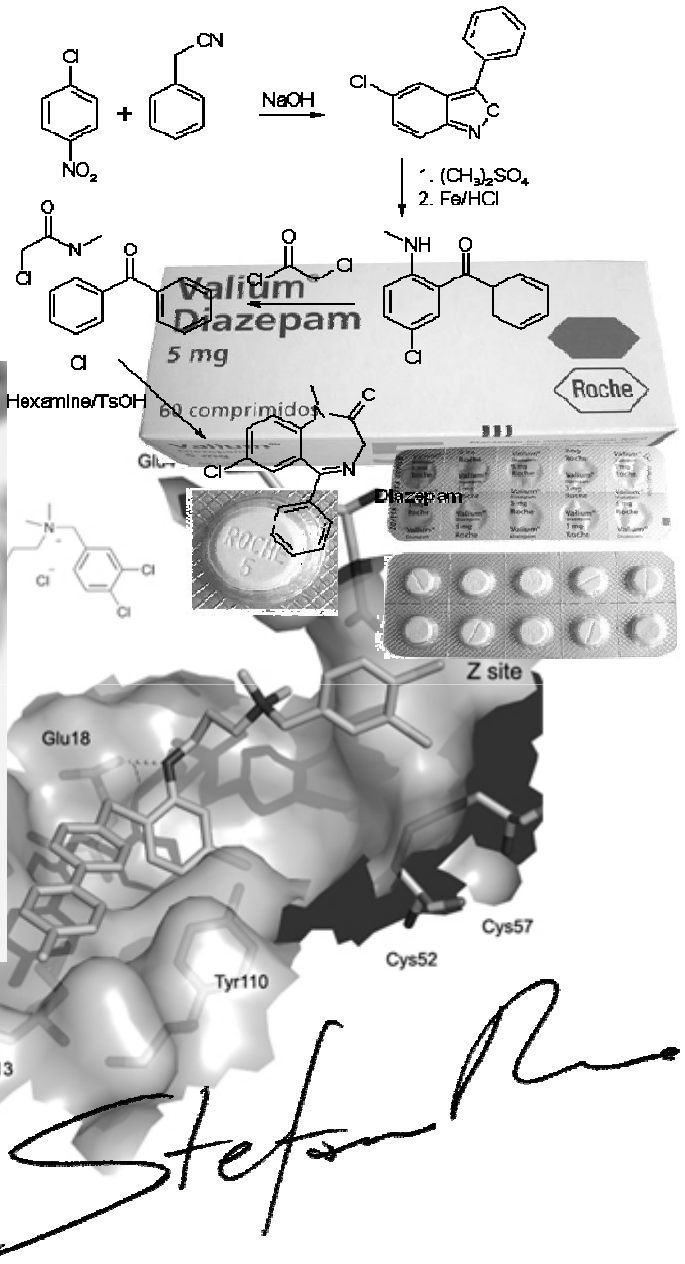
Chimica Farmaceutica e Tossicologica – Parte II

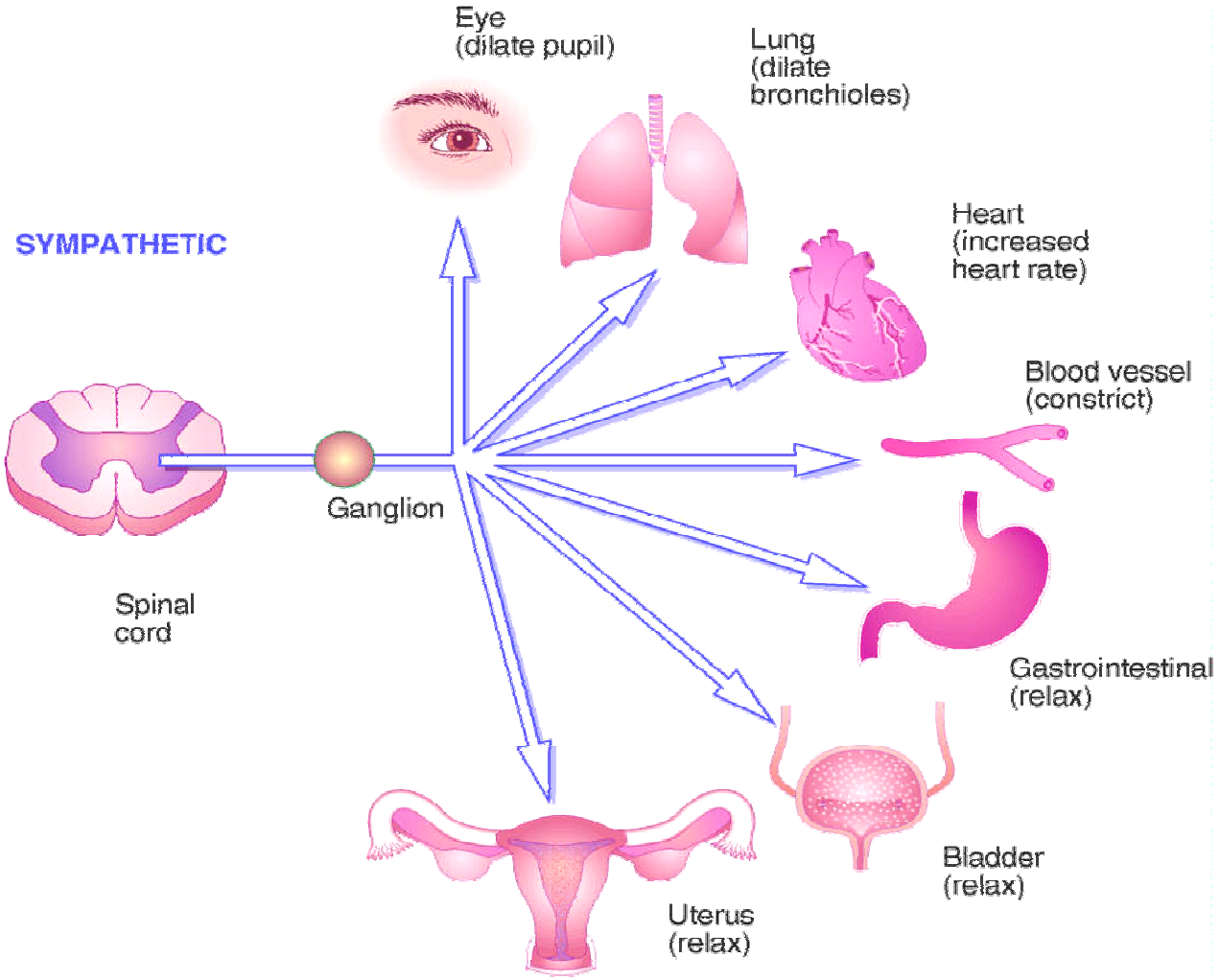


ADRENERGICI & ANTIADRENERGICI

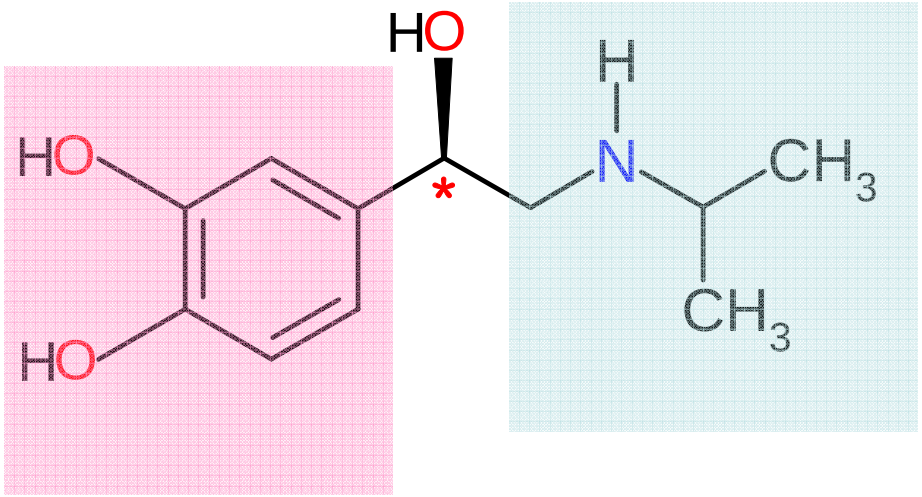
Parte II

12. Adrenergic Antagonists

Adrenergic nervous system

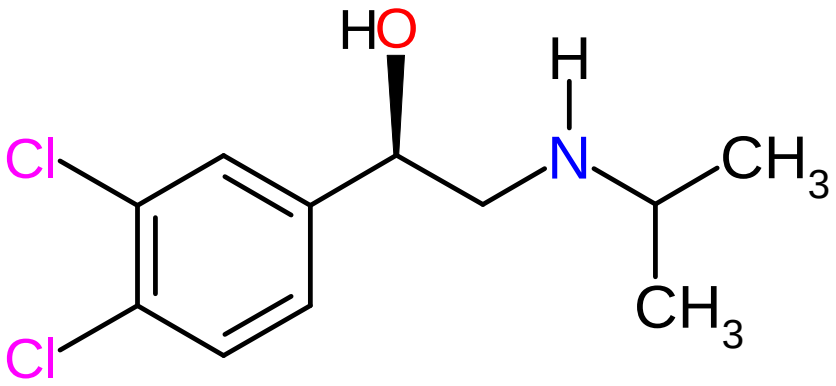


13. Adrenergic Antagonists: β-blockers



Crucial for the agonistic behavior

Greater selectivity for β–receptors

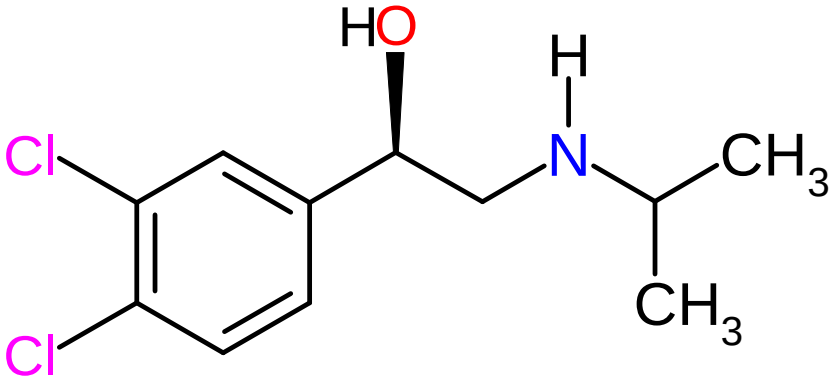


Isoprenaline (full agonist)

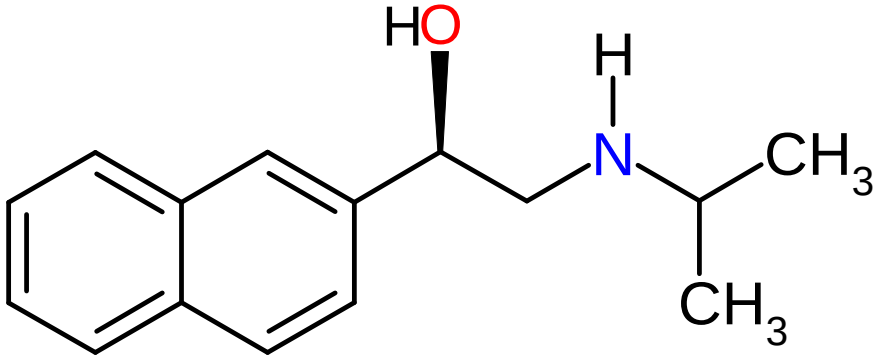
Dichloroisoprenaline (partial agonist)

Dichloroisoprenaline, also known as dichlorosisoproterenol, was the first beta blocker ever to be developed. It is non-selective for the β1-adrenergic and β2-adrenergic receptors. DCI has low potency and acts as a partial agonist/antagonist at these receptors.

13. Adrenergic Antagonists: β-blockers



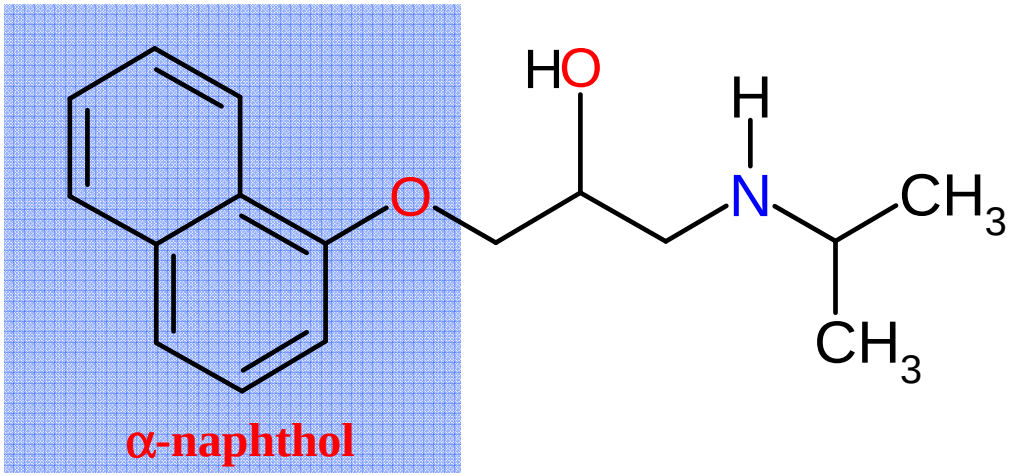
Dichloroisoprenaline (partial agonist)



Pronethalol (antagonist)

Pronethalol was the first ***non-selective*** beta blocker clinical candidate discovered by Sir James Black and John Stephenson of ICI Pharmaceutical in 1960. It was never used clinically due to carcinogenicity in mice, which was thought to result from formation of a carcinogenic naphthalene epoxide metabolite.

13. Adrenergic Antagonists: β-blockers



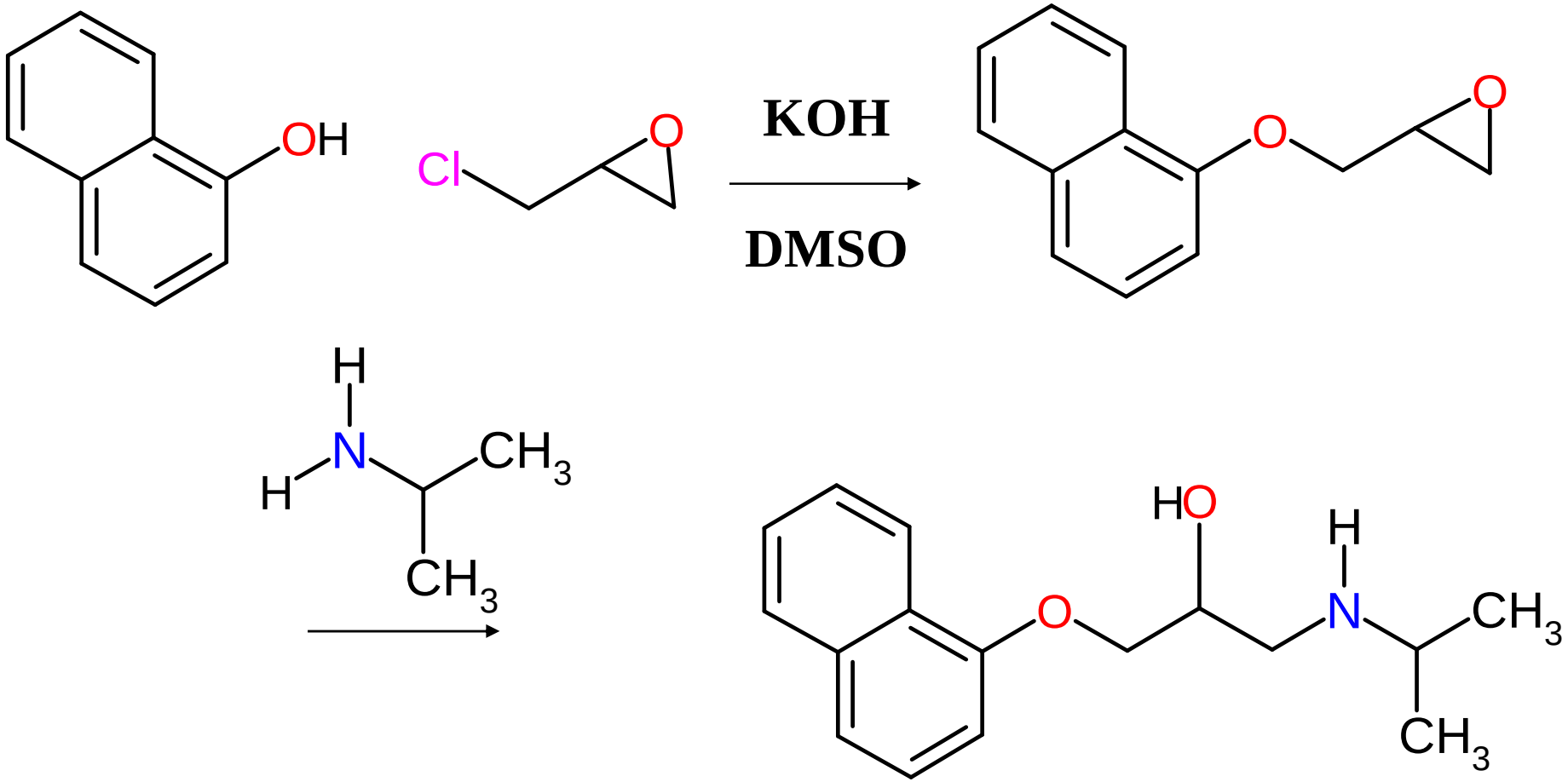
Propranolol

(*RS*)-1-(isopropylamino)-3-(1-naphthyloxy)propan-2-ol

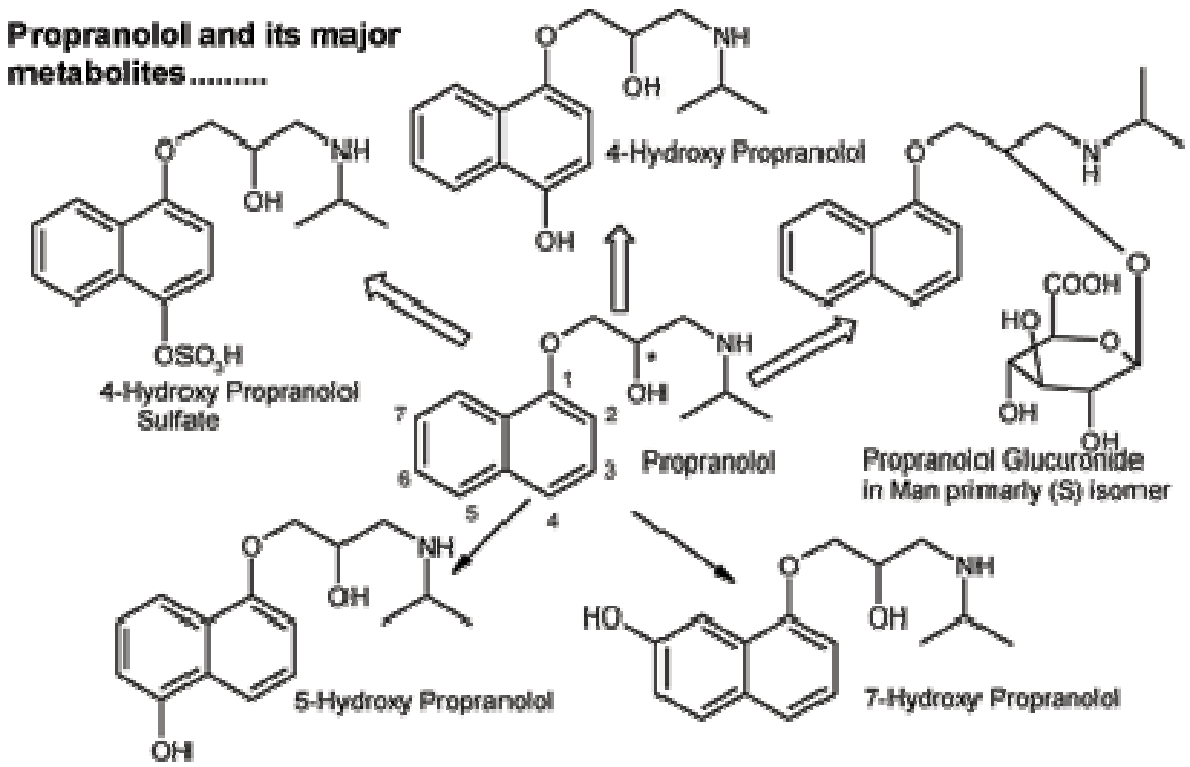
Propranolol is a non-selective beta blocker, that is, it blocks the action of epinephrine and norepinephrine on both β1- and β2-adrenergic receptors. This results in a reduction in resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension. Propranolol is a racemic compound; the *S*-(-)isomer is responsible for adrenergic blocking activity. Propranolol is a highly lipophilic drug (logP=3.0) achieving high concentrations in the brain.

13. Adrenergic Antagonists: β-blockers

Synthesis Path



13. Adrenergic Antagonists: β-blockers



Propranolol is rapidly and completely absorbed, with peak plasma levels achieved approximately 1–3 hours after ingestion. Despite complete absorption, propranolol has a variable bioavailability due to extensive first-pass metabolism. The main metabolite 4-hydroxypropranolol, with a longer half-life (5–7.5 hours) than the parent compound (3–4 hours), is also pharmacologically active.

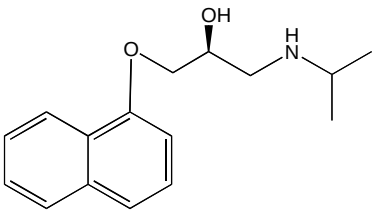
13. Adrenergic Antagonists: β-blockers

James W. Black :

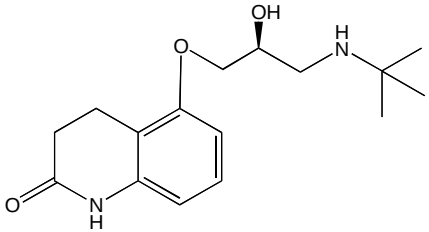
Sir James Whyte Black, (14 June 1924 – 22 March 2010) was a Scottish doctor and pharmacologist. He spent his career both as researcher and as an academic at several universities. Black established the physiology department at the University of Glasgow, where he became interested in the effects of adrenaline on the human heart. He went to work for ICI Pharmaceuticals in 1958 and, while there, developed propranolol, a beta blocker used for the treatment of heart disease. Black was also responsible for the development of cimetidine, a drug used in a similar manner to treat stomach ulcers. He was awarded the Nobel Prize for Medicine in 1988 for work leading to the development of propranolol and cimetidine.

13. Adrenergic Antagonists: β-blockers

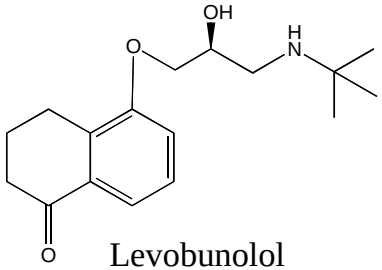
13.1 Non selective β1 and β2



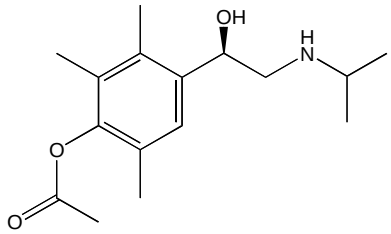
Propranolol



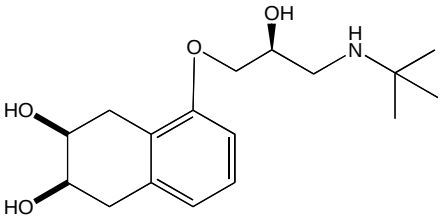
Carteolol



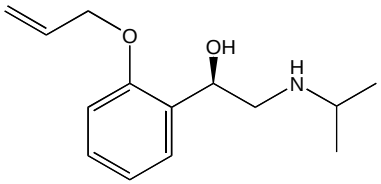
Levobunolol



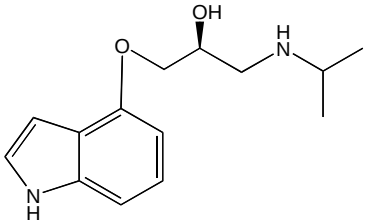
Metipranolol
(OptiPranolol, Glaucoma)



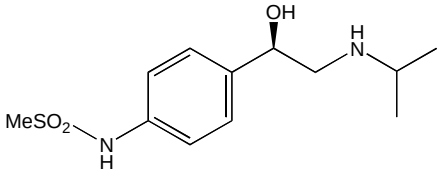
Nadolol
(Corgard, blood pressure, chest pain)



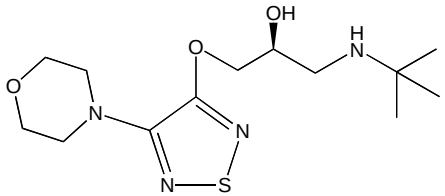
Oxprenolol



Pindolol



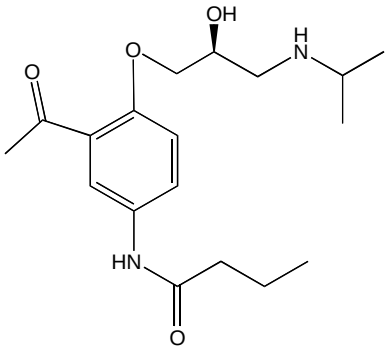
Sotalol
(also inhibits inward potassium channels in the heart)



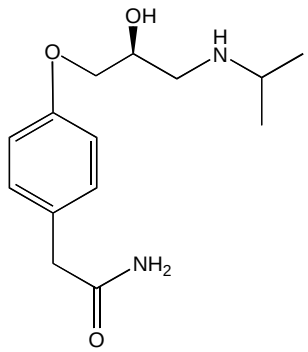
Timolol
(oral form is Blocadren)
(Opthalmic form Timoptol or Timoptic)

13. Adrenergic Antagonists: β-blockers

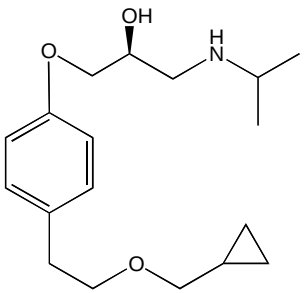
13.2 Selective β1



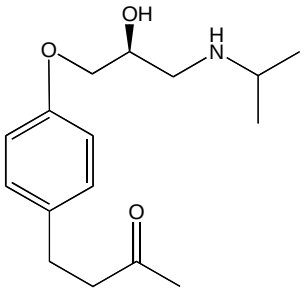
Acebutolol



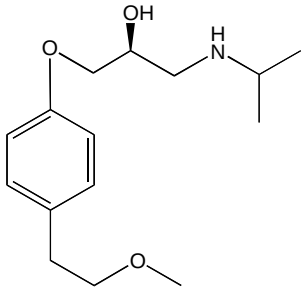
Atenolol



Betaxolol
(Betoptic, Lokren)



Esmolol
(Brevibloc)



Metoprolol
(Lopressor, Novartis)
(also Toprol-XL,
Betaloc (AstraZeneca)

1976

13. Adrenergic Antagonists: β-blockers

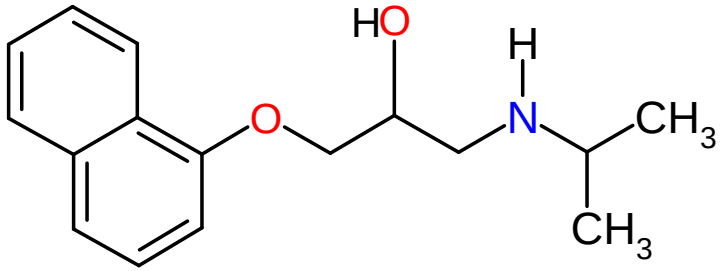
13.2 Selective β1

Cardio-selectivity and asthma

Atenolol is a so-called **β**1-selective (or 'cardioselective') drug. That means that it exerts greater blocking activity on myocardial β1-receptors than on β2 ones in the lung. The β2 receptors are responsible for keeping the bronchial system open. If these receptors are blocked, bronchospasm with serious lack of oxygen in the body can result. However, due to its cardioselective properties, the risk of bronchospastic reactions if using atenolol is reduced compared to nonselective drugs as propranolol. Nonetheless, this reaction may also be encountered with Atenolol, particularly with high doses. Extreme caution should be exerted if Atenolol is given to asthma patients, who are particularly at risk; the dose should be as low as possible. If an asthma attack occurs, the inhalation of a β2-mimetic antiasthmatic, such as hexoprenaline or salbutamol, will usually suppress the symptoms.

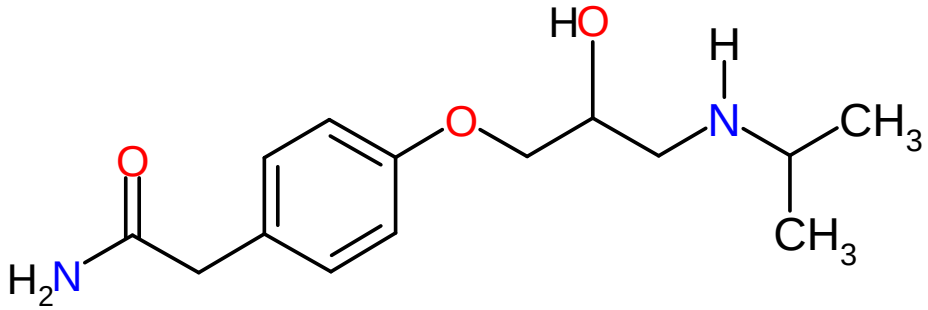
13. Adrenergic Antagonists: β-blockers

13.2 Selective β1



Propranolol

logP = 3.0



Atenolol

(*RS*)-2-{4-[2-hydroxy-3-(propan-2-ylamino) propoxy]phenyl}acetamide

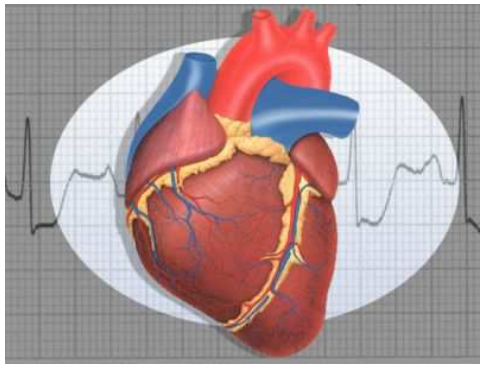
logP = 0.5

Atenolol is a **selective** β1 receptor antagonist, a drug belonging to the group of beta blockers. Introduced in 1976, Atenolol was developed as a replacement for Propranolol in the treatment of hypertension. *Unlike Propranolol, Atenolol does not pass through the blood-brain barrier thus avoiding various central nervous system side effects*.

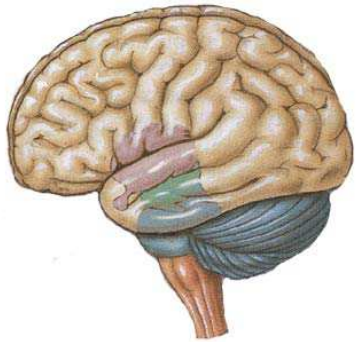
Atenolol is one of the most widely used β-blockers and was once first-line treatment for hypertension.

13. Adrenergic Antagonists: β-blockers

13.2 Selective β1: CNS side effects



↑ logP

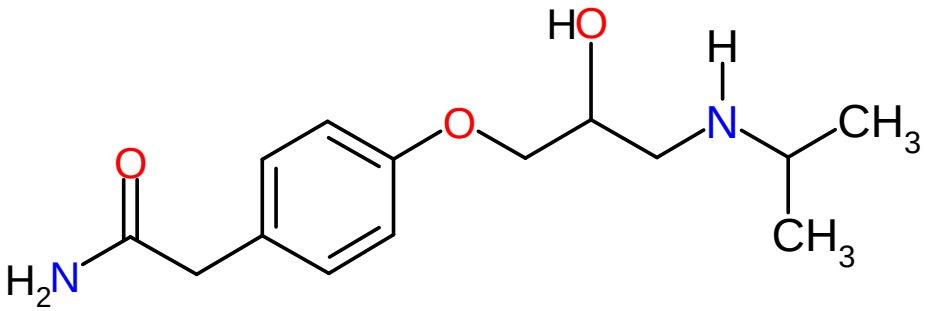


	logP
Propranolol	3.0
Betaxolol	2.4
Pindolol	1.9
Esmolol	1.7
Metoprolol	1.6
Timolol	1.2
Atenolol	0.5

lethargy
nightmares
confusion
loss of memory
depression

13. Adrenergic Antagonists: β-blockers

13.2 Atenolol absorption and excretion



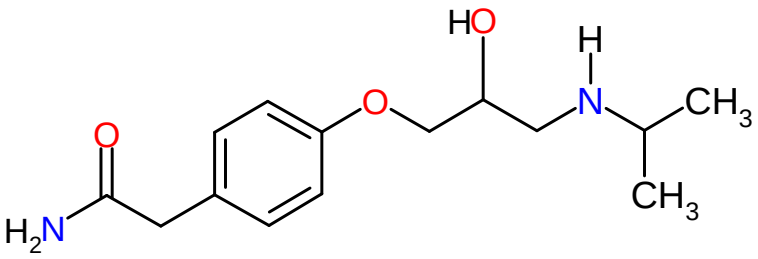
Atenolol
logP = 0.5

REMEMBER: as already described for Pirenzepine, also for **Atenolol** only approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces.

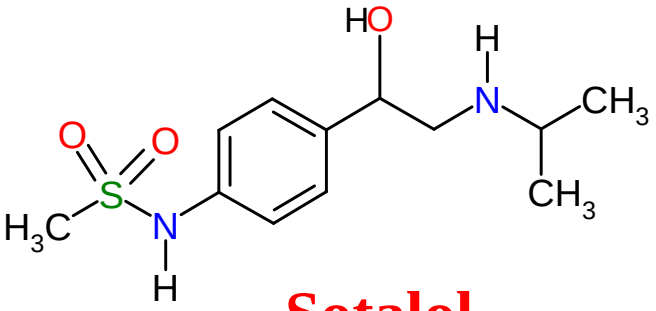
Moreover, unlike Propranolol or Metoprolol, but like Nadolol, Atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion.

13. Adrenergic Antagonists: β-blockers

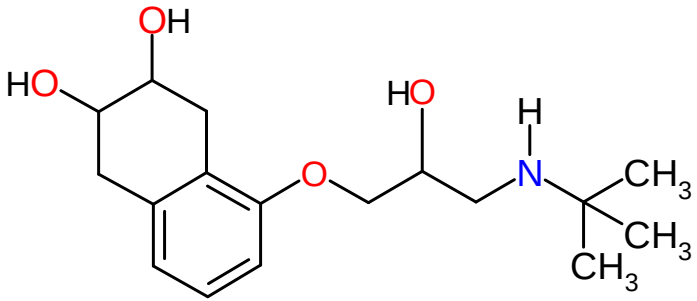
13.2 Other *low logP* β-blockers



Atenolol
logP = 0.5



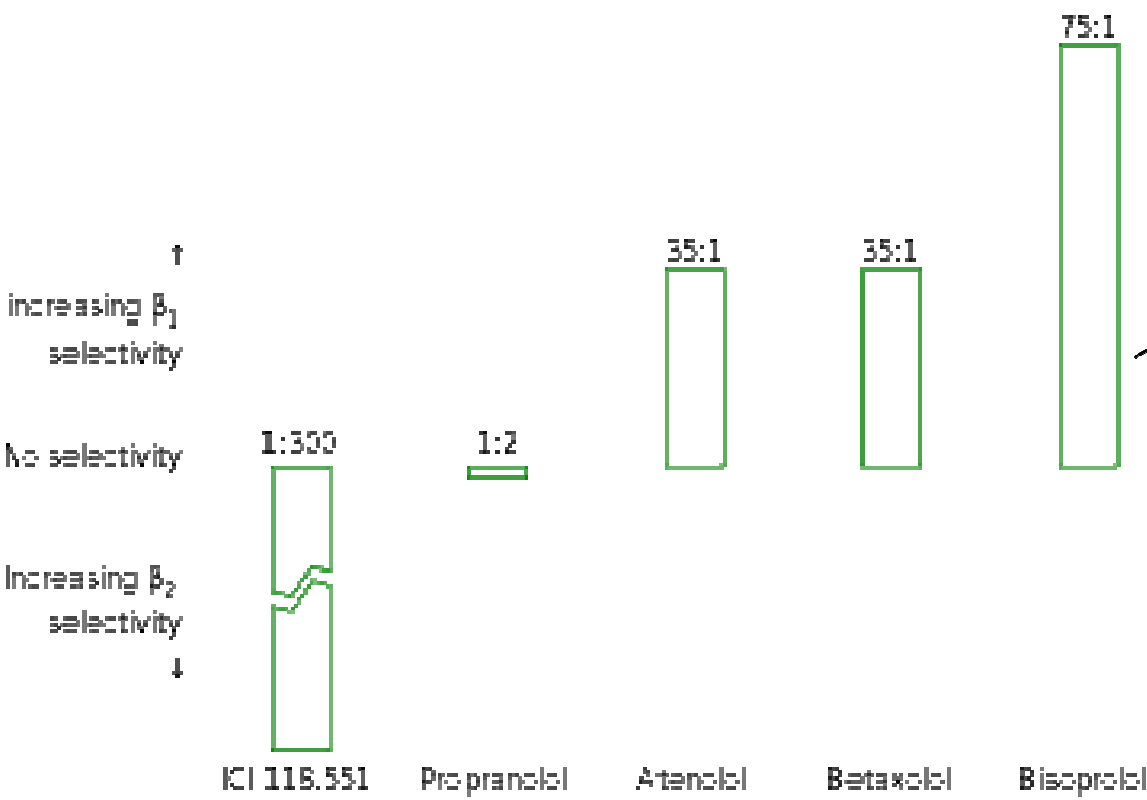
Sotalol
logP = 0.3

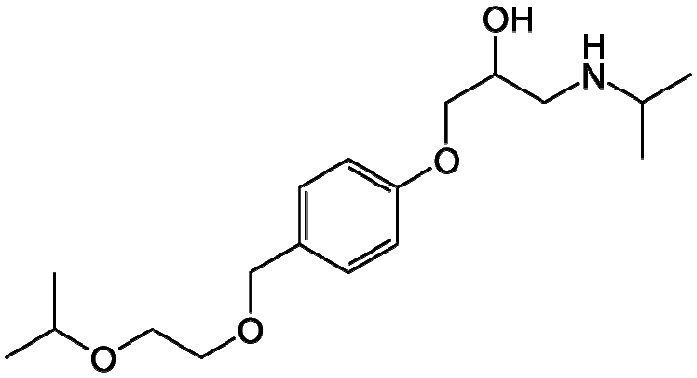


Nadolol
logP = 0.8

13. Adrenergic Antagonists: β-blockers

13.2 Selective β1

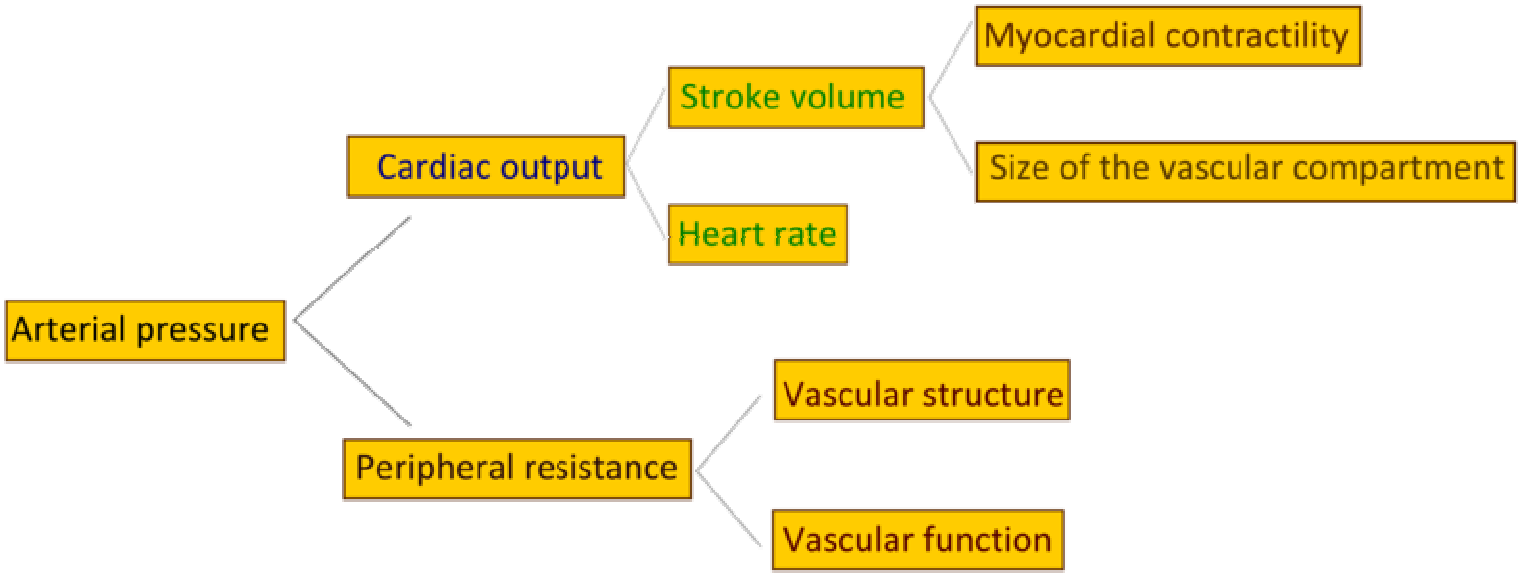




logP = 2.2

1992

Hypertension treatments:

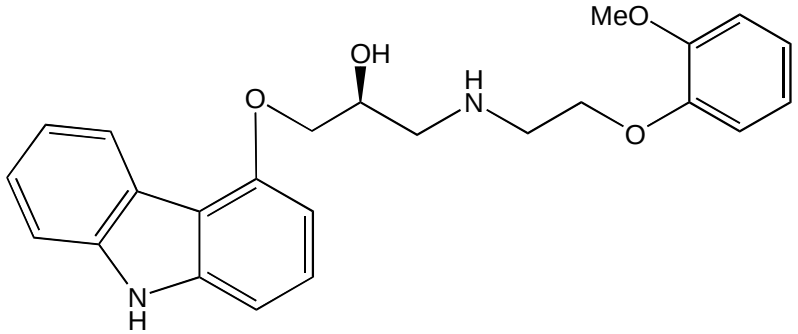


First line therapy:

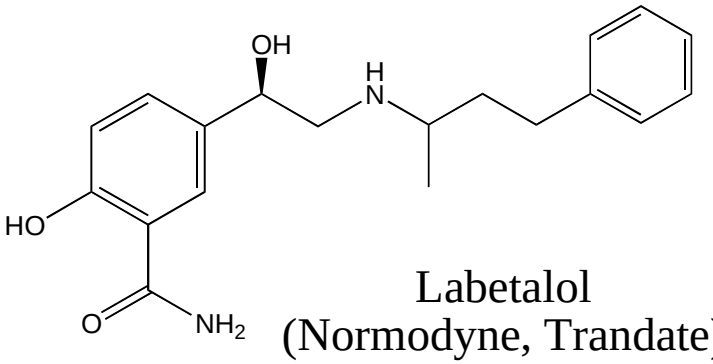
a. ACE inhibitor (or angiotensin-converting-enzyme inhibitor);
b. calcium antagonists;
c. Diuretics;
d. Beta-blockers

13. Adrenergic Antagonists: β-blockers

13.3 Non selective β1 and β2 plus α1 antagonism



Carvedilol
(Coreg, GSK)
(Dilatrend, Eucardic, Roche)

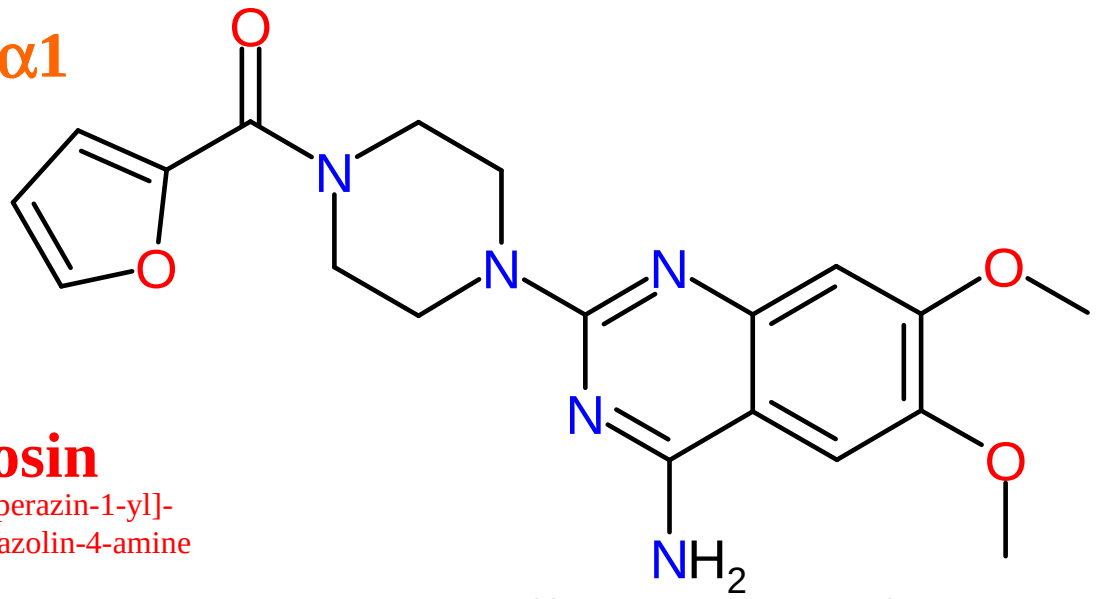


Labetalol
(Normodyne, Trandate)

In addition to blocking both β1- and β2-adrenergic receptors, **carvedilol** and **labetalol** also display α1-adrenergic antagonism, which confers the added benefit of reducing blood pressure through vasodilatation.

12. Adrenergic Antagonists: α-blockers

12.1 Selective α1



Prazosin

2-[4-(2-furoyl)piperazin-1-yl]-
6,7-dimethoxyquinazolin-4-amine

Prazosin is *orally active* and has a minimal effect on cardiac function due to its *alpha-1 receptor selectivity*. The antihypertensive characteristics of prazosin make it a *second-line choice* for the treatment of high blood pressure.

Prazosin is also useful in treating urinary hesitancy associated with *prostatic hyperplasia* by blocking alpha-1 receptors, which control constriction of both the prostate and ureters. Although not a first line choice for either hypertension or prostatic hyperplasia, it is a choice for patients who present with both problems concomitantly.

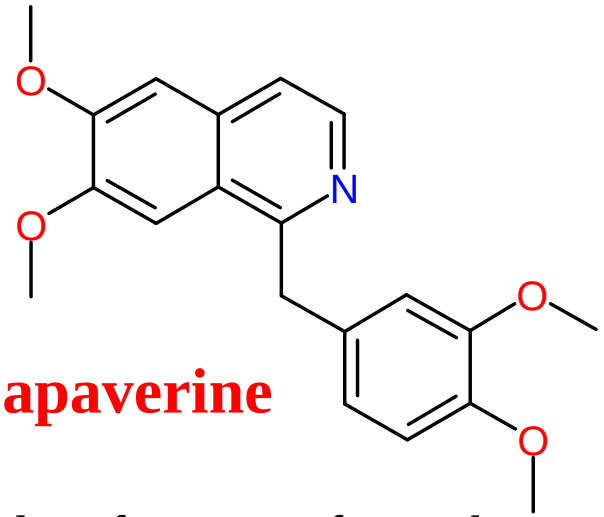
Prazosin has shown to be effective in treating *severe nightmares* in children, associated with post-traumatic disorders (PTSD) symptoms.

12. Adrenergic Antagonists: α-blockers

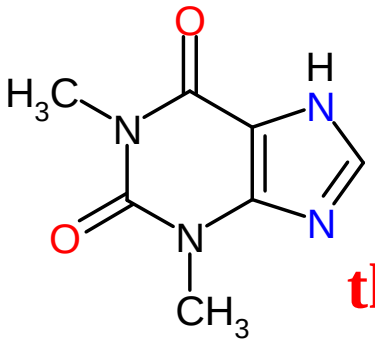
Discovery of Prazosin

In the light of the role that the cyclic nucleotides, cAMP and cGMP, play in the regulation of vascular smooth muscle tone and the rate and force of cardiac contraction more specifically their goal was to discover novel, highly effective ***inhibitors of phosphodiesterase***.

Several prototype structures were synthesized which incorporated structural features of the natural substrate and of ***papaverine*** and ***theophylline*** both inhibitors of phosphodiesterase.



papaverine

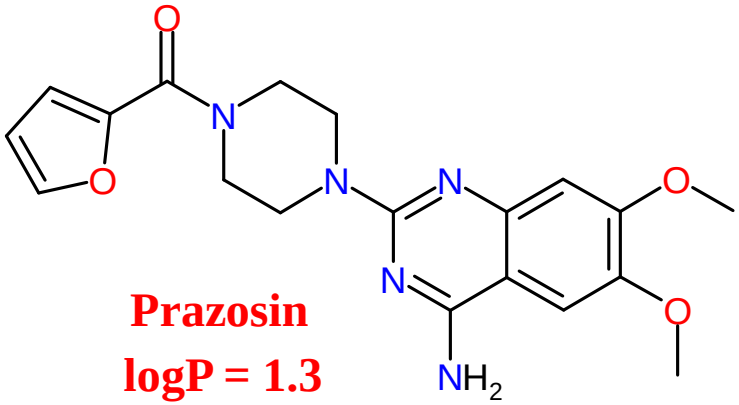


theophylline

This lead to the identification of a sub-series of efficacious analogues from which ***prazosin*** was selected for clinical development.

12. Adrenergic Antagonists: α-blockers

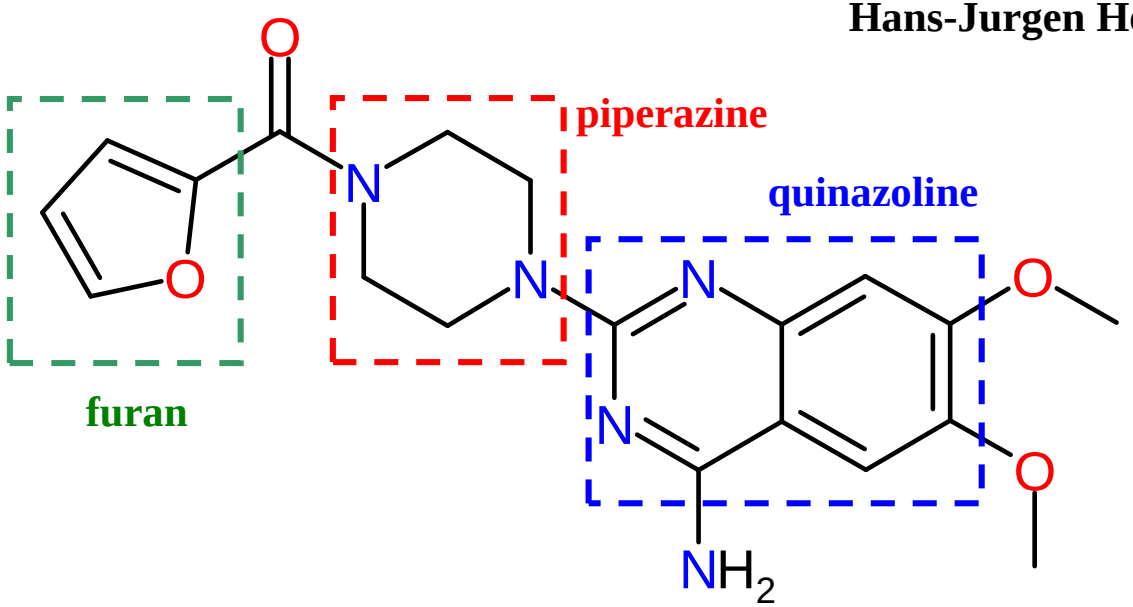
12.1 Selective α1



Prazosin

logP = 1.3

Hans-Jurgen Hess, Ph.D.



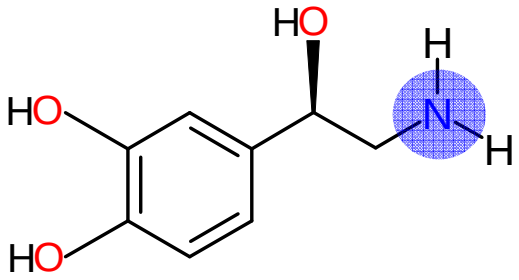
piperazine

quinazoline

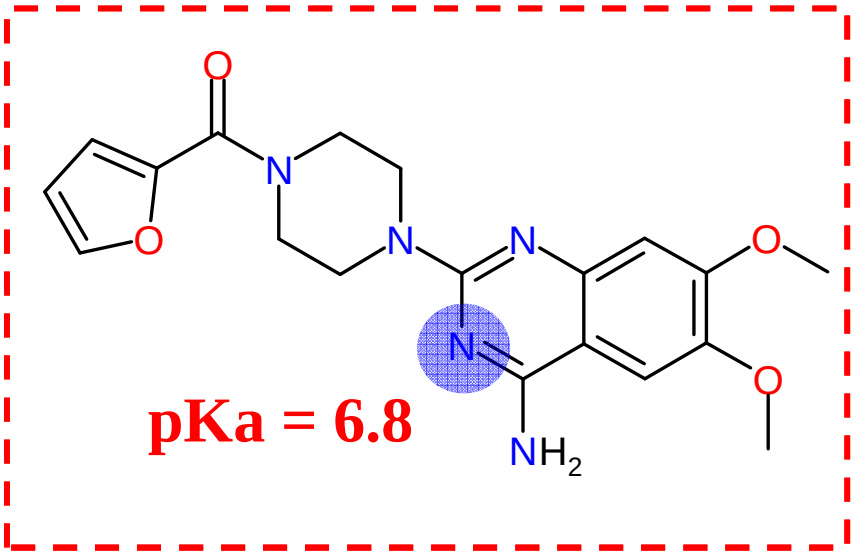
furan

12. Adrenergic Antagonists: α-blockers

Do you remember….

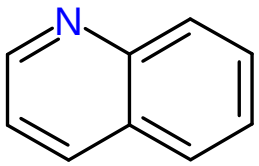


pKa = 8.6



pKa = 6.8

quinoline



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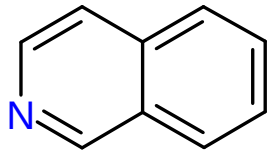
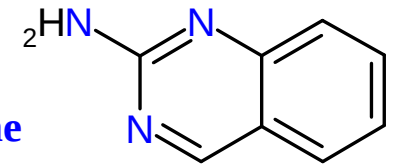
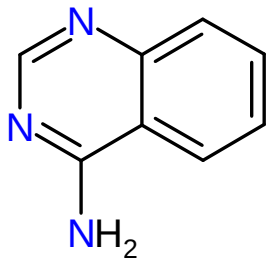


pKa = 5.1

isoquinoline

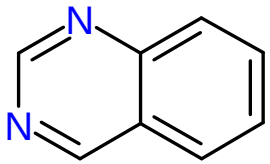


pKa = 4.4



pKa = 5.7

quinazoline



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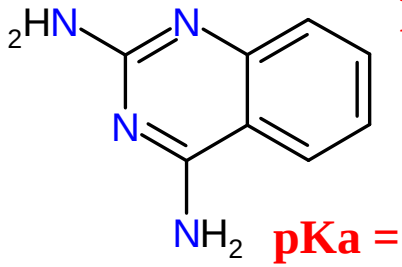
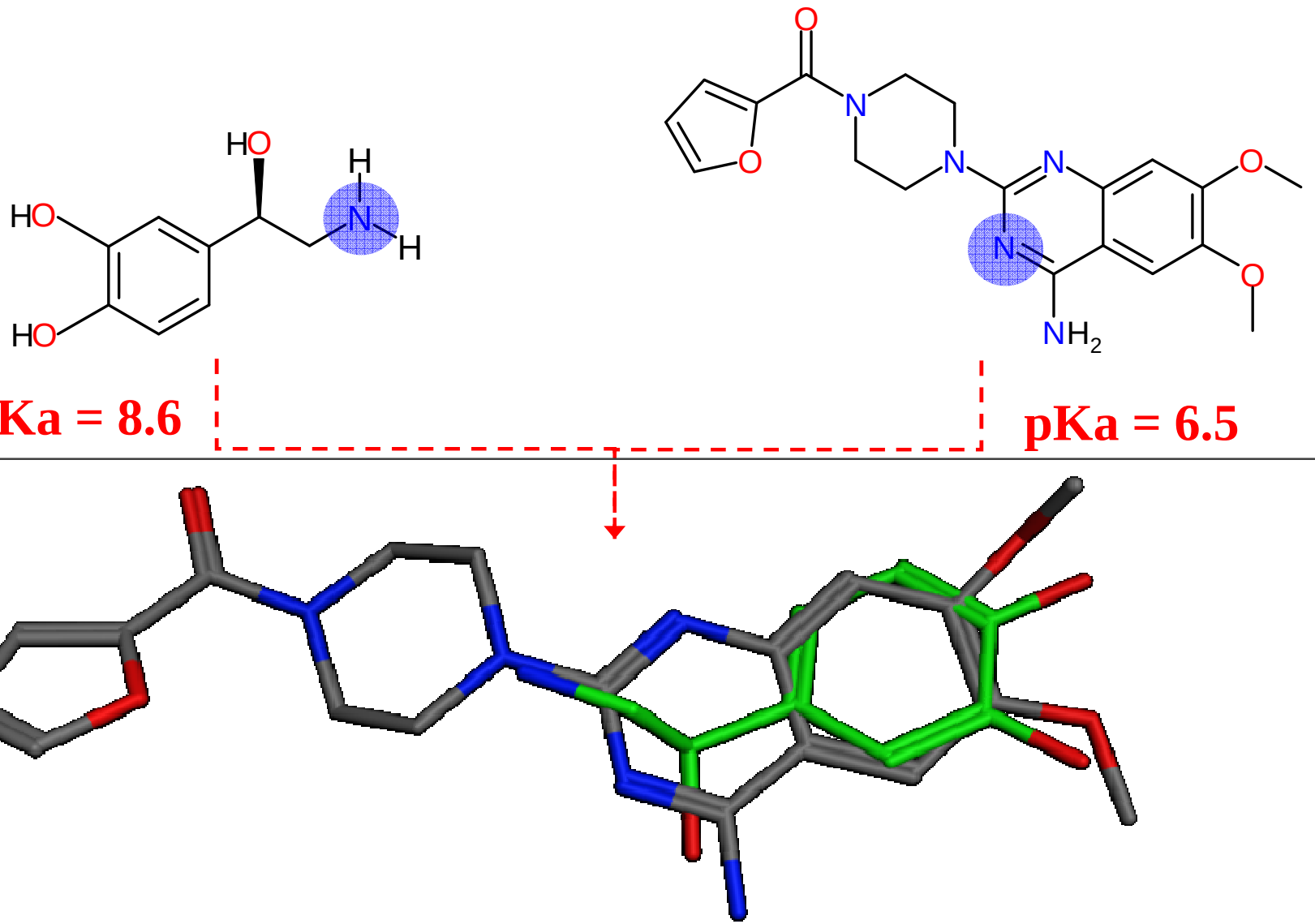


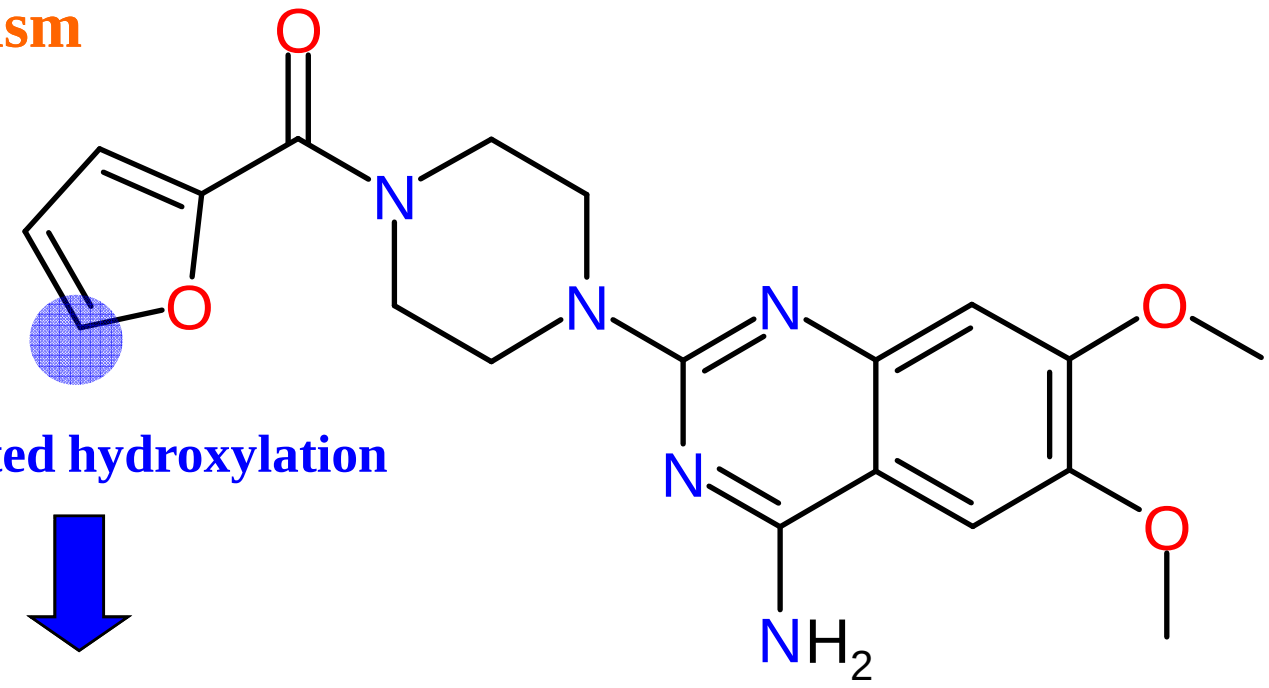
pKa = 7.1

12. Adrenergic Antagonists: α-blockers

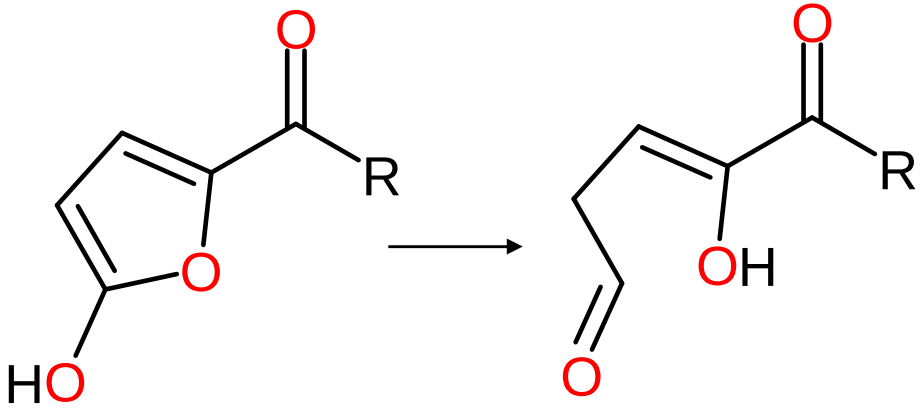


12. Adrenergic Antagonists: α-blockers

Furan metabolism

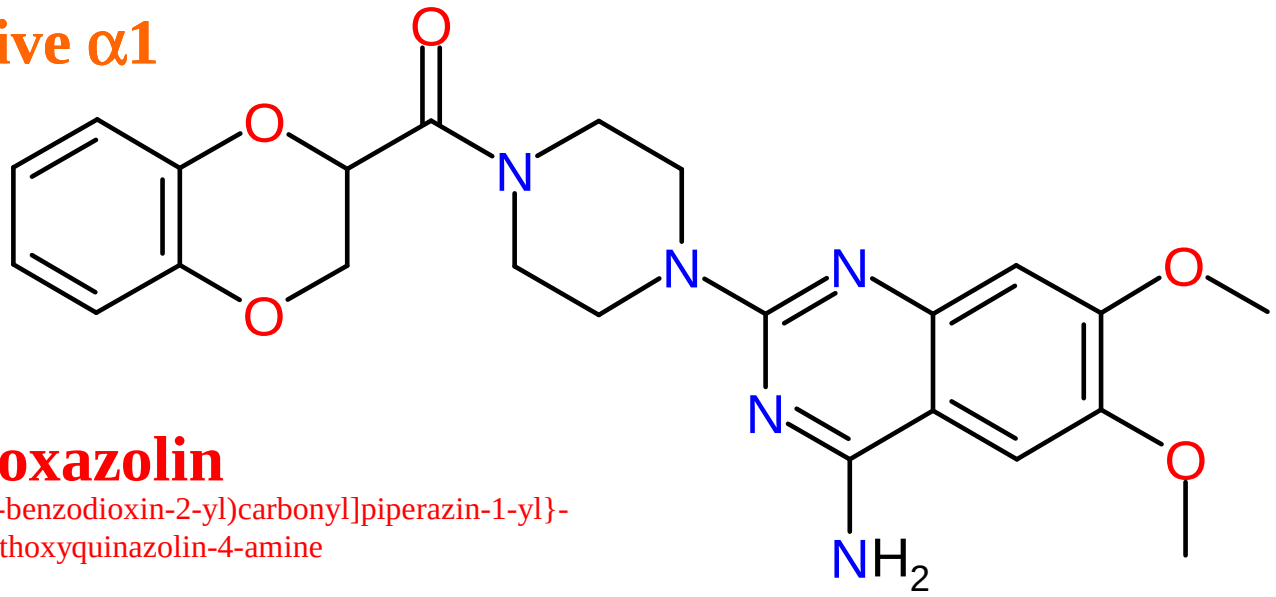


P450-mediated hydroxylation



12. Adrenergic Antagonists: α-blockers

12.1 Selective α1



Doxazolin

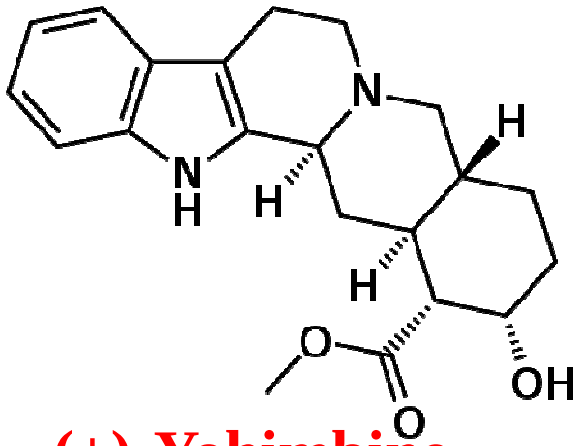
(*RS*)-2-{4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]piperazin-1-yl}--6,7-dimethoxyquinazolin-4-amine

Doxazosin, a quinazoline compound sold by Pfizer under the brand names Cardura and Carduran, is an alpha-blocker (*α1 selective*) used to treat high blood pressure and benign prostatic hyperplasia. It is sold as a racemic mixture.

On 2005, the FDA approved a sustained release form of doxazosin, to be marketed as **Cardura XL** for the preferential treatment of benign prostatic hyperplasia.

12. Adrenergic Antagonists: α-blockers

12.2 Selective α2



(+)-Yohimbine

17α-hydroxy-yohimban-16α-carboxylic acid methyl ester

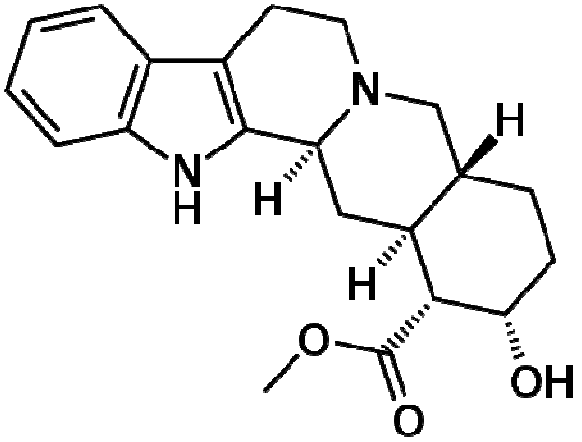
Pausinystalia yohimbe

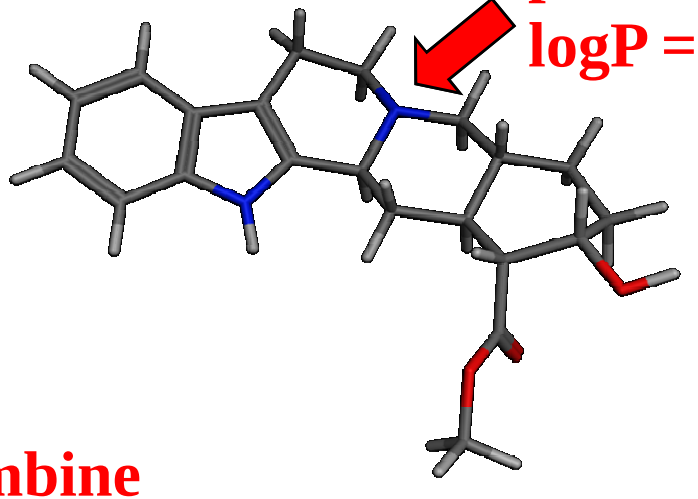
Yohimbine (or **Aphrodine**) is an alkaloid with stimulant and aphrodisiac effects found naturally in *Pausinystalia yohimbe* (Yohimbe).

Yohimbine *has high affinity for the α2-adrenergic receptor*, moderate affinity for the α1-adrenergic, 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1F, 5-HT2B, and D2 receptors, and weak affinity for the 5-HT1E, 5-HT2A, 5-HT5A, 5-HT7, and D3 receptors. It behaves as an antagonist at α1-adrenergic, α2-adrenergic, 5-HT1B, 5-HT1D, 5-HT2A, 5-HT2B, and D2, and as a partial agonist at 5-HT1A.

12. Adrenergic Antagonists: α-blockers

12.2 Selective α2

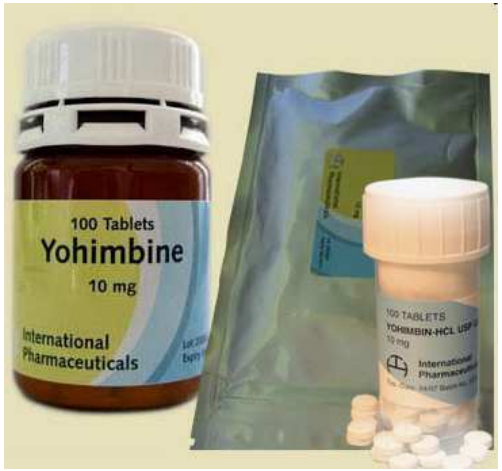




(+)-Yohimbine

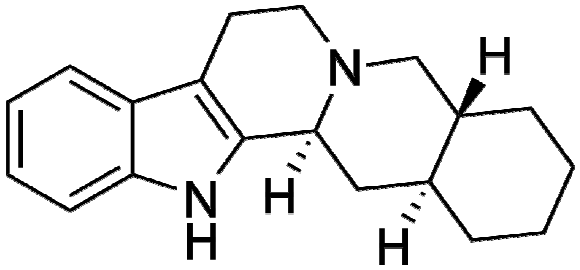
Yohimbine awakens the libido and gives an all-round boost to male sexual performance

Before the advent of Viagra, this pharmaceutical extract from the Yohimbe plant was a key treatment for male impotence.



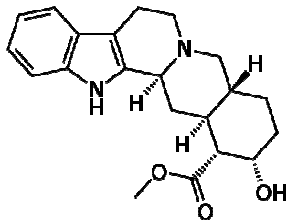
12. Adrenergic Antagonists: α-blockers

Yohimban alkaloids:

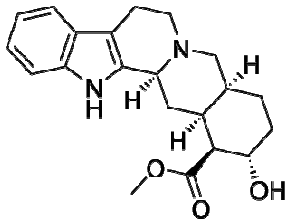


Yohimban

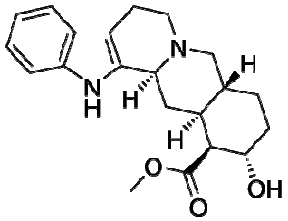
1,2,3,4,4a,5,7,8,13,13b,14,14*a*-dodecahydro-indolo [2',3':3,4]pyrido[1,2-*b*]isoquinoline



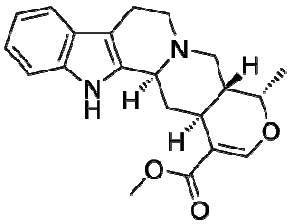
Yohimbine
mainly α2



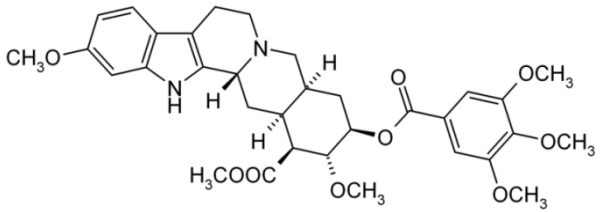
Rauwolscine
mainly α2



Corynanthine
α1 > α2



Ajmalicine
α1 > α2

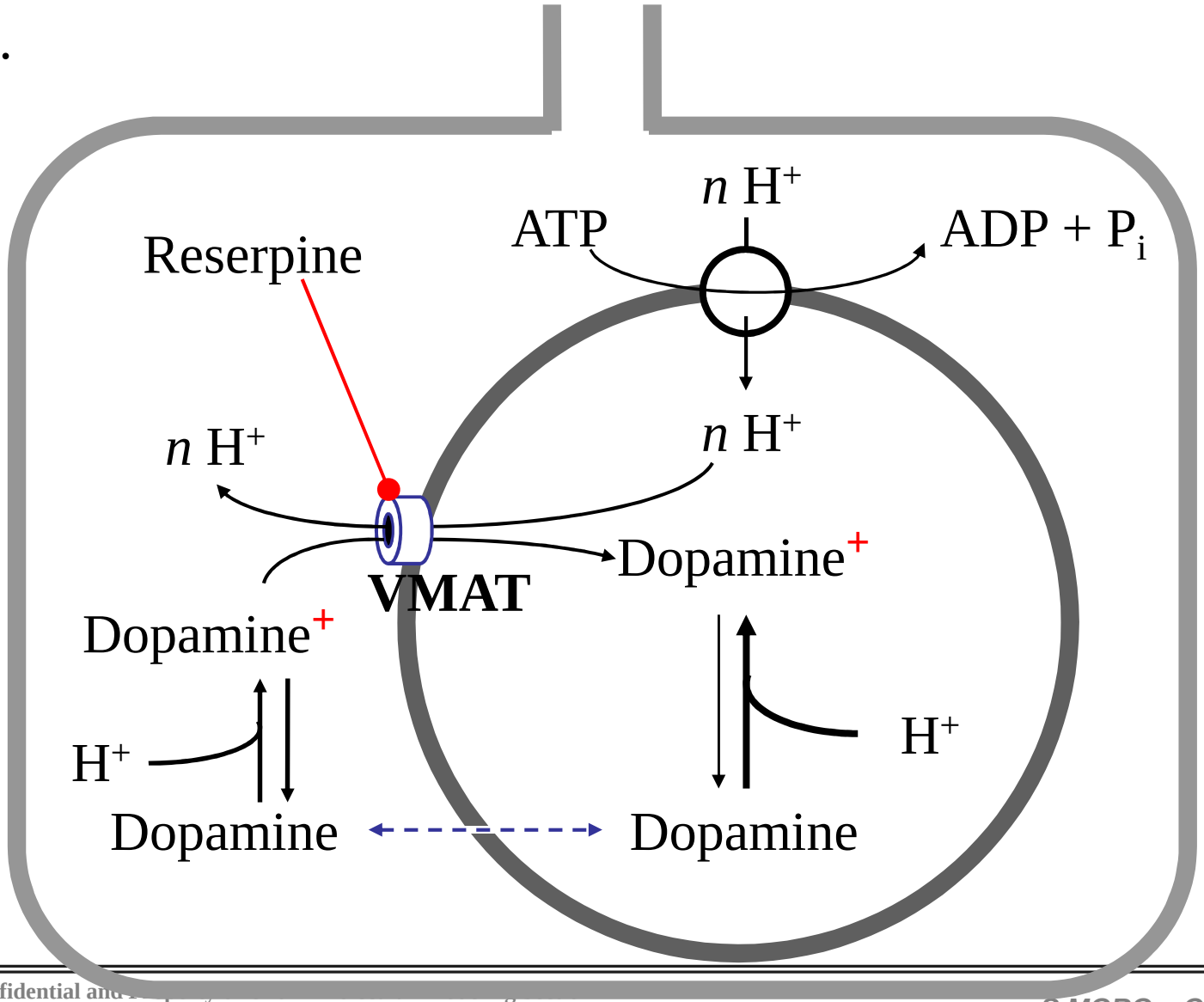


Reserpine

Reserpine almost irreversibly blocks the uptake (and storage) of norepinephrine (i.e. noradrenaline) and dopamine into synaptic vesicles by inhibiting the Vesicular Monoamine Transporters (VMAT).

12. Adrenergic Antagonists: α-blockers

Reserpine inhibits the vesicular accumulation of catecholamines and of serotonin.

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Stefano Moro
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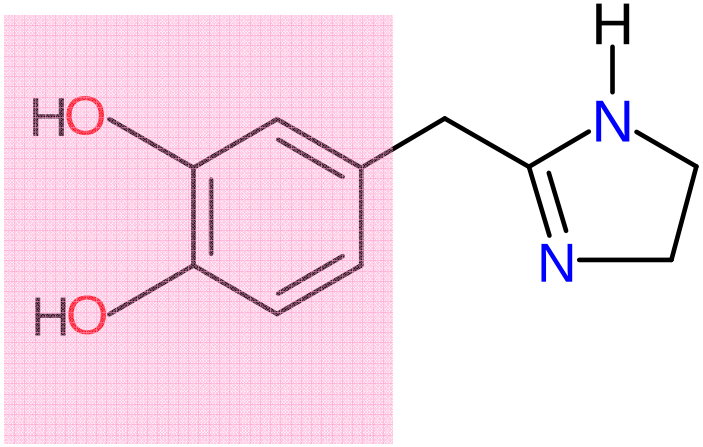
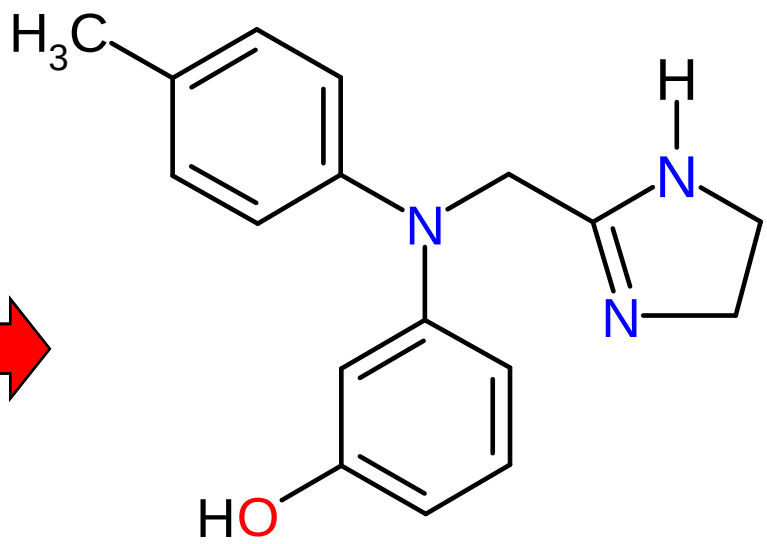
DATE
SCENE
TAKE

12. Adrenergic Antagonists: α-blockers



Crucial for the agonistic behavior

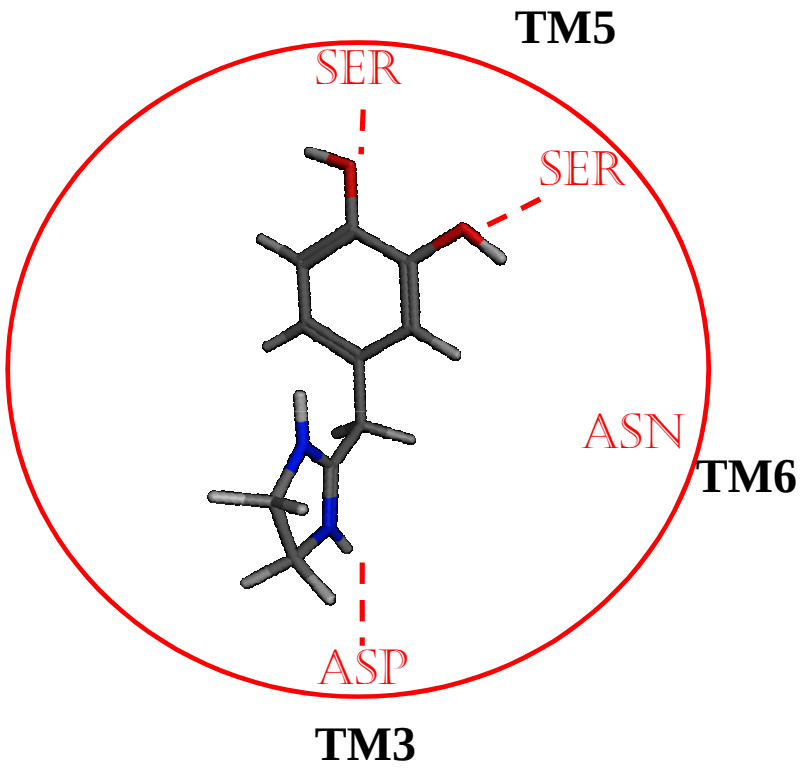


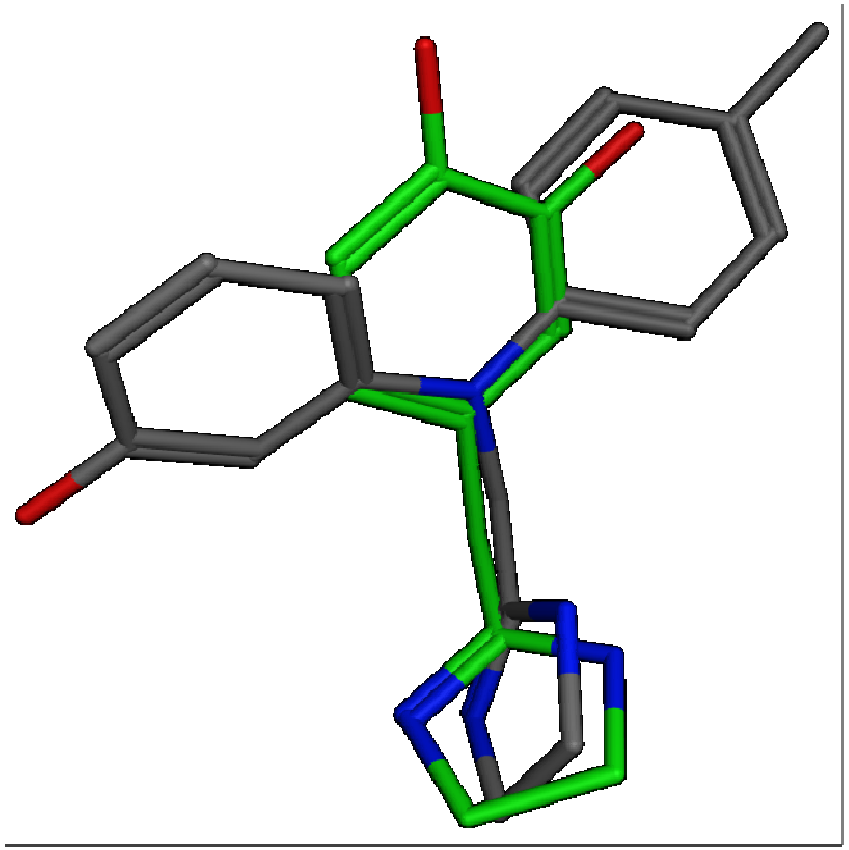
Phentolamine

3-[4,5-dihydro-1*H*-imidazol-2-ylmethyl-(4-methylphenyl)-amino]phenol

Phentolamine is a reversible ***nonselective*** alpha-adrenergic antagonist. Its primary action is **vasodilatation** due to α1 blockade. The primary application for phentolamine is for the control of hypertensive emergencies, most notably due to pheochromocytoma.

12. Adrenergic Antagonists: α-blockers





Do you have a new good idea?