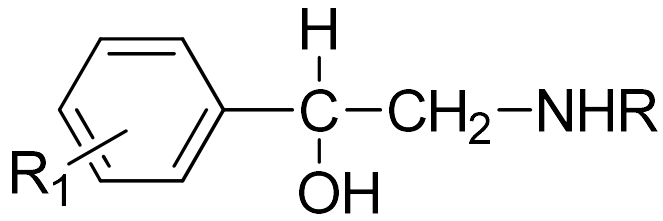
SAR of sympathomimetic drugs

The common structural features required for adrenergic agents are a substituted benzene ring and a primary or secondary aliphatic amino group separated by 2 carbon atoms from benzene ring.

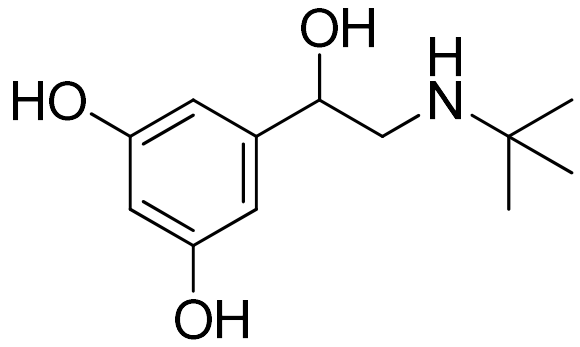


- The agent in this class have a hydroxyl group on the β-carbon atom of the side chain.
- Hydroxy substituted carbon must be in R absolute configuration for maximum direct activity.

Substitution on the amino group

- The receptor selectivity depends on the size of the alkyl group present on the nitrogen atom.
- Increase in the size from hydrogen in nor-adrenaline to isoproterenol decreases activity at α-receptor and increases activity at β-receptor.
- Substitution of amino group with a tertiary butyl group also provide selectivity for different β receptors.

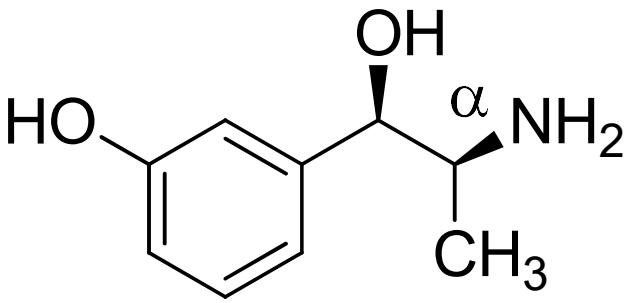
e.g. Terbutaline is a selective β_2 agonist whereas, isoprenaline is a non-selective β agonist.



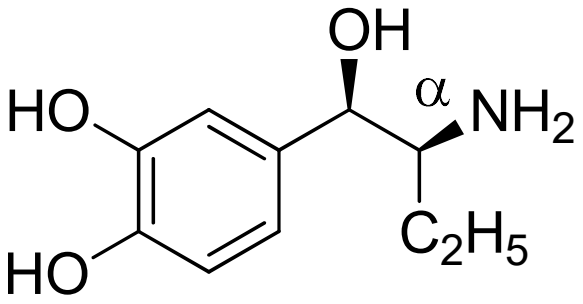
Terbutaline

Substitution on the α-carbon atom in the side chain

- Small alkyl groups like methyl or ethyl may be present on the α-carbon atom. Such substitution slow the metabolism carried out by Mono amine oxidase.
- An ethyl group in this position diminish α-activity and afford compound having β activity.

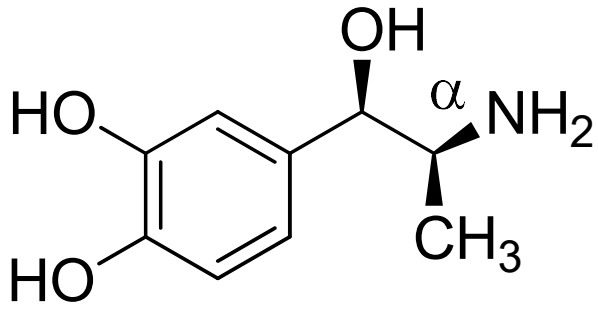


Metaraminol



Ethyl nor-epinephrine

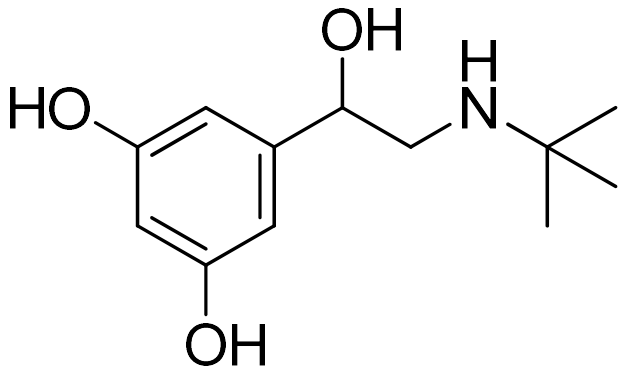
- Substitution on this carbon introduce another asymmetric center producing pairs of diastereomers, which can have significantly different biological activity.
- e.g. maximum direct activity in streoisomer of α-methyl nor-epinephrine reside with the streoisomer having 1R, 2S absolute configuration. While 1R, 2R streoisomer is indirectly activity.



1R,2S- methyl nor-epinephrine

Substitution on the aromatic ring

- Compound having both 3,4-dihydroxy group on benzene ring are active at both α and β receptors and they rapidly metabolize COMT.
- Change in substitution pattern to 3,5-dihydroxy as in terbutaline gives good oral activity and selectivity for β_2 receptor.



Terbutaline