Topic: Salmeterol

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Drug Description

Molecular formula: $C_{25}H_{37}NO_4$

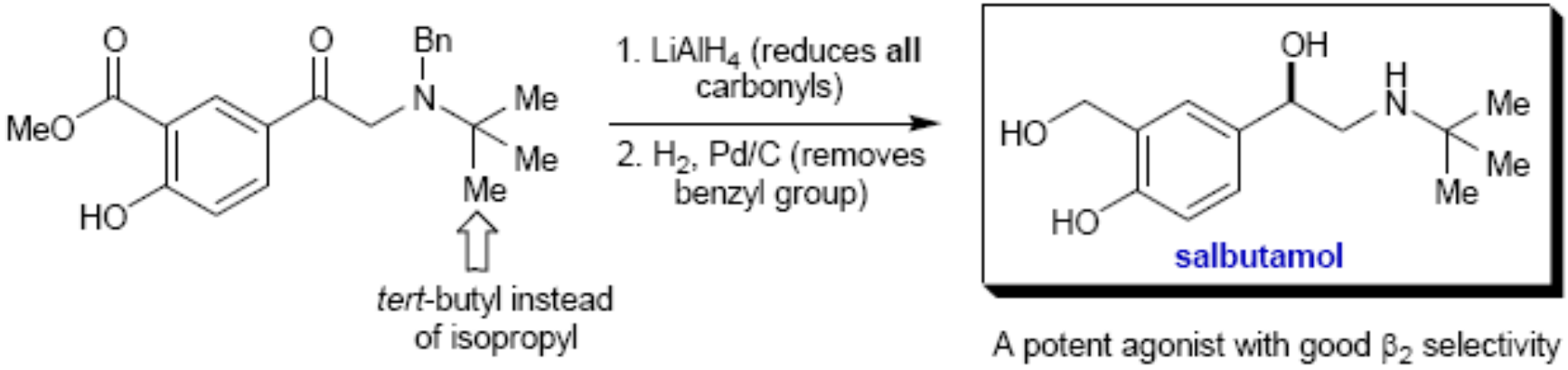
Systematic name:
(*RS*)-2-(hydroxymethyl)-4-{1-hydroxy-2-[6-(4-phenylbutoxy)
hexylamino]ethyl}phenol

Drug Description

- Use to treat asthma and chronic obstructive pulmonary disease (COPD)
- available as a metered-dose inhaler(dry powder to inhale by mouth using an inhaler)
- The duration of its action lasts approximately 12 hours.

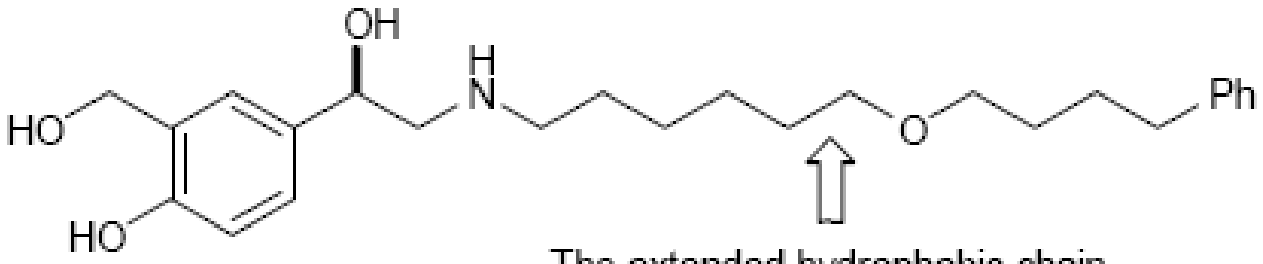
Lead compound discovery

Process of manufacture of Salmeterol from Salbutamol:



A potent agonist with good β_2 selectivity

- The next generation compound was one called **salmeterol**:



Molecular modification

- 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 head of salbutamol that binds to the active site of the β_2-adrenergic receptor , coupled to a long aliphatic side chain that profoundly increases the lipophilicity(dissolve in fat/oil) of the molecule.

Molecular modification

- Concept: molecule diffuses laterally through the cell membrane to approach the β_2AR. The side chain then interacts with an exo-site

- 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 of action of salmeterol

Formulation development

- consisted of a branch chain of phenethyl and it was found to be longer acting (6 hrs) 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.

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.

Safety and human trial

- Pre-clinical Research --- Salmeterol xinafoate induced merciful tumors of smooth muscle in the mesovarium of rats and the uterus of mice
- salmeterol is not considered to cause a significant hazard to man.

- Clinical Research---- similar study was taken on human → Result: no clinically relevant serious adverse cardiac effects have been observed in studies in man

- although salmeterol relieves asthma symptoms, it also promotes bronchial inflammation and sensitivity without warning.

Approval for marketing

- Approval has been granted to market salmeterol in over 100 countries
- 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
- there has been an estimated 45 million patient years of exposure to salmeterol-containing products.