UPC2208 Molecular Courtship

Wheezy? Breathe Easy!

Examining the Use of Salbutamol in Asthma Treatment

Mayank Keoliya A0200908M

Rachelle Marie Chua Hui Ling A0223115X

Srinithi Rethinakumar A0194074B

Table of Contents

1.0 Introduction

As one of the world's major noncommunicable diseases, asthma is a chronic airway inflammatory disease of the lungs that affects more than 339 million people globally[1]. In particular, asthma affects the air passages of the lungs and the air flow within them. It is "characterized by an abnormal responsiveness of the airways to stimuli that are ineffective in normal subjects"[2]. Individuals with asthma experience bronchospasms — the constriction of the muscular walls of the bronchioles (where oxygen passes into blood) in the lungs — as well as mucus secretion into the airways. These result in a narrowing of the airways as well as the blockage of it, resulting in difficulties in breathing as it decreases the rate at which air can flow in and out of the lungs. Factors such as cold air, exertion and dust can trigger these asthma symptoms.

While there is no definitive cure for asthma, it is easily treatable through medication. The most common type of treatment to control the constriction of bronchial muscles comes in the form of inhalers. Inhalers puff a dose of the medication into an individual's mouth, which then gets inhaled into the airways. This causes **bronchodilation,** which increases the volume of air that can pass through the airways.

In this paper, we focus on two such drugs that treat asthma by causing bronchodilation, namely, atropine and salbutamol. Atropine, introduced in western medicine in the early 1800s, was one of the first treatments used for asthma[3]. It was suggested as an effective form of asthma therapy in 1927 by Francis Rackermann in the first edition of Russell LaFeyette Cecil's *Textbook of Medicine*[4], one of the most important and widely-consulted medical textbooks in the United States to date[5]. However, atropine was phased out for its ineffectiveness and eventually replaced by other drugs such as Salbutamol. Salbutamol, first introduced in 1966[6], currently

exists on the World Health Organization's List of Essential Medicines as one of the safest and most effective drugs for asthma treatment[7]. It is a widely prescribed drug, being the seventh most commonly prescribed drug in the United States with over 60.5 million prescriptions[8]. While both drugs function as bronchodilators, salbutamol is a short-acting beta$_2$(β_2)-agonist (SABA) that acts on the β_2-adrenergic receptor to specifically relaxes the smooth muscles in the lungs while atropine is an anticholinergic (an agent that inhibits the parasympathetic nervous system) that is non-specific in its muscle relaxation.

Through an exploration of atropine and salbutamol from a molecular courtship perspective, this report aims to illuminate the reasons as to why atropine in its inhaled formula is ineffective and has been phased out of use, while salbutamol has remained as an effective drug in asthma treatment for over half a century. To do so, this report focuses on the structure, function, and mechanism of action of the two drugs to conclude on their effectiveness at a molecular level. It also compares salbutamol, a short-term beta$_2$(β_2)-agonist (SABA), with salmeterol, a long-term beta$_2$(β_2)-agonist (LABA) that is derivative of salbutamol, to conclude on the differences between short-term and long-term beta$_2$(β_2)-agonists and their consequent different functions in asthma treatment. Finally, we conclude with a brief discussion of the further applications of salbutamol in society.

2.0 Investigating Atropine vs Salbutamol

2.1 Atropine

Atropine is derived from the components of *Atropa belladonna*, which is commonly known as the deadly nightshade. It is well known as a non-selective inhibitor (blocker) of **muscarinic receptors**[9]. The following diagram is the molecular structure of atropine (Fig. 1).

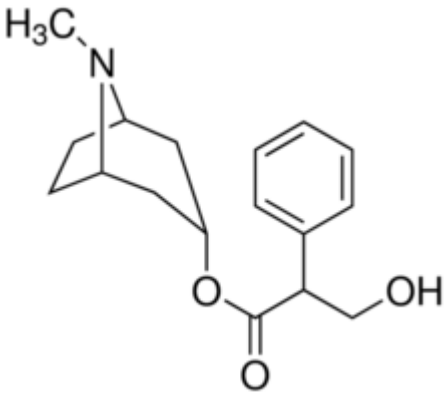


Figure 1: Molecular structure of Atropine

To understand the workings of atropine, the function of muscarinic receptors and their relationship with atropine must first be established. Muscarinic receptors are involved in the processes related to the body when one is resting, feeding or relaxed[10]. Only the M1, M2 and M3 subtypes of muscarinic receptors are well known and the details regarding their roles are as summarised in the table below[11]:

Subtype	**Location** - Function
M1	**Brain** - M1 receptors are involved in higher cognitive processes such as learning and memory
M2	**Heart** - Activation of M2 receptor results in lower cardiac output

M3	**Smooth Muscles** - Activation of M3 receptor results in the contraction of smooth muscle. It can cause stomach cramps, and **contraction** of the bladder muscles (used to treat urinary retention) and **bronchial smooth muscles.** **Secretions** - Sweating, tearing, salivation and **bronchial secretion** are also effects of this receptor. It also causes constrictor pupillae muscles in the eye to contract.

For the purpose of this paper, we will focus on the M3 receptor subtype. The activation of this receptor results in the contraction of bronchial smooth muscles and bronchial secretion (mucus). Both of these lead to difficulties in breathing due to the consequential narrowing of airways in the lungs. Hence, targeting the M3 receptor and managing to **antagonise** its action is useful in treating asthma by easing breathing difficulties. A **receptor antagonist** is a type of receptor ligand or drug that blocks or dampens a biological response by binding to and blocking a receptor rather than activating it like an **agonist**. Atropine was found to have the ability to antagonise muscarinic receptors including subtype M3.

Molecular Interaction Diagram of Atropine with Muscarinic Receptor

Now that we understand more about atropine's structure, the molecular interaction diagram of atropine binding/docking at the muscarinic receptor is shown below (Fig. 3)[12,13]. The active sites in the diagramThere are a considerable number of hydrogen bonds and pi-pi interactions between the phenylalanine (PHE) amino acid residue and the aromatic ring of atropine. There are also London dispersion forces between the tryptophan (TRP) amino acid and the carbon ring of atropine. The hydrogen bonds found between asparagine (ASN) and atropine are probably very strong due to the resonance effect of the amide groups found in ASN.

Resonance effect of the amide group of ASN

The amide bond exists in resonance structure as shown below (Fig. 2). The lone pair on the nitrogen is able to delocalise, causing the oxygen in the amide group to become negative. Due to the resonance effect, the oxygen is now more negatively charged, making it a better H-bond acceptor. This strengthens the muscarinic receptor's affinity to atropine.

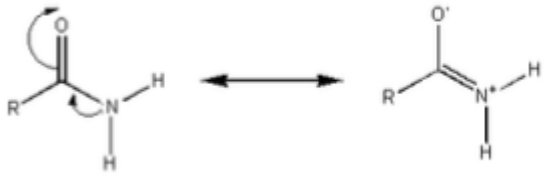


Figure 2: Resonance effect found in ASN

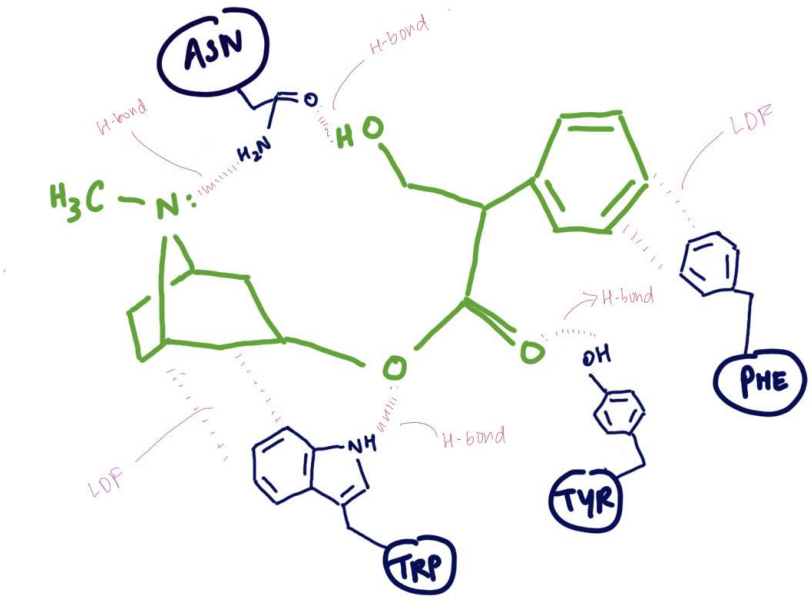


Figure 3: Docking of atropine in the active site of muscarinic receptor, M3

As seen from the figure above, there are strong intermolecular forces of attraction between atropine and the active site of the muscarinic receptor, which allows atropine to dock at the active site. This would block the usual ligand, acetylcholine, from binding to the receptor in order to activate it, preventing the contraction of the bronchial smooth muscles. Hence, in the

presence of an antagonist like atropine, bronchial muscles will relax instead of contract, making atropine a bronchodilator drug.

2.2 Salbutamol

Salbutamol has been marketed as a **racemic mixture**, although β_2-agonist activity resides almost exclusively in the **(R)-enantiomer**. A racemic mixture consists of equal parts of two enantiomers. Enantiomers are isomers that are mirror images of each other and rotate plane-polarized light in an equal but opposite direction. Salbutamol consists of the enantiomers, R-salbutamol and S-salbutamol (Fig. 4). Both enantiomers differ in their agonistic function and S-salbutamol is found to trigger adverse effects in patients which then led to the development of an enantiomerically pure R-salbutamol formulation known as **levosalbutamol**[14]. While both levosalbutamol and salbutamol are marketed as asthma medication, this paper will focus on salbutamol as a racemic mixture, as it is more commonly used by asthmatic patients.

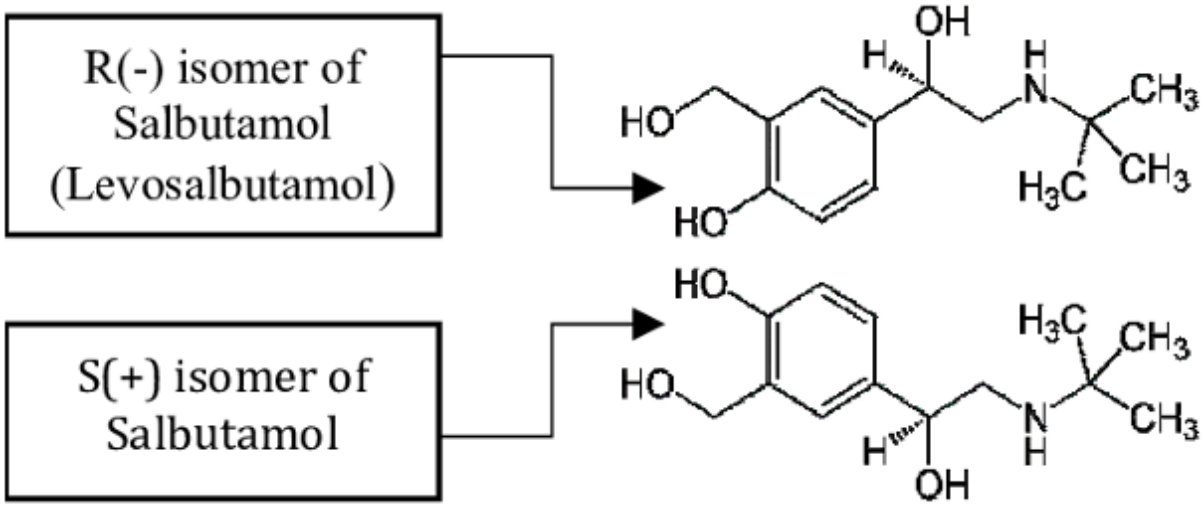


Figure 4: Structures of enantiomers, R-salbutamol and S-salbutamol[15]

Before moving on to the drug, here is a brief description on the function of a β_2-receptor and its role in bronchodilation. Agonising the β_2-receptor in the smooth muscles of the lungs, will lead to the stimulation of the adenylyl cyclase enzyme, which leads to the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Increased levels

of cAMP leads to the relaxation of bronchial smooth muscles. Hence, in a patient suffering from an asthma attack, this drug will provide immediate relief by dilating the bronchial muscles, allowing them to breathe easier.[16]

2.2.1 Salbutamol Racemic Mixture

There is a controversy about the racemic mixture of salbutamol as 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. Compared to S-salbutamol, R-salbutamol binds to the β_2-receptor with 150 times the affinity. Additionally, S-salbutamol, like atropine, has been found to cause toxicity and is known to bind to muscarinic receptors, resulting in bronchial muscle contraction[17]. The following sections will explore possible reasons as to why the enantiomers could have opposing effects.

2.2.2 R-salbutamol

Other than the relaxation of smooth muscle, R-salbutamol also has several other beneficial effects on the lungs like the increased clearing of mucus[18] in the lungs and the ability to some extent, reduce acute inflammation, which is another symptom of asthma.

Molecular Interaction Diagram of R-salbutamol with β_2-receptor

Pi-pi interactions exist between the aromatic ring in R-salbutamol and PHE amino acid found in the active site of the β2-receptor. There is also hydrogen bonding present between the amino acids, serine (SER), aspartic acid (ASP), asparagine (ASN) and R-salbutamol as illustrated below. The intermolecular forces of attraction allow for the binding of R-salbutamol to the β2-receptor. Upon binding of the agonist R-salbutamol to the receptor, downstream molecules are activated, resulting in the dilation of the bronchial muscles.

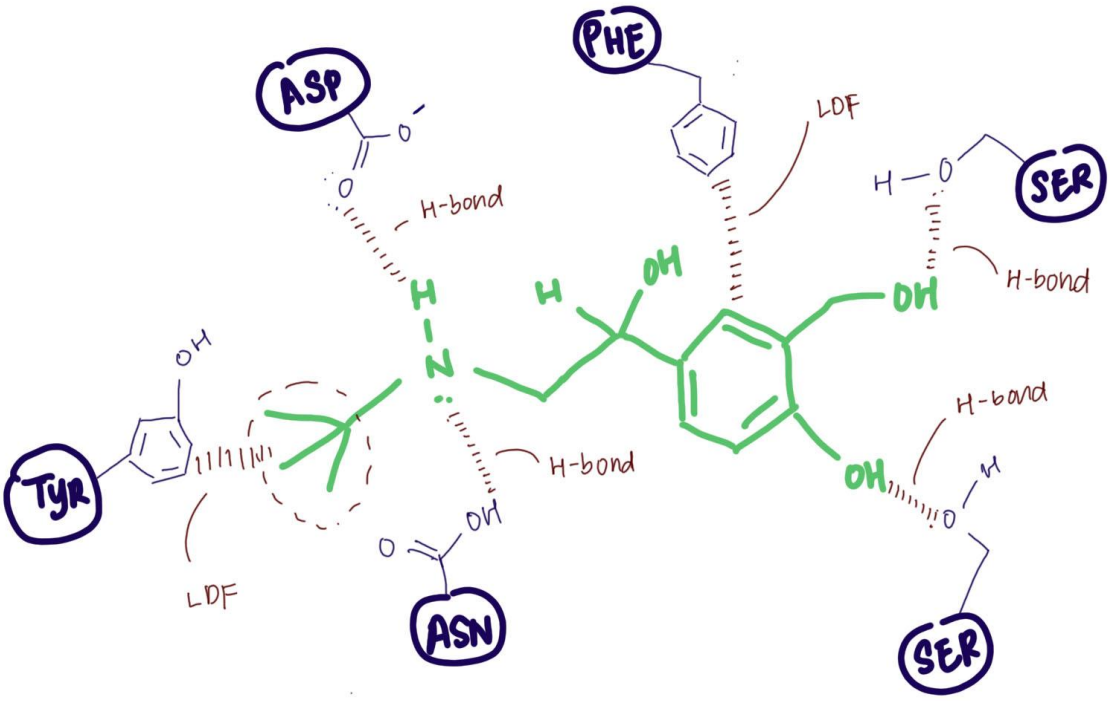


Figure 5: Docking of R-salbutamol in the active site of β2-receptor[19]

2.2.3 S-salbutamol

As mentioned previously, S-salbutamol has a lower affinity to β_2-receptors. It also binds to the muscarinic receptor, acting as an agonist. This binding results in the initiation of muscle contraction of the bronchial smooth muscles— the opposite effect of R-salbutamol. The following interaction diagrams can give an insight as to why this could be so.

Molecular Interaction Diagram of S-salbutamol with β_2-receptor

Due to the conformation of S-salbutamol, which can be visualised as a mirror image of R-salbutamol, some of the amino acid residues like ASP in the active site will be unable to form hydrogen bonds with S-salbutamol. As discussed previously, the hydrogen bonding by ASP is strong due to the resonance of the amide group in ASP. Hence, this further supports the fact that the bonding of S-salbutamol to the active site of the β2-receptor is not as strong as its

enantiomer. In fact, as the following only depicts a possible 2D arrangement of the docking of salbutamol in the active site, it is possible that S-salbutamol has even weaker docking in the active site if the 3D arrangement was considered. This could also explain why S-salbutamol has much lower affinity to β2-receptor than R-salbutamol.

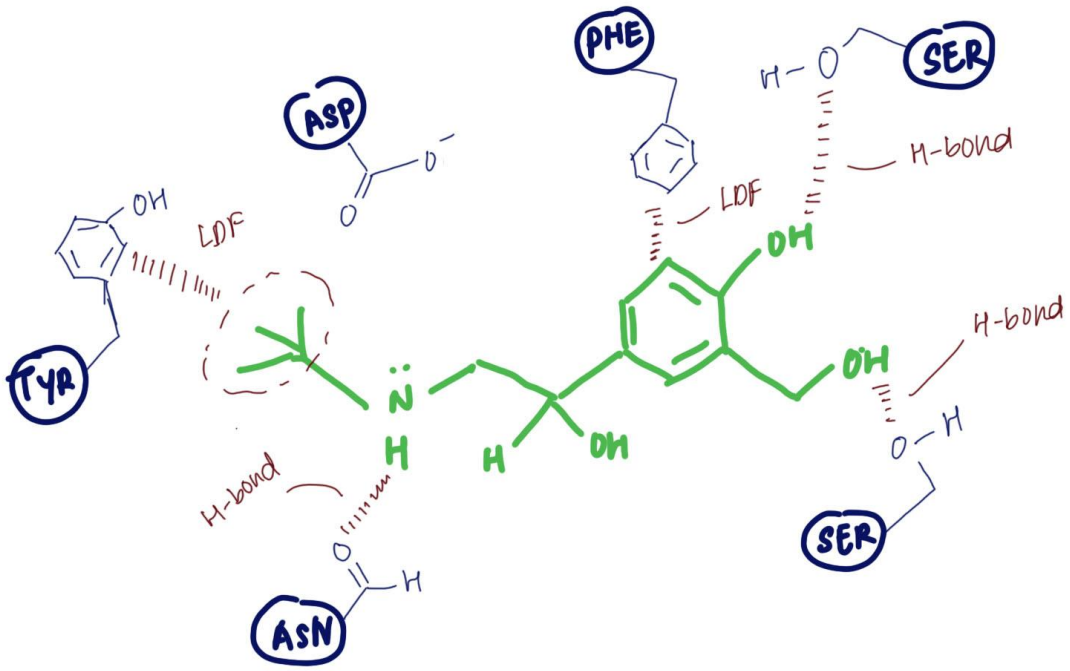


Figure 6: Docking of S-salbutamol in the active site of β2-receptor

Molecular Interaction Diagram of S-salbutamol with Muscarinic Receptor

There is hydrogen bonding between the tyrosine (TYR), ASN, TRP and SER residues and the alcohol groups on the aromatic ring of salbutamol. The molecular docking of S-salbutamol in the active site of the muscarinic receptor seems stronger with the β2-receptor due to the presence of more hydrogen bonds. This could be why S-salbutamol preferentially binds to the muscarinic M3 subtype receptors, resulting in unwanted effects like bronchial constriction.

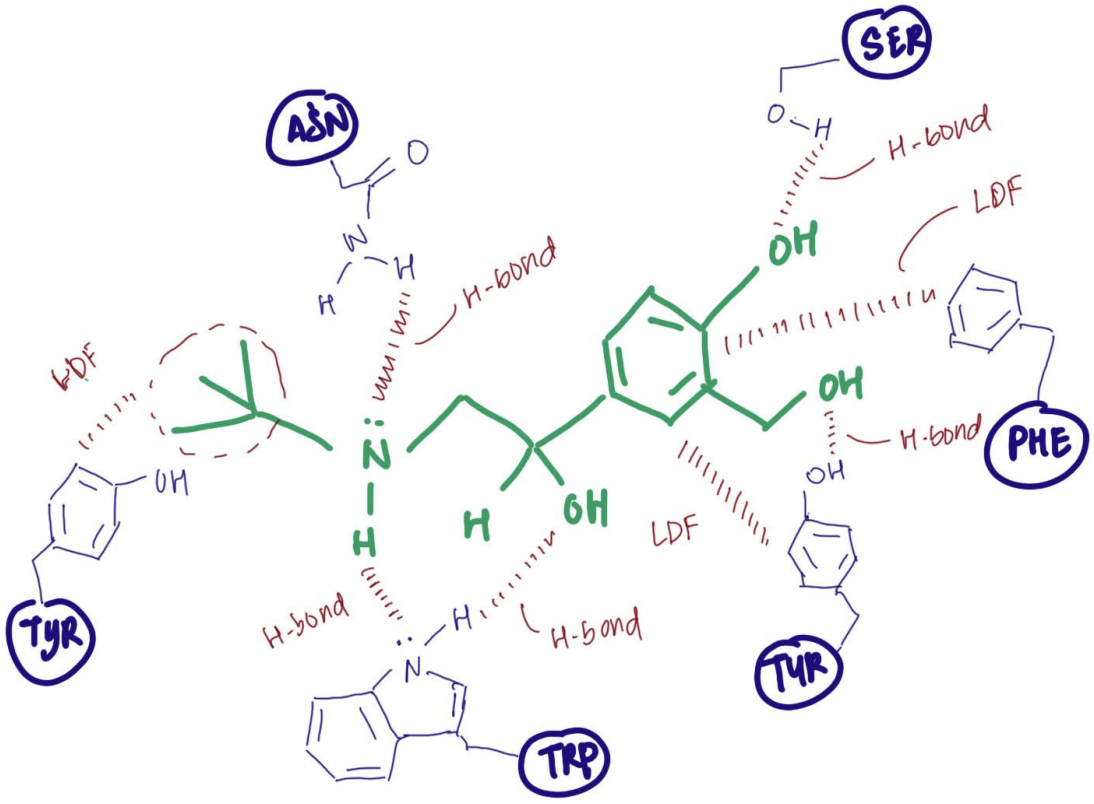


Figure 7: Docking of S-salbutamol in the active site of muscarinic receptor M3

2.3 Discontinuation of Atropine and Efficacy of Salbutamol as Bronchodilator Drug

As mentioned previously, atropine is no longer used as a bronchodilator drug. There are two reasons for this. Firstly, atropine has poor solubility in water and thus, is not effective for use as an inhalant drug. Atropine is naturally present as a white, crystalline solid. To be stored in inhalers, it must be dissolved in water. However, it has low solubility in water— 455ml water dissolves only 1g of atropine[20]. This low solubility can be explained by examining the intermolecular forces of attraction between atropine molecules, between water molecules, and between water (the solvent) molecules and atropine (the solute) molecules.

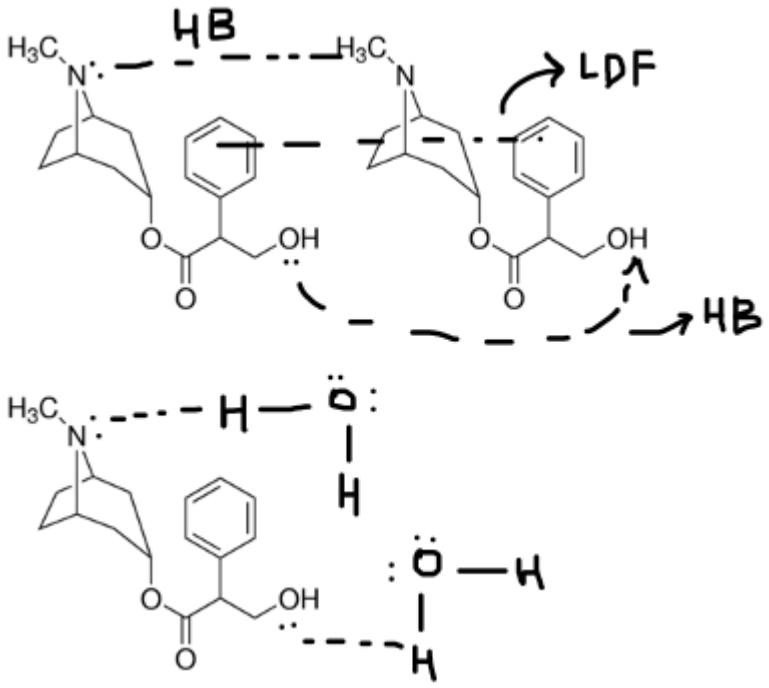


Figure 8: Intermolecular forces of attraction between atropine and water molecules

The intermolecular forces of attraction between atropine molecules are very strong, especially due to the London dispersion forces between the aromatic rings in the atropine molecule. There are also hydrogen bonds between the oxygen in the alcohol groups and nitrogen in the amine group in the atropine molecule. However, in the interaction between atropine and water, there is only hydrogen bonding, as presented above. Since the forces of attraction between the atropine molecules are stronger than those between atropine and water, it can be concluded that the solubility of atropine is poor. Hence, this is one of the two reasons atropine is rendered unfit for mass use in inhalers.

The second reason is mainly due to the fact that it interacts with many of the other muscarinic receptor subtypes apart from M3. Hence, antagonising M1 and M2 results in could affect cognitive process and arterial function respectively. The effects of atropine as a non-selective antagonist of all muscarinic receptors can be found in the table below.

Subtype	Location - Function
M1	**Brain** - In therapeutic doses, in human beings, atropine has only little or no action on the central nervous system (CNS). 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

As can be seen above, while administering atropine relaxes bronchial muscles, it also causes many other unwanted effects. Hence, due to its lack of specificity as a drug in relieving patient symptoms, it was discontinued as a bronchodilator and replaced by drugs like salbutamol that avoid such negative impacts.

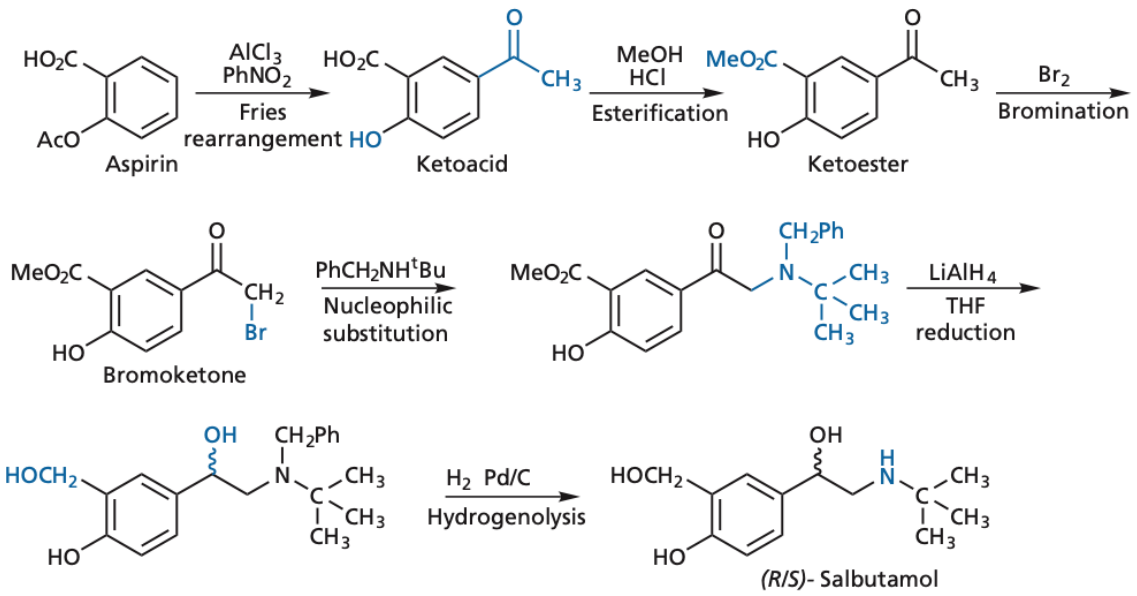
Salbutamol is a more successful drug than atropine as it is selective for only one type of receptor, the β_2-receptors. However, as mentioned previously, the S isomer of salbutamol does have some selectivity for muscarinic receptors that result in the unwanted physiological

response of bronchial muscle contraction. Salbutamol is thus marketed as a racemic mixture to minimise the negative activity of S-salbutamol. Levosalbutamol, containing only the R-salbutamol that is uniquely selective for β_2-receptors and not muscarinic receptors, is an alternate option. Levosalbutamol causes fewer adverse effects than salbutamol. It avoids causing conditions such as tremors, palpitation, tachycardia, and nervousness. However, while levosalbutamol seems like the better option of the two, the high cost of production of this enantiomerically pure drug has deterred the wide-spread use of it[21]. Hence, salbutamol, the racemic mixture, remains the more popular of the two treatment options.

3.0 Short-term vs Long-term Asthma Treatment

3.1 Synthesis of Salbutamol

One of the most popular methods for the synthesis of salbutamol is through the chemical modification of aspirin. To examine why this is so, this section explores the chemical process of turning aspirin into salbutamol, focusing on how the favourable courtship between reagents, solvents and catalysts leads to a good yield of salbutamol. The following synthesis of salbutamol through aspirin was suggested by Ganellin et al in 1993[22]:



Synthesis of salbutamol.

Figure 9: Overview of synthesis of salbutamol using aspirin

The synthesis of salbutamol through aspirin occurs in a 6-step process:

1. Fries rearrangement
2. Esterification
3. Bromination
4. Nucleophilic substitution by tertiary amine
5. Reduction by lithium aluminium hydride (LAH)
6. Hydrogenolysis

In this paper, we focus on **Fries rearrangement**, **bromination**, and the **reduction by LAH**, since their mechanisms are relevant to the concepts explored in this module. The explanation of the remaining steps is outside the ambit of this paper.

Firstly, the **Fries rearrangement** involves the breaking of one end of the ester linkage, and thus the migration of the acetyl group (CH_3-C=O) to the benzene ring itself. We transform aspirin (an ester) to a ketone. Aluminium chloride ($AlCl_3$) acts as a catalyst here.

In analysing the mechanism of Fries rearrangement, we consider the $AlCl_3$ molecule. The Al atom has 6 electrons in its valence shell - 3 of its own, and 3 bonding electrons. It is short of an octet, and is thus electron deficient. As an electrophile, it will form a courtship with the carbonyl oxygen atom from the electron-rich aspirin. This is because in aspirin, the carbonyl oxygen (in the C=O bond) is more electron-rich than the phenyl oxygen (C-OH bond), as the latter has electrons delocalized in the aromatic benzene ring. $AlCl_3$ thus attacks at the more nucleophilic carbonyl oxygen, and forms a marriage with it, forming the ketoacid (the second step in Fig. 10).

At this point, evidence shows that there occurs an intramolecular rearrangement of the $AlCl_3$ complex. However, its precise mechanism is not known[23]. A possible theory is that the carbonyl oxygen is not stable when it has a positive charge, and thus it pulls the electrons of the polar Al-O bond toward itself, resulting in the formation of the $AlCl_3$ marriage at the phenyl oxygen.

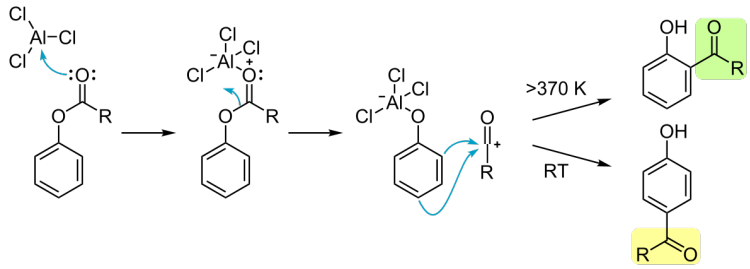


Figure 10: Fries rearrangement on phenyl acetate

There is now a positive charge at the phenyl group, which pulls electrons from the adjacent carbon atom. The acetyl group leaves as an electrophilic ion. The $AlCl_3$-phenoxide courtship

also cleaves, leaving us with a phenoxide ion. Note the resonance structures of the phenoxide ion:

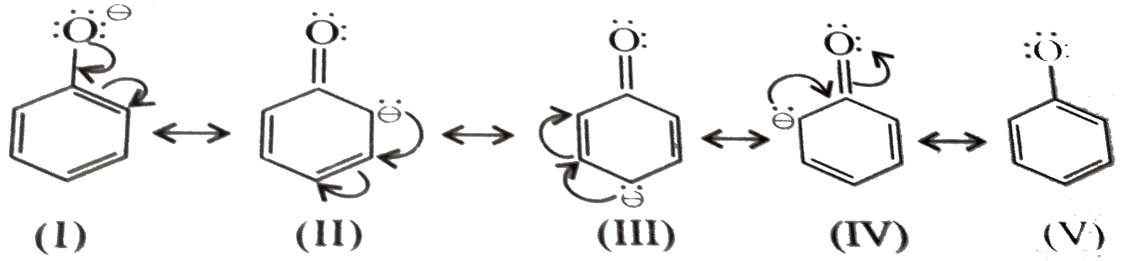


Figure 11: Resonance structures for the phenoxide ion

In this discussion, note that *ortho* refers to the carbon atom adjacent to the C-O bond, *meta* refers to the carbon atom two positions away from the C-O bond, and *para* refers to the carbon atom three positions away from the C-O bond, i.e directly opposite the bond.

The negative charge is present at the ortho (structure II and IV) and para (structure III) carbons only, thus these are relatively more nucleophilic than the carbon at the meta position (which is neutral across all resonance structures). The electrophilic carbocation attacks at either the ortho or para position. The para position is preferred at low temperatures due to less steric hindrance and the thermodynamic stability of the ortho isomer.

After Fries rearrangement, esterification results in another intermediate compound called a **ketoester.** This ketoester is subject to **bromination,** which is the replacement of a hydrogen in the acetyl group with a Br atom. This is an electrophilic substitution, and any acid can be used as a catalyst.

The bromine molecule is a weak electrophile due to negligible polarity of the Br-Br bond, thus causing the lack of an inductive effect. The α-carbon (*ortho* carbon adjacent to the C=O bond), is a weak nucleophile due to the polar nature of the C=O bond that pulls electrons away from

it. This α-carbon must be made more nucleophilic (i.e more electron-rich) to aid the attack by an electrophilic Br atom later in Step 2 (Fig. 13). This is achieved by the introduction of an acid catalyst in Step 1 (as seen in Fig. 12). The oxygen atom, being electron-rich, becomes protonated. The acid residue (B^-) is strongly nucleophilic, and removes one of the α-hydrogen atoms. The α-carbon forms a C=C double bond with the electrons from the broken C-H bond, leading to formation of a C=C-OH group (called an **enol**) and the regeneration of the catalyst.

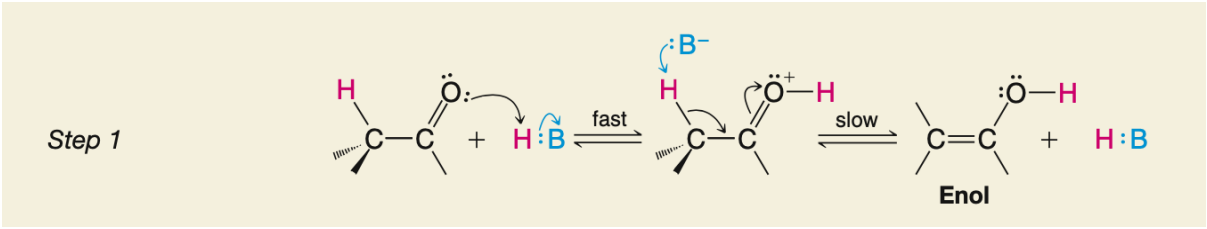


Figure 12: Step 1 of bromination - formation of C=C-OH group

In Step 2 (Fig. 13), the electron cloud on the Br-Br bond is momentarily asymmetric, leading to formation of weak $\boldsymbol{\delta^+}$ and $\boldsymbol{\delta^-}$ charge on the Br atoms. The $\boldsymbol{\delta^+}$ Br atom, being electrophilic, attacks the electron-rich C=C bond. The lone-pair on the O atom then reforms the C=O ketonic bond. This is a favourable step, since the resulting Br^- anion is a good leaving group. The H in the O-H bond becomes acidic due to formal +ve charge on the O atom.

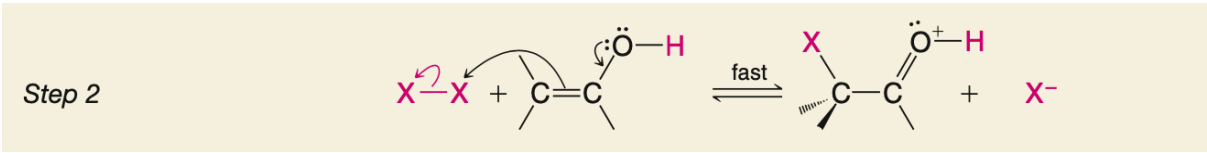


Figure 13: Step 2 of bromination - addition of bromine atom

In Step 3 (Fig. 14), the nucleophilic Br^- anion attacks the acidic H atom and removes it, resulting in the formation of HBr. Note that subsequent bromination will be discouraged, since the Br atom will pull electrons away from the carbonyl oxygen (inductive effect), making it a weaker nucleophile and discouraging its protonation.

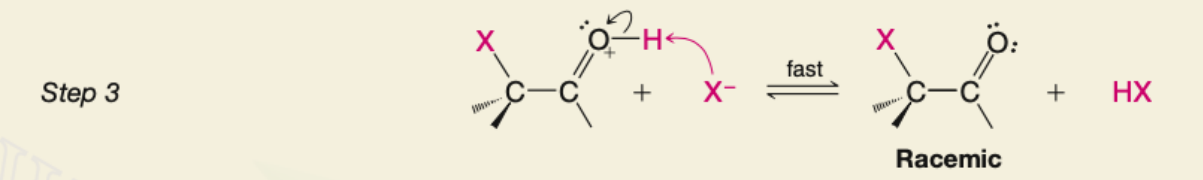


Figure 14: Step 3 of bromination - removal of proton (H^+)

After bromination, nucleophilic **substitution** of the newly added Br atom and two adjacent H atoms by the amino group occurs. **Reduction** of the C=O bond occurs next, using lithium aluminium hydride (Fig. 15) as the reagent[24].

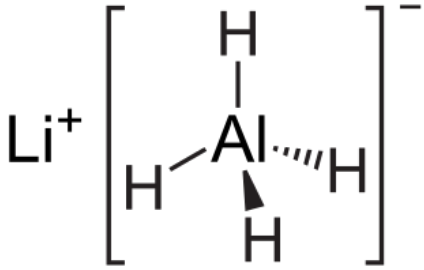


Figure 15: Molecular structure of lithium aluminium hydride

In the first step (Fig. 16), the negatively charged hydride anion attacks the carbon atom, which is electron-poor due to the tendency of oxygen to pull shared electrons to itself (inductive effect). This results in the addition of an H atom at the C=O bond.

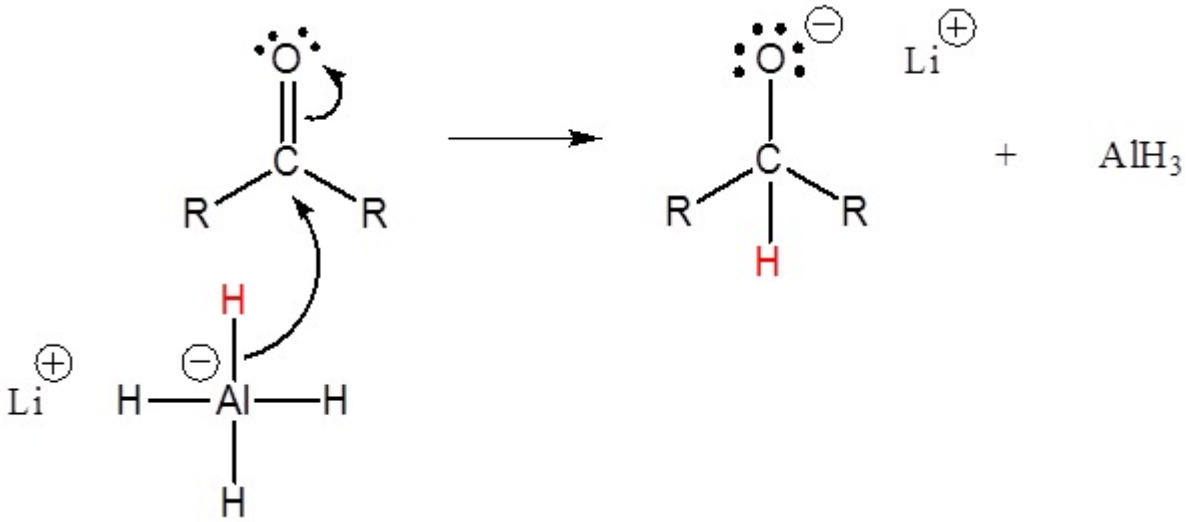


Figure 16: Nucleophilic attack by hydride anion

At this stage (Fig. 17), water is added to the mixture. While the acidity of the O-H bond in H_2O is low (i.e the H atom has a lower tendency to leave), the negatively charged O atom is a strong enough nucleophile to pull the H atom toward itself, and form a marriage to give the reduced alcohol, as well as LiOH as a byproduct.

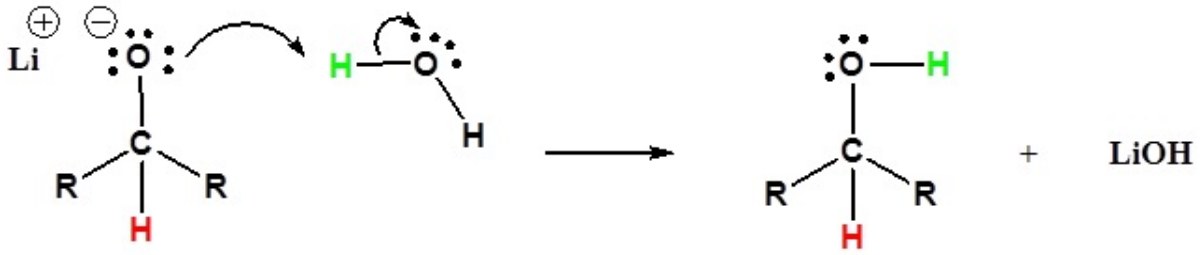


Figure 17: Addition of proton (H^+)

Finally, **hydrogenolysis** (breaking of a C-C bond) results in the removal of the phenyl benzene group to give salbutamol. Now that we have covered the synthesis of salbutamol and established its chemistry, the following sections will compare and contrast salbutamol, a short-acting β_2-agonist (SABA), and salmeterol (Fig. 18), a long-acting β_2-agonist (LABA). Both these drugs are used in the treatment of asthma, but to differing effects.

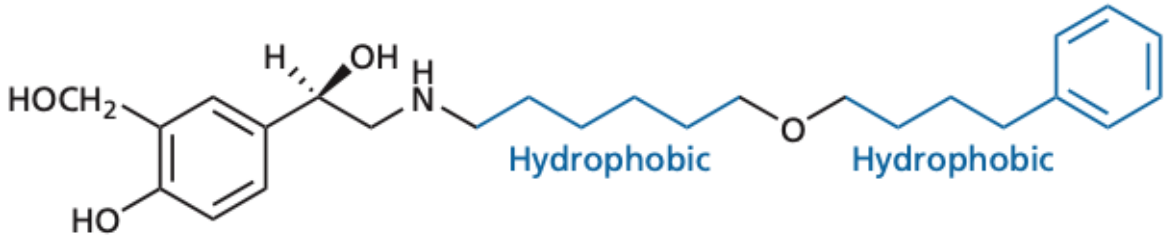


Figure 18: Structure of salmeterol

3.2 Absorption and Metabolism of SABA and LABA

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, while **duration of action**

is the amount of time this effect lasts. In this context, SABAs have short duration, while LABAs have long duration of action.

Salbutamol is a SABA drug (lasting ~3 hours in duration of action) with a **fast onset** of action. Because of this, it is used as a "rescue" medication to provide quick relief from acute asthma symptoms. Salmeterol, its long-chained relative, is a LABA drug (~12 hours duration) and has a **slow onset** of action. It is thus used to treat patients with chronic asthma who need regular treatment. It is also used to cope with nocturnal asthma— a condition which usually occurs at about 4 a.m. (commonly called the morning dip).[25] In this section, we will analyse the different mechanisms of **absorption** and **metabolism** of salbutamol and salmeterol in the body and examine how these differences affect their duration and onset of action.

3.2.1 Absorption of Salbutamol and Salmeterol

β_2 receptors are embedded in the bronchioles of lungs and are exposed to an aqueous fluid. Bronchiole cells (and their lipid cell membranes) are adjacent to the receptors. Recall that lipids are hydrophobic fatty acids (Fig. 19).

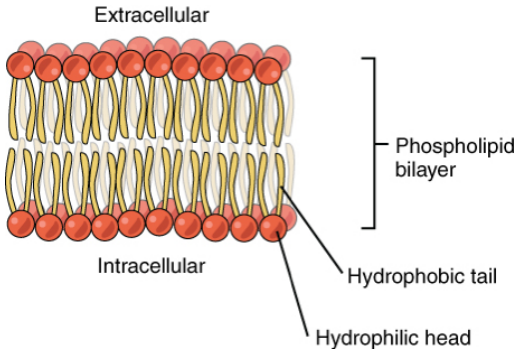


Figure 19: Lipid bilayer in bronchiole

When a drug is inhaled, it is absorbed into the lungs via the biophase. The drug then interacts with the β_2 receptor and the lipid membrane (also called the lipid bilayer), and these interactions contribute to the drug's' onset and duration of action. The exact mechanism of

this interaction is not known yet. In this paper, we will discuss the diffusion microkinetic theory, a mechanism proposed by Anderson et al[26]. The essential feature of the model is that the lipid membrane acts as a depot for drugs with moderate to high lipophilicity.

The dimensions (length x breadth x height) of the beta-2 receptor molecule are: 18×33×45 Å. We will consider only the length dimension. The corresponding length of salmeterol is 25 Å. Since the length of beta-2 receptors is 18 Å exactly, it is not possible for salmeterol to fit in beta-2 receptors completely, and at an orientation conducive for the pharmacophore (phenyl-ethanol-amine) to court the receptor effectively. It violates both distance and orientation criteria for good intermolecular courtship.

However, salmeterol does not get inserted into the β_2 receptor completely - only its pharmacophore is. The saligenin head (benzene ring and -OH group) is merely angled into the receptor. The rest of the salmeterol molecule remains outside the receptor. One might then wonder - if the courtship between these drugs and the beta-2 receptor is incomplete, why does the drug not simply get washed away by the incoming aqueous fluid? In other words, why does the drug "stick" around for a longer period of time?

The answer is that the hydrophobic parts of LABA "stick" to the lipid bilayers in the membranes of neighbouring cells. The lipids have short polar components which extend out in the polar biophase, and long non-polar components beneath them. An example is DOPC (Fig. 20a). The London forces between the tail of LABA molecules and the lipid molecules holds them in place.

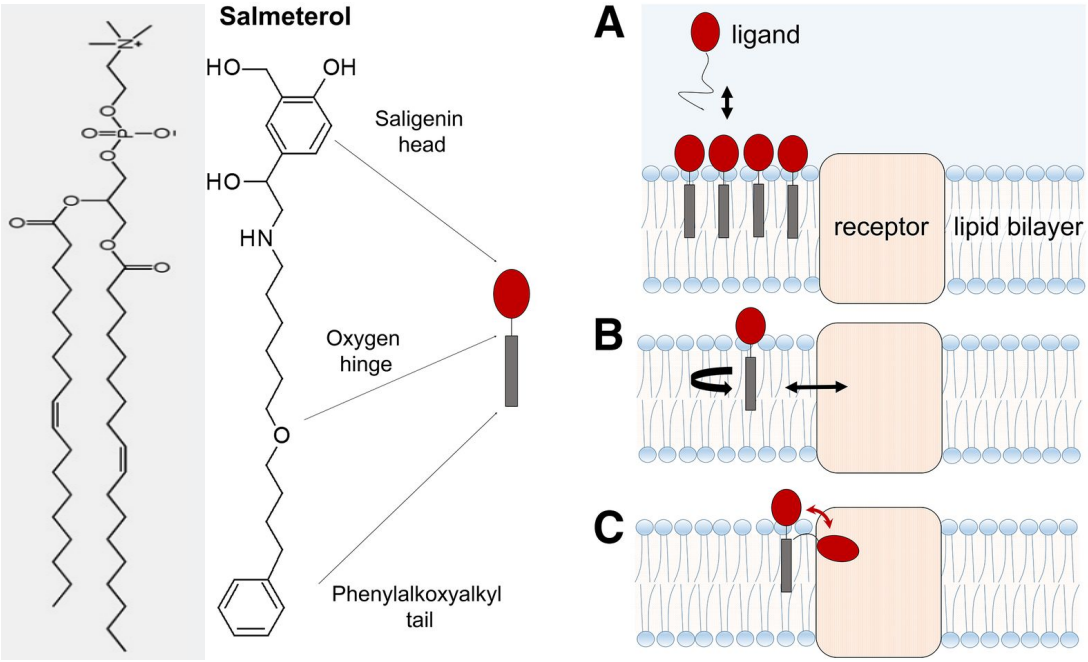


Figure 20: (a) Dioleoyl-phosphatidyl-choline (DOPC); (b) Salmeterol in lipid bilayer

Salbutamol, lacking a hydrophobic tail, has unfavourable interactions with the lipid molecules, and thus it quickly diffuses into the aqueous biophase. Here, it favourably interacts directly with β_2 receptors due to its pharmacophore. This leads to its **fast onset of action**. However, once in the aqueous biophase, it is deactivated by the MAO enzyme. Further, since it only exhibits a courtship (not a marriage) with the beta-2 receptors, it is easily washed away by incoming aqueous fluids. This leads to its **low duration of action**.

Salmeterol, with a long hydrophobic tail, has a strong courtship with lipids (Fig. 20b). In fact, it is 10,000 times more lipid-soluble than salbutamol. and its interaction with the β-adrenoceptor is energetically unfavourable causing **slow onset** but **long duration** of action.

3.2.2 Metabolism of Salbutamol and Salmeterol

Once any drug enters the lungs, it can be degraded by enzymes, such as catechol-O-methyltransferase (COMT) or monoamine oxidase (MAO). The enzymes change the

pharmacophore and render the drug ineffective, such that the drug is then said to be **metabolized**. COMT metabolizes drugs with catechol rings (benzene ring with adjacent C-OH bonds), while MAO metabolizes those with amine groups (Fig. 22) .

Both salbutamol and salmeterol are not metabolized by the COMT enzyme, since they do not have the catechol ring. However, salbutamol with its amine groups is metabolized by MAO. The following figure depicts the metabolism of epinephrine, which will inform our discussion of salbutamol as it has a similar chemical structure, and thus undergoes a similar metabolism.

A key step in the metabolism by MAO is **dealkylation**, or the cleavage of all N-C bonds attached to the amino group. Thus, resistance to MAO depends on the number of carbon atoms attached to the nitrogen. These C-N bonds must must be broken before MAO can act to oxidatively deaminate the nitrogen, as shown below:

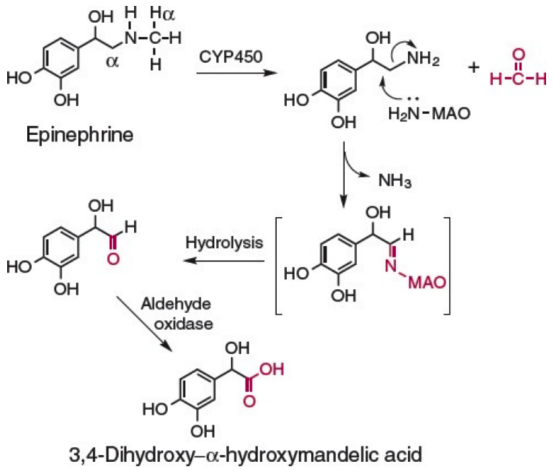


Figure 22: Metabolism of a drug with amine group by MAO

Drugs with tertiary butyl groups such as salbutamol are slowly dealkylated, whereas those with aralkyl substituents such as salmeterol are resistant to N-dealkylation. Thus, salmeterol tends to stay in the body for longer, which further enhances its duration of action.

4.0 Further Applications of Salbutamol

In addition to its benefits as a bronchodilator for asthma treatment in humans, salbutamol is also useful in treating acute airway obstruction in most animals due to the fact that it binds only to β_2 receptors, and thus has fewer side effects. In particular, it is used to treat bronchospasms and coughs in cats and dogs, and can be used in the emergency treatment of asthma in cats[27].

However, while salbutamol brings about positive effects in bronchodilation, it can also be abused beyond the purposes of its use. Abuse of salbutamol via asthma inhaler misuse occurs both in asthmatic and nonasthmatic individuals. Worryingly, it encourages risky behavior amongst non-prescribed users of inhalers. In a 2004 school-based American study, it was found that 15% of 8th and 9th graders used non-prescribed asthma inhalers, with 10.7% of the student population borrowing inhalers from others to use. This misuse was seen to be related to perceived benefits of stimulation such as increased alertness and expanded lung capacity, and the effect of fluorocarbon propellants such as mild stimulation, euphoria and intoxication. Such abuse of non-prescribed inhalers is postulated to be "part of a cluster of risky behaviours" as their use is "significantly associated with higher rates of other drug use" such as marijuana, ecstasy and cocaine, as well as smoking and overindulgence in alcohol. In contrast, asthmatic students who only used their inhalers as prescribed were no more likely to abuse alcohol and drugs than non-users of inhalers.[28]

Beyond the casual abuse of the drug by youths, salbutamol has also been used for doping in professional sports. While the complete ban against β_2-agonists such as inhaled salbutamol in the Olympics has been lifted since 1986, Olympic athletes are still required to provide medical proof to be permitted to use inhaled β_2-agonists[29]. As seen in the previous section, salbutamol's behaviour as a β_2-agonist results in the release of chemicals (cAMP and adenylyl cyclase) that

temporarily increase oxygen flow in the lungs. This might appeal to individuals for the perceived advantage in performance, especially in intensive fast-paced sports that require high levels of oxygen intake. However, salbutamol is mainly reported to have performance-enhancing abilities when it is injected or taken orally— its performance-enhancing effects when inhaled are rather insignificant due to the lower concentration of it in the lungs[26]. Despite this insignificance, cases of inhaled salbutamol doping still occur, with the most notable case in recent times being that of British cyclist Chris Froome in a 2017 international cycling competition[30]. Thus, while salbutamol on the whole has positive effects in the management of asthma, it is still important to regulate its use such that it does not become misused by individuals.

5.0 References

(1) Asthma https://www.who.int/news-room/fact-sheets/detail/asthma (accessed Mar 28, 2021).

(2) Novelli, F.; Malagrinò, L.; Dente, F. L.; Paggiaro, P. Efficacy of Anticholinergic Drugs in Asthma. *Expert Rev. Respir. Med.* **2012**, *6* (3), 309–319. https://doi.org/10.1586/ers.12.27.

(3) Gross, N. J.; Skorodin, M. S. Anticholinergic, Antimuscarinic Bronchodilators. *Am. Rev. Respir. Dis.* **1984**, *129* (5), 856–870. https://doi.org/10.1164/arrd.1984.129.5.856.

(4) Asthma | One Hundred Years of Treatment and Onward | American Journal of Respiratory and Critical Care Medicine https://www-atsjournals-org.libproxy1.nus.edu.sg/doi/full/10.1164/rccm.200502-257OE (accessed Mar 28, 2021).

(5) Medical modelling of obesity: a transition from action to experience in a 20th century American medical textbook - Chang - 2002 - Sociology of Health & Illness - Wiley Online Library https://onlinelibrary-wiley-com.libproxy1.nus.edu.sg/doi/full/10.1111/1467-9566.00289 (accessed Mar 28, 2021).

(6) Landau, R.; Achilladelis, B.; Scriabine, A. *Pharmaceutical Innovation: Revolutionizing Human Health*; Chemical Heritage Press: Philadelphia, 1999.

(7) WHO model list of essential medicines https://www.who.int/publications-detail-redirect/WHOMVPEMPIAU2019.06 (accessed Mar 28, 2021).

(8) The Top 300 of 2021 https://clincalc.com/DrugStats/Top300Drugs.aspx (accessed Mar 28, 2021).

(9) Encyclopedia of Toxicology - 2nd Edition https://www.elsevier.com/books/encyclopedia-of-toxicology/anderson/978-0-08-054800-5 (accessed Mar 28, 2021).

(10) Lofton, A. Atropine. In *Encyclopedia of Toxicology (Second Edition)*; Wexler, P., Ed.; Elsevier: New York, 2005; pp 190–192. https://doi.org/10.1016/B0-12-369400-0/00094-6.

(11) Eglen, R. M. Overview of Muscarinic Receptor Subtypes. In *Muscarinic Receptors*; Fryer, A. D., Christopoulos, A., Nathanson, N. M., Eds.; Handbook of Experimental Pharmacology; Springer: Berlin, Heidelberg, 2012; pp 3–28. https://doi.org/10.1007/978-3-642-23274-9_1.

(12) Kamath, V. B.; Lobo, R.; Pai, V.; Pai, A. Structure Activity Relationship of Atropine Analogues with Muscarinic Acetyl Choline M1 Receptor: A Molecular Docking Based Approach. *undefined* **2016**.

(13) Wess, J.; Blin, N.; Mutschler, E.; Blüml, K. Muscarinic Acetylcholine Receptors: Structural Basis of Ligand Binding and G Protein Coupling. *Life Sci.* **1995**, *56* (11–12), 915–922. https://doi.org/10.1016/0024-3205(95)00028-5.

(14) Westerhof, F. J.; Zuidhof, A. B.; Kok, L.; Meurs, H.; Zaagsma, J. Effects of Salbutamol and Enantiomers on Allergen-Induced Asthmatic Reactions and Airway Hyperreactivity. *Eur. Respir. J.* **2005**, *25* (5), 864–872. https://doi.org/10.1183/09031936.05.00102203.

(15) Figure 1. Structural formula of Salbutamol enantiomers. https://www.researchgate.net/figure/Structural-formula-of-Salbutamol-enantiomers_fig2_315521017 (accessed Mar 28, 2021).

(16) Salbutamol - Mechanism, Indication, Contraindications, Dosing, Adverse Effect, Interaction, Renal Dose, Hepatic Dose | Drug Index | Pediatric Oncall https://www.pediatriconcall.com/drugs/salbutamol/934 (accessed Mar 28, 2021).

(17) Salbutamol https://go.drugbank.com/drugs/DB01001 (accessed Mar 28, 2021).
(18) Almeida, M. J. Albuterol for Bronchiectasis - Bronchiectasis News Today.
(19) Fig 3. Molecular interaction diagrams of salbutamol deduced from... https://www.researchgate.net/figure/Molecular-interaction-diagrams-of-salbutamol-deduced-from-molecular-docking-A_fig3_320544912 (accessed Mar 28, 2021).
(20) Atropine (International Programme on Chemical Safety Evaluation, 2002) http://www.inchem.org/documents/antidote/antidote/atropine.htm (accessed Mar 28, 2021).
(21) Levalbuterol vs. Albuterol: Which Works Better? *The Checkup*, 2019.
(22) Ganellin, C. R.; Roberts, S. M. *Medicinal Chemistry: The Role of Organic Chemistry in Drug Research*, 2nd edition.; Academic Press: London, 1993.
(23) March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 8th Edition | Wiley https://www.wiley.com/en-us/March%27s+Advanced+Organic+Chemistry%3A+Reactions%2C+Mechanisms%2C+and+Structure%2C+8th+Edition-p-9781119371793 (accessed Mar 28, 2021).
(24) Reduction of Carbonyls to Alcohols Using Metal Hydrides - Chemistry LibreTexts https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Supplemental_Modules_(Organic_Chemistry)/Aldehydes_and_Ketones/Reactivity_of_Aldehydes_and_Ketones/Reduction_of_Carbonyls_to_Alcohols_Using_Metal_Hydrides (accessed Mar 28, 2021).
(25) Martins, J. An Introduction to Medicinal Chemistry, Fifth Edition- Graham L. Patrick.
(26) Anderson, G.; Lindén, A.; Rabe, K. Why Are Long-Acting Beta-Adrenoceptor Agonists Long-Acting? *Eur. Respir. J. Off. J. Eur. Soc. Clin. Respir. Physiol.* **1994**, *7*, 569–578. https://doi.org/10.1183/09031936.94.07030569.
(27) Cavanagh, K. Plumb's Veterinary Drug Handbook. Pocket — 7th Edition. *Can. Vet. J.* **2012**, *53* (12), 1284.
(28) BOYD, C. J.; TETER, C. J.; MCCABE, S. E. Pilot Study of Abuse of Asthma Inhalers by Middle and High School Students. *J. Adolesc. Health Off. Publ. Soc. Adolesc. Med.* **2004**, *34* (6), 531–534. https://doi.org/10.1016/j.jadohealth.2003.07.023.
(29) Fitch, K. D. B2-Agonists at the Olympic Games. *Clin. Rev. Allergy Immunol.* **2006**, *31* (2), 259–268. https://doi.org/10.1385/CRIAI:31:2:259.
(30) Heuberger, J. A. A. C.; van Dijkman, S. C.; Cohen, A. F. Futility of Current Urine Salbutamol Doping Control. *Br. J. Clin. Pharmacol.* **2018**, *84* (8), 1830–1838. https://doi.org/10.1111/bcp.13619.