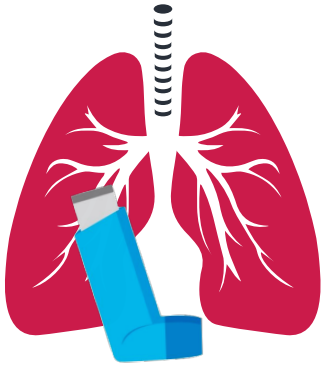


Wheezy? Breathe Easy!

Examining the use of salbutamol in asthma treatment

1 Asthma

Symptoms and Treatment

Asthma

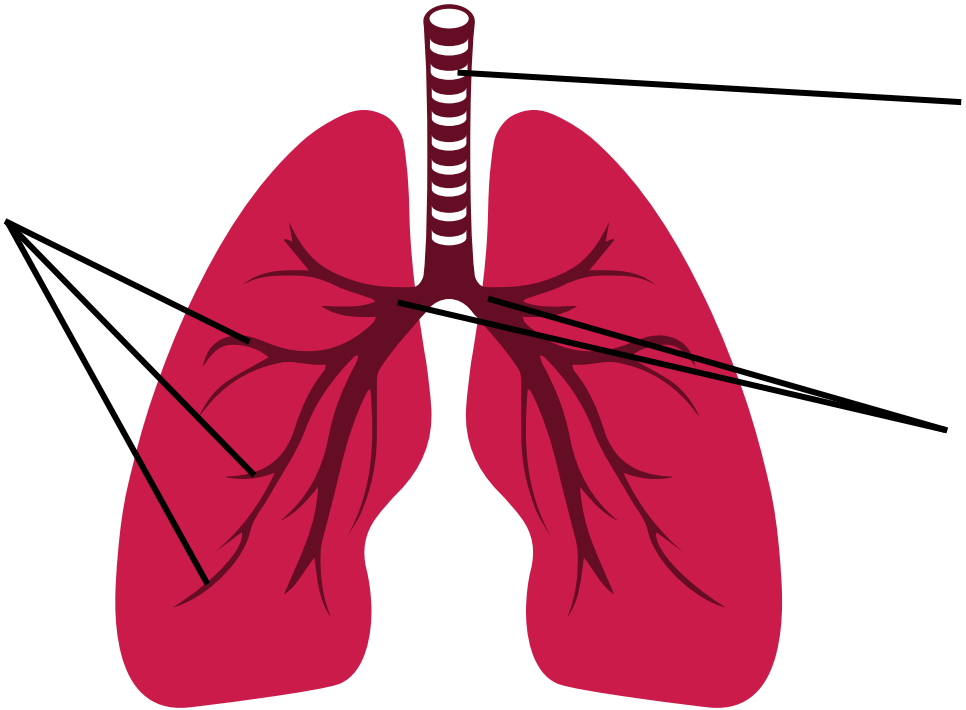
- Chronic airway inflammatory disease of the lungs
  - Affects the air passages of the lungs and the air flow within them
- “characterized by an abnormal responsiveness of the airways to stimuli that are ineffective in normal subjects” (Novelli, Malagrina, Dente & Paggiaro, 2012)
- Trigger → Constriction → Difficulty breathing

>339 million people globally

Lungs

Bronchioles
Bronchioles are air passages inside the lungs that branch off like tree limbs from the bronchi.

The bronchioles deliver air to tiny sacs called alveoli where oxygen and carbon dioxide are exchanged.



Trachea (windpipe)
Allows the passage of inhaled air from the mouth/nose to the bronchi of the lungs.

(Primary) bronchi
A bronchus is a passage or airway in the respiratory system that conducts air into the lungs.

Triggers

Air pollution & dust

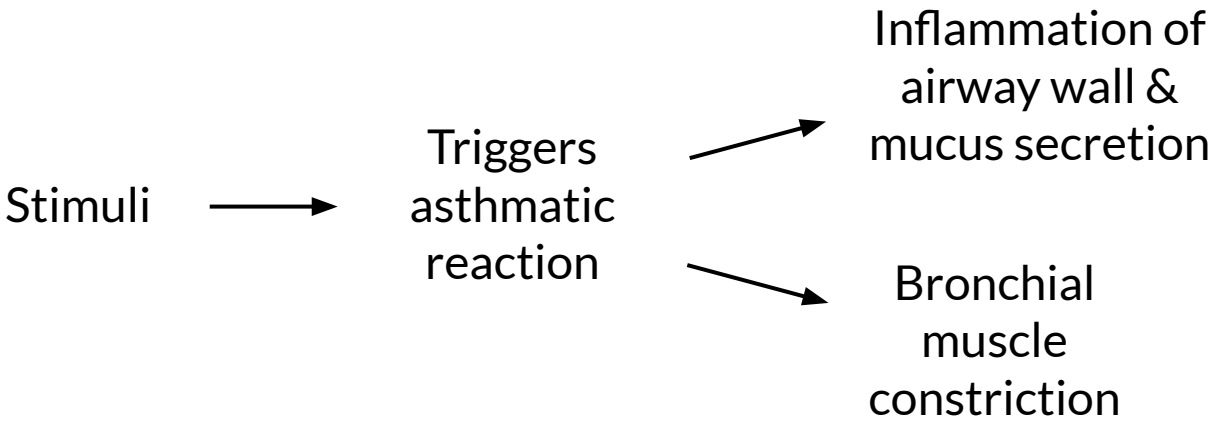
Smoking

Alcohol consumption

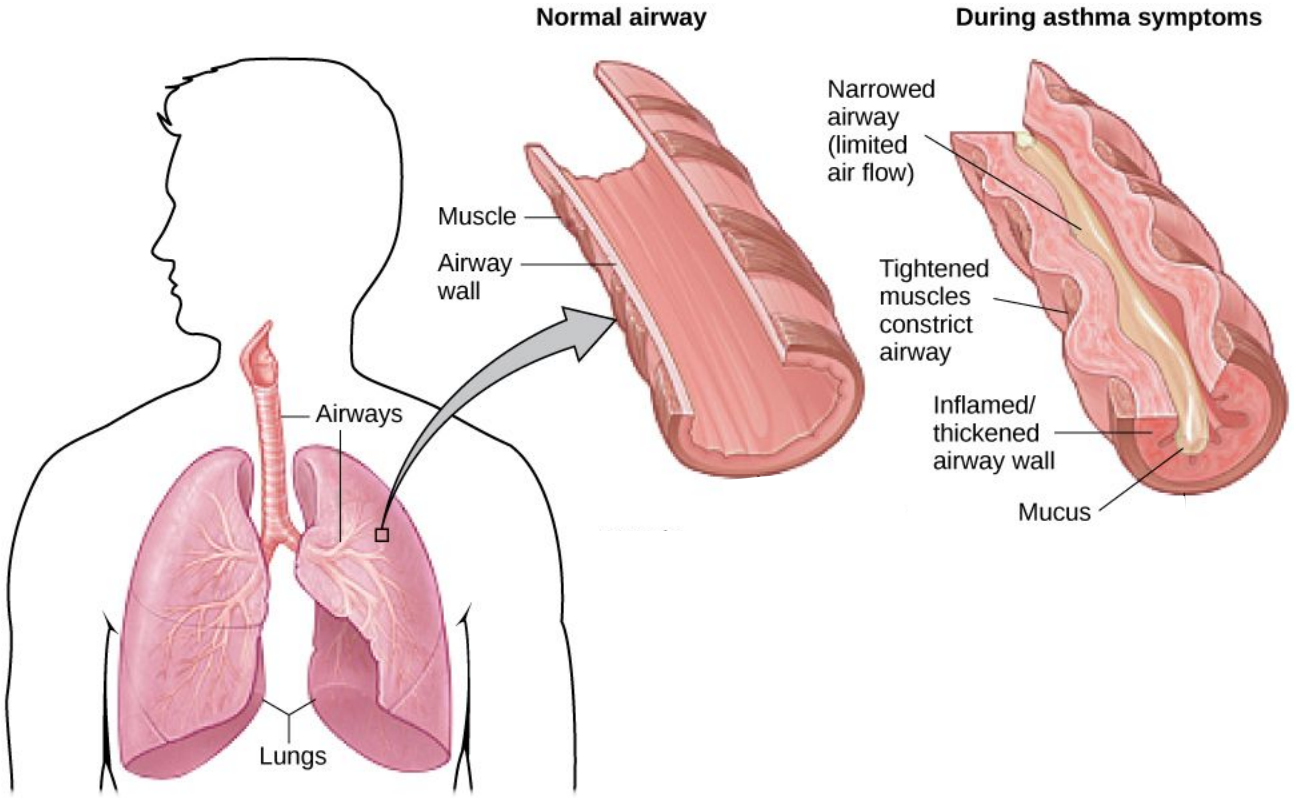
Exercise

Heightened emotions

Cold weather

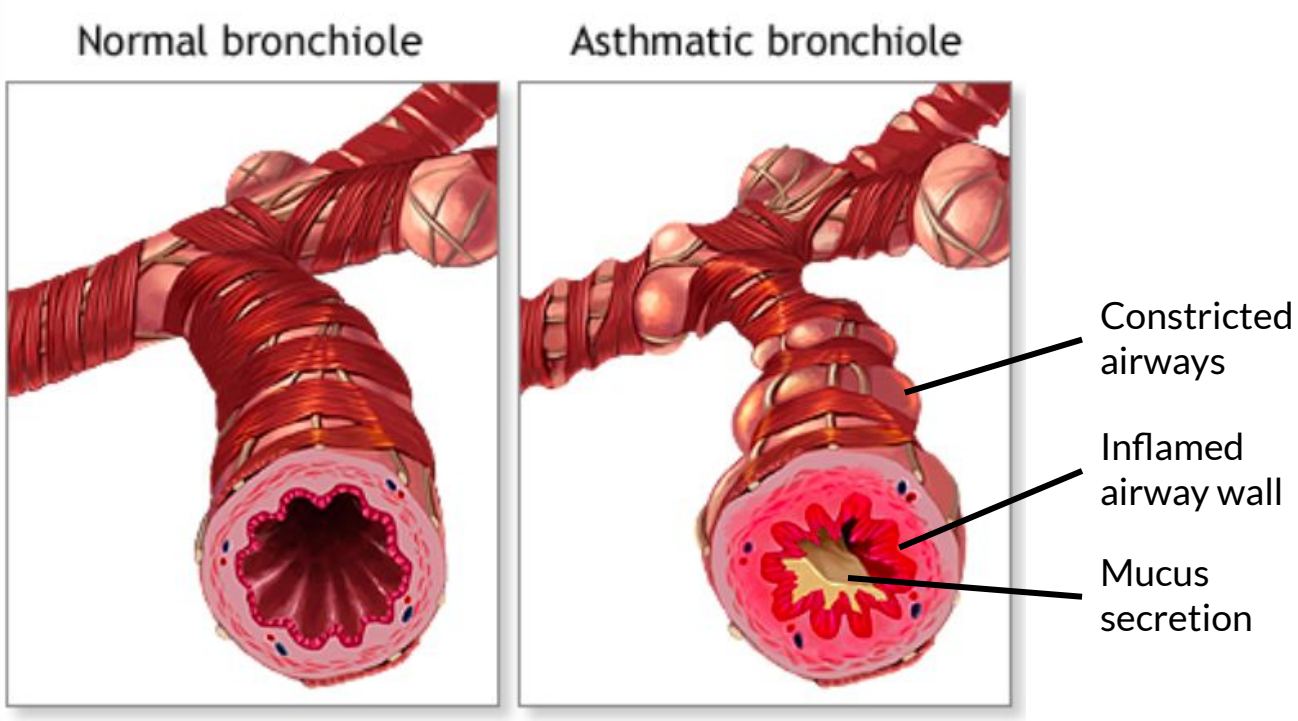

Stimuli
Triggers asthmatic reaction
Inflammation of airway wall & mucus secretion
Bronchial muscle constriction

Asthmatic reaction



Asthmatic reaction

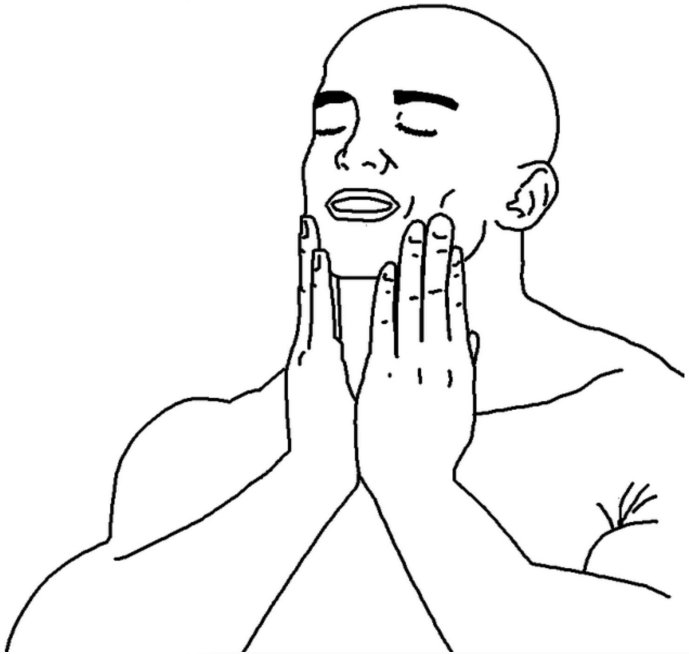
Airway cross-section of bronchioles



Narrowed & blocked airways → reduced airflow in lungs → difficulties breathing

Asthmatic reaction

Normal bronchiole



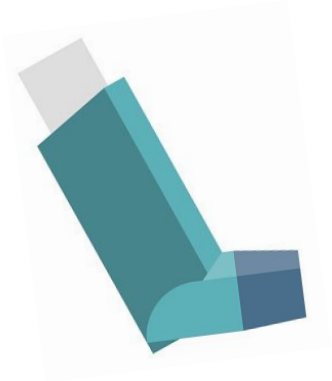
Asthmatic bronchiole

Narrowed & blocked airways → reduced airflow in lungs → difficulties breathing

Treatment

Focuses on reversing the effects of bronchial muscle constriction through **bronchodilation**

Medicine used to treat asthma thus must have bronchodilating effects



~~Atropine~~ **INEFFECTIVE**

Salbutamol

- WHO's List of Essential Medicines
- 7th most common prescribed drug in US

Question:

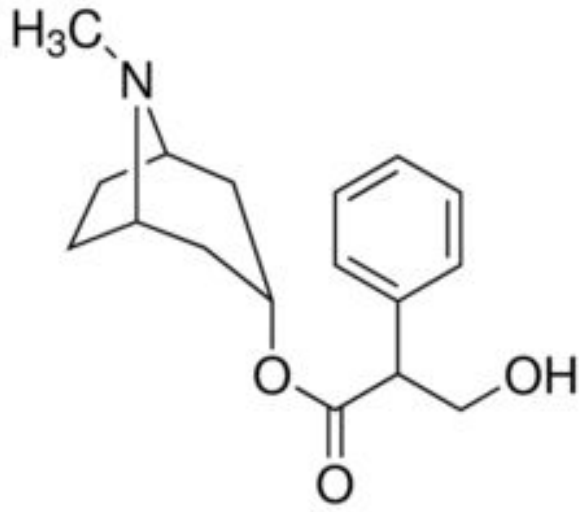
What exactly makes atropine ineffective and salbutamol effective?

2 Atropine & Salbutamol

Examining asthma treatment drugs and their efficacy

Atropine

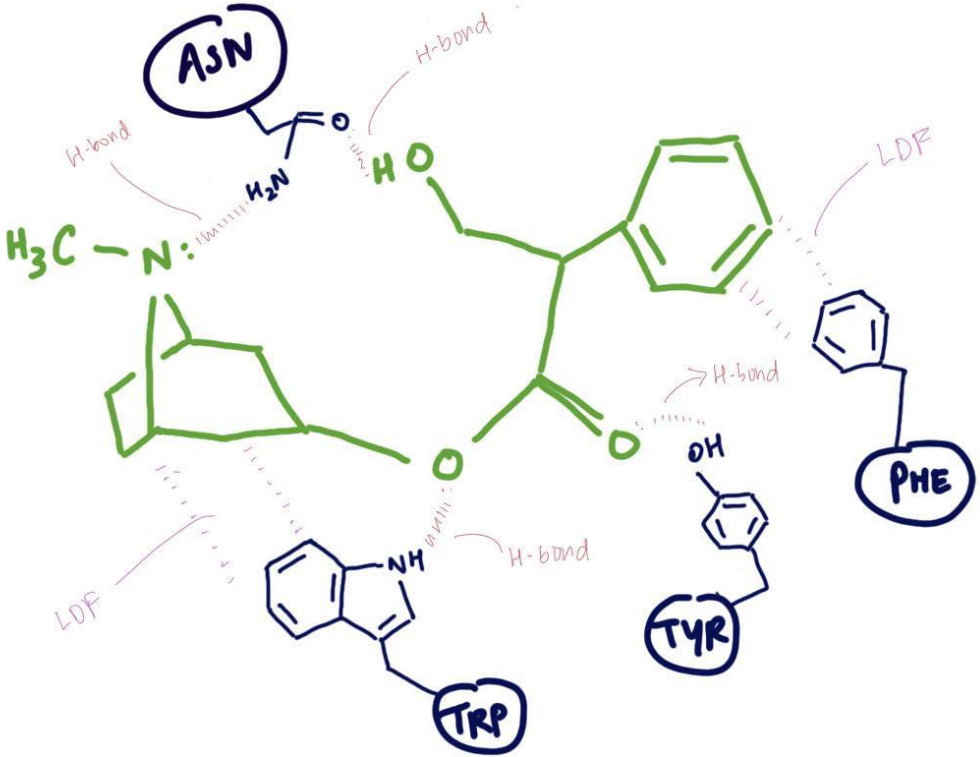
- Derived from components of the Belladonna, commonly known as a deadly nightshade
- Non-selective inhibitor of muscarinic receptors



Muscarinic Receptors

Subtype	**Location** - Function
M1	**Brain** - Central muscarinic receptors are involved in higher cognitive processes such as learning and memory
M2	**Heart** - Decrease in cardiac output. Produces a fall in arterial pressure
M3	**Smooth Muscles** - Contraction of smooth muscle. It causes an increase in peristaltic activity of the gastrointestinal tract, which can cause pain, and **contraction** of the bladder detrusor muscles (used to treat urinary retention) and **bronchial smooth muscles** **Sweating, lacrimation, salivation and bronchial secretion** are also effects of this receptor. It also causes constrictor pupillae muscles in the eye to contract.

Atropine with Muscarinic Receptor



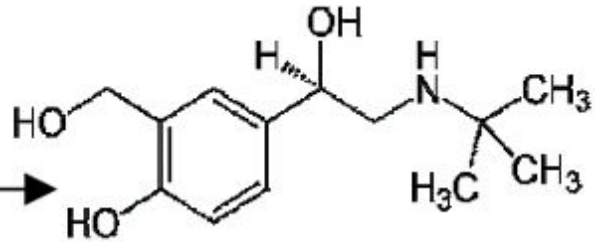
Atropine with Muscarinic Receptor

1. Block the usual ligand, acetylcholine, from binding to the receptor
2. Preventing the contraction of the bronchial smooth muscles
3. Bronchodilation = Asthma relief

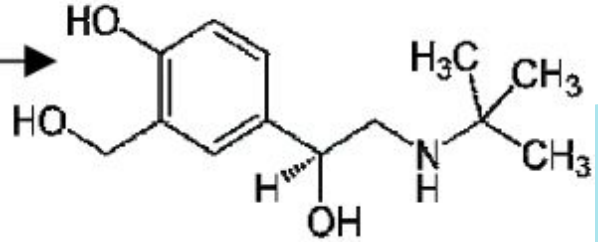
Salbutamol

- Short-acting β2 adrenergic receptor agonist used in the treatment of asthma
- Exist as racemic mixture
  - Enantiomers: R-salbutamol and S-salbutamol

R(-) isomer of Salbutamol (Levosalbutamol)



S(+) isomer of Salbutamol



How Salbutamol works

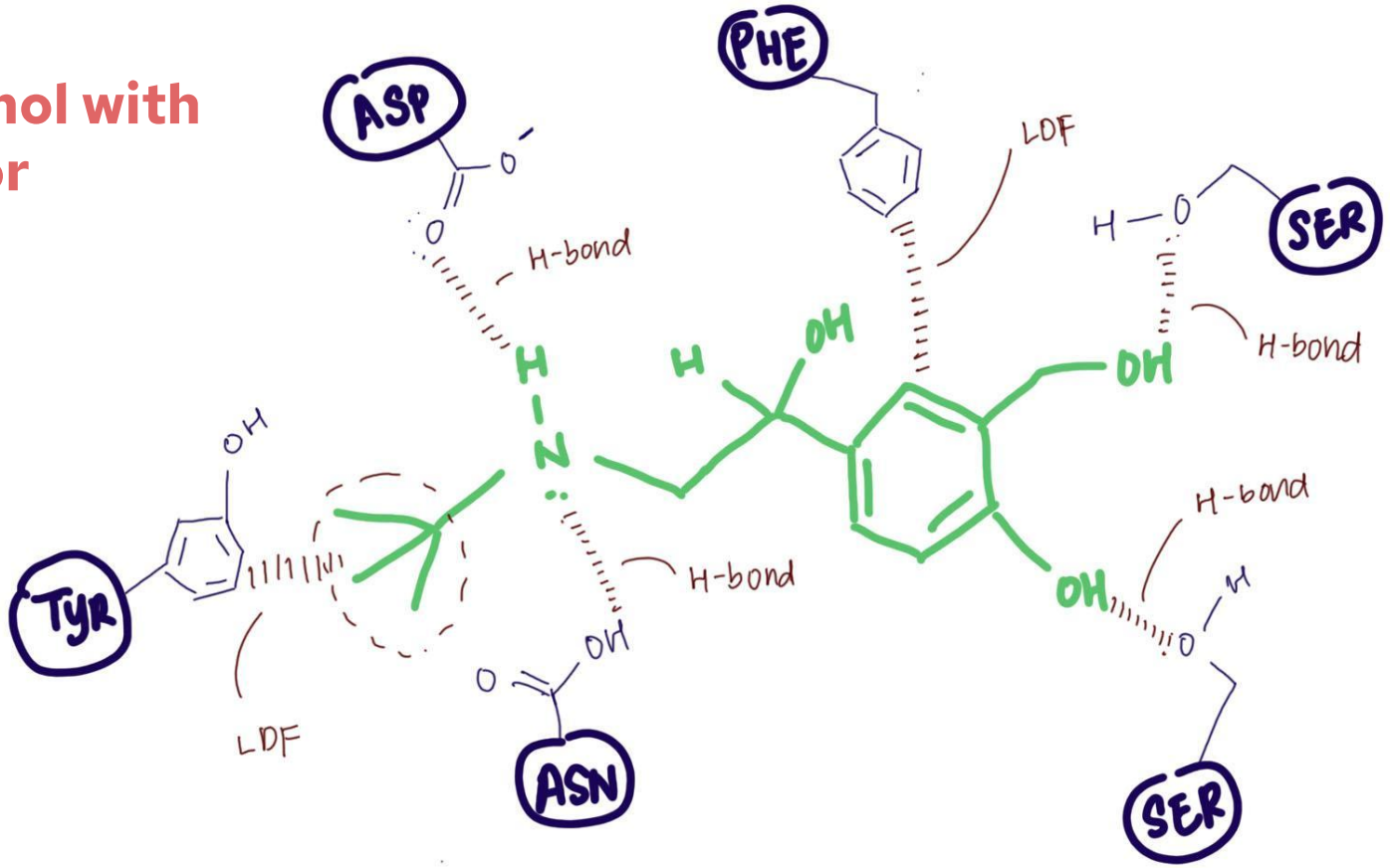
1. Agonise the β2-receptor in the smooth muscles of the lungs
2. Stimulation of adenylyl cyclase
3. Conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP)
4. Increased levels of cAMP → relaxation of bronchial smooth muscles
5. Asthma relief!

Racemic Mixture – Salbutamol

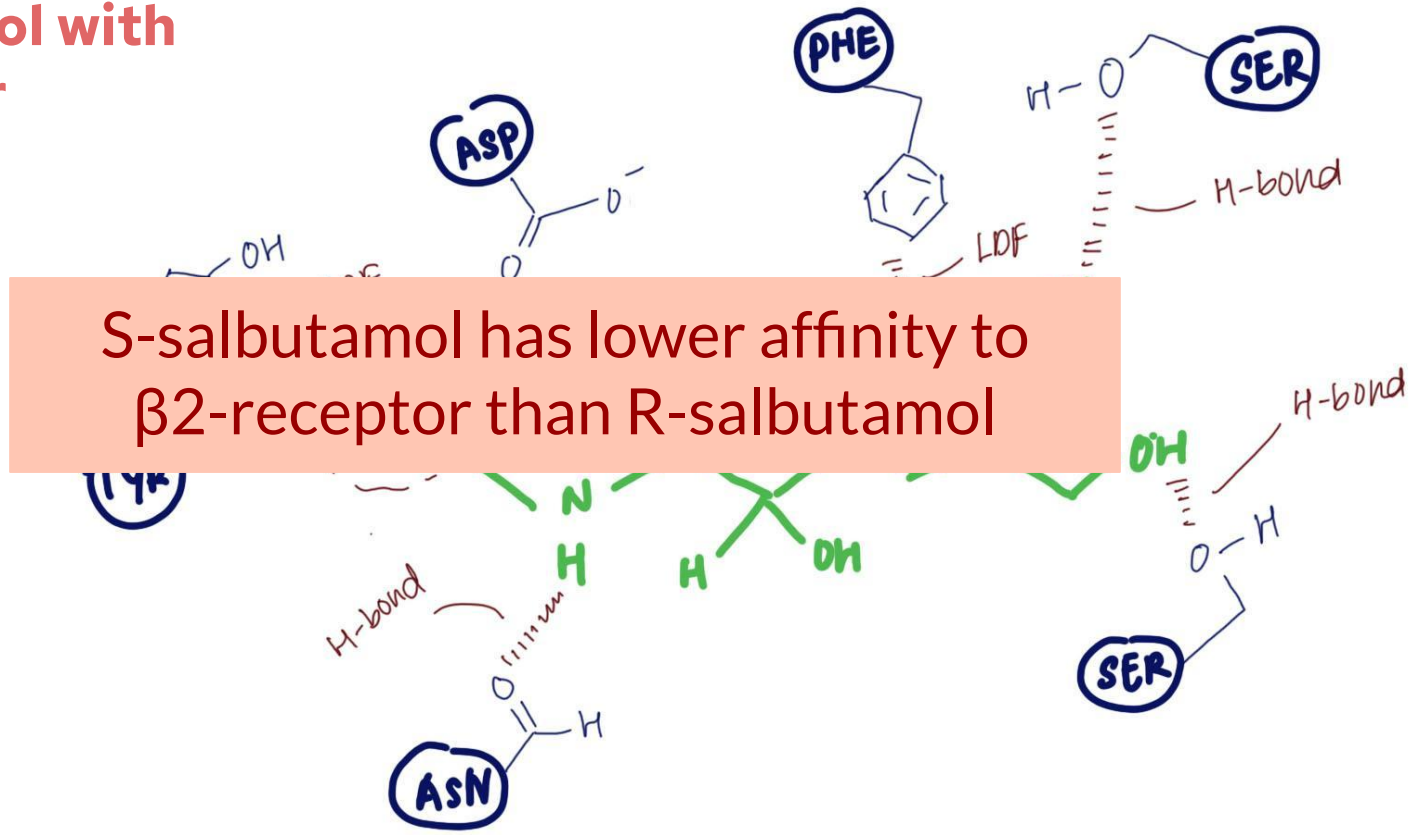
The two isomers R and S-salbutamol have been found to have opposing effects

- R-salbutamol causes smooth muscle to relax whereas S-salbutamol causes smooth muscle to contract
- The R-isomer has 150 times greater affinity for the beta2-receptor than the S-isomer and the S-isomer has been associated with toxicity

R-salbutamol with β2-receptor

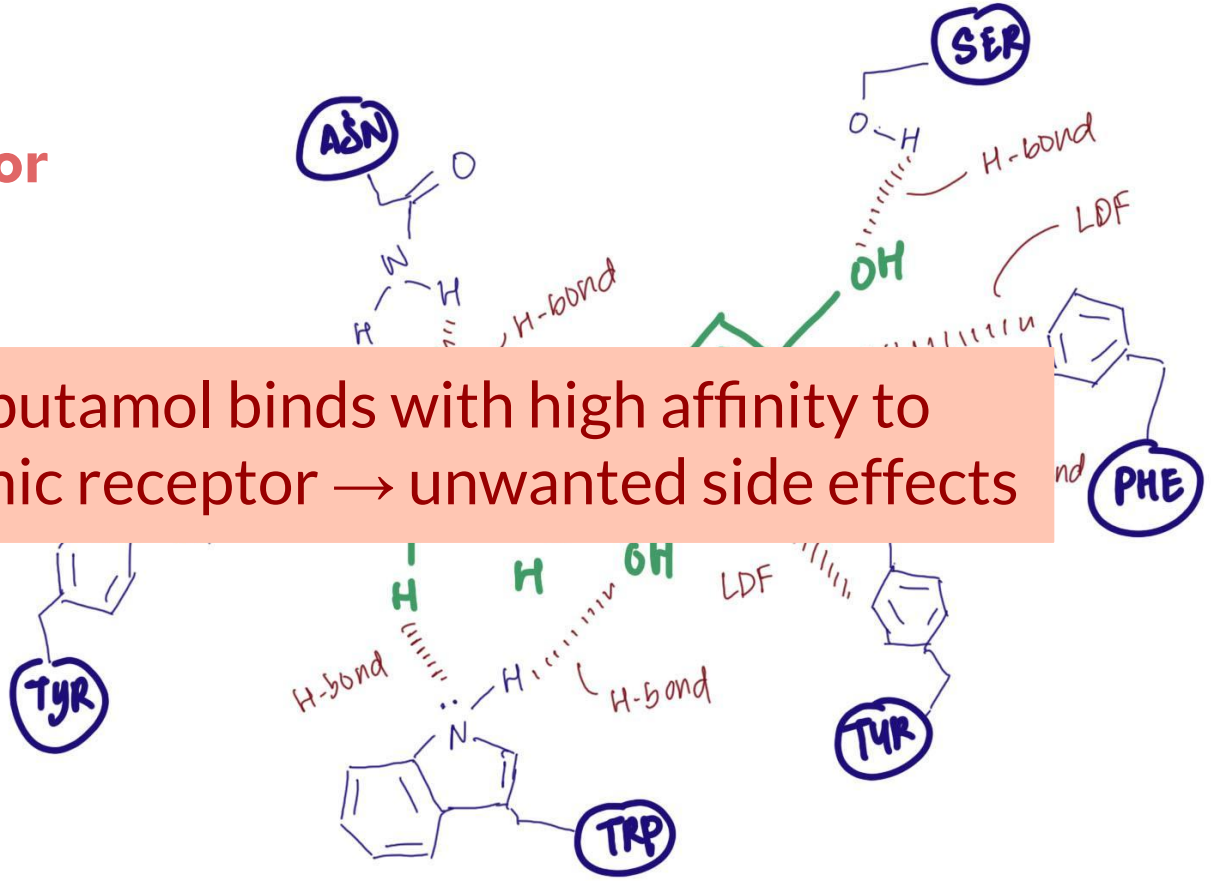


S-salbutamol with β2-receptor



S-salbutamol has lower affinity to β2-receptor than R-salbutamol

S-salbutamol with muscarinic receptor



S-salbutamol binds with high affinity to muscarinic receptor → unwanted side effects

Levosalbutamol

- Contains only **R-salbutamol** that is uniquely selective for β2-receptors
- Enantiomerically pure
- Levosalbutamol causes fewer adverse effects than salbutamol

High cost of production of this enantiomerically pure drug has deterred the widespread use of it

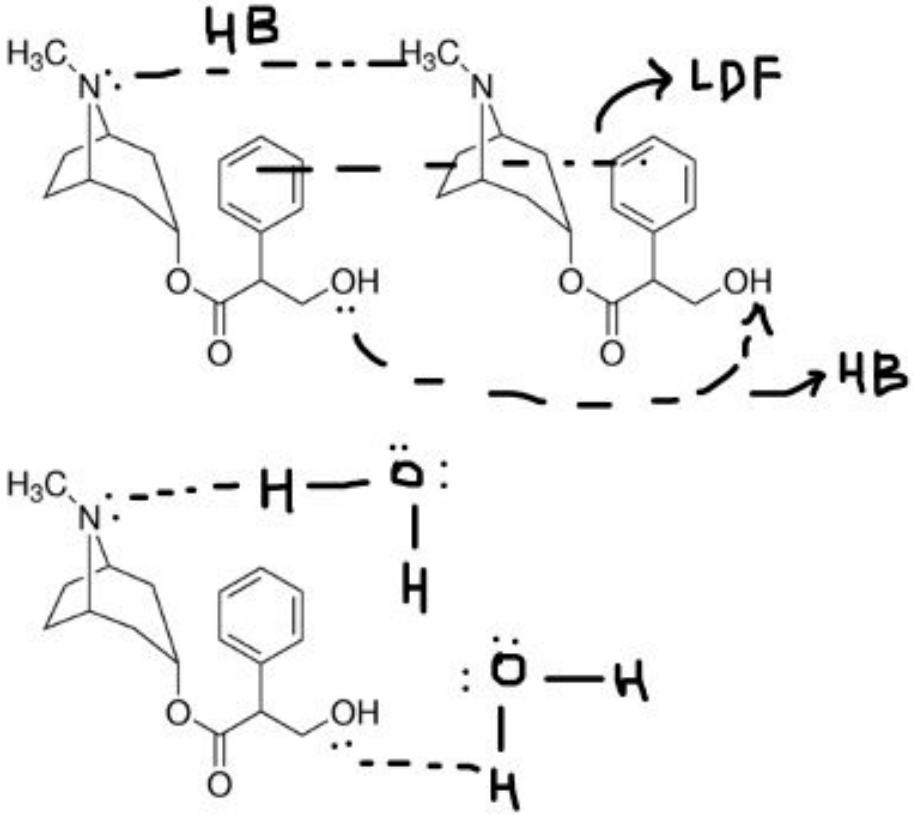
- Salbutamol is still the more popular option
  - Racemic mixture helps to offset unwanted effects of S-salbutamol

Discontinuation of Atropine

1. **Poor solubility** for administration with an inhaler

1. Too many **side effects** → non-selective inhibitor

Poor solubility for administration with an inhaler

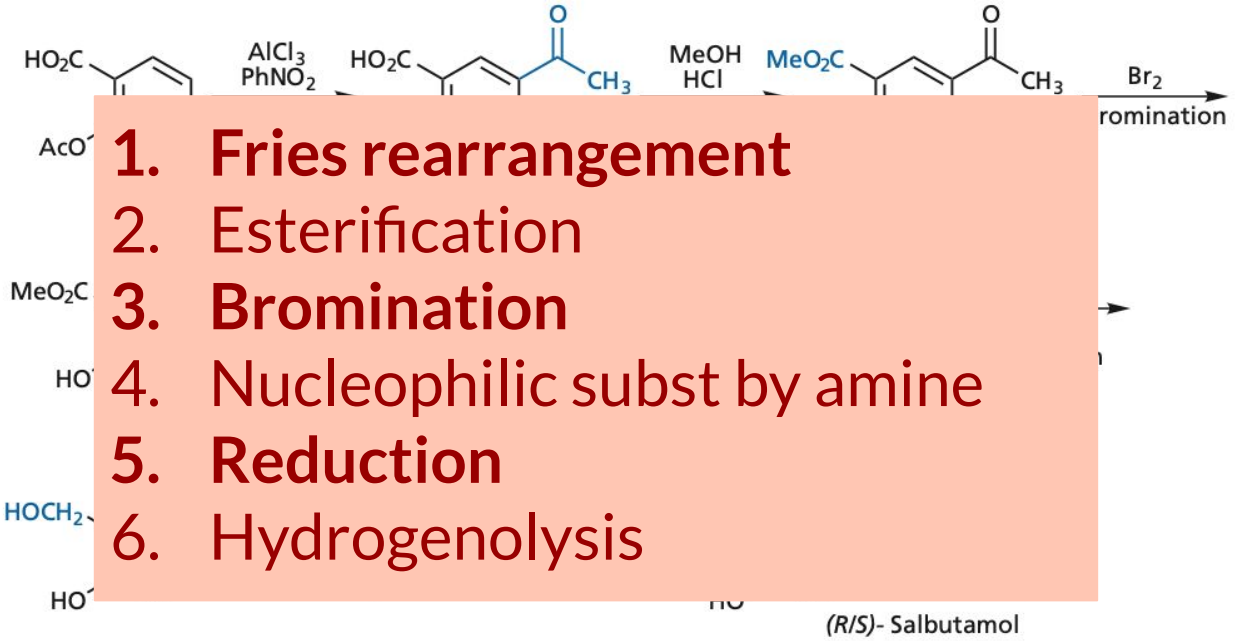


Side effects due to non-selectivity

Subtype	**Location** - Function
M1	**Brain** - In therapeutic doses, in human beings, atropine has only little or no action on the central nervous system. It may cause mild restlessness; higher doses can cause agitation and disorientation. In toxic doses it can result in CNS depression which causes circulatory and respiratory collapse.
M2	**Heart** - Atropine causes tachycardia by blocking cardiac M2. The tachycardia is modest, as there is no effect on the sympathetic system. It only inhibits the existing parasympathetic tone.
M3	**Smooth Muscles** - Bronchial, biliary and urinary tract smooth muscle are all relaxed by atropine. Incontinence due to bladder overactivity is reduced by muscarinic antagonists **Inhibition of secretions -** Salivary, lacrimal, bronchial and sweat glands are inhibited by atropine, producing an uncomfortably dry mouth and skin

3A Synthesis of Salbutamol

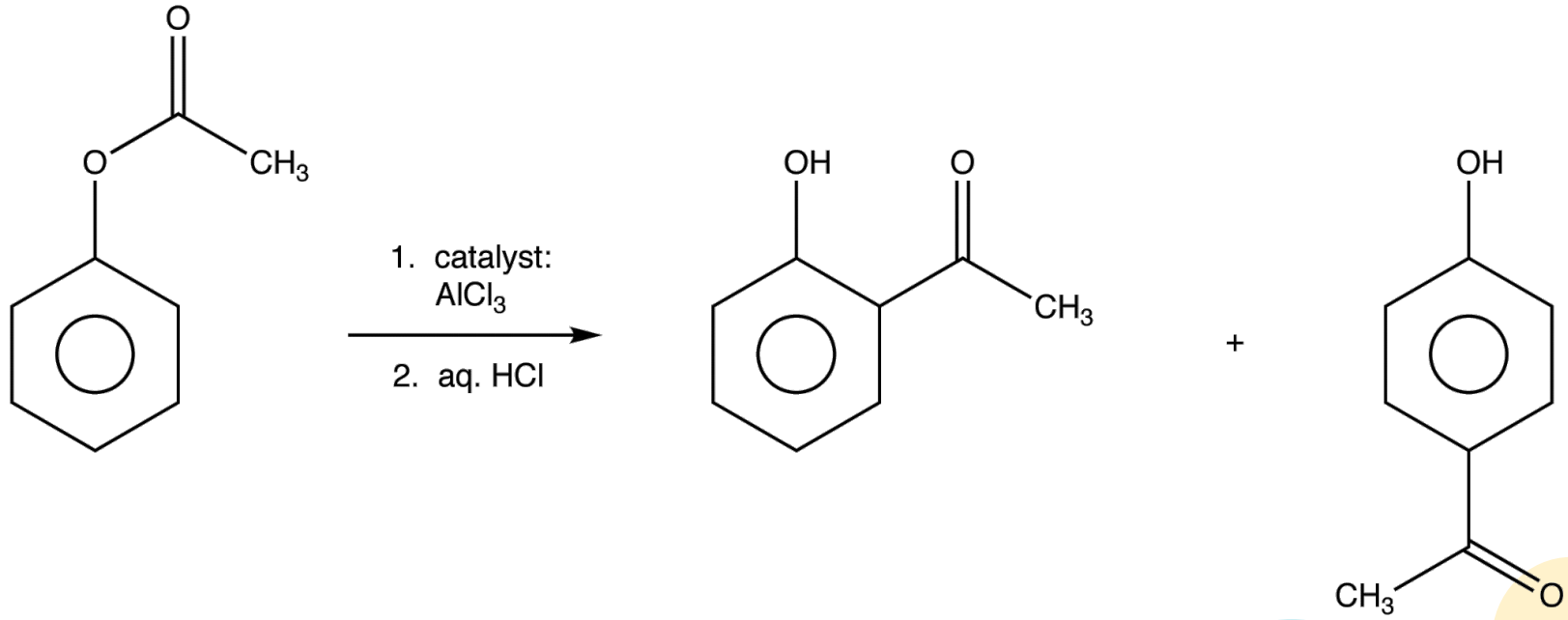
Synthesis from aspirin



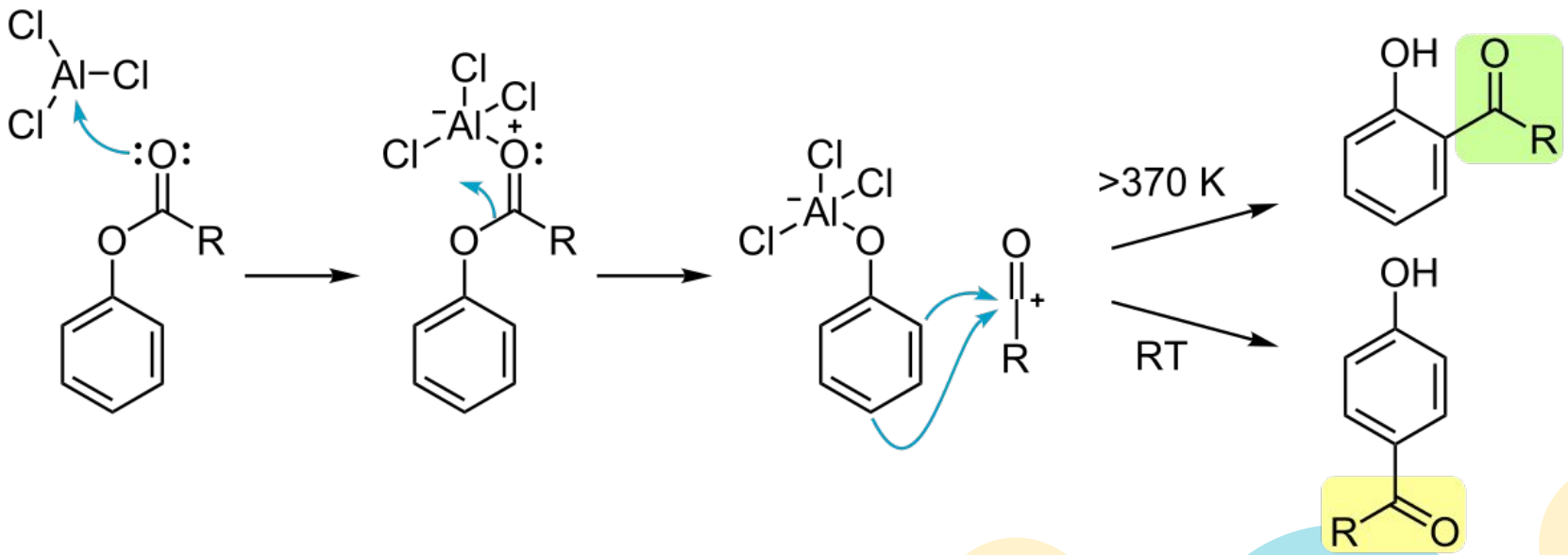
1. **Fries rearrangement**
2. Esterification
3. **Bromination**
4. Nucleophilic subst by amine
5. **Reduction**
6. Hydrogenolysis

Synthesis of salbutamol.

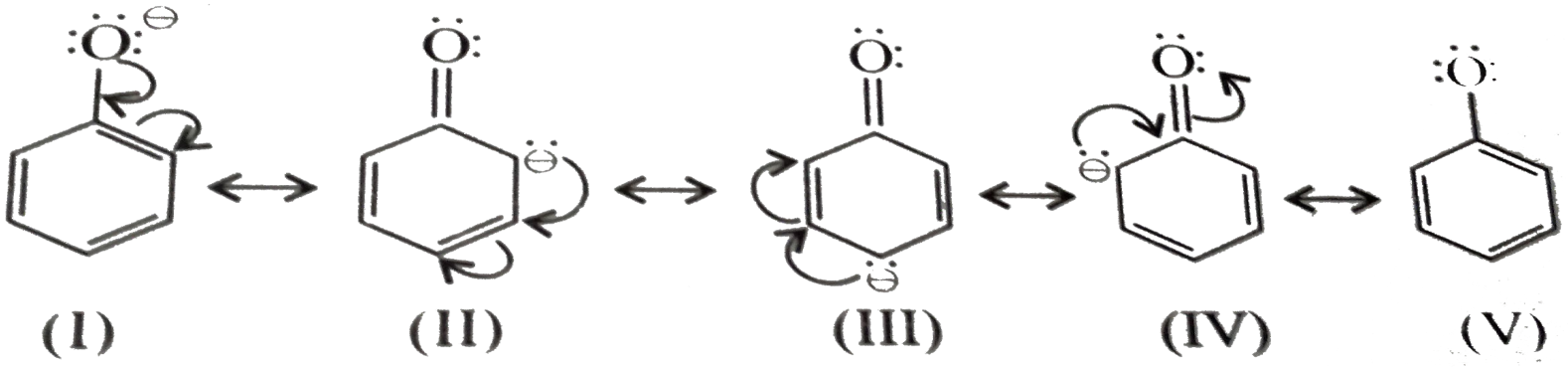
1. Fries rearrangement



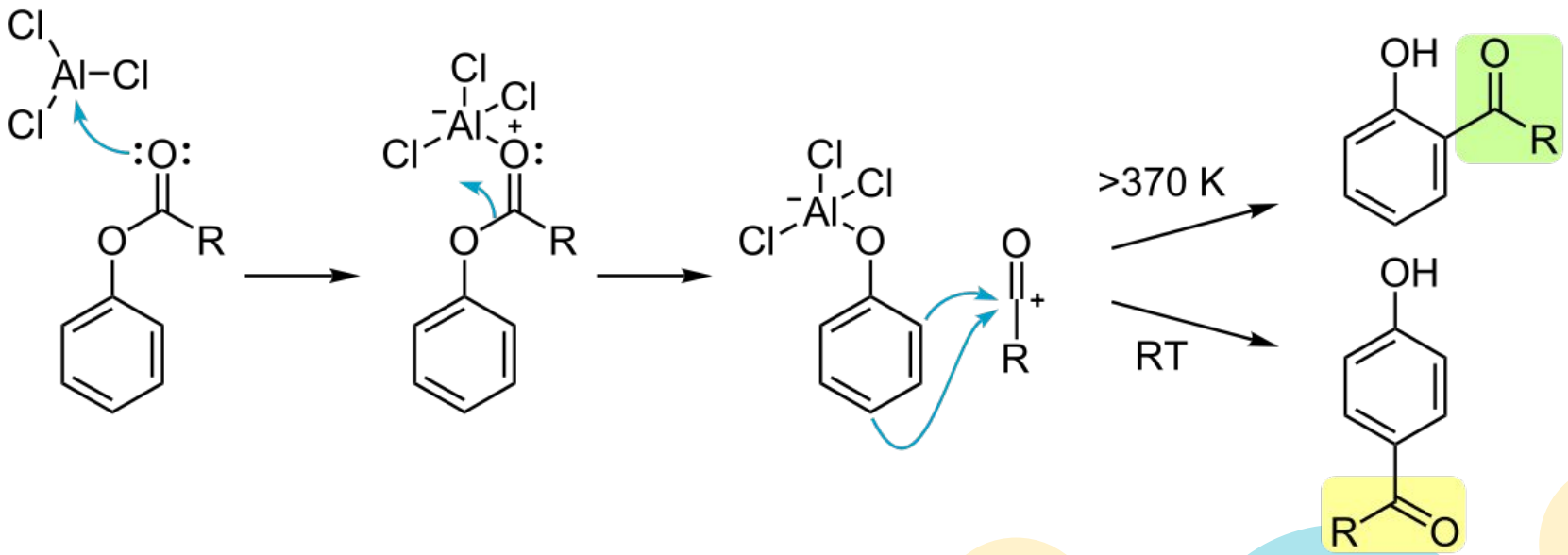
1. Fries rearrangement



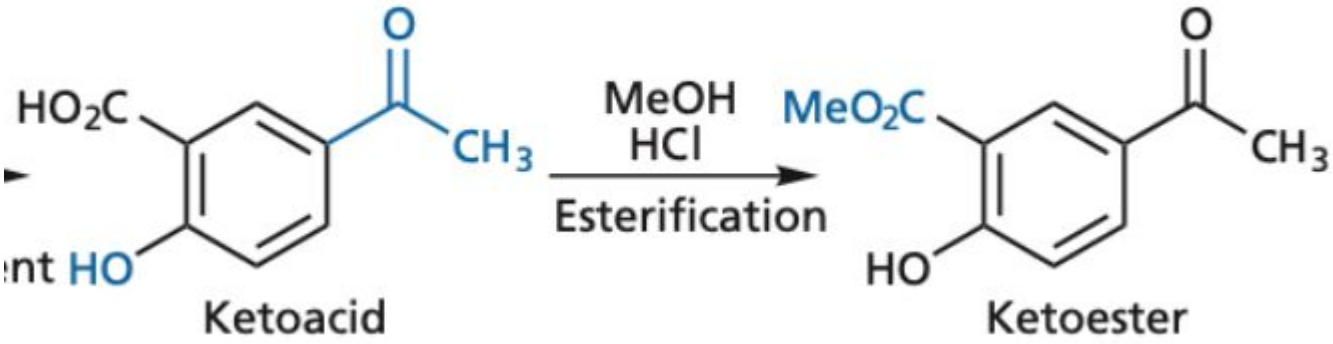
1. Fries rearrangement



1. Fries rearrangement

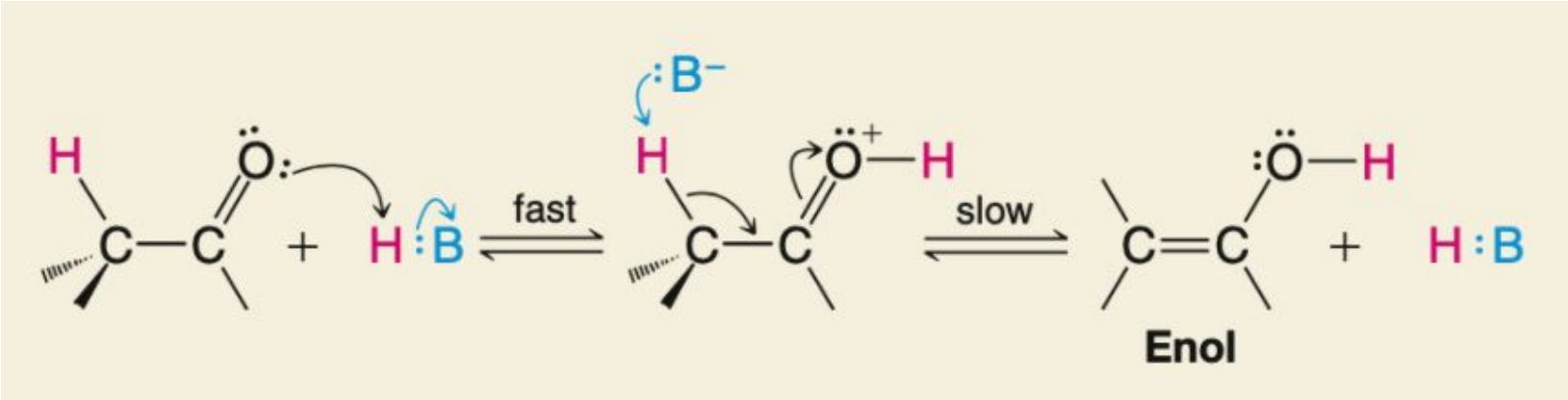


2. Esterification



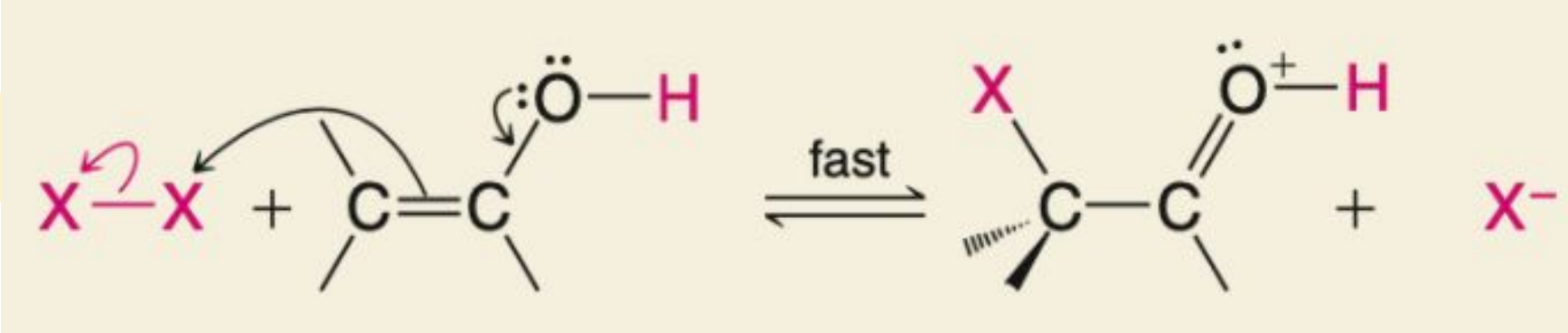
3. Bromination

3a. Bromination – Step 1



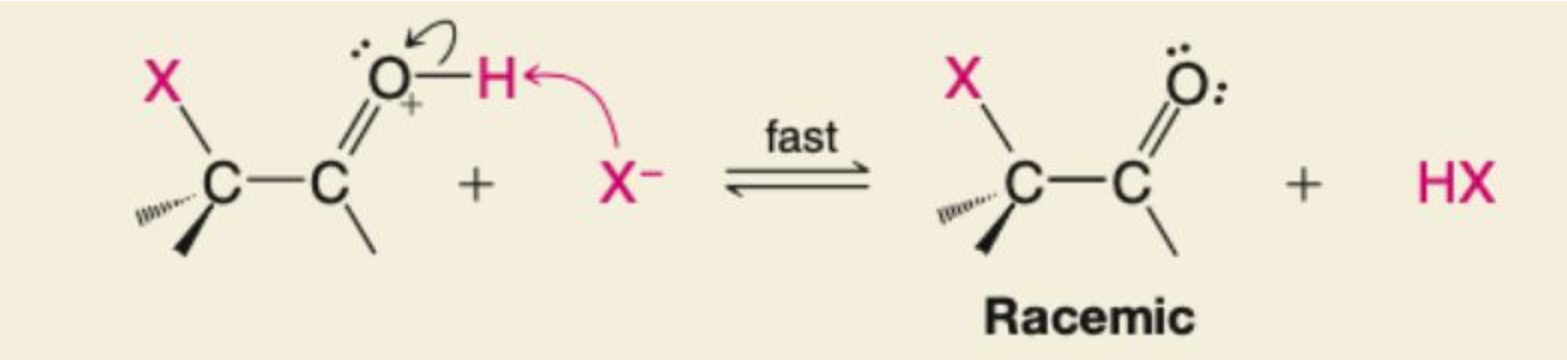
formation of C=C-OH group

3b. Bromination – Step 2



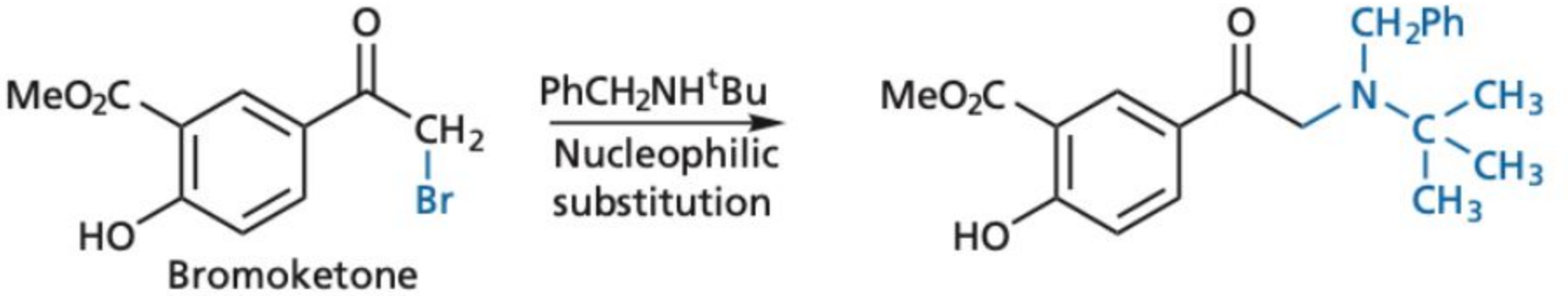
addition of bromine atom

3c. Bromination – Step 3

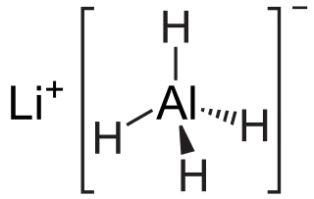


removal of proton (H^+)

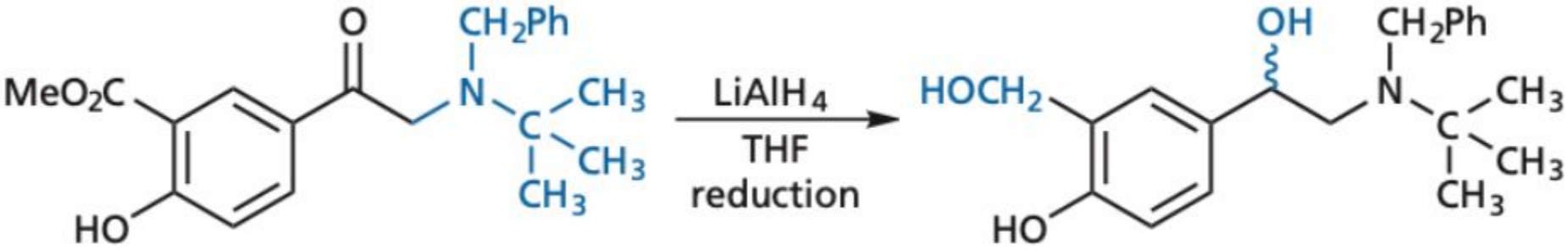
4. Nucleophilic subst by amine



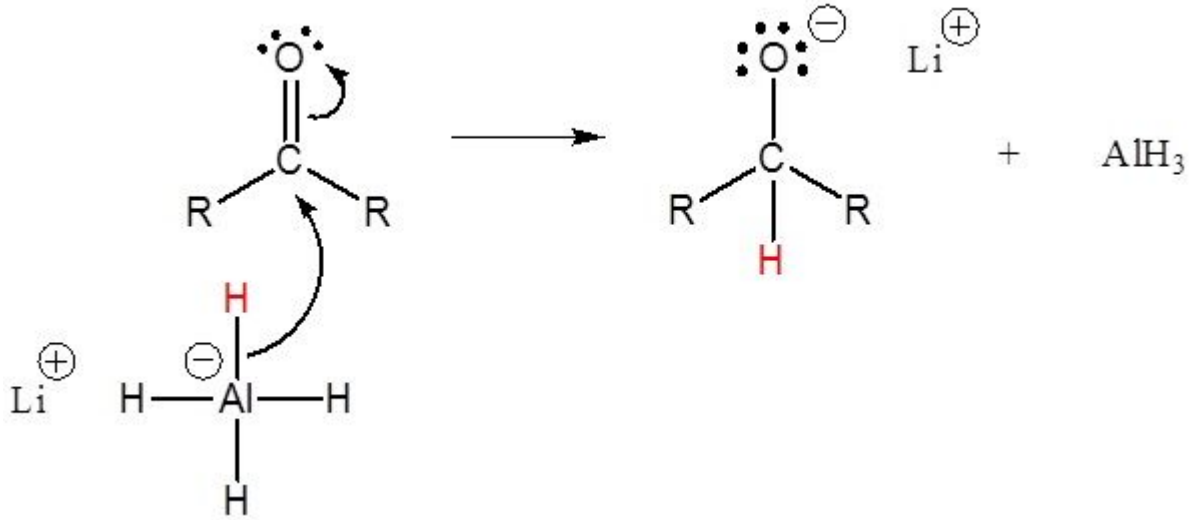
5. Reduction by LAH



LAH molecule

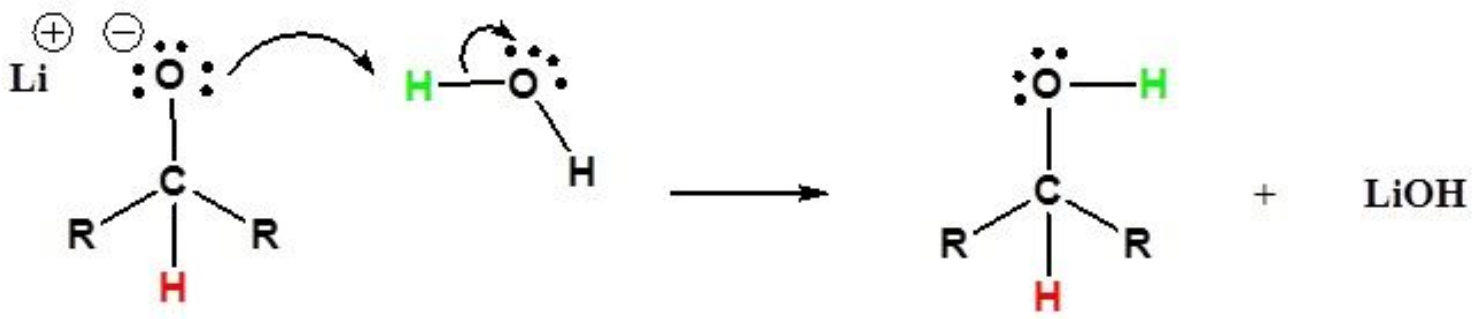


5a. Reduction by LAH – Step 1



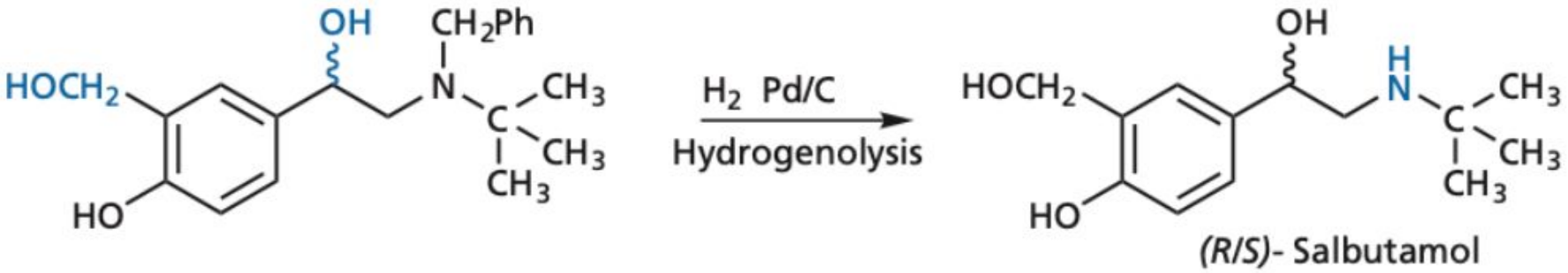
Nucleophilic attack by hydride anion

5b. Reduction by LAH – Step 2

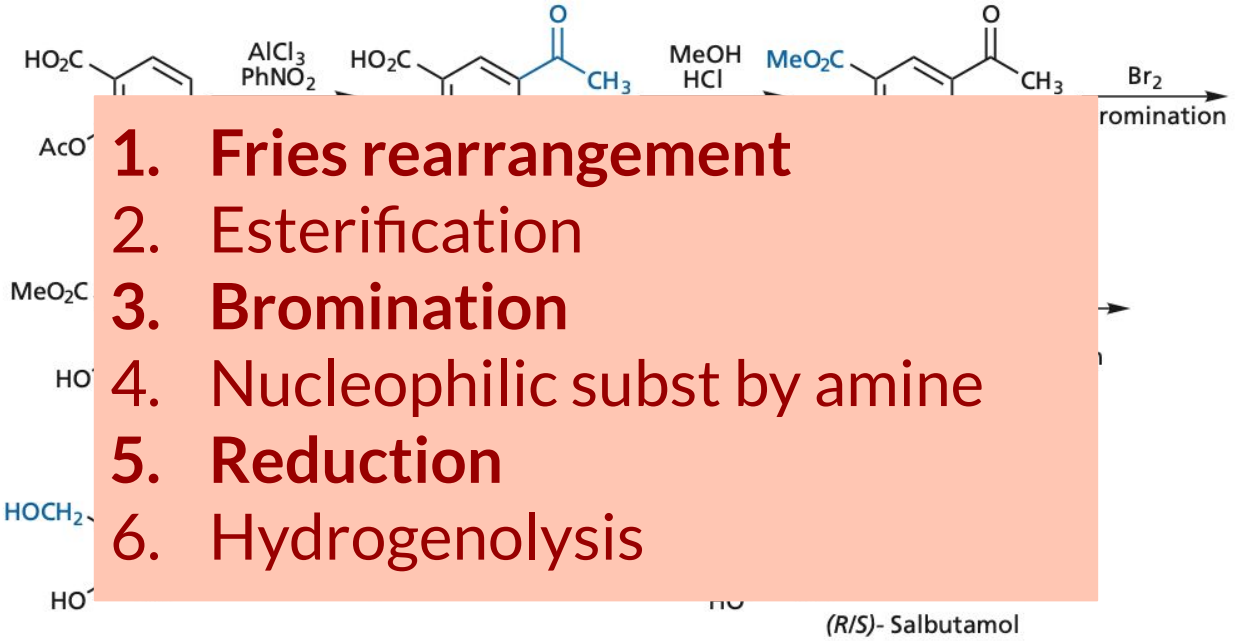


Addition of proton (H^+)

6. Hydrogenolysis



Synthesis from aspirin



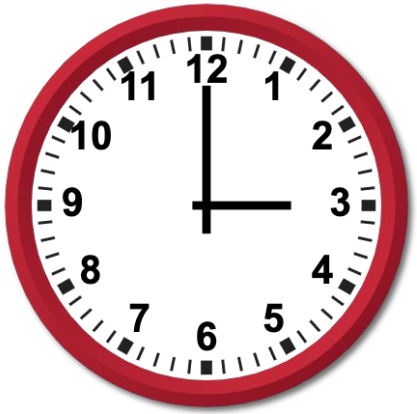
1. **Fries rearrangement**
2. Esterification
3. **Bromination**
4. Nucleophilic subst by amine
5. **Reduction**
6. Hydrogenolysis

Synthesis of salbutamol.

3B Short-acting vs long-acting asthma drugs

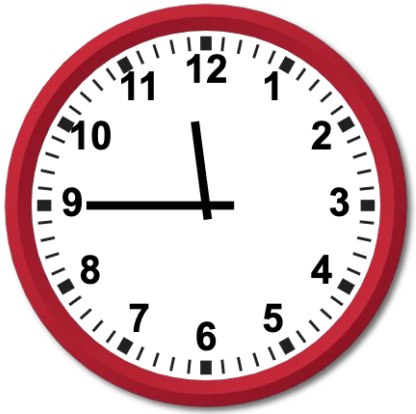
Overview & Key Terms

- When an agonist binds (i.e has strong courtship) to a receptor, it produces chemicals that cause a biological effect, such as bronchodilation.
- In biochemistry, **onset** of action refers to the amount of time a drug takes to start producing this biological effect,
- **Duration** of action is the amount of time this effect lasts.



SABA

Long-acting **beta-2 agonist**
Salbutamol
Typically fast onset

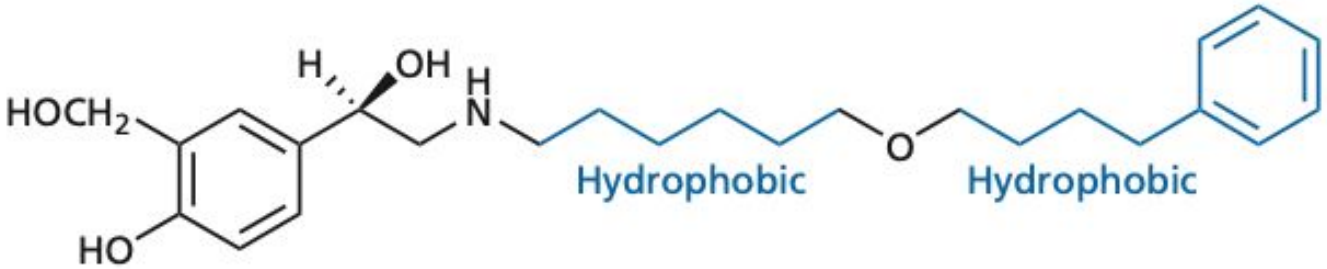


LABA

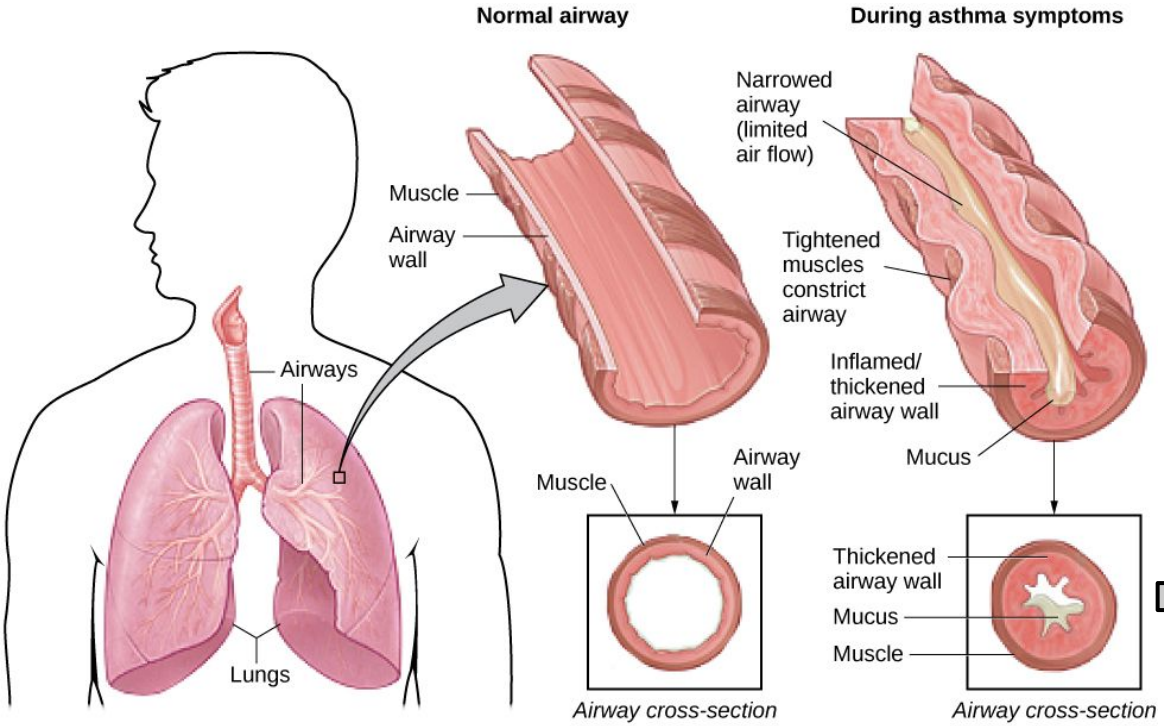
Long-acting **beta-2 agonist**
Salmeterol
Typically slow onset

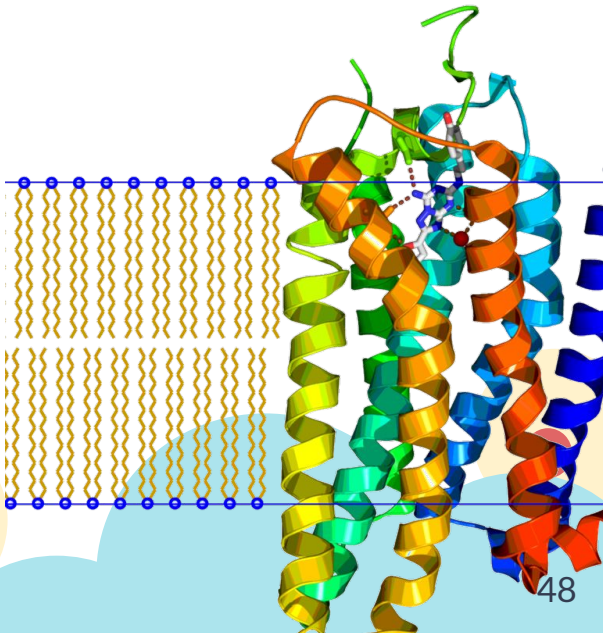
Salmeterol

- ~12 hours of duration, thus it is a LABA
- Long-chained relative of salbutamol (same **pharmacophore**), differs from salbutamol primarily in **absorption**

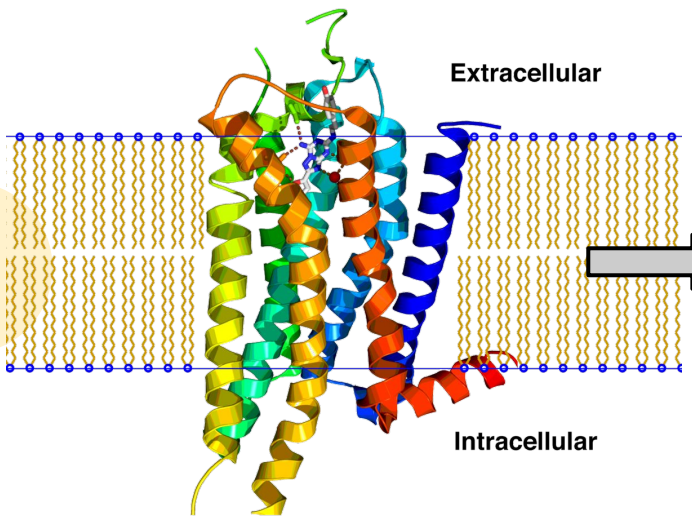


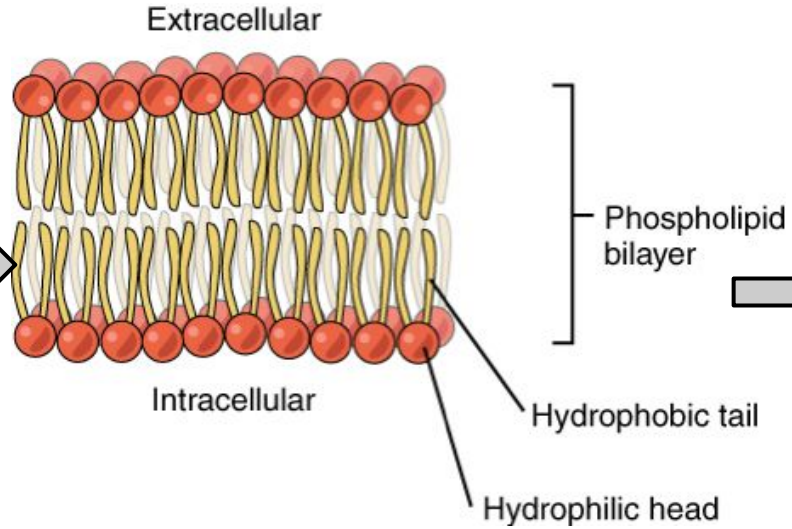
Zooming In

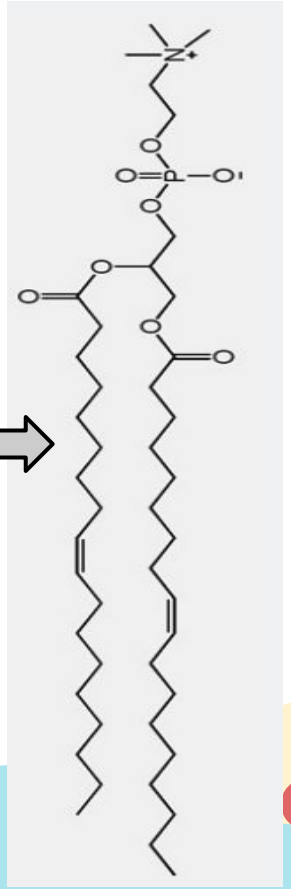

Normal airway
During asthma symptoms
Airways
Lungs
Muscle
Airway wall
Muscle
Airway wall
Airway cross-section
Narrowed airway (limited air flow)
Tightened muscles constrict airway
Inflamed/ thickened airway wall
Mucus
Thickened airway wall
Mucus
Muscle
Airway cross-section

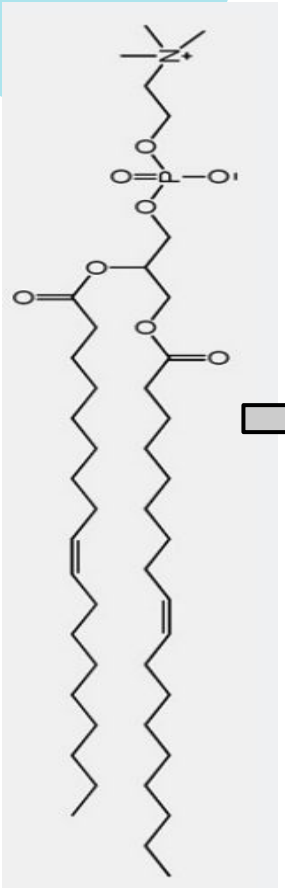


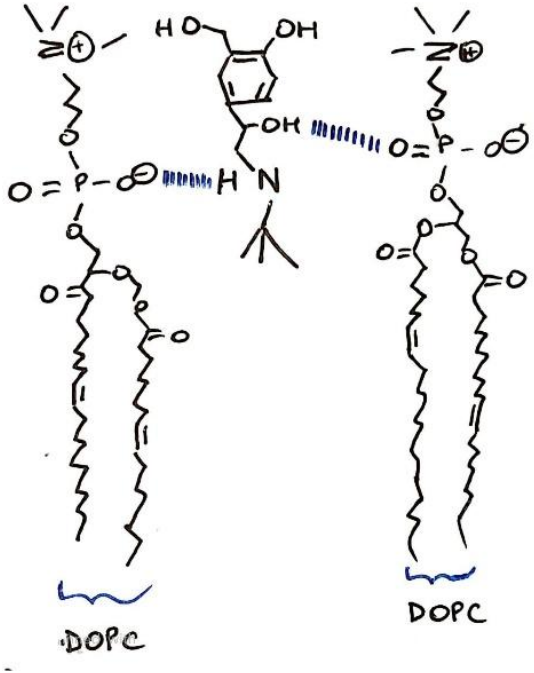
Zooming In


Extracellular
Intracellular

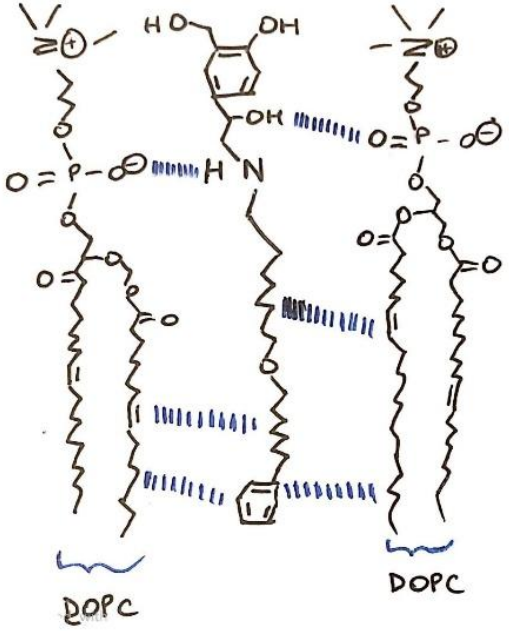

Extracellular
Intracellular
Phospholipid bilayer
Hydrophobic tail
Hydrophilic head





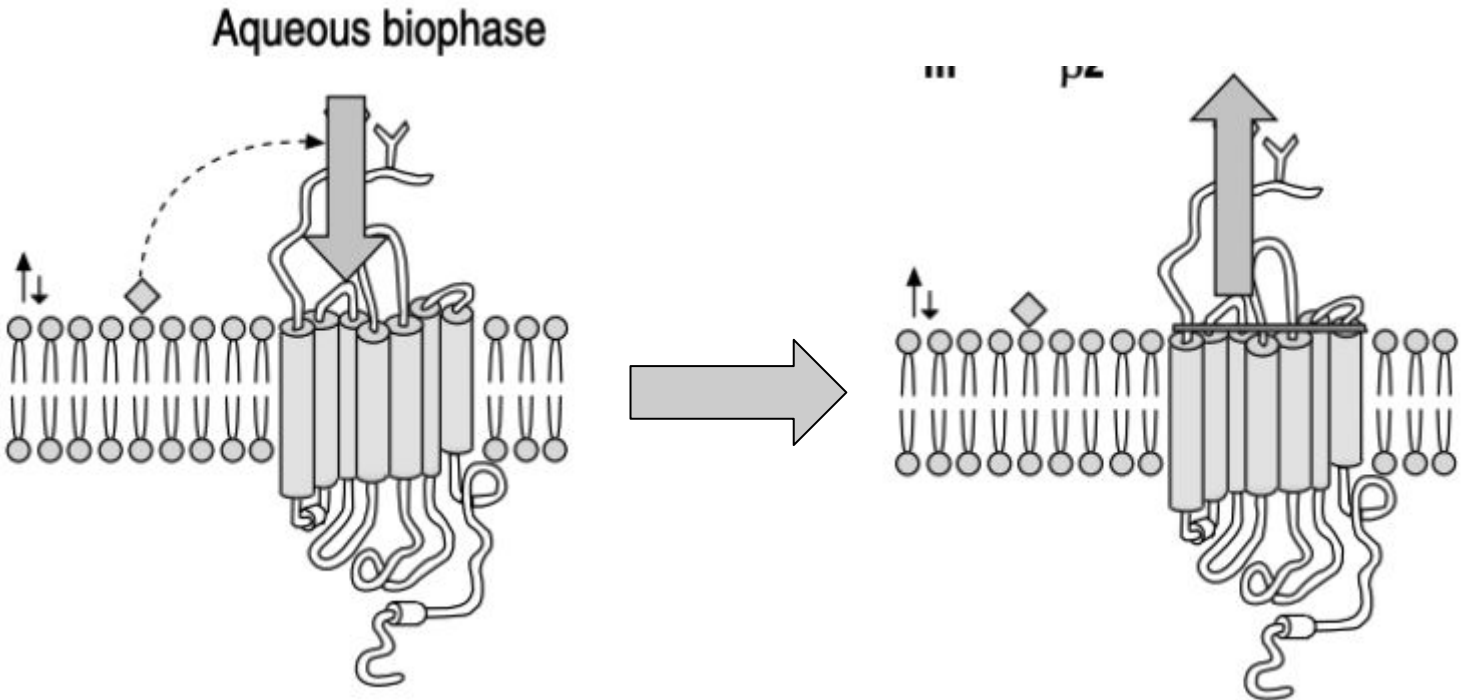


Salbutamol



Salmeterol

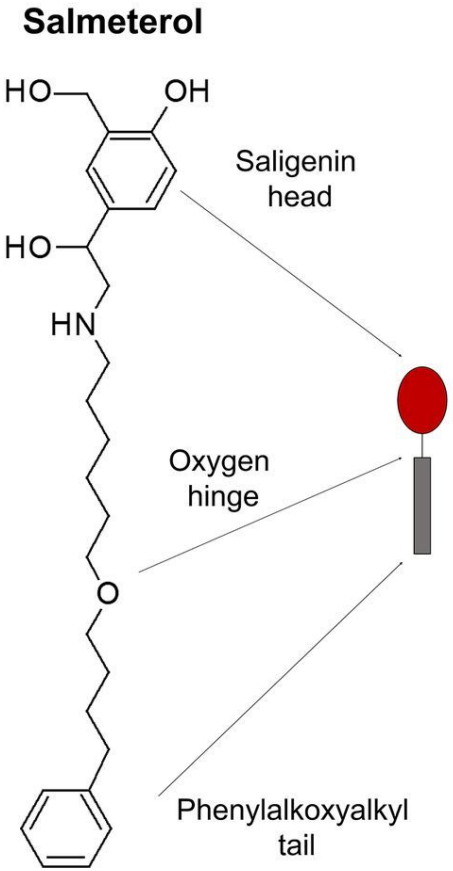
Absorption of Salbutamol

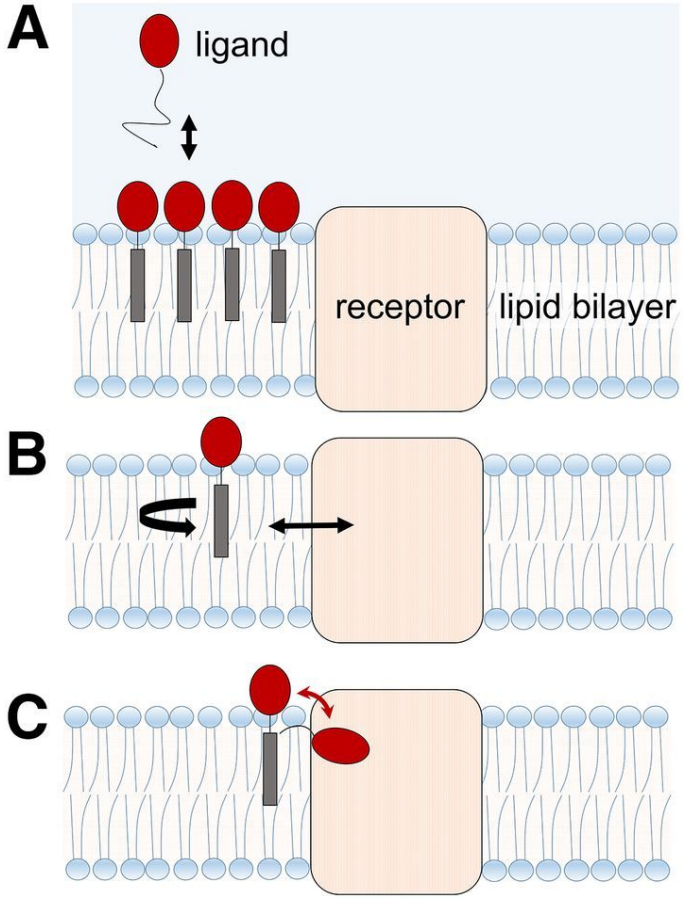


Diffuses *in* rapidly - **fast onset**

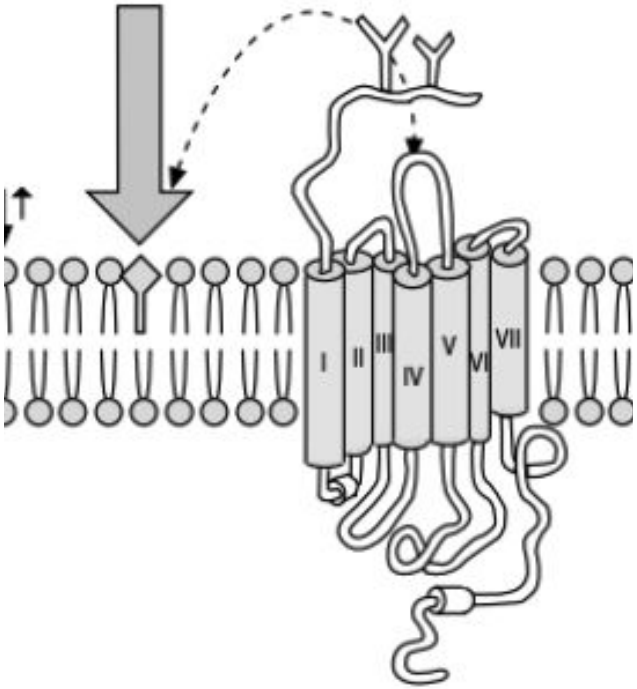
Diffuses *out* rapidly - **short duration**

Absorption of Salmeterol

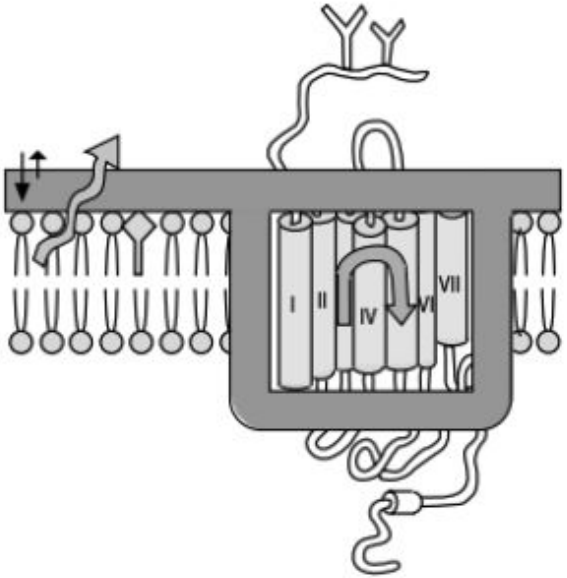




Absorption of Salmeterol



Diffuses *in* slowly - **slow onset**



Diffuses *out* slowly - **long duration**

4 Further Applications of Salbutamol

Further Applications of Salbutamol

- Salbutamol, as a bronchodilator, is also treat acute airway obstruction in most animals
  - Chosen because it binds only to β_2 receptors,, thus having fewer side effects
- Used to treat bronchospasms and coughs in cats and dogs
- Can be used in the emergency treatment of asthma in cats
- But not all of its applications are positive

Abuse of Salbutamol

- Abuse of salbutamol occurs both in asthmatic and nonasthmatic individuals
  - Encourages risky behaviour amongst non-prescribed users of inhalers

- **2004 school-based American study:**
  - 15% of 8th and 9th graders used non-prescribed inhalers
  - 10.7% of the student population borrowed the inhalers from people they knew

- Misuse attributed to perceived benefits of stimulation (e.g. increased alertness, expanded lung capacity) and the effects of fluorocarbon propellants (e.g. mild stimulation, euphoria and intoxication)

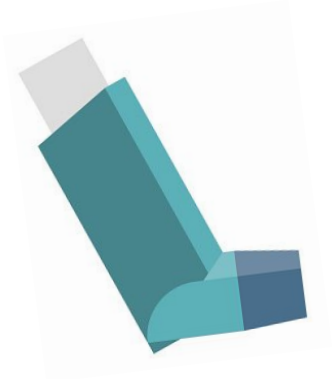
- Abuse of inhalers "part of a cluster of risky behaviour", "significantly associated with higher rates of other drug use"

Abuse of Salbutamol

- Doping in professional sports:
- While Salbutamol is not banned in professional sports, its use is highly regulated.
- Recall: Salbutamol is a β_2-agonist that temporarily increases oxygen flow in the lungs via the release of chemicals (cAMP and adenylyl cyclase)
    - Appeals to individuals for the perceived advantage in performance, especially in intensive fast-paced sports that require high levels of oxygen intake
- However, salbutamol's performance-enhancing effects when inhaled are rather insignificant as compared to injection or oral forms of it because of its lower concentration in the lungs v/s bloodstream

Abuse of Salbutamol

Chris Froome, cyclist
2017 Vuelta a España
Doping controversy



Wheezy? Breathe Easy!

Q & A

Thank you!