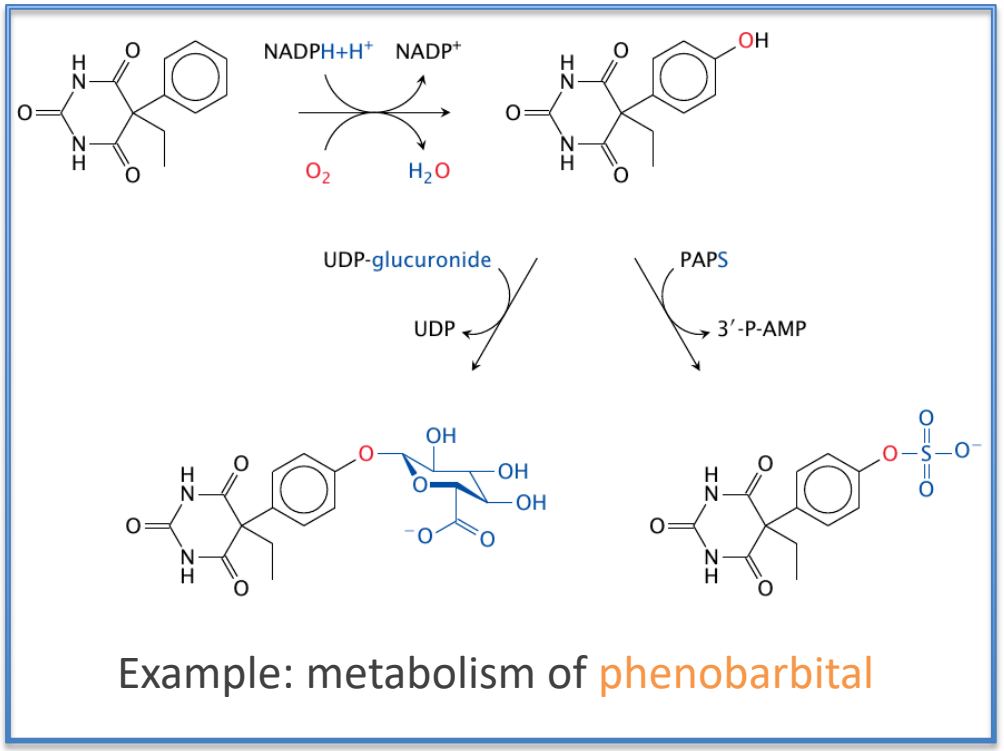
Kidneys take care of the **polar** compounds



Liver takes care of the hydrophobic compounds, either they become polar or excreted via **feces**

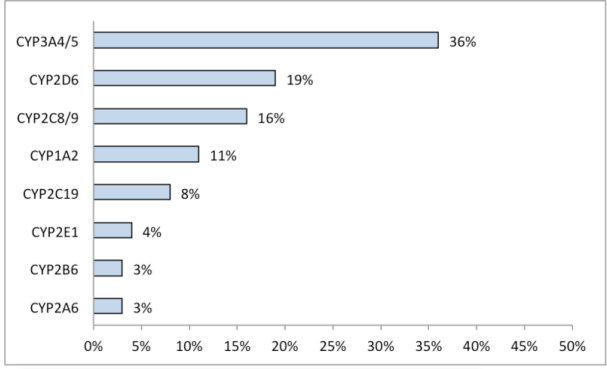
Metabolism of Drugs: Phases 1 and 2

- P1: Functionalization – adding a functional group for further reactions, or cleavage. Injection, IM or SQ skips P1
  - Oxidation
  - Hydrolysis
  - Reduction
- P2: Conjugation
  - Glucuronidation
  - Sulfation
  - Acetylation
  - Glutathione Conjugation
  - Methylation
  - Amino Acid Conjugation
- P3: ATP-dependent exporter from cells -> Urine or Bile



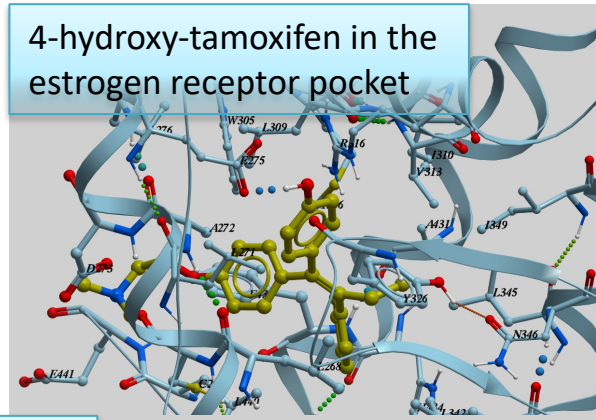
Cytochrome P450

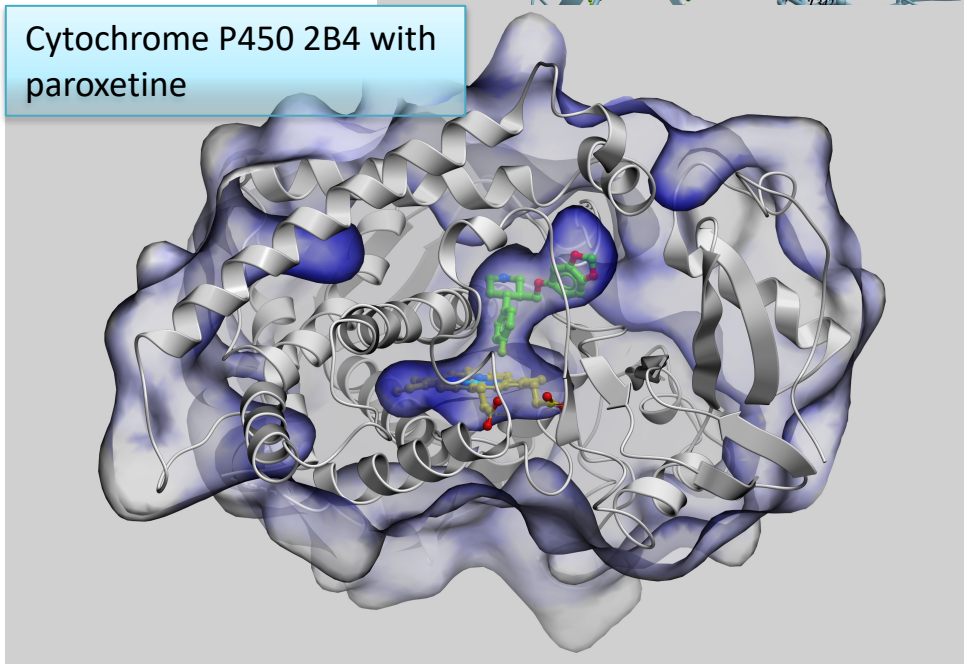
as drug-inducers. Drugs inhibiting CYPs



- **R-H** + O_2 + 2e => **R-OH** + H_2O (uses NADPH)
- Adding One Oxygen: **mono-oxygenase**
- R-OH is then modified by polar *sulfate or sugars*
- **Inhibitors**: bergamottin, dihydroxy-bergamottin, and paradicin-A in grapefruit juice (and other juices) have been found to *inhibit* CYP3A4 , may lead to overdose
- Saint-John's Wort *induces* CYP3A4, but also *inhibits* CYP1A1, CYP1B1, and CYP2D6, - no action
- Tobacco smoking induces CYP1A2, ..
- Other **inducers**:

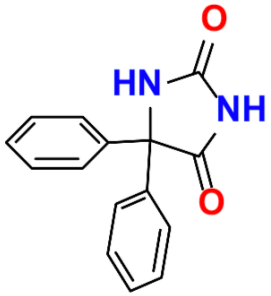
CYP	Drug Inducer	Fold-ind.
1A2	PPI (Omeprazole, ..)	14-20
2B6	Phenobarbital	5-10
2C8,9 2C19	Rifampin	2-4 20
3A4	Rifampin; Carbamazepine	4-31





Metabolism Converts a Fat-Soluble Compound to A Water Soluble Compound

Metabolism is mostly an Enzymatic Process

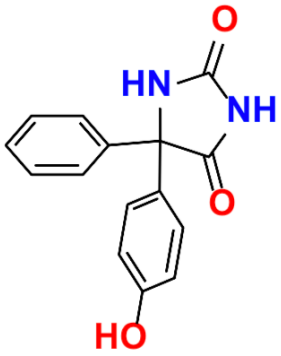


Phenytoin
An Anticonvulsant

Highly Lipophilic
Insoluble in Water

Functionalization

Cytochrome P450

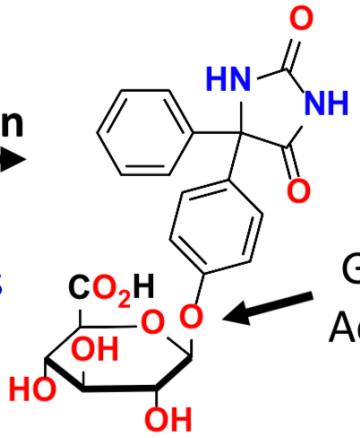


4-Hydroxyphenytoin

Slightly Water Soluble

Conjugation

Glucuronsyl
Transferases



Glucuronic
Acid Moiety

Glucuronide Conjugate of
4-hydroxyphenytoin

Very Water Soluble

Metabolism of a Drug is a Detoxification Pathway!!

Allows the human body to cope with exposure to foreign "nasty" compounds

Leads to inactivation of the active drug

Excretion

Credit: Satjit Brar, Pharm.D., Ph.D. , Lecture on Drug Metabolism, Course: SPPS 263A, 2020

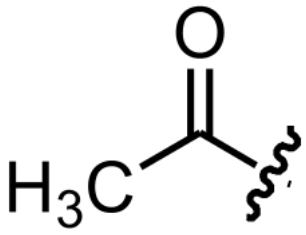
Problematic permeability

- Natural products (big and polar)
  - permeability a major problem
- Peptidomimetics (long and polar)
  - permeability a major problem
- RNAi, miRNA, siRNA and its precursors
  - possible solutions: liposome, nanoparticle, ..
- CNS targets (tight barrier)
  - Blood-brain permeability a major problem

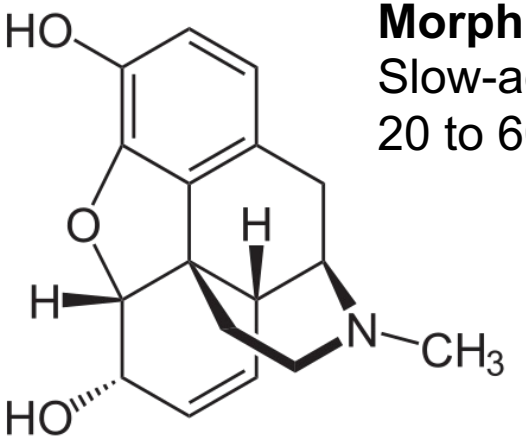
Pro-Drugs

- **”a pharmacologically *inactive* compound that is *converted* to an *active* drug by a metabolic biotransformation”** (Albert, “Selective Toxicity”, 1951)
- Possible Goals:
  - Improve permeability by adding an enzymatically cleavable group, e.g. Heroin vs Morphine
  - Add a carrier to the right destination, e.g. Valcyclovir for CNS
  - Deliver a neutral precursor, then make a highly charged drug from a prodrug *inside* the cell, eg. Acyclovir

Morphine vs Heroin



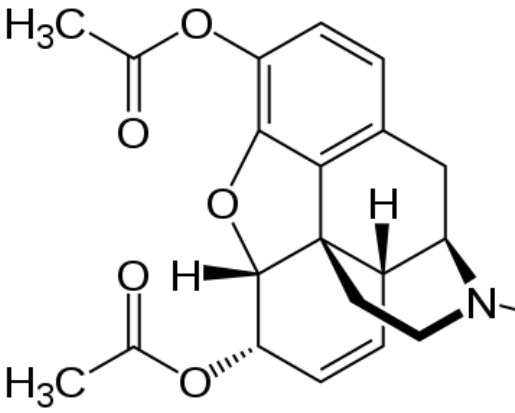
Acetyl group



Morphine
Slow-acting, Onset: 20 to 60 min

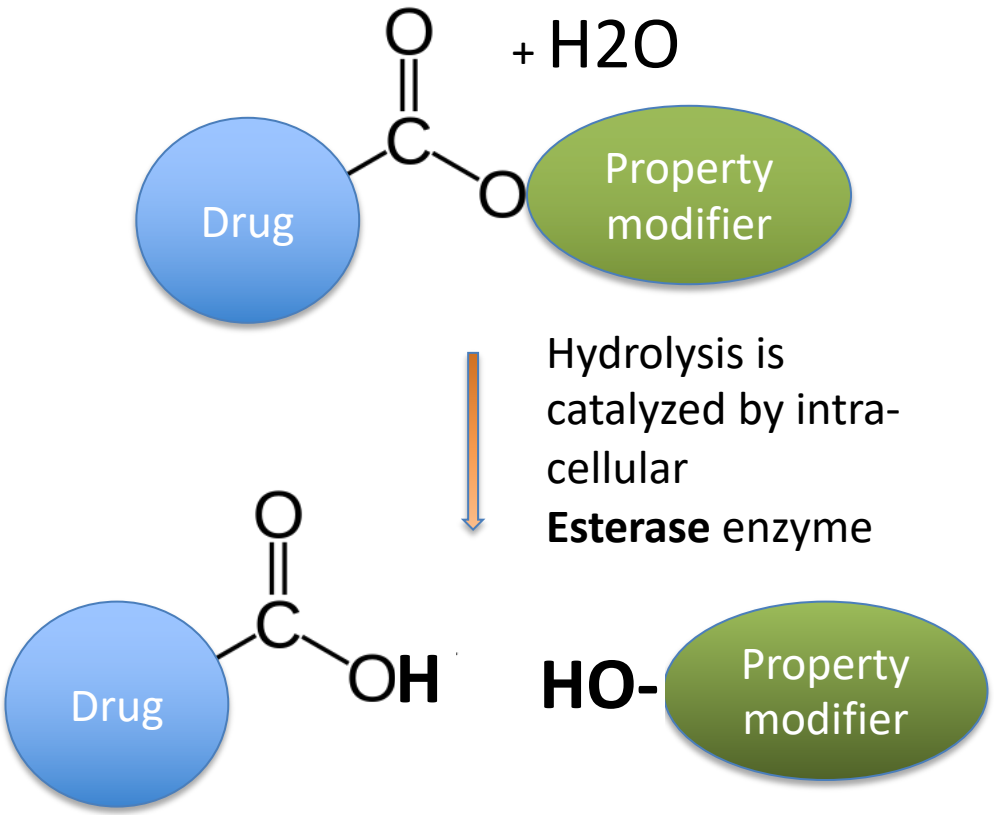
Heroin "pro-drug" activation mechanism

- 1st pass metabolism in liver deacetylates it into morphine, but ..
- if injected, it avoids 1st pass metabolism
- Acetyl groups increase CNS permeation (it is more fat-soluble)
- Gets deacetylated in the brain

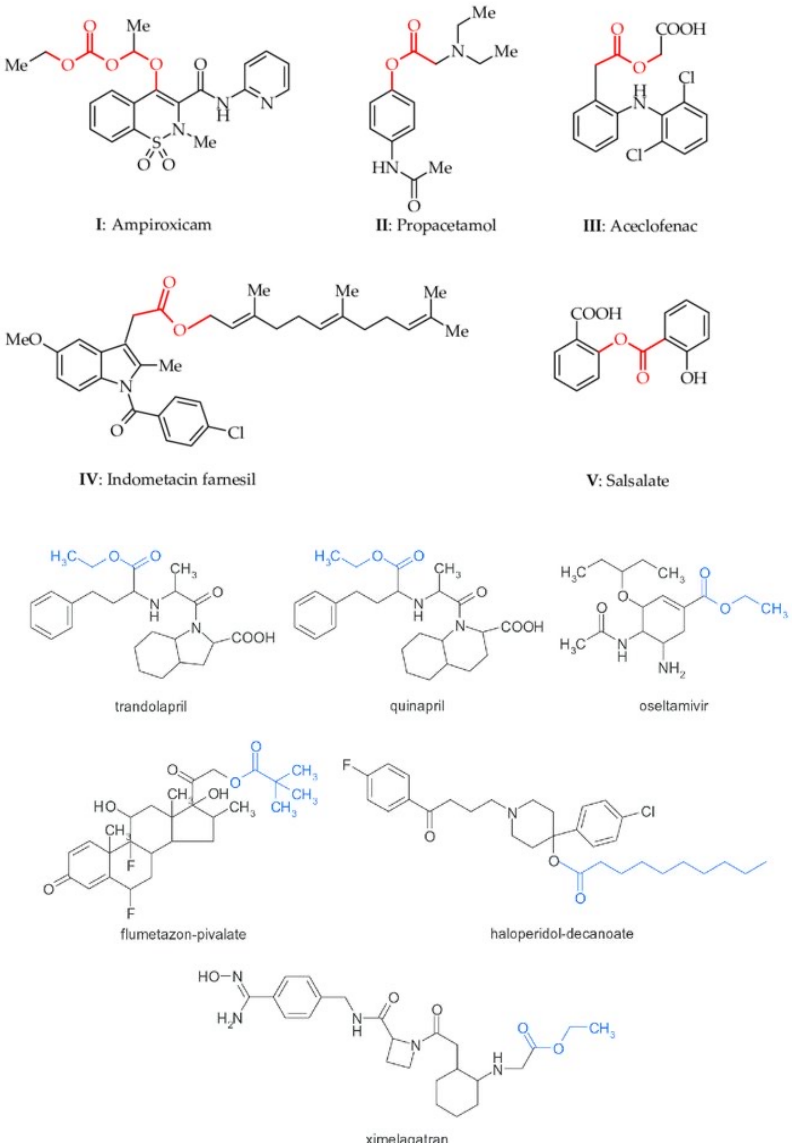


Heroin
Diacetyl-morphine
IM, SQ, oral
Onset: 1-2 min
2 to 3 times more potent than morphine

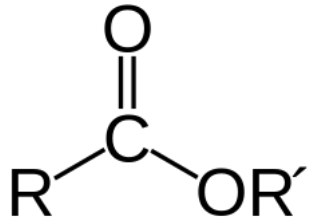
Ester-prodrugs



The Ester moiety can be flipped to create Drug-OH and Modifier-COOH products

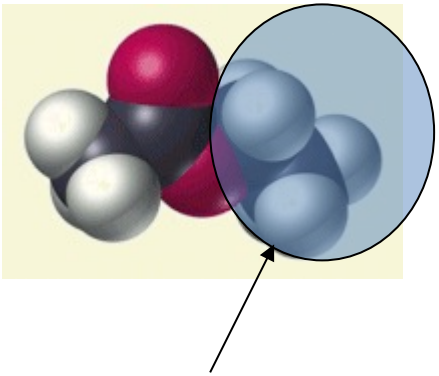


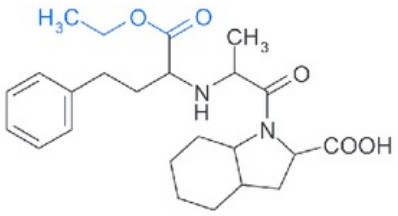
Esters and hydrolysis

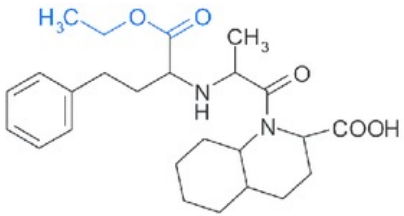


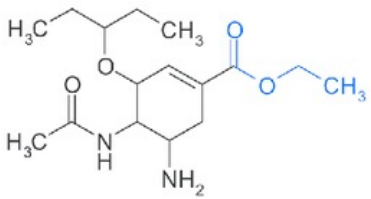
A carboxylate ester

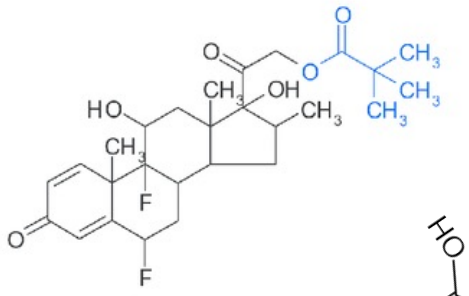
- Ethyl esters are frequently used as a pro-moiety, other carboxylic acids are OK too
- They can be hydrolyzed *non-enzymatically* or with cellular **esterase** enzymes

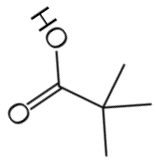

A lipophilic tail

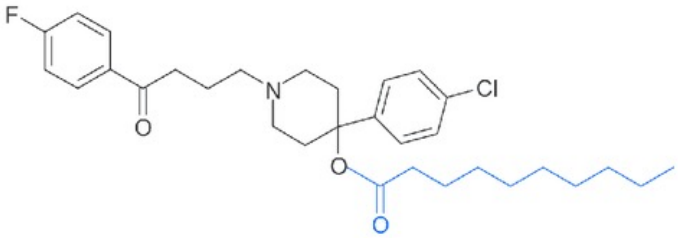

trandolapril


quinapril


oseltamivir


flumetazon-pivalate

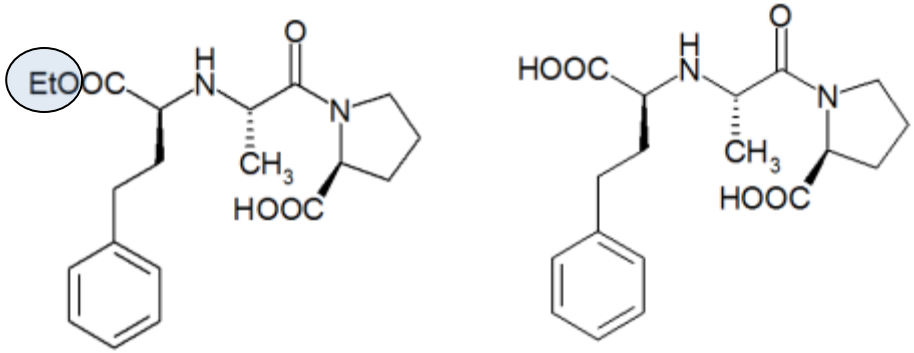

Pivalic acid


haloperidol-decanoate

Examples: Prodrugs to fix **permeability**

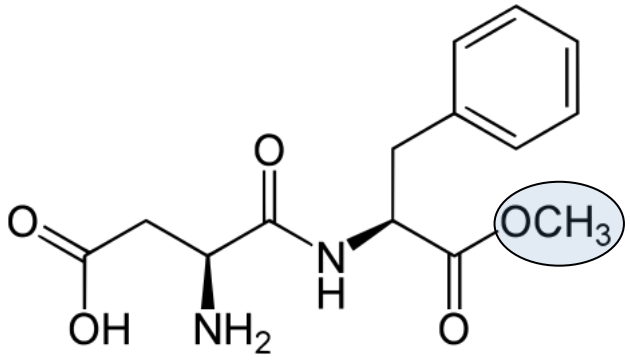
- Enapril (ACE inhibitor, hypertension) is hydrolyzed to Enaprilat by esterase. Byproduct: ethanol

Enapril + H2O to Enaprilat + ethanol



- Aspartame/NutraSweet

  Byproduct: methanol



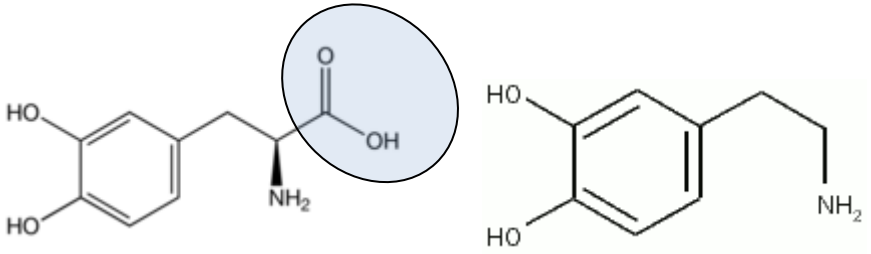
+H2O

Beware of methyl esters

Prodrug: how to trick the Brain

- **Pretend to be an amino acid**
  - Prodrug Strategy: Attach a CNS transportable amino acid to the CNS-active ingredient

- **Levodopa to Dopamine by *decarboxylase***
  - Brain has a *specific transport* system for L-amino acids

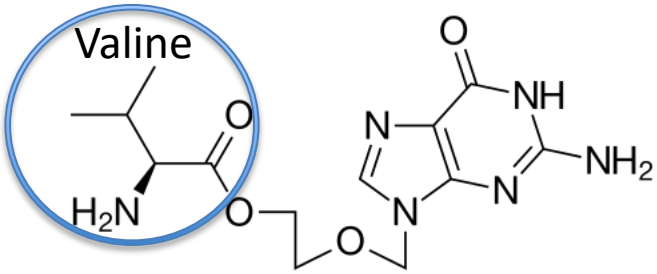


Dopamine

- Many other tricks ..

Acyclovir improved: Valacyclovir

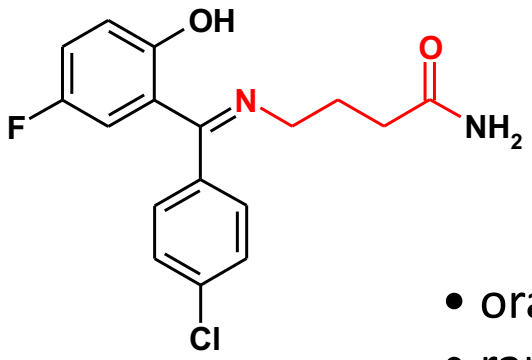
- Adding one more group to the pro-drug
- *Problem*: acyclovir has poor oral bioavailability (15-20%)
- Design: attach valine ester to improve bioavailability
- P1 liver metabolism: esterase cleaves off Valine



Bioavailability: 55%

Pro-drug: Increased BB permeability

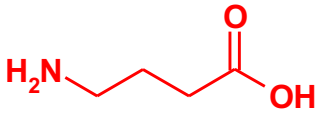
Prodrug:



Progabid

- orally active
- rapid penetration of blood-brain barrier

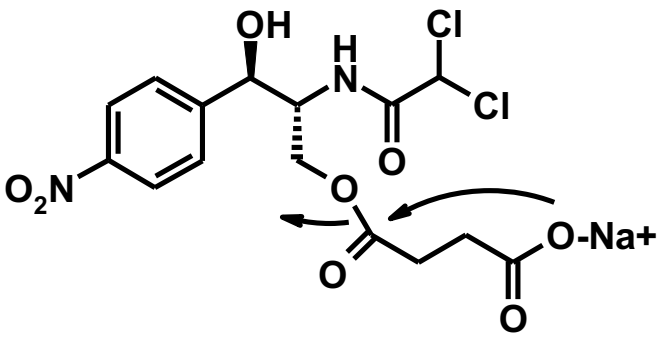
Drug:



GABA (gamma-amino butyric acid)

- anti-convulsive neurotransmitter
- orally inactive
- no penetration of blood-brain barrier

Prodrugs to improve solubility

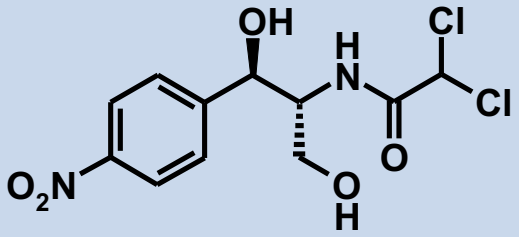


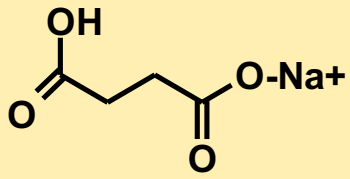
Chloramphenicol Succinate

Esterase

or Water

Chloramphenicol





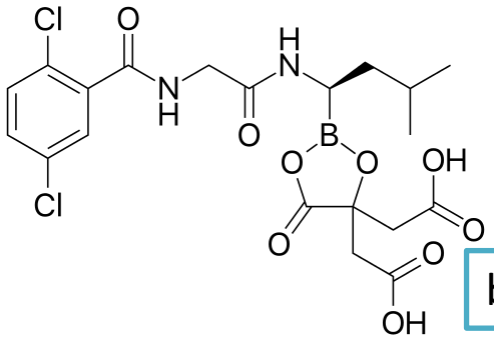
Sodium succinate

Multiple myeloma, Protecting Covalent Proteasome Inhibitor, **Ixasomib citrate**

Goal: protect a **reactive boronic acid** functional group, ensure high protein binding

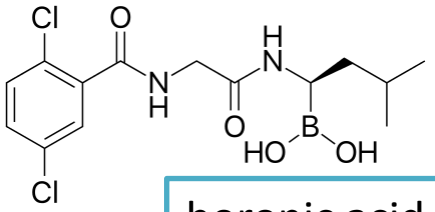
Ninlaro is a 2-nd gen proteasome inh (PI), first **oral** PI, better than 1st-gen Bortezomib, or IV Carfilzomib

Ixazomib citrate (**Ninlaro**,MLN9708), the **prodrug**



boronic ester

Ixazomib (Takeda, 2016)



boronic acid

IC is taken orally as a boronic ester prodrug; ester rapidly hydrolyzes under physiological conditions to ixazomib inside cell. Absolute bioavailability is 58%, and highest blood plasma-concentration of ixazomib is reached after one hour. Plasma protein binding is 99%

MOA: Covalently and reversibly inhibits the protein proteasome subunit β5. Induces apoptosis, Lenolido-synergy

ADRs: Common side effects of the **ixazomib+lenalidomide+dexamethasone** study therapy included diarrhoea (42% vs 36% under placebo+Len+Dex), constipation (34% versus 25%), thrombocytopenia (low platelet count; 28% vs 14%), peripheral neuropathy (28% vs 21%), nausea (26% vs 21%), peripheral oedema (swelling; 25% vs 18%), vomiting (22% vs 11%), and back pain (21% vs 16%).

Multi-Step Prodrugs : Nucleoside analogs

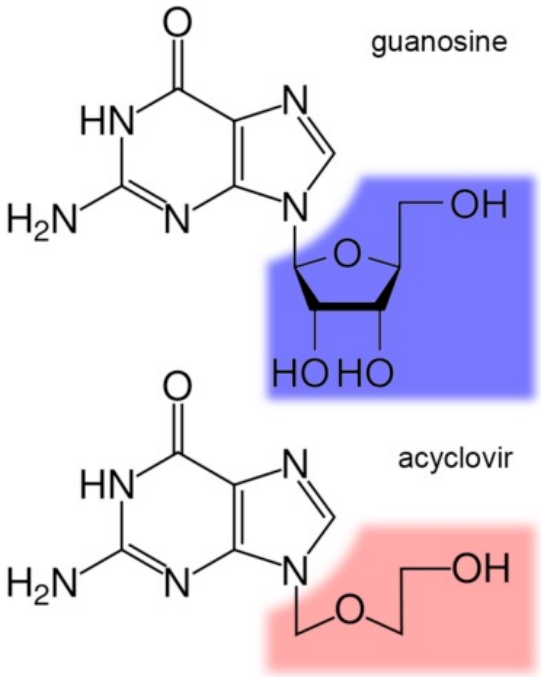
Acyclovir/ACV (HSV1,2, Varicella zoster V, EBV)

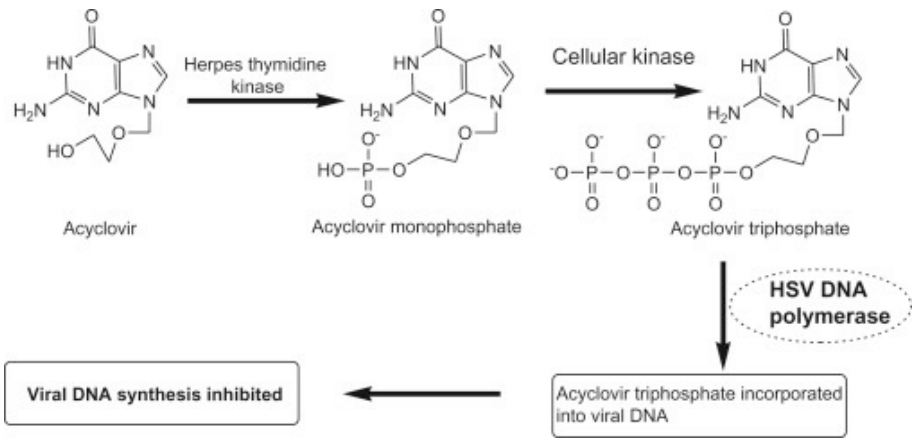
- Inhibitor of viral DNA polymerase is *Acyclovir-tri-phosphate (ACV-TP)*

Prodrug Aims**:** to administer an **uncharged** (no phosphate) **precursor of nucleoside triphosphate analog** and to be **active only inside infected cells**

Steps:

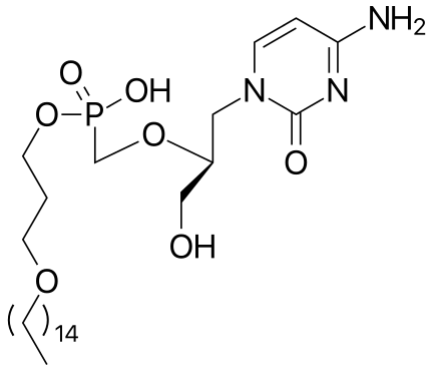
- ACV drug gets into many cells and is not activated
- Only in Herpes-infected cells there is **viral thymidine kinase** that adds the 1st phosphate ACV -> ACT-MP
- Host kinases add two more : ACV-MP -> **ACT-TP**

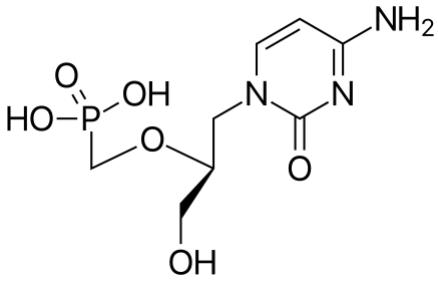




Antiviral: BrinCidofovir/Tempexa vs Cidofovir/Vistide

prodrug





CMV/cytomegalovirus retinitis

Brincidofovir (oral) approved in the US in June 2021
Drug against dsDNA viruses and associated diseases: ***Smallpox* caused by Variola virus**, *CMV* and *Ebola* (2014)

Adding a lipid leads to release Cidofovir inside the cell, not in blood plasma, higher intracellular concentration

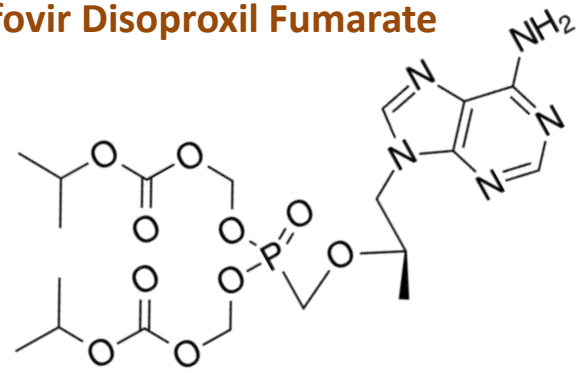
Cidofovir (topical or injectable/IV) approved in the US in June 1996
Very nephrotoxic.

Cidofovir itself is a prodrug. Its active metabolite, **cidofovir diphosphate**, inhibits viral replication by selectively inhibiting viral DNA polymerases

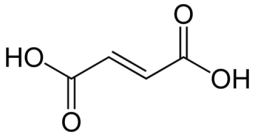
Tenofovir disoproxil, a nucleotide analog Hepatitis B,HIV

Targets: Reverse Transcriptase, Polymerases. Goal of prodrug: keep and protect 1st phosphate

Tenofovir Disoproxil Fumarate

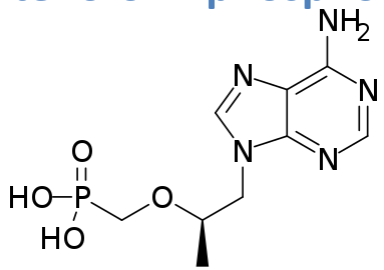


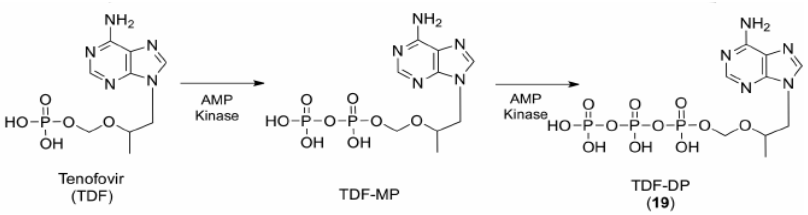
Fumaric Acid



well tolerated with low discontinuation rates

tenofovir phosphonate

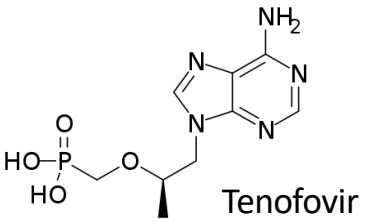




Tenofovir disoproxil is a pro-drug form of tenofovir phosphonate, which is liberated intracellularly and converted to tenofovir disphophate.[21] It is marketed by Gilead Sciences (as the fumarate, abbreviated TDF)

ADRs of TD: potential onset of **lactic acidosis or liver damage.** Long term use of T.D. is associated with nephrotoxicity (as Fanconi syndrome) and bone loss

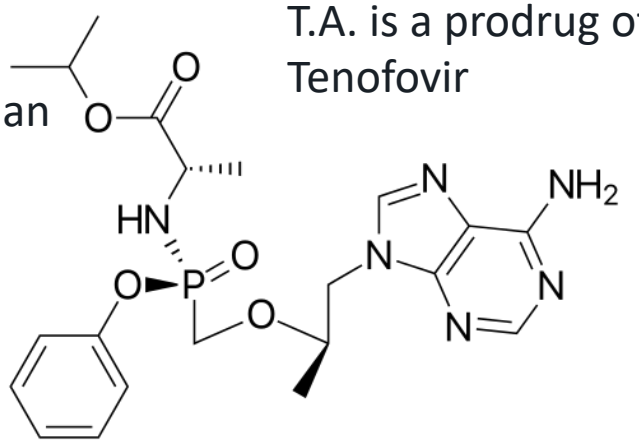
Tenofovir alafenamide fumarate, Vemlidy,



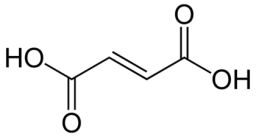
Tenofovir

T.A. is a prodrug of Tenofovir

Alafenamide is an alanine ester



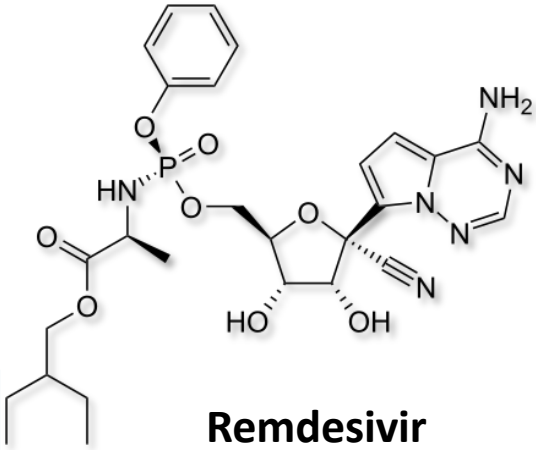
Fumaric Acid



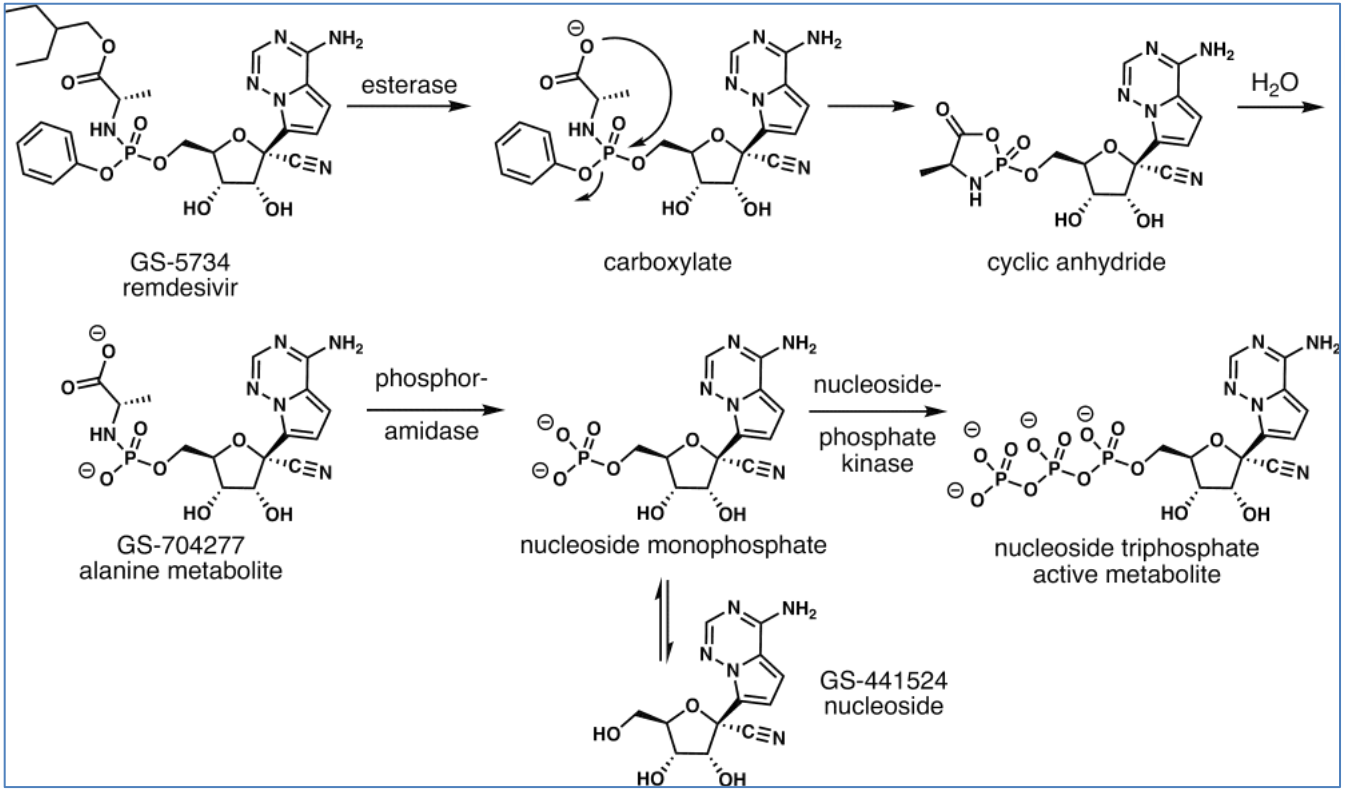
Tenofovir **Alafenamide** Fumarate, TAF, has greater antiviral activity ***and better distribution into lymphoid tissues*** compared to Tenofovir **Disoproxil** Fumarate

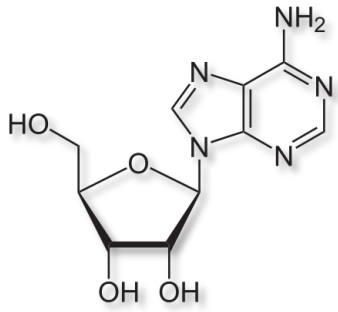
Similar Prodrug: **Remdesivir** vs Covid-19

- First developed for Hepatitis C, investigated for Ebola and Marburg
- Contains the 1st phosphate



Remdesivir





Adenosine