Pharmaceutical Chemistry

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Drugs & Pharmaceuticals

Drug discovery, design and development; Basic Retrosynthetic approach. Synthesis of the representative drugs of the following classes: analgesics agents, antipyretic agents, anti-inflammatory agents (Aspirin, paracetamol, Ibuprofen); antibiotics (Chloramphenicol); antibacterial and antifungal agents (Sulphonamides; Sulphanethoxazol, Sulphacetamide, Trimethoprim); antiviral agents (Acyclovir), Central Nervous System agents (Phenobarbital, Diazepam),Cardiovascular (Glyceryl trinitrate), antilaprosy (Dapsone), HIV-AIDS related drugs (AZT- Zidovudine).

Fermentation

Aerobic and anaerobic fermentation. Production of (i) Ethyl alcohol and citric acid, (ii) Antibiotics; Penicillin, Cephalosporin, Chloromycetin and Streptomycin, (iii) Lysine, Glutamic acid, Vitamin B2, Vitamin B12 and Vitamin C.

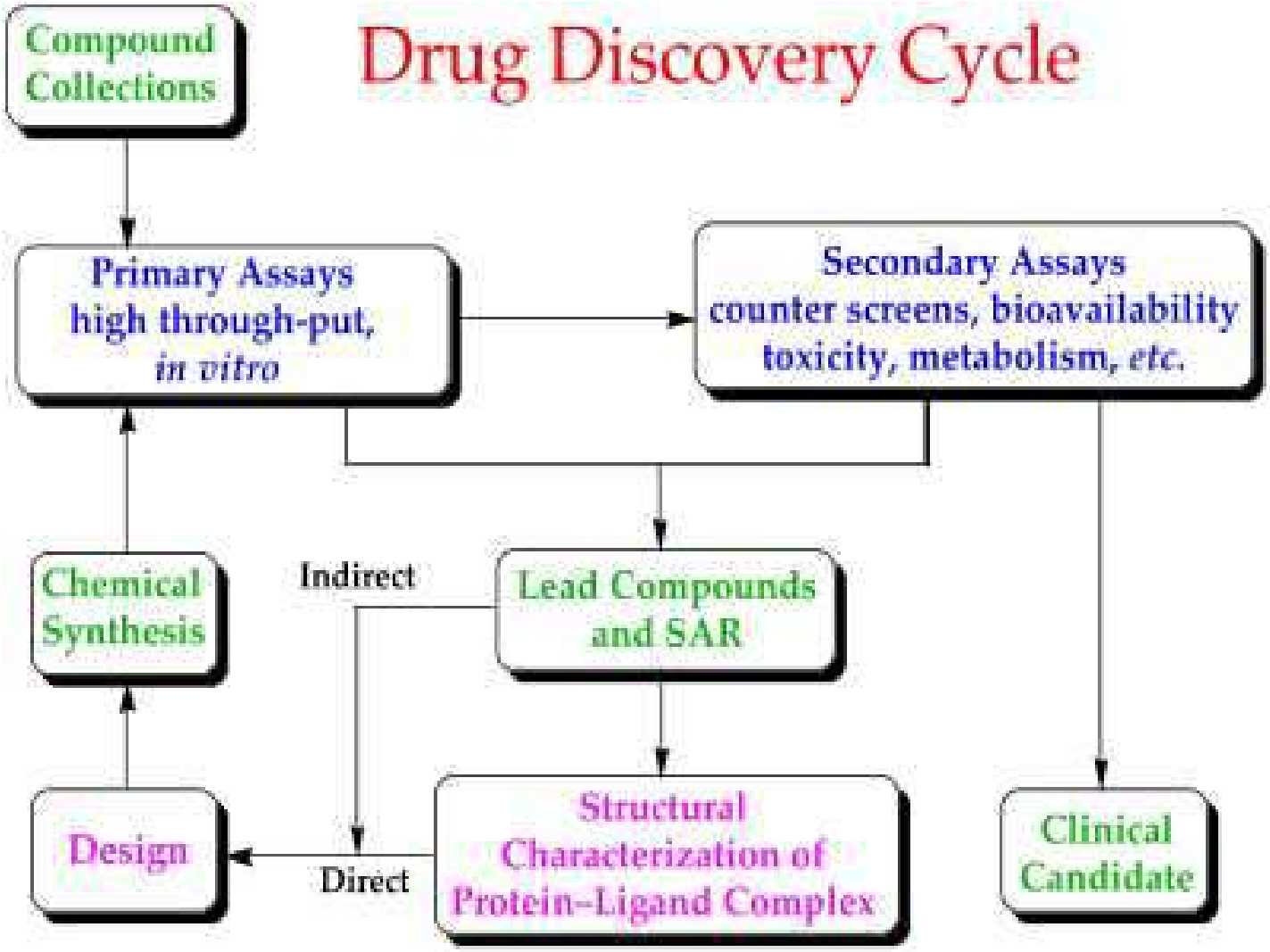
I will discuss Drugs and Pharmaceuticals portions only in this slide show

What is Drug Discovery

- In the fields of medicine and pharmacology, drug discovery is the process by which new candidate medications are discovered

- Historically, drugs were discovered by identifying the active ingredient from traditional remedies or by serendipitous discovery, as with penicillin

- Modern drug discovery involves the identification of screening hits, medicinal Chemistry and optimization of those hits to increase the affinity, selectivity (to reduce the potential of side effects), efficacy/potency, metabolic stability (to increase the half-life), and oral bioavailability. Once a compound that fulfills all of these requirements has been identified, the process of drug development can continue. If successful, clinical trials are developed

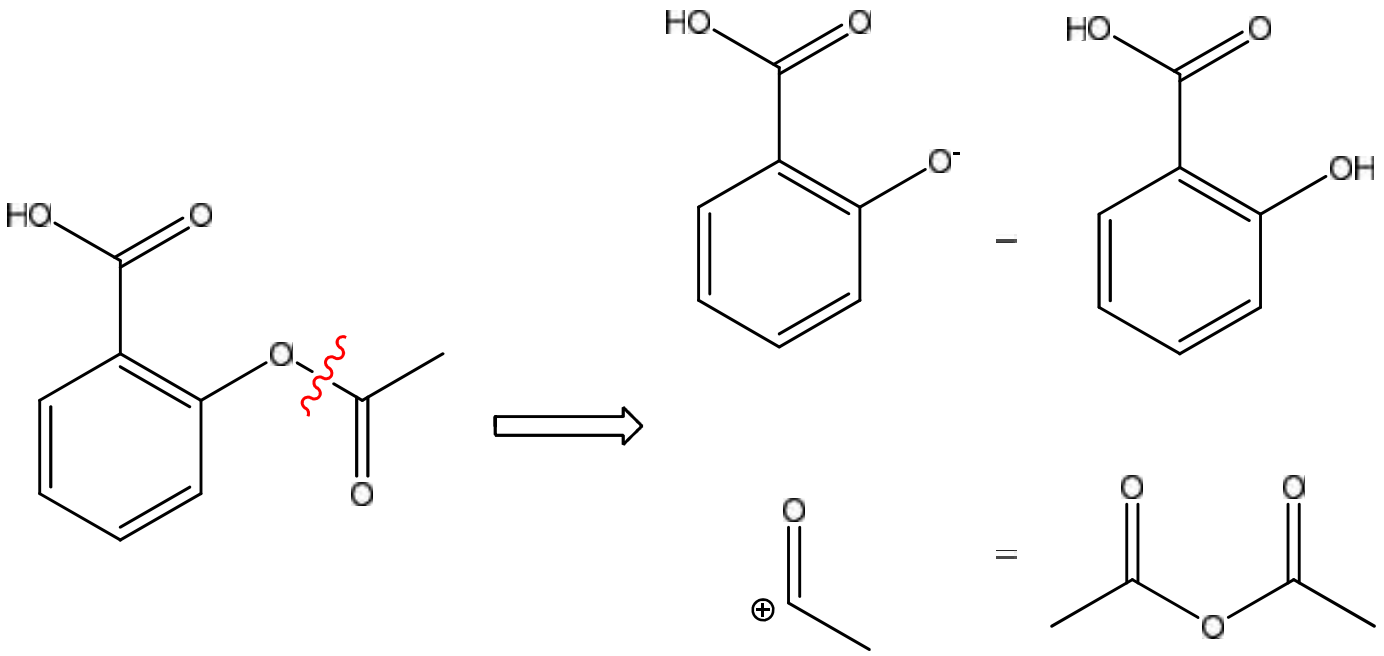

Drug Discovery Cycle
Compound Collections
Primary Assays high through-put, in vitro
Secondary Assays counter screens, bioavailability toxicity, metabolism, etc.
Chemical Synthesis
Indirect
Lead Compounds and SAR
Design
Direct
Structural Characterization of Protein–Ligand Complex
Clinical Candidate

What is Retrosynthtic approach

- **Retrosynthetic analysis** is a technique for solving problems in the planning of organic syntheses.
- This is achieved by transforming a target molecule into simpler precursor structures regardless of any potential reactivity/interaction with reagents.
- Each precursor material is examined using the same method. This procedure is repeated until simple or commercially available structures are reached.
- These simpler/commercially available compounds can be used to form a synthesis of the target molecule

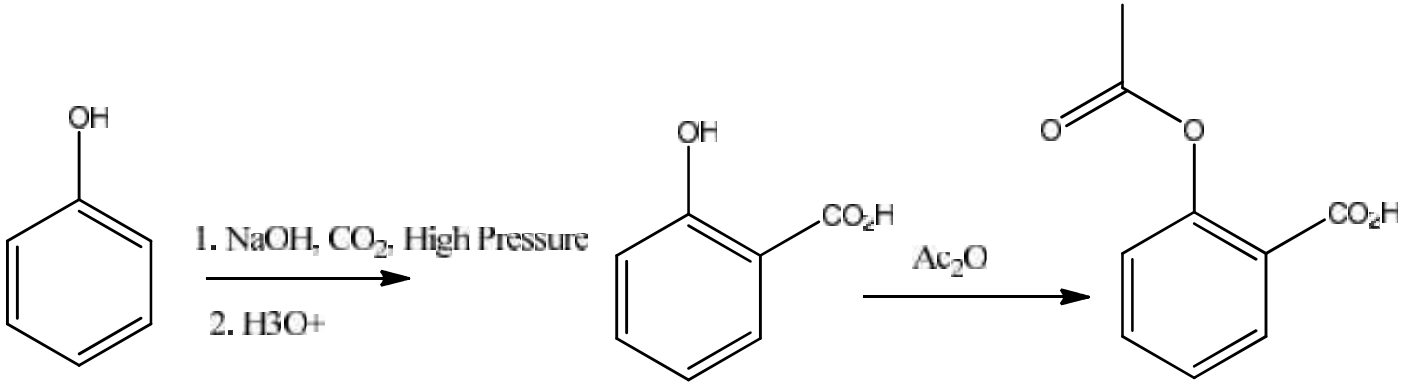
BASIC APPROACH OF RETROSYNTHESIS

Retrosynthetic and Synthetic approach of Aspirin (common analgesic)

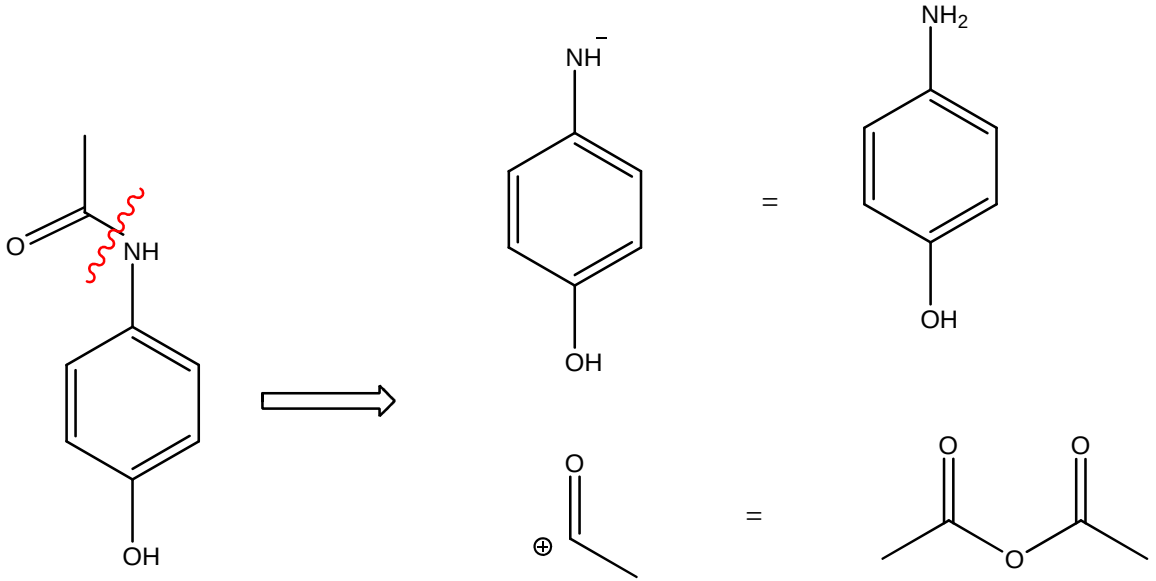


Retrosynthetic Aprroach of Aspirin

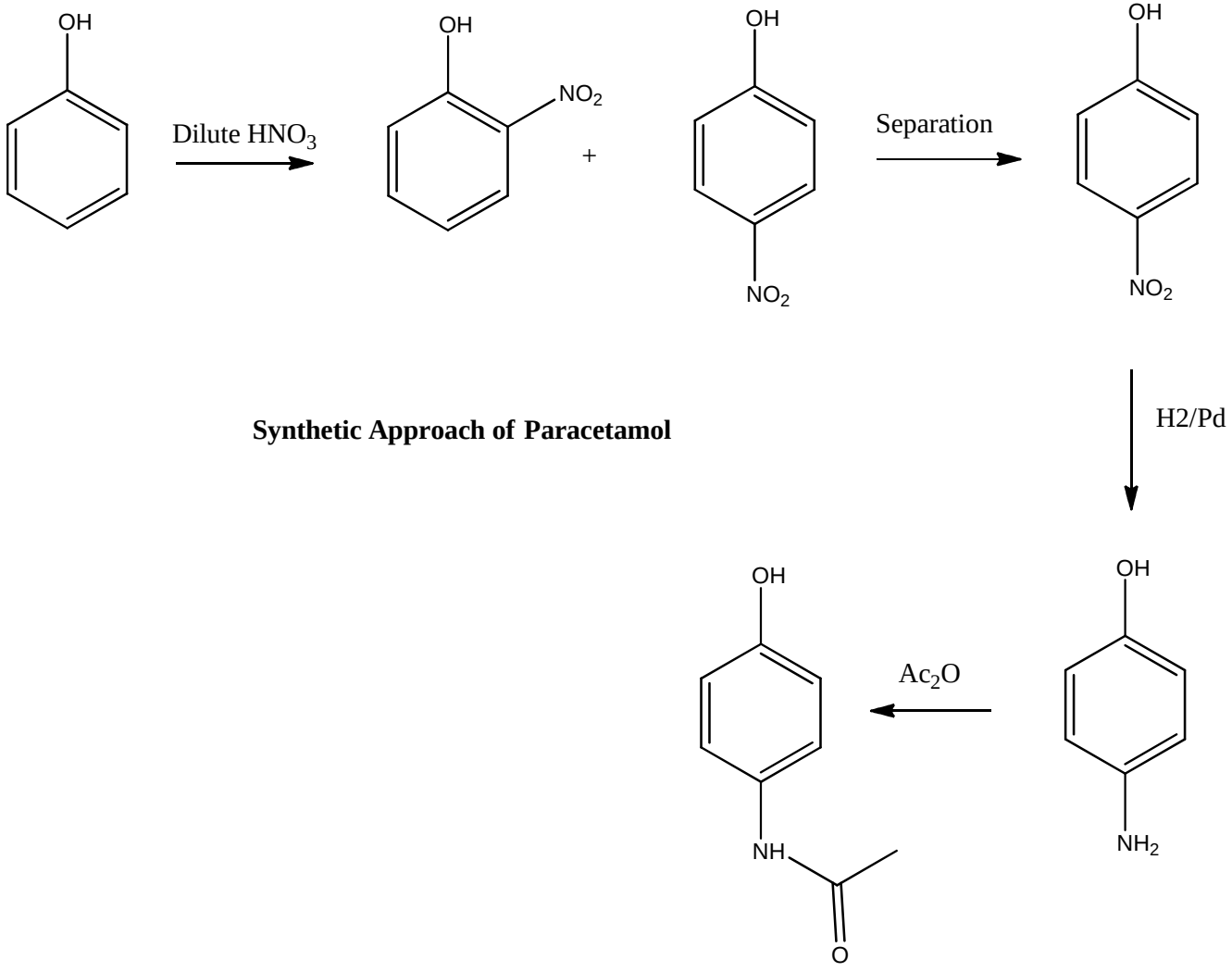
Synthetic Approach of Aspirin



Retrosynthesitic and synthetic approach of Paracetamol (Anti Pyretic)

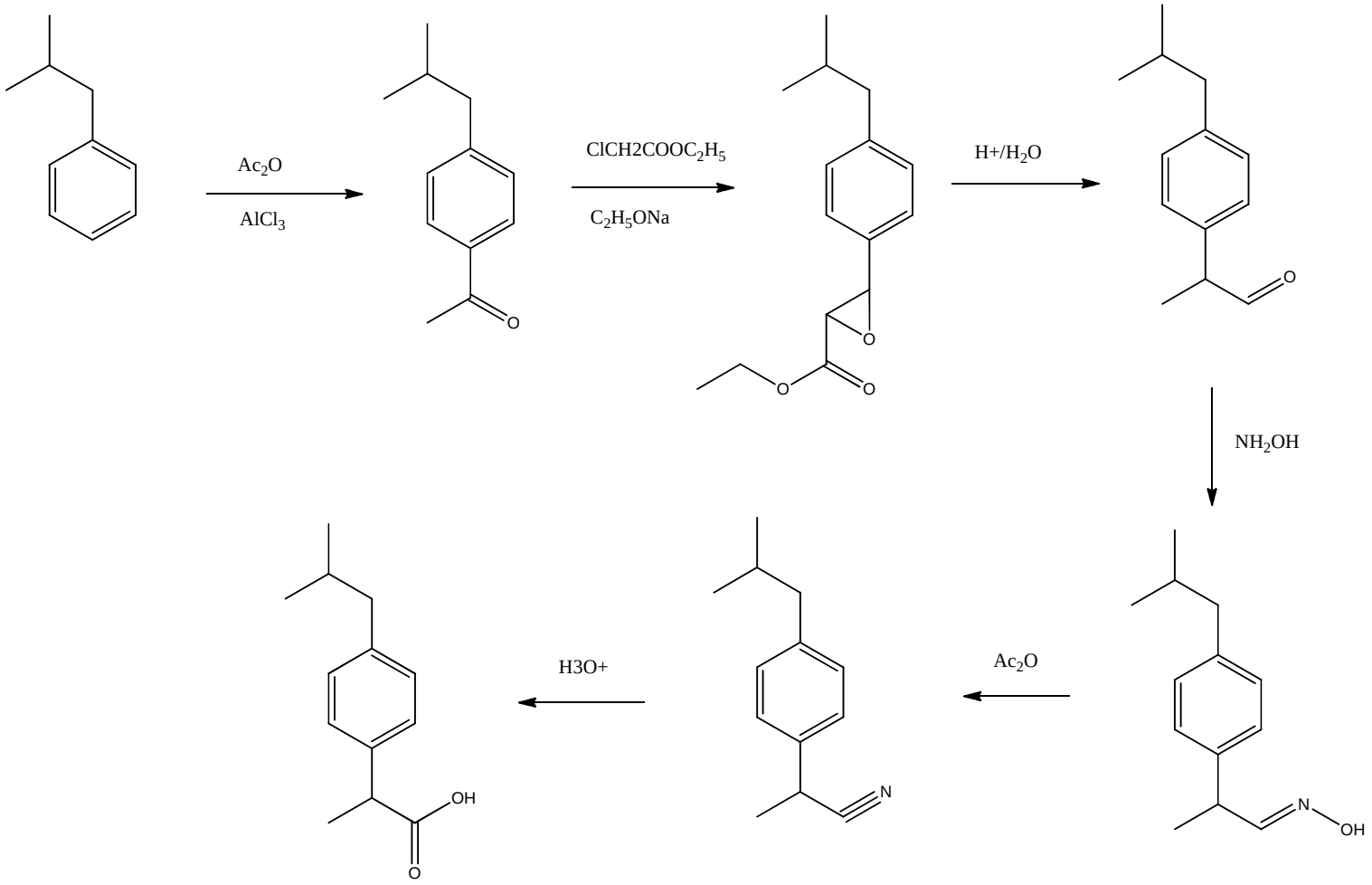


Retrosynthetic approach of Paracetamol

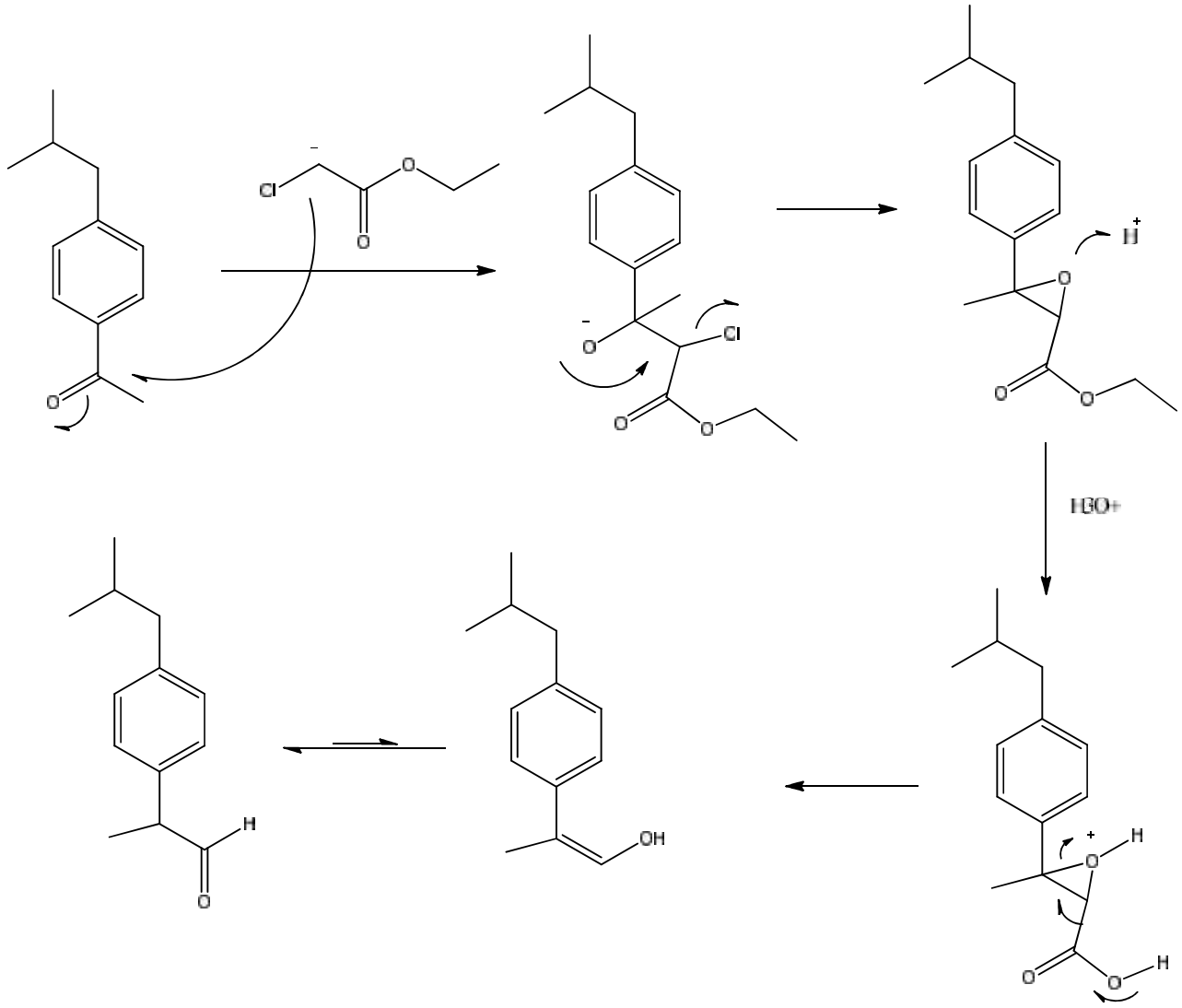


Synthetic Approach of Paracetamol

Ibuprofen synthesis (Anti-inflammatory drugs)



Mechanism of some important steps



Antibiotics

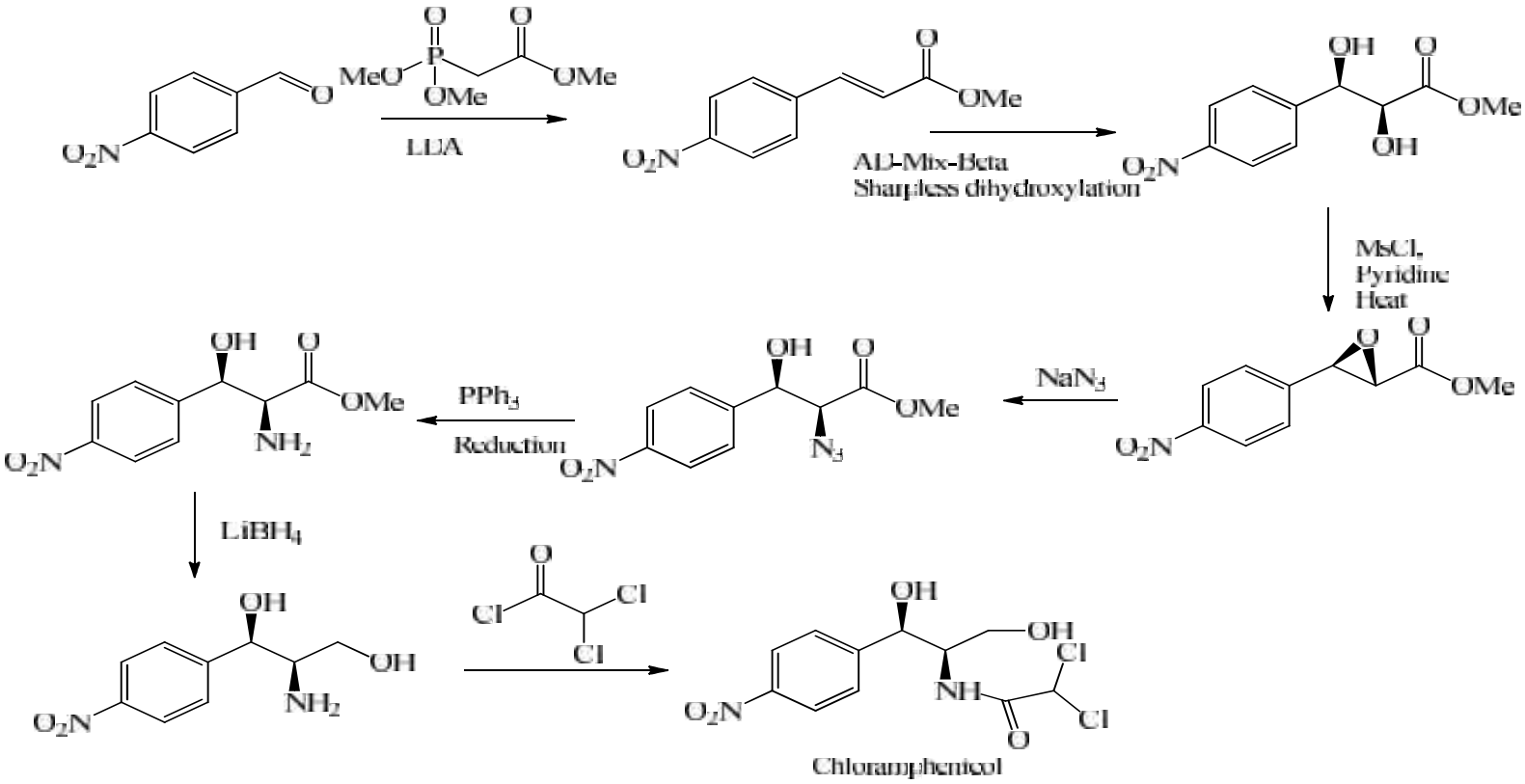
Antibiotics are chemical substances produced by various species of microorganisms, which in low concentration destroy or inhibit the other species of microorganisms. In the present usage the term antibiotic includes chemically related and derived substances.

Antibiotics have prevented millions of deaths and radically changed healthcare during the last century. There are dozens of different types of antibiotics, with each of them grouped into different classes. The following list includes eight of the most common classes of antibiotics, what they are generally used for and some of the potential side effects: 1. Penicillins, 2. Cephalosporins 3.Sulfonamides, 4. Fluoroquinolones, 5. Macrolides, 6. Tetracyclines, 7. Aminoglycosides, 8. Carbapenems.

Chloramphenicol

Chloramphenicol is an antibiotic useful for the treatment of a number of bacterial infections. This includes as an eye ointment to treat conjunctivitis. By mouth or injection into a vein, it is used to treat meningitis, plague, cholera and typhoid fever. Its use by mouth or by injection is only recommended when safer antibiotics can not be used

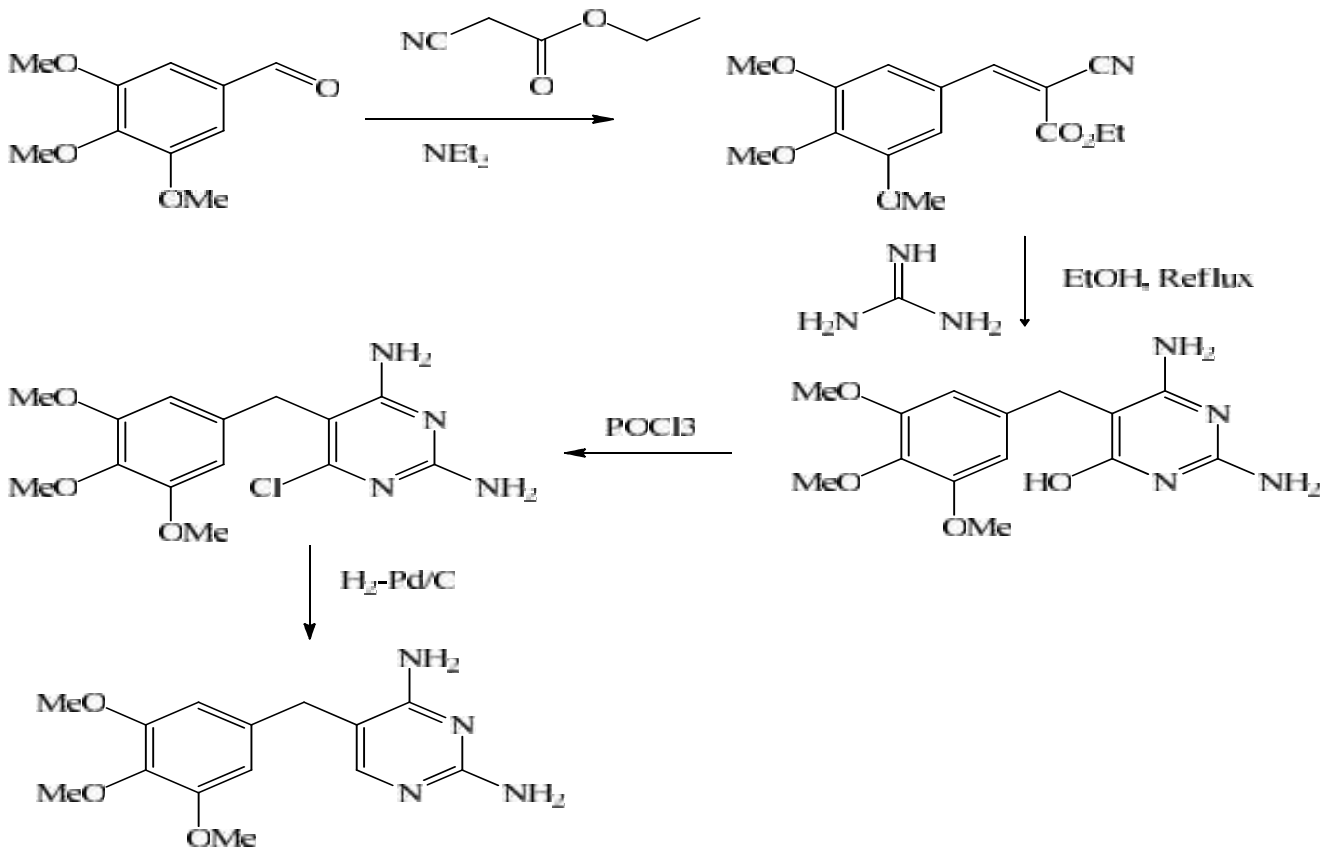
Synthetic route of Chloramphenicol



Trimethoprim

Trimethoprim is an antibiotic used mainly in the treatment of bladder infections. Other uses include for middle ear infections and travelers diarrhea

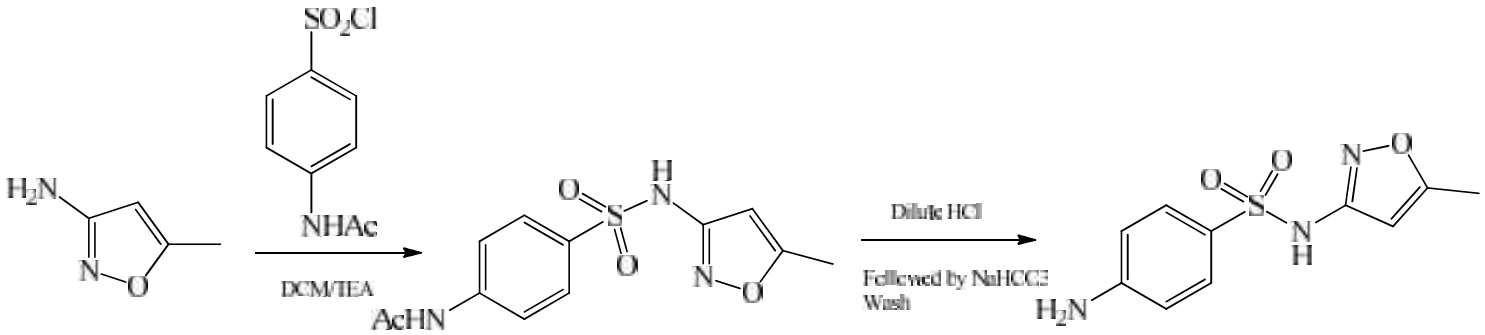
Trimethoprim Synthesis



Sulfamethoxazole

Sulfamethoxazole is an antibiotic. It is used for bacterial infections such as urinary tract infections, bronchitis and prostatitis and is effective against both gram negative and positive bacteria such as Listeria monocytogenes and E-coli

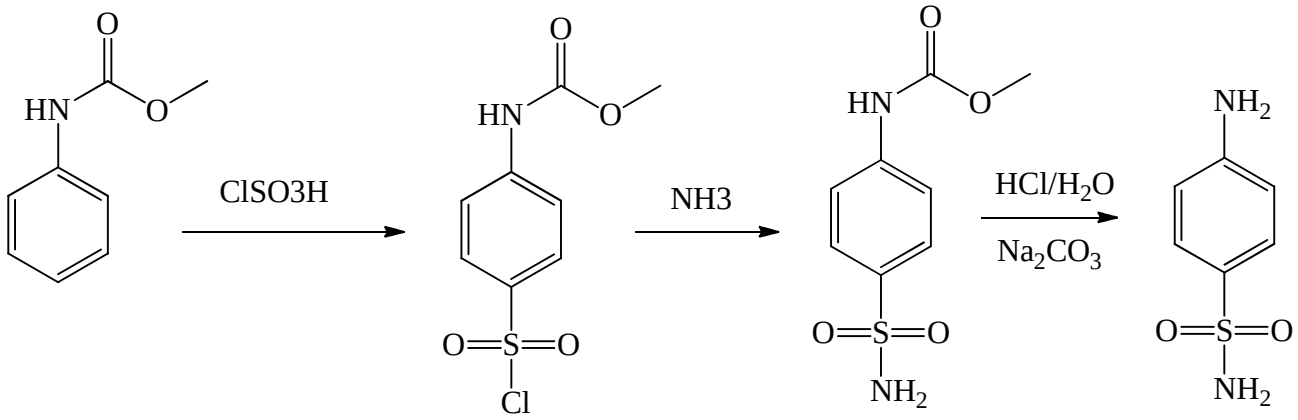
Sulfamethoxazole Synthesis



Sulfacetamide

Sulfacetamide 10% typical lotion, sold under the brand name klaron or ovace, is approved for the treatment of acne and seborrhea dermatitis. It also has anti-inflammatory properties when used to treat blepharities or conjunctivitis. It is believed to work by limiting the presence of folic acid which bacteria need to survive

Sulfacetamide Synthesis



Antiviral Agents

The diseases due to viral infections are more frequent. The viral infections are possibly responsible for over 60% of the human illness, whereas only 15% may be due to bacterial infections. The well know viral diseases include common cold, influenza, bronchitis, hepatitis, herpes gastroenteritis, rabbis, chicken pox, small pox, measles and mumps

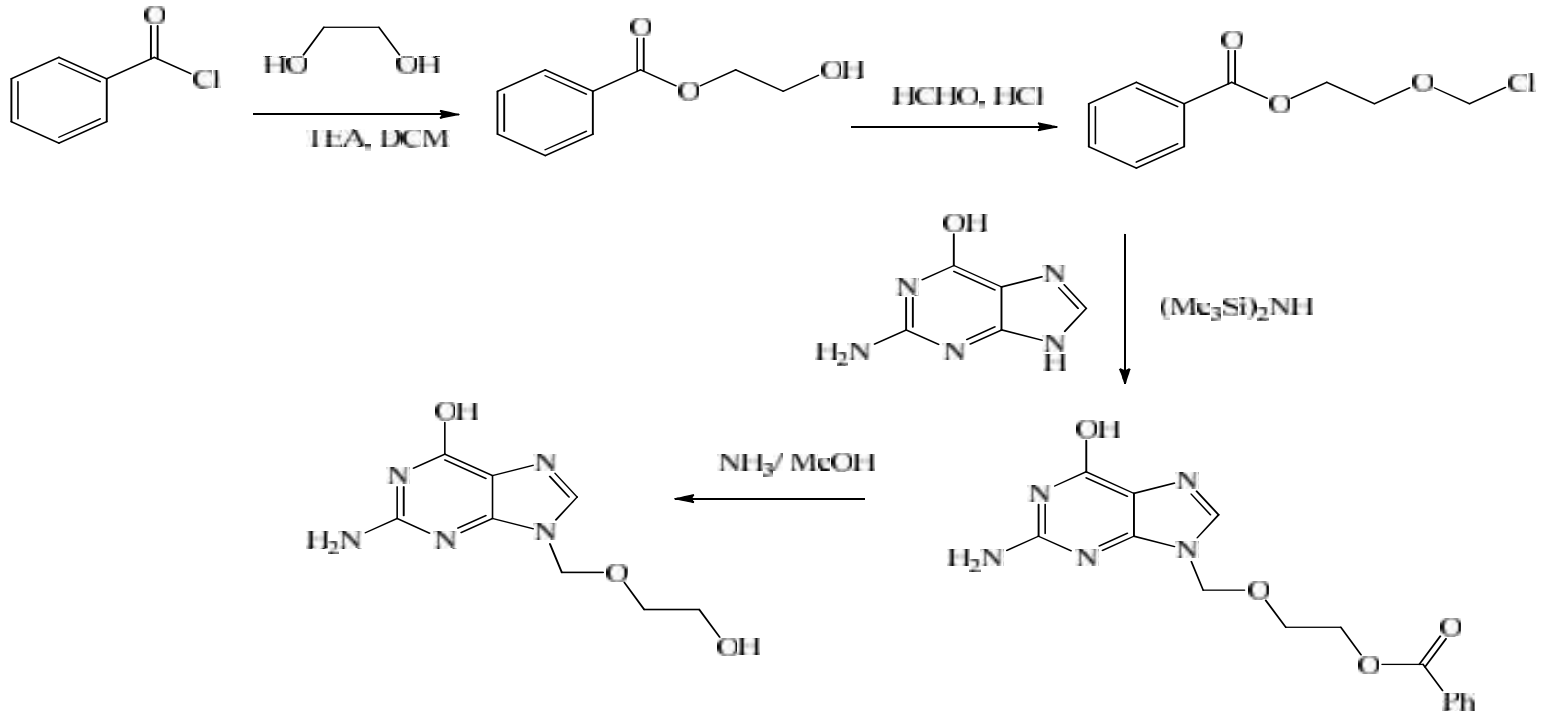
Antivirals agents are compounds that help the body fight off certain viruses that can cause disease. Antiviral drugs are also preventive. They can protect from getting viral infections or spreading a virus to others.

Antiviral medicines work differently depending on the drug and virus type. Antivirals can: Block receptors so viruses can't bind to and enter healthy cells. Boost the immune system, helping it fight off a viral infection. Lower the viral load (amount of active virus) in the body.

Acyclovir

Acyclovir is an antiviral medication. It is primarily used for the treatment of herpes simplex virus infections, chicken pox and shingles. Acyclovir is converted by viral thymidine kinase to acyclovir monophosphate, which is then converted by host cell kinase to acyclovir triphosphate. ACV-TP in turn, competitively inhibits and inactivates HSV-specified DNA polymerases preventing further viral DNA synthesis without affecting the normal cellular processes.

Acyclovir Synthesis

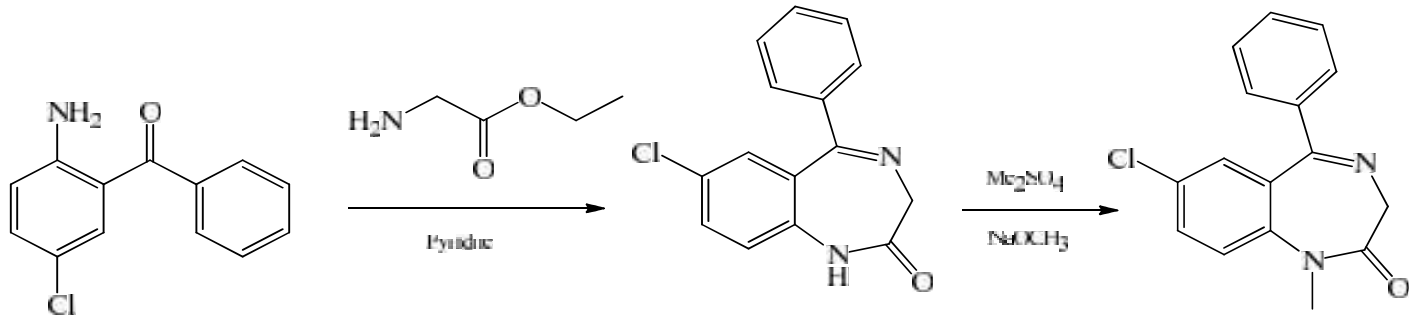


Central Nervous System Agents

Central Nervous System (CNS) depressants are medicines that include sedatives, tranquilizers, and hypnotics. These drugs can slow brain activity, making them useful for treating anxiety, panic, acute stress reactions, and sleep disorders. Drugs that are classified as CNS depressants include: Alcohol. Barbiturates. Benzodiazepines. We will discuss here the synthesis aspects diazepam and phenobarbitol

Diazepam, first marketed as valium, is a medicine of the benzodiazepine family that typically produces a calming effect. It is commonly used to treat a range of conditions including anxiety, alcohol withdrawal syndrome, muscle spasms, seizures, trouble sleeping and restless legs syndrome

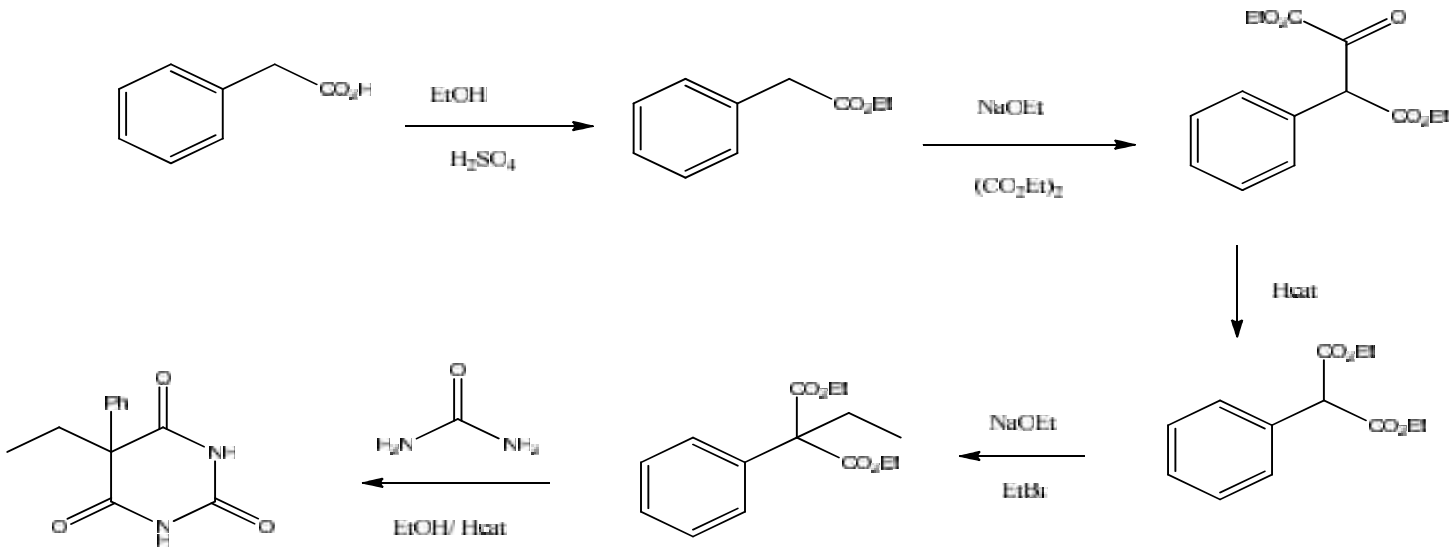
Diazepam Synthesis



Phenobarbital

Phenobarbital, also known as phenobarbitone, is a medication recommended by WHO for the treatment of certain types of epilepsy in developing country. In the developed world it is commonly used to treat seizure in young children. Though its action on GABA receptors, Phenobarbitol increases flux of chloride ions into a neuron which decreases excitatory glutamate signaling is also believed to contribute to the hypnotic/ anticonvulsant effect that is observed with the barbiturates.

Phenobarbitol Synthesis:

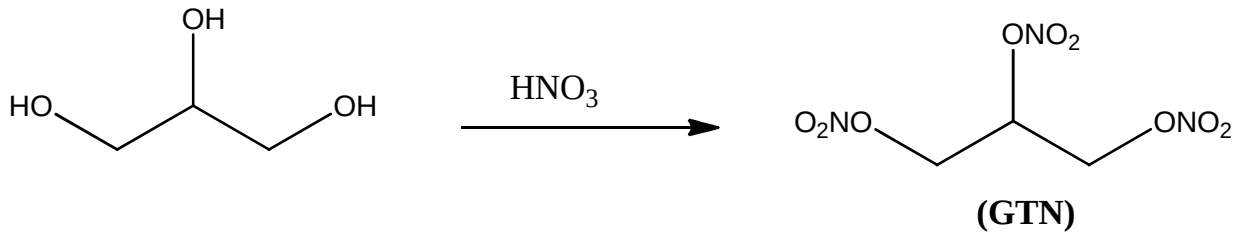


Cardiovascular agents

Cardiovascular agents are medicines that are used to treat medical conditions associated with the heart or the circulatory system (blood vessels), such as arrhythmias, blood clots, coronary artery disease, high or low blood pressure, high cholesterol, heart failure, and stroke

Nitroglycerine, also known as glyceryl trinitrate (GTN), is a medication used for heart failure, high blood pressure, and to treat and prevent chest pain from not enough blood flow to the heart or due to cocaine. This is taken by mouth, under the tongue, applied to skin, or by injection into a vain

Synthesis of Glyceryltrintritrate:



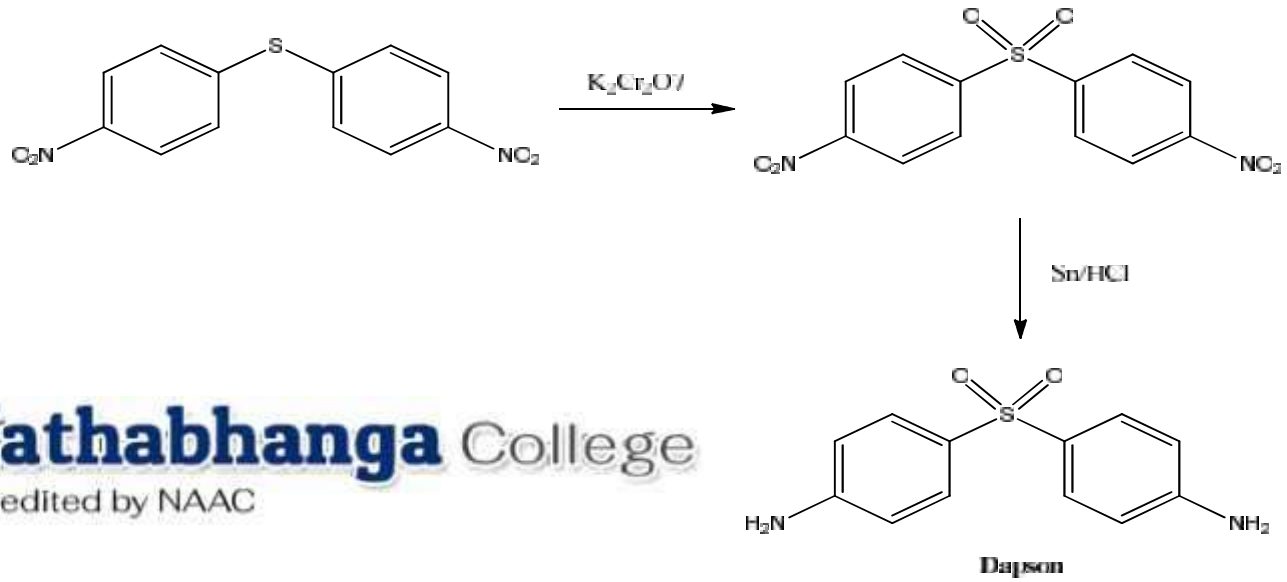
(GTN)

Leprostatic Agents

A leprostatic agent is a drug that interferes with proliferation of the bacterium that causes leprosy

Dapson, also known as diaminodiphenyl sulfone (DDS) is an antibiotics commonly used in combination with rifampilin and clofazimine for the treatment of leprosy. It is a second line medication for the treatment and prevention of pneumocystis pneumonia and for the prevention of toxoplasmosis in those who have poor immune functions.

Synthesis of Dapson:



Dapson

HIV-AIDS related drugs

Zidovudine (ZDV), also known as azidothymidine (AZT, is an antiretroviral medication used to prevent and treat HIV/AIDS. AZT is a thymidine analogue, AZT works by selectively inhibiting HIV reverse transcriptase, the enzyme that the virus uses to make DNA copy of its RNA. Reverse transcription is necessary for production of HIV's double-stranded DNA, which would be subsequently integrated into the genetic material of the infected cell.

Synthesis of Zidovudine: