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Activation of Prodrugs Depend on the Metabolism of These Prodrugs

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Abstract

Prodrugs depend on enzymatic processes, essentially in the liver, but can also occur in other tissues to release the active metabolite. These metabolic biotransformations are often enzymatically controlled, ensuring the drug becomes pharmacologically active at its site of action. Metabolism may occur at the target site (e.g., in viruses, where drugs are phosphorylated) or in the liver or other tissues. For example, codeine is activated by demethylation to morphine, which is a more active analgesic than codeine. Clopidogrel oxidized to 2-oxoclopidogrel which is active and 2-oxoclopidogrel which is metabolized in two active thiol metabolite. Enalapril is a prodrug that is metabolized to enalaprilat, the active form. L-Dopa is a prodrug that is converted into dopamine in the brain by decarboxylation. Azathioprine is metabolized to mercaptopurine, which is immunosuppressive. Sulfasalazine is a prodrug metabolized by azoreductase and converted to 5-aminosalicylic acid and sulfapyridine, which are more active than sulfasalazine. Prontosil is a prodrug converted into sulfanilamide, which is more active than prontosil. Salicin is a glycoside that is metabolized into salicylic acid, which is active as an analgesic. Valacyclovir is metabolized into acyclovir, which is an active antiviral.

Keywords: prodrugs, active drugs, metabolism, oxidation, hydrolysis, dealkylation

1. Introduction

Codeine is a narcotic drug when metabolized by dealkylation (demethylation), of codeine, which is used as antitussive more than analgesic when metabolized by oxidative dealkylation convert into morphine which used a narcotic analgesic more than codeine. This process activates the codeine by changing it into morphine and makes it more active than codeine.

Clopidogrel is a prodrug, meaning it is inactive needs to be metabolized into an active form to be effective, this process occur in the liver, where is

the clopidogrel oxidized in clopidogrel which further metabolized to the active thiol metabolite, this metabolite (thiol metabolite) binds to receptor on platelets which inhibit ADP from binding and preventing platelet aggregation.

Enalapril is a prodrug metabolized in the liver by its active form, enalaprilat, which is an ACE inhibitor that is currently available in USA. The metabolism occurs via cleavage of its ester group by the esterase enzyme and converts enalapril to enalaprilat, which is active as an ACE inhibitor.

Levodopa is a prodrug which is able to cross blood-brain barrier due to resemble amino acid; so penetrate to the brain, hence L-Dopa metabolized through several pathways, the decarboxylation it is the main process where L-Dopa convert to dopamine which is unable to cross the blood-brain barrier; so that L-Dopa which is prodrug is preferable to used in treatment of parkinsonism.

Azathioprine is an immunosuppressant that undergoes metabolism in the body through multiple pathways, primarily converting to 6-mercaptopurine, further metabolized by various enzymes into an active metabolite via the hypoxanthine phosphoribosyl transferase pathway, where 6-mercaptopurine is converted into its metabolite form 6-thioguanine nucleotide, which is incorporated into DNA and RNA, disrupting cellular processes and causing immunosuppression.

Sulfasalazine is a prodrug which used orally and inactive compound which is metabolized (hydrolyzed) in the intestine and convert into two active compounds (sulfapyridine) which is antibacterial and 5-amino salicylic acid which is anti-inflammatory, the 5-amino salicylic acid not absorbed from intestine and remain in the colon to treat the ulcerative colitis, in addition to antibacterial agent sulfapyridine.

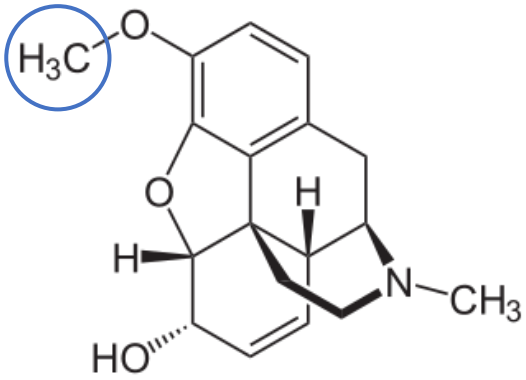
Prontosil is the compound which is revolute the sulfa drugs era where it is a red dye act as a prodrug i.e. inactive invitro but in vivo metabolized where it reduced by reductase enzyme which result from intestinal flora and cleavage the prontosil into sulfanilamide which is active antibacterial and the first sulfa drug detected and try amino benzene, the other compound resulted from prontosil.

Salicin found in willow park is metabolized into salicylic acid and sugar part where the salicin is a glycoside (sugar part and non-sugar part), the salicylic acid is non-sugar part which has anti-inflammatory and analgesic properties, the cleavage of salicin in gastrointestinal tract and the salicylic acid is metabolized via bind with glycine and form salicyluric acid which is easily excreted, which easily detected in the urine.

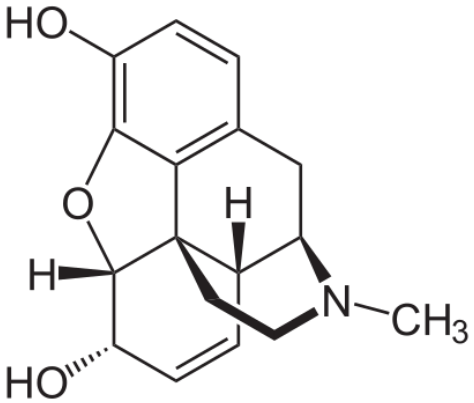
Valacyclovir is a prodrug which converted to acyclovir and L-Valine through first pass intestinal and/or hepatic metabolism, acyclovir is the active drug which is also activated by phosphorylation to act as antiviral drug, and β-Lactamase inhibitors e.g., penicillins and cephalosporins, many of them are considered as prodrugs, e.g., ampicillin and amoxicillin, where the amino group of ampicillin may be metabolized via oxidative deamination and converted to benzylpenicillin (penicillin G). Also, amoxicillin, which has a phenolic OH and an amino group, may be converted to benzylpenicillin (penicillin G); hence, the metabolism of many drug derivatives may result in the lead drug of the class, e.g., penicillins and cephalosporins.

2. Pharmacology and Chemistry

(1) Codeine:



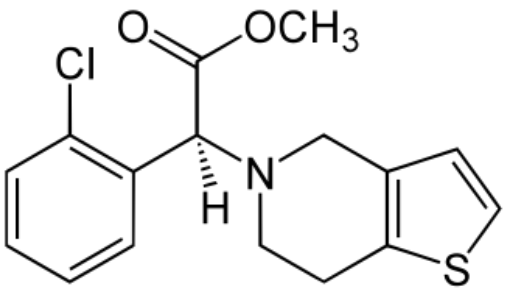
Codeine



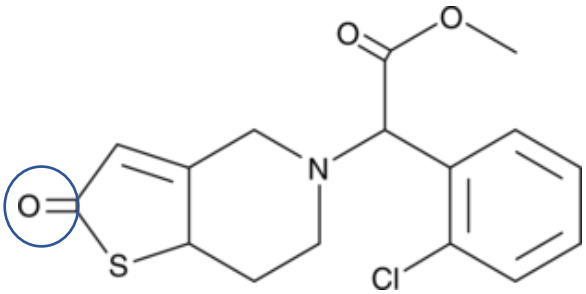
Morphine

Codeine is an opioid compound used to relieve mild and moderate pain in people who suffer from moderate pain and know respond to non-steroidal anti-inflammatory drugs (NSAIDs). Codeine is used to relieve cough and has a moderate analgesic compared to morphine; so codeine is metabolized by oxidative dealkylation and converted to morphine, which has more analgesic activity than codeine.

(2) Clopidogrel:



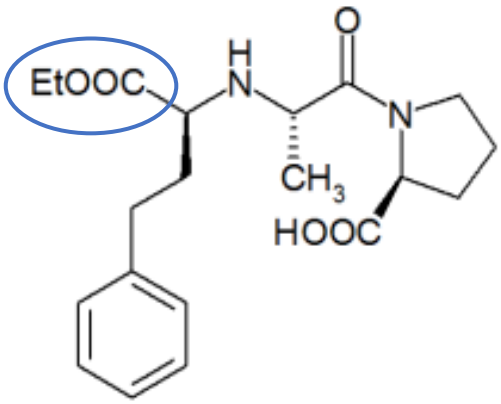
Clopidogrel



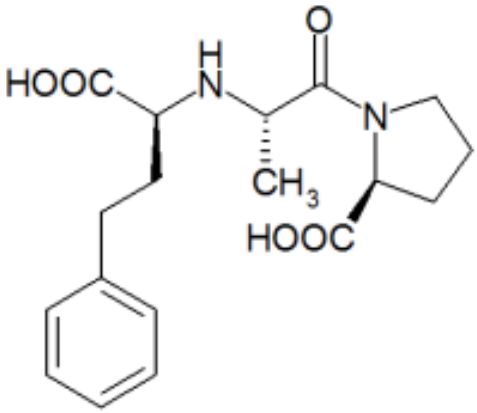
Oxoclopidogrel

Clopidogrel is metabolized into oxoclopidogrel, which is active as an antiplatelet clopidogrel approved for managing unstable angina which may cause myocardial infarction (MI), where the oxoclopidogrel prevents platelet aggregation and inhibits clot formation. In addition, into the fibrinolytic of the oxoclopidogrel which is more active than clopidogrel.

(3) Enalapril:



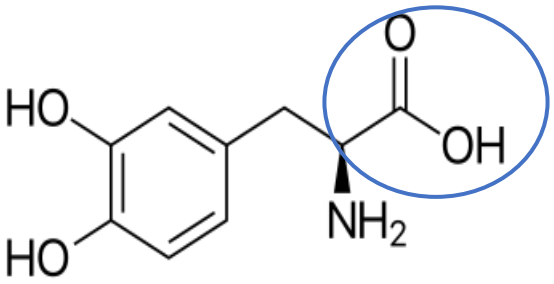
Enalapril



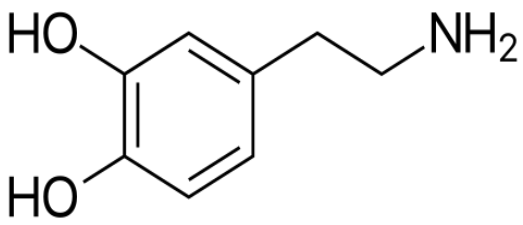
Enalaprilat

Enalapril is an angiotensin-converting enzyme inhibitor (ACE I) which converts into enalaprilat, the active metabolite, which treat the hypertension via inhibit the vasoconstriction of blood vessels; hence increases the blood supply and oxygen to the heart.

(4) L-Dopa:



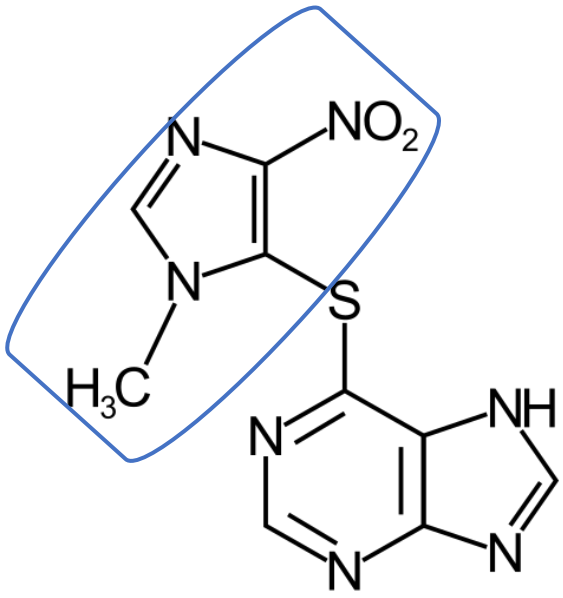
L-Dopa



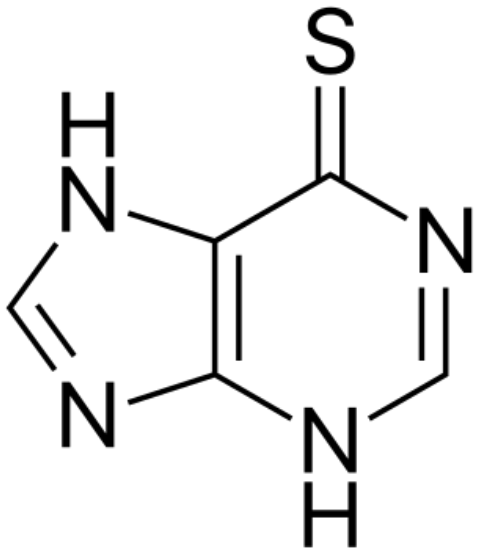
Dopamine

L-Dopa used to treat the motor symptoms of Parkinson's disease, L-Dopa is similar to amino acids; hence carried by amino acid carrier and cross blood-brain barrier, dopamine is lipophilic more than L-Dopa and not cross the blood-brain barrier; so the L-Dopa metabolized in the brain by decarboxylase enzyme and converted to dopamine which treated the parkinsonism where helps to alleviate symptoms like tremor, stiffness, and slow movements and may treat encephalitis or brain injury which maybe cause parkinsonism.

(5) Azathioprine:



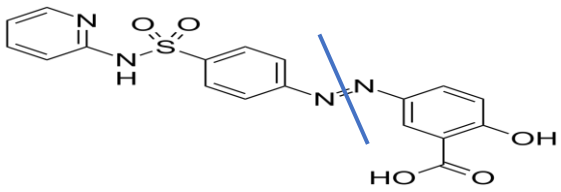
Azathioprine



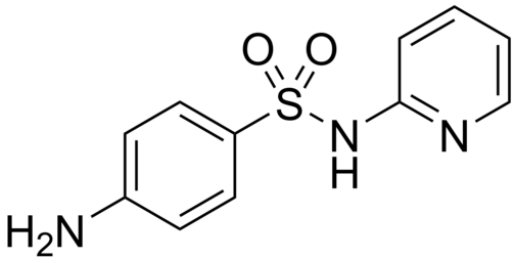
6-Mercaptopurine

Azathioprine is an immunosuppressive after metabolized into 6-mercaptopurine. It is used to treat rheumatoid arthritis, and granulomatosis with polyangiitis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus (SLE) and in kidney transplant to prevent rejection; hence, as azathioprine is considered a prodrug needs to be metabolized to active 6-mercaptopurine.

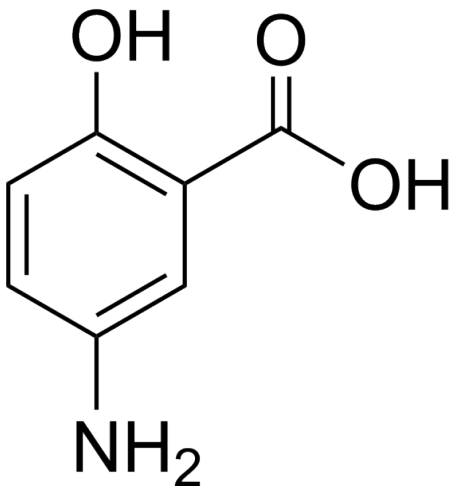
(6) Sulfasalazine:



Sulfasalazine



Sulfapyridine

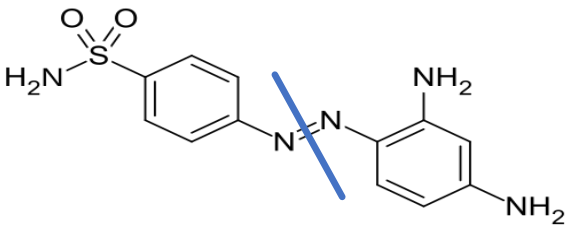


5-aminosalicylic acid

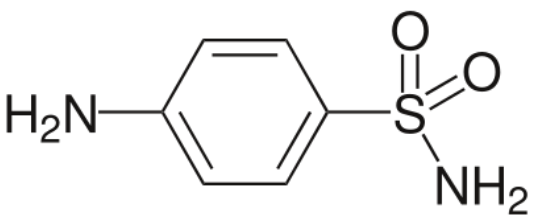
Sulfasalazine is a prodrug that needs to be cleaved between the two nitrogen to result in 5-aminosalicylic acid, which is anti-inflammatory and analgesic, and sulfapyridine, which is antibacterial.

Sulfasalazine is used in the treatment of inflammatory bowel disease, including ulcerative colitis and Crohn's disease. It is also indicated for use in rheumatoid arthritis and used in other types of inflammatory arthritis, e.g., psoriatic arthritis and reactive arthritis; so the sulfasalazine inactive prodrug needs to be activated by metabolism to become active compounds.

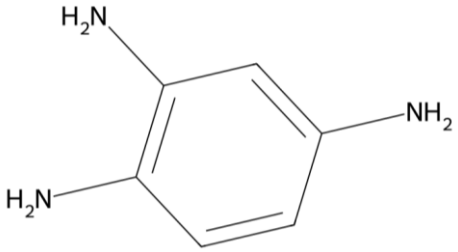
(7) Prontosil:



Prontosil



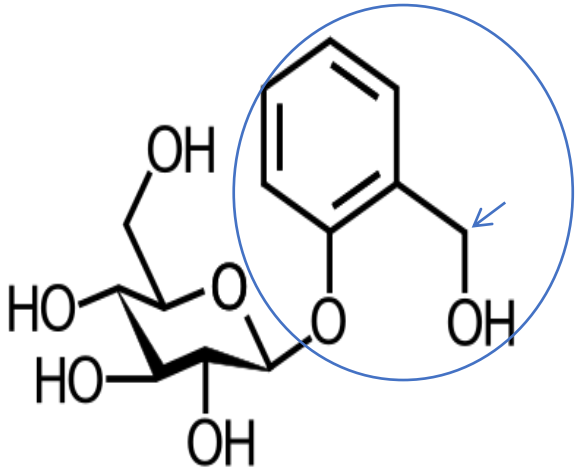
Sulfanilamide



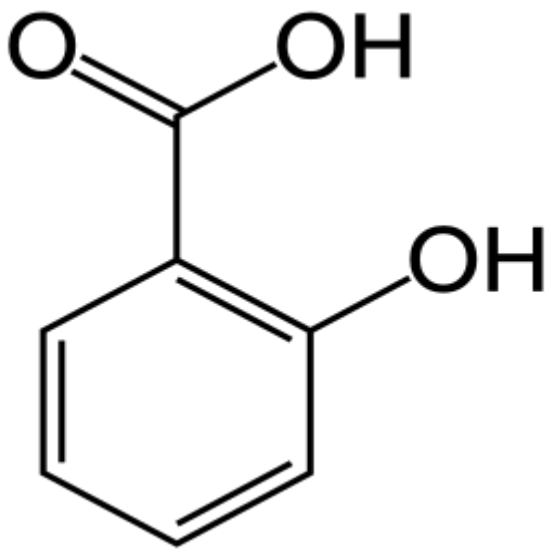
1,2,4-Triaminabenzene

Prontosil is sulfonamide antibacterial was one of the first effective drugs for treating bacterial infections caused by streptococci, it works by being converted in the body to sulfanilamide through metabolism by azoreductase enzyme; hence, sulfanilamide which resulted from prontosil inhibit the folic acid synthesize required for the growth and division of bacteria. Sulfanilamide was initially effective in puerperal fever and meningitis caused by meningococcus.

(8) Salicin:



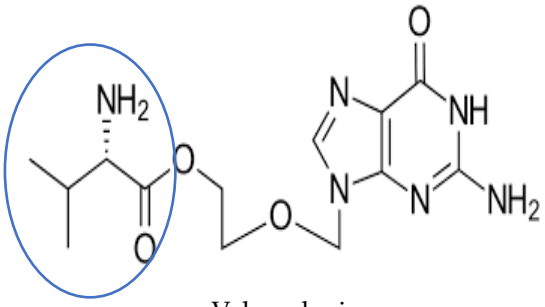
Salicin



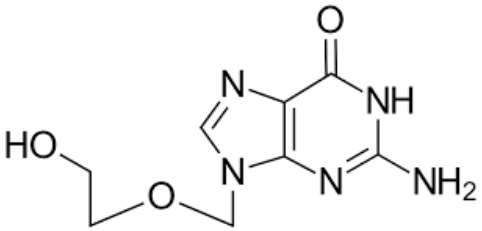
Salicylic acid

Salicin is a glycoside obtained from Salix, which is used in medicine for the relief of pain and inflammation, where it is precursor to salicylic acid, which is used in the treatment. Salicin is a prodrug that needs activation through cleavage of the glycosidic linkage between the glycone part and aglycon part, which is active, but salicin as is inactive. Salicin is used to reduce cartilage degeneration in osteoarthritis, potentially slowing disease progression the Salicylic acid also has a role in reducing the risk of cardiovascular diseases. Salicin has neuroprotective properties.

(9) Valacyclovir:



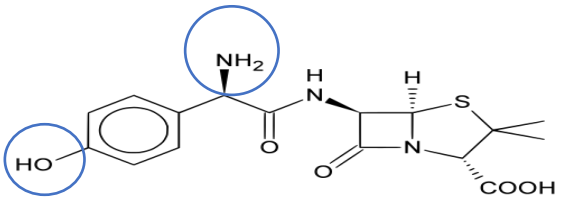
Valacyclovir



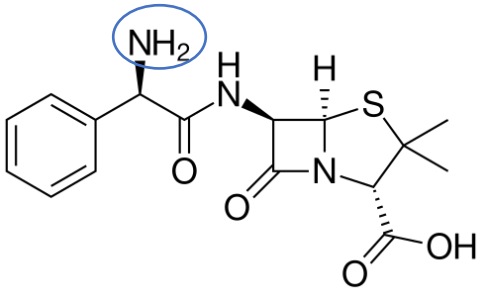
Acyclovir

Valacyclovir is a prodrug need to activate into an acyclovir through break valacyclovir into valine amino acid and acyclovir, which used in treatment of herpes virus infections including herpes labialis, also known as cold sores, herpes zoster also known as shingles, and herpes simplex also known as genital herpes in adults, it is also used to treat chicken pox and cold sores in children; hence valacyclovir is inactive when metabolized into acyclovir become active, further activated through phosphorylation.

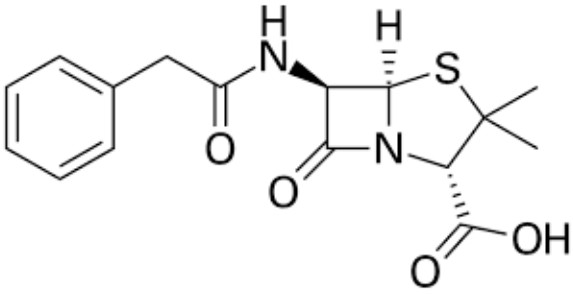
(10) Ampicillin and amoxicillin:



Amoxicillin



Ampicillin



Benzylpenicillin

Ampicillin and amoxicillin are active prodrugs which are metabolized into benzylpenicillin become has longer duration (Ampicillin and Amoxicillin) more than benzylpenicillin, in this case the ampicillin and amoxicillin when metabolized retained with antibacterial properties, the penicillin used in treatment of a wide range of bacterial infection including those of the skin, throat, lungs and urinary tract maybe

used in treatment of pneumonia, air infections, dental abscesses and some sexually transmitted diseases (STD) in some cases penicillin can be uses to prevent rheumatic fever following streptococcal infection, the penicillins inhibit the cell wall of bacteria via inhibits the formation of peptidoglycan cross linkage; hence weakening the cell wall and cause bacterial rupture.

3. Conclusion

The pharmacological and biochemical significance of prodrugs, demonstrating how inactive or less active compounds are metabolically transformed into therapeutically active agents. Prodrugs such as codeine, clopidogrel, enalapril, levodopa, azathioprine, sulfasalazine, prontosil, salicin, valacyclovir, and certain β-lactam derivatives undergo specific metabolic pathways—oxidative dealkylation, enzymatic cleavage, reduction, phosphorylation, or ester hydrolysis—that enhance their bioavailability, selectivity, and therapeutic efficacy.

This metabolic activation allows for improved pharmacokinetics, targeted drug delivery, reduced adverse effects, and expanded clinical applications. Examples include levodopa's ability to cross the blood–brain barrier before conversion to dopamine for Parkinson's disease management, sulfasalazine's site-specific release of anti-inflammatory and antibacterial components in the colon, and clopidogrel's conversion to an active thiol metabolite for antiplatelet activity.

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