AL Chemistry Group Project

Topic: Salmeterol (A bronchodilator)

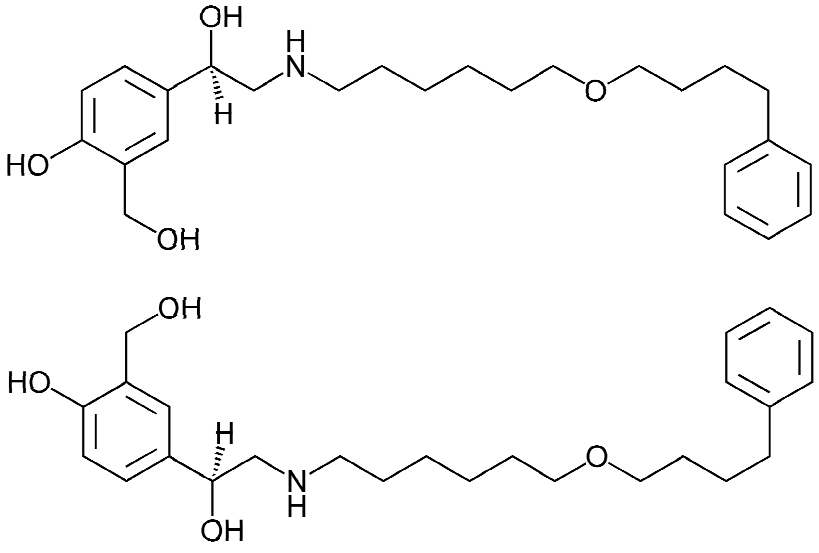
A typical inhaler, of Serevent (salmeterol)

i.Drug Description

Salmeterol is a long-acting beta2-adrenergic receptor agonist drug that is currently prescribed for the treatment of **asthma** and **chronic obstructive pulmonary disease (COPD)**. It is currently available as a metered-dose inhaler (MDI) or a proprietary "disk-styled" inhaler that releases a powdered form of the drug.

Inhaled salmeterol works like other beta 2-agonists, causing bronchodialation by relaxing the smooth muscle in the airway so as to treat the exacerbation of asthma. It comes as a dry powder to inhale by mouth using an inhaler. The duration of its action lasts approximately 12 hours.

Salmeterol's formula:



Systematic name:

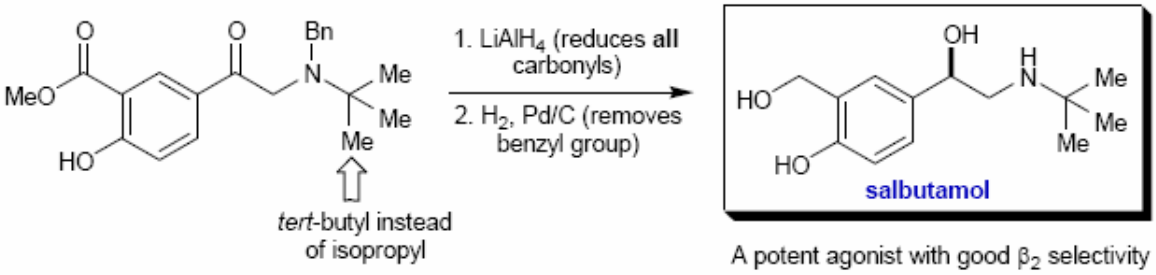
(*RS*)-2-(hydroxymethyl)-4-{1-hydroxy-2-[6-(4-phenylbutoxy) hexylamino]ethyl}phenol

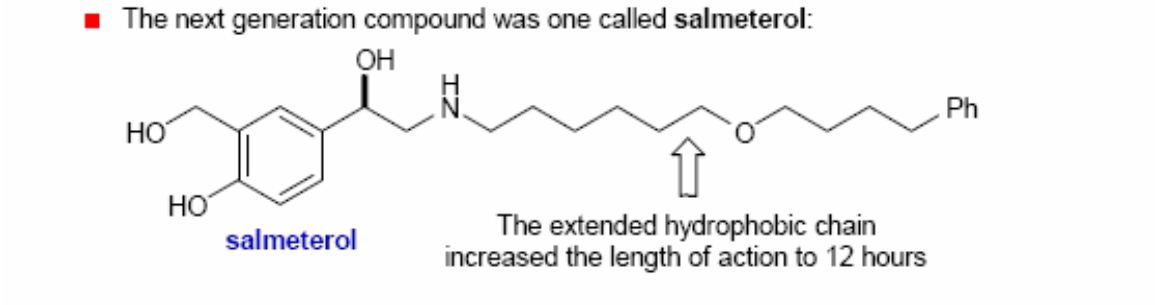
Molecular formula:

$C_{25}H_{37}NO_4$

ii.Lead compound discovery

. Process of manufacture of Salmeterol from Salbutamol





iii.Molecular modification

Salmeterol is a highly selective β_2-agonists with a bronchodilating effect lasting for at least 12 h after a single inhalation . Its molecular structure contains long-acting inhaled β_2-agonists (LABA). Salmeterol is the result of a specific research program designed to achieve prolonged duration of action by molecular modification of the short-acting β_2-agonists salbutamol. The resulting 25 Å molecule consists of the saligenin head of salbutamol that binds to the active site of the β_2-adrenergic receptor (β_2AR), coupled to a long aliphatic side chain that profoundly increases the lipophilicity of the molecule. The concept has been proposed that the molecule diffuses laterally through the cell membrane to approach the β_2AR. The side chain then interacts with an auxiliary binding site (exo-site), a group of highly hydrophobic amino acids within the fourth domain of the β_2AR. Binding to the exo-site prevents dissociation of salmeterol from the β_2AR and allows the active saligenin head to repeatedly engage the active site of the receptor. This mechanism would account for the long duration of the effect but slow onset of action of salmeterol .

iv.Formulation development

Salmeterol consisted of a branch chain of phenethyl and it was found to be longer acting (6 hrs) than salbutamol as a bronchodilatator in man. Comparison of the calculated logP values showed that Salmeterol had a logP one unit greater than salbutamol. During the recent Modification of the aryl ether group in Salmeterol, it was a great success that this improved the compound with significantly increased durations of action had been developed.

Reference:

- **log P** A measure of the hydrophobicity/hydrophilicity of the drug.

log P - Quite an important issue: $P = \frac{\text{Concentration of drug in organic phase}}{\text{Concentration of drug in aqueous phase}}$ (**octanol** most commonly used as the organic solvent)

log P too high - drug is too hydrophobic - it remains in membranes and can't be excreted
lop P too low - drug is too hydrophilic - it will not cross membranes

v.History&Market

History timeline:

1980-- Salmeterol, marketed and manufactured by GlaxoSmithKline

1990—It was released as Serevent but the product was under license from Allen & Hanburys

2005--The American FDA released a health advisory, alerting the public to findings that show the use of Long-acting β_2-agonists could lead to a worsening of symptoms, and in some cases death.

vi.Safety and human trial

1. Pre-clinical Research

Salmeterol xinafoate had been extensively evaluated in animal toxicity tests. Significant toxicities occurred only at doses in excess of those recommended for human use and were those expected for a potent beta2-adrenoreceptor agonist and glucocorticosteroid.

In long term studies, salmeterol xinafoate induced merciful tumors of smooth muscle in the mesovarium(卵巢繫膜) of rats and the uterus of mice. Rodents are sensitive to

the formation of these pharmacologically- induced tumours. That's why, salmeterol is not considered to cause a significant hazard to man.
Co-administration of salmeterol and fluticasone propionate(drug similar to salmeterol) were also examined.
It was found that this resulted in some cardiovascular interactions at high doses. In rats, mild atria myocarditis(心肌炎)and focal coronary arteritis(動脈炎) were transient effects that resolved with regular dosing. In dogs, heart rate increases were greater after co-administration than after salmeterol alone.

2.Clinical Research

To test whether the co-administration of salmeterol and fluticasone propionate had some adverse effects on human, a similar study was taken on human. The result had shown that no clinically relevant serious adverse cardiac effects have been observed in studies in man. Co-administration did not modify other class-related toxicities in animals.
Besides, The use of inhaled salmeterol is still recommended in asthma guidelines for the resulting improved symptom control, further concerns have been raised, by a large meta-analysis of the pooled results from 19 trials with 33,826 participants, that salmeterol may increase the small risks of asthma deaths and this additional risk is not reduced with the additional use of inhaled steroids.
This seems to occur because although salmeterol relieves asthma symptoms, it also promotes bronchial inflammation and sensitivity without warning.

vi.Approval for marketing

Approval has been granted to market salmeterol in over 100 countries. Salmeterol was first approved as a CFC-MDI (chlorofluorocarbon-containing metered dose inhaler) in the United Kingdom (UK) in 1990 and in the United States (US) in 1994. Salmeterol was later developed as **SEREVENT® DISKUS®†** (salmeterol xinafoate inhalation powder).
This powder formulation is available worldwide, and was approved in the United Stated (US) in 1997. Additionally, salmeterol is a component of **ADVAIR**, which was first approved in Sweden in 1998 and the US in 2000. Consistent with the Montreal Protocol and the resulting phase out of CFCs, GlaxoSmithKline elected to discontinue salmeterol CFC-MDI in the US in 2002 as part of the process to remove all CFC-containing products from the marketplace.
As of April 30, 2005 the worldwide exposure to salmeterol alone was estimated to be 24.3 million patient years for treatment of asthma and COPD. Additionally, worldwide exposure to salmeterol administered with fluticasone propionate (FP) in a single device was estimated to be 20.9 million patient years. Therefore, in total there has been an estimated 45

million patient years of exposure to salmeterol-containing products.

Reference :

- http://www.chem.ed.ac.uk/teaching/chem4-5/resources/lectures/moduleN/medchemnotes.pdf
- **Wikipedia**