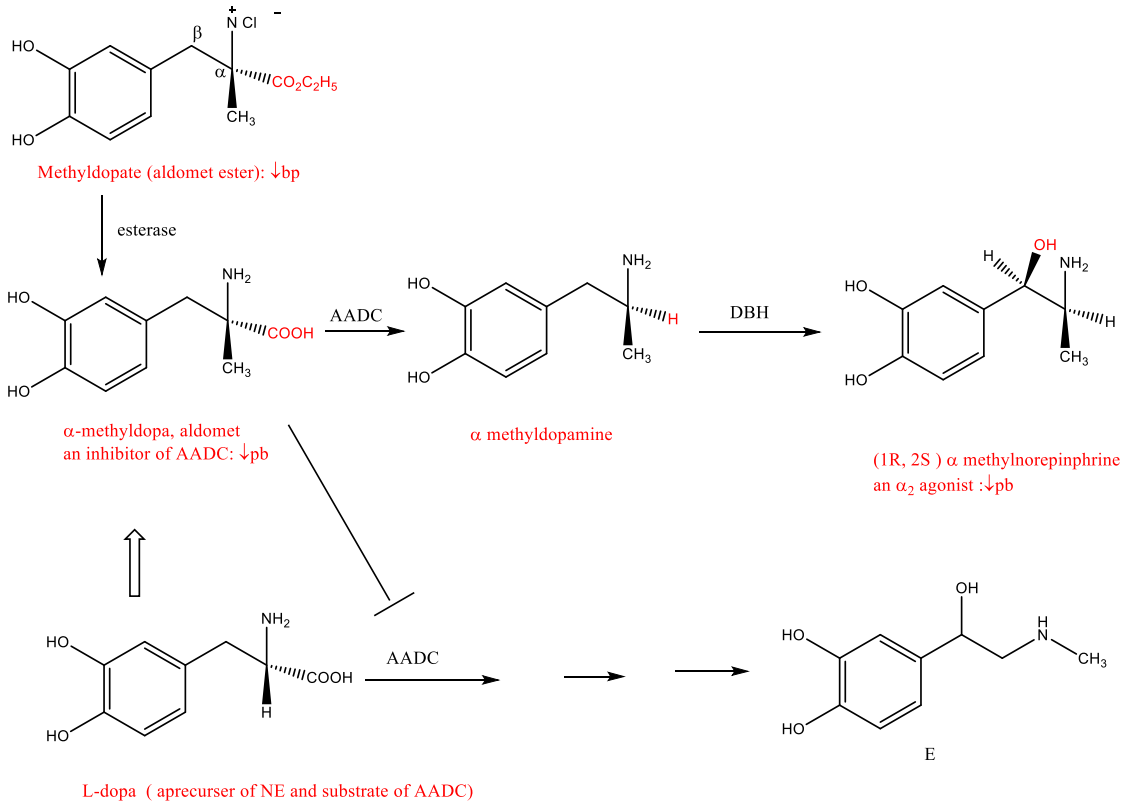
6. Methyldopa (L-α-methyldopa, Aldomet®)



Its metabolism in the CNS to its active metabolite (α-methylnorepinephrine). Methyldopa is transported actively into CNS via an aromatic amino acid transporter, where it is decarboxylated by AADC in the brain to (1R,2S)-α-methyldopamine. This intermediate, in turn, is stereospecifically β-hydroxylated by DBH to give the (1R,2S)-α-methylnorepinephrine. This active metabolite is a selective **α_2-agonist** because it has correct (1R,2S) configuration. It act centrally to decrease sympathetic outflow and lower blood pressure.

Methyldopa is used **only by oral administration** because its zwitterionic character limits its solubility. **The ester hydrochloride salt of methyldopa**, methyldopate (Aldomet ester), was developed as a **highly water-soluble derivative** that could be used to make parenteral preparations.

DUAL α- AND β-AGONISTS/ANTAGONISTS

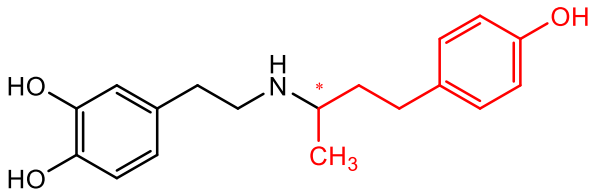
Dobutamine (Dobutrex) is a positive inotropic agent[1] administered intravenously for congestive heart failure. It resembles DA structurally but possesses a bulky 1-(methyl)- 3-(4-hydroxyphenyl)propyl group on the amino group.

[1] Mean increase force of heart rate

It possesses a center of asymmetry, and both enantiomeric forms are present in the racemic mixture used clinically. The **(-) isomer** of dobutamine is a potent **α_1-agonist**, which is capable of causing marked pressor responses. In contrast, (+)-dobutamine is a potent **α_1-antagonist.**

Importantly, the effects of these two isomers are mediated via β_1-receptors. Both isomers appear to be full agonists, but the (+) isomer is a more potent β_1-agonist than the (-) isomer (approximately tenfold)

Dobutamine contains a catechol group and is orally inactive and thus is given by intravenous infusion

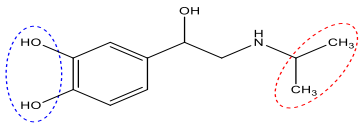


doputamine
oxidized slightly by air
COMT metabolism and conjugation→
oral inactive and short DOA

β-ADRENERGIC RECEPTOR AGONISTS

1. Isoproterenol (Isuprel)

Di-OH result in:
sensetive to air and light
metabolism by COMT, sulfate and glucuronide conjugation→
poor absorption and short DOA



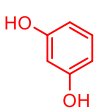
isoproterenol

isopropyl group result in:
↑β activity, virtually no α activity
resistance to MAO

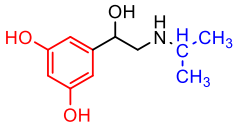
Is a nonselective and prototypical **β-agonist (β2/β1 = 1)**. The principal reason for its poor absorption characteristics and relatively short DOA is its facile metabolism by sulfate and glucuronide conjugation of the phenolic OH groups and o-methylation by COMT. Because it is a catechol, it is sensitive to light and air.

Because of an isopropyl substitution on the nitrogen atom, it has virtually no α-activity. However, it does act on both β_1- and β_2-receptors. It thus can produce an increase in cardiac output by stimulating cardiac β_1-receptors and can bring about bronchodilation through stimulation of β_2- receptors in the respiratory tract.

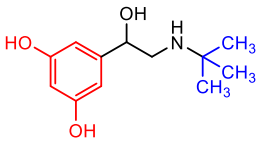
2. Metaproterenol (Alupent®), terbutaline (Bricanyl®)



resorcinal



metaproterenol
3′,5′ di OH group result in:
↑β_2 activity
not metabolized by COMT→
oral active and longer DOA



terbutaline
bulk N-R group result in:
↑β_2 activity and virtually no α activity
not metabolized by MAO
oral active and longer DOA

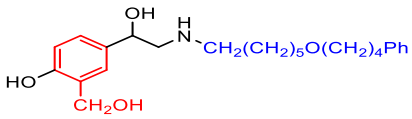
Belong to the structural class of resorcinol bronchodilators that have 3-,5-diOH groups of the phenyl ring.

They relax the bronchial musculature in patients with asthma but cause less direct cardiac stimulation than do the nonselective β-agonists.

Because metaproterenol has a β-directing N-isopropyl group and it is less β_2 selective than either terbutaline have β_2-directing t-butyl groups) and hence is more prone to cause cardiac stimulation.

They are much more effective when given orally, and they have a longer DOA. This is because they are resistant to the metabolism by either COMT or MAO.

3. Salmeterol



salmeterol

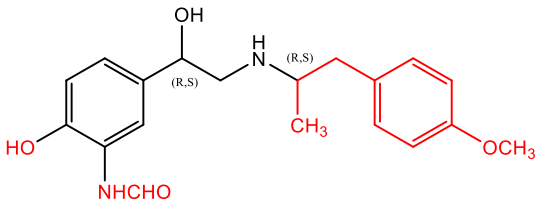
Selective β_2- agonists whose selectivity results from **replacement of the meta-OH group** of the aromatic ring with a **hydroxymethyl moiety.**

It has an **N-phenylbutoxyhexyl** substituent in combination with **a β-OH** group and a **salicyl phenyl ring** for optimal direct-acting β_2-receptor selectivity and potency.

This drug associates with the β_2-receptor slowly resulting in slow onset of action and dissociates from the receptor at an even slower rate.

It is resistant to both MAO and COMT and highly lipophilic (log P = 3.88). It is thus very long acting (12 hours), an effect also attributed to the highly lipophilic phenylalkyl substituent on the nitrogen atom, which is believed to interact with a site outside but adjacent to the active site

4. Formoterol



formoterol

A lipophilic (log P =1.6) and long-acting β_2-agonist. It has **3-formylamino** (β-directing) and **4-OH** groups on one phenyl ring and a lipophilic β-directing **N-isopropyl-p-methoxyphenyl** group on the nitrogen atom. Its long DOA (12 hours), which is comparable to that of salmeterol, has been suggested to result from its association with the membrane lipid bilayer, from which it gradually diffuses to provide prolonged stimulation of β_2 receptors and its resistance to MAO and COMT.

Formoterol possesses two chiral centers and is used as the racemic mixture of the (R,R) and (S,S) enantiomers. There is no clinical advantage for using (R,R)- formoterol as bronchodilators compared with the racemic mixture because of its high potency and low dose.