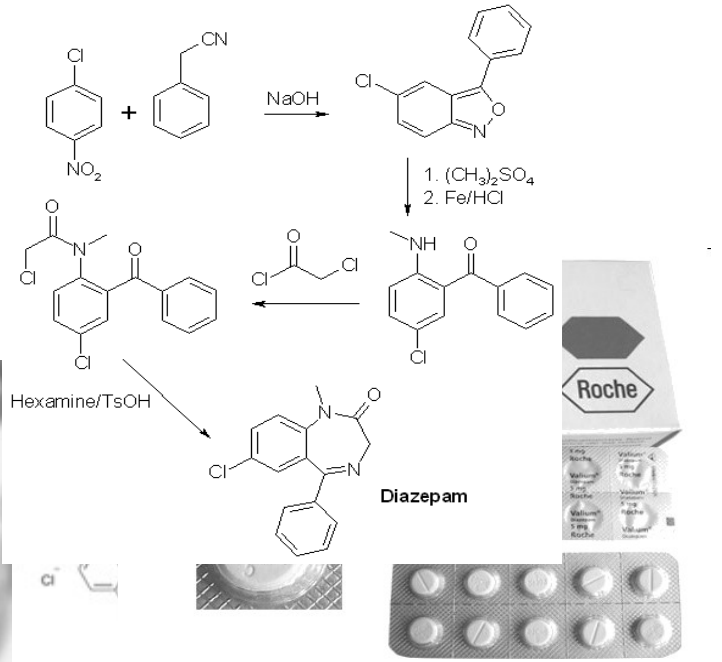
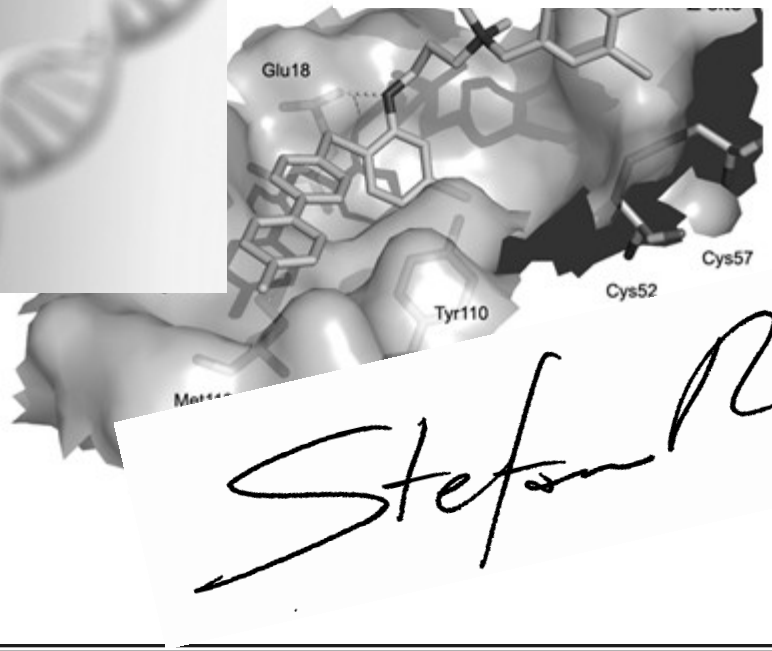
Chimica Farmaceutica e Tossicologica – Parte II





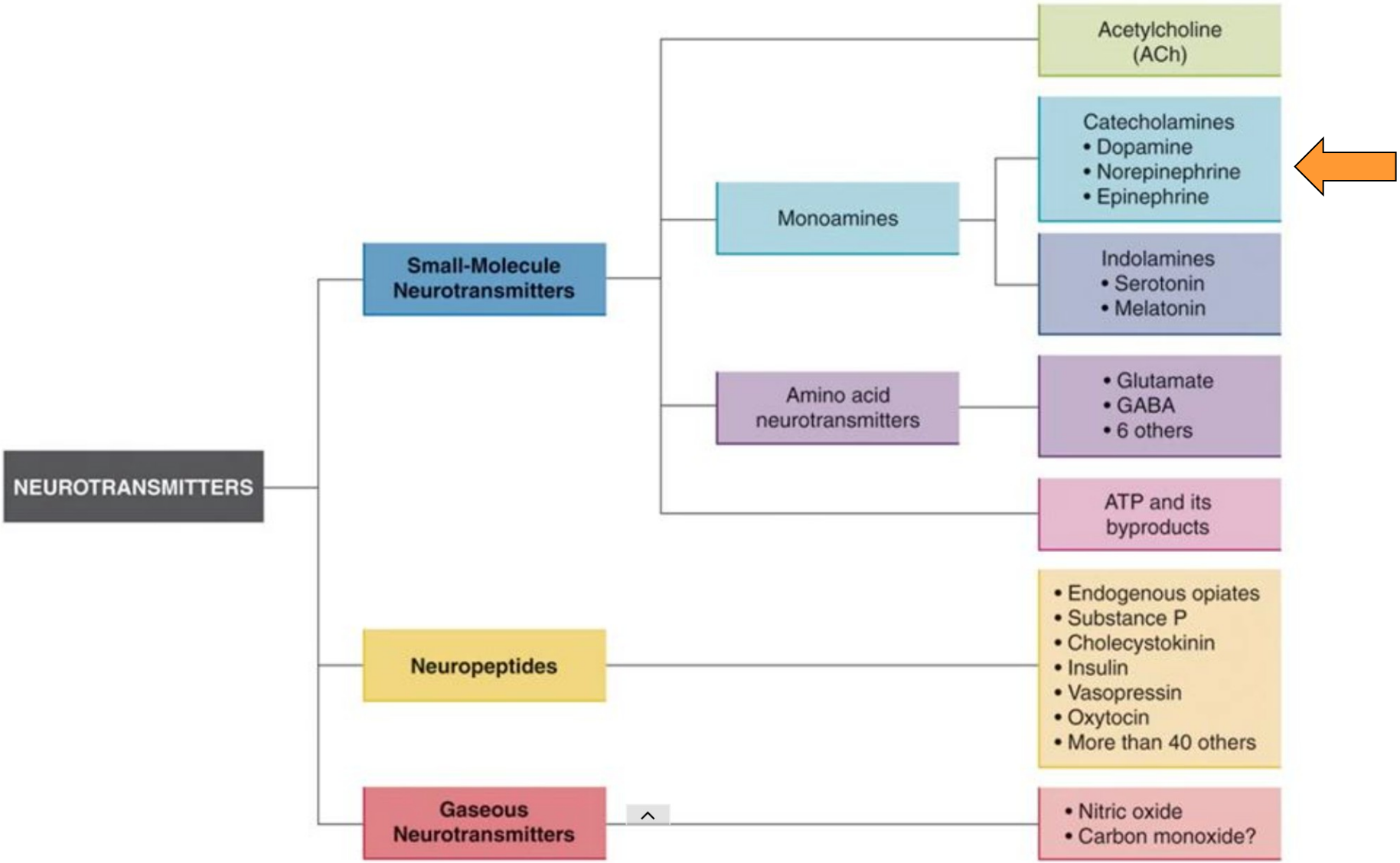
ADRENERGICI & ANTIADRENERGICI

Parte I

Mi ripeto ancora… la più importante per noi!

NON CONFONDEREMO MAI LA *CALCOLATRICE* CON LE *CIFRE* CHE ESSA PRODUCE!!!

0. Propedeutic...



credits: https://slideplayer.com/slide/7815788/

1. Nerve Transmission

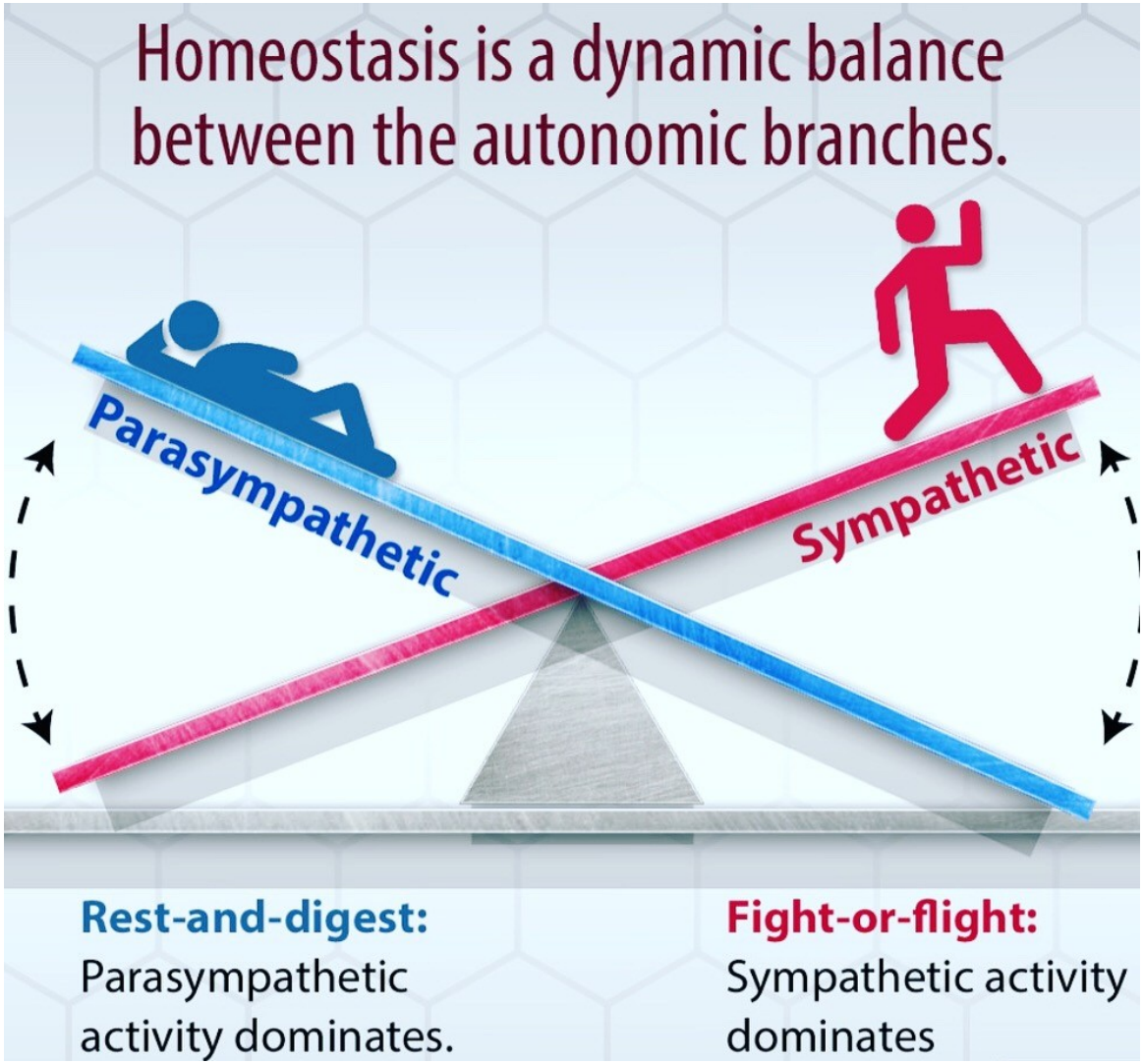
Adrenergic nervous system

BODY TISSUE/ORGAN	SYMPATHETIC RESPONSE*	PARASYMPATHETIC RESPONSE*
Eye	Dilates pupils	Constricts pupils
Lungs	Dilates bronchioles	Constricts bronchioles and increases secretions
Heart	Increases heart rate	Decreases heart rate
Blood vessels	Constricts blood vessels	Dilates blood vessels
Gastrointestinal	Relaxes smooth muscles of gastrointestinal tract	Increases peristalsis
Bladder	Relaxes bladder muscle	Constricts bladder
Uterus	Relaxes uterine muscle	
Salivary gland		Increases salivation

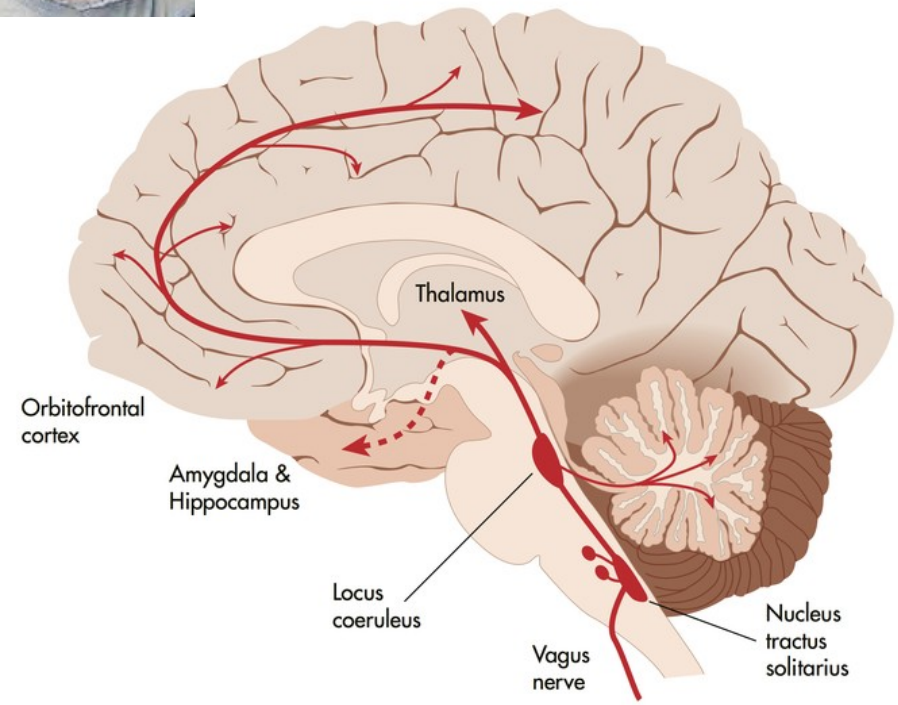
*The sympathetic and parasympathetic nervous systems have opposite responses on body tissues and organs.

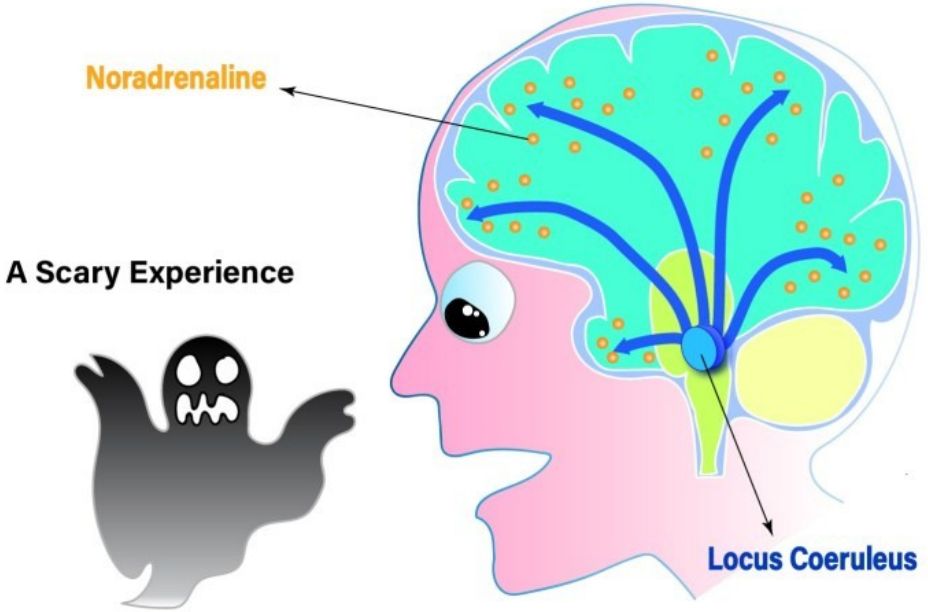
1. Nerve Transmission

Adrenergic nervous system



Locus coeruleus… and fear learning!

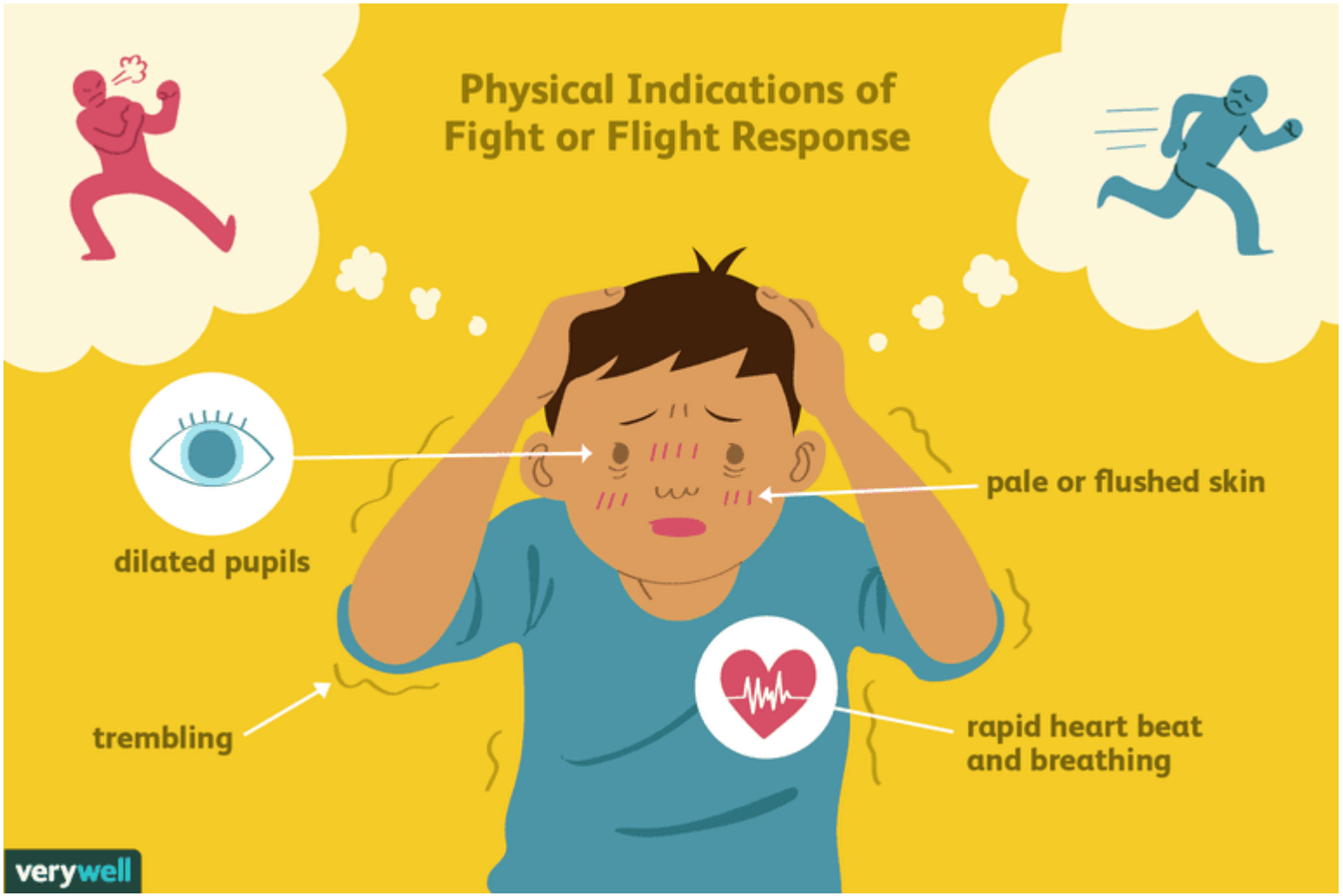




It turns out that the neural cells of the *locus coeruleus* are blue because they make and release a specific kind of chemical signal, or neurotransmitter, called *noradrenaline*. Noradrenaline is a stress signal, released by the locus coeruleus when an animal is experiencing fear and stress.

credits: http://sitn.hms.harvard.edu/flash/2018/mysterious-fear-learner-locus-coeruleus/

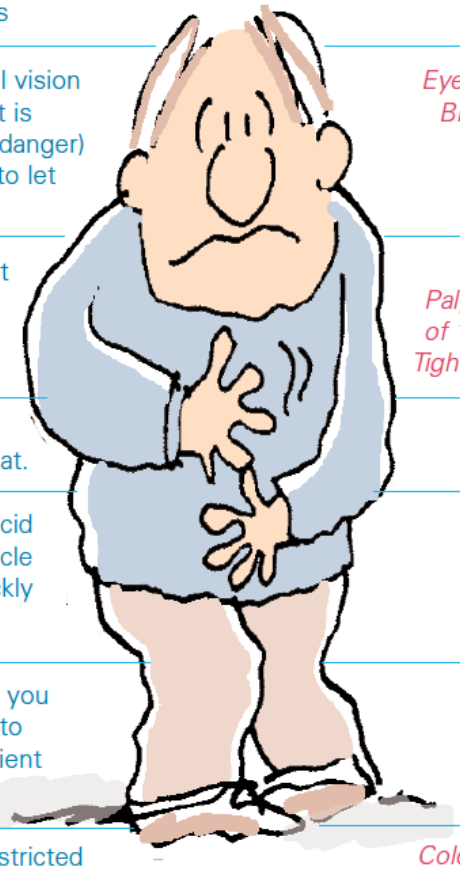
Fight or Flight response...



credits: Illustration by Joshua Seong. © Verywell, 2018

Fight or Flight response...

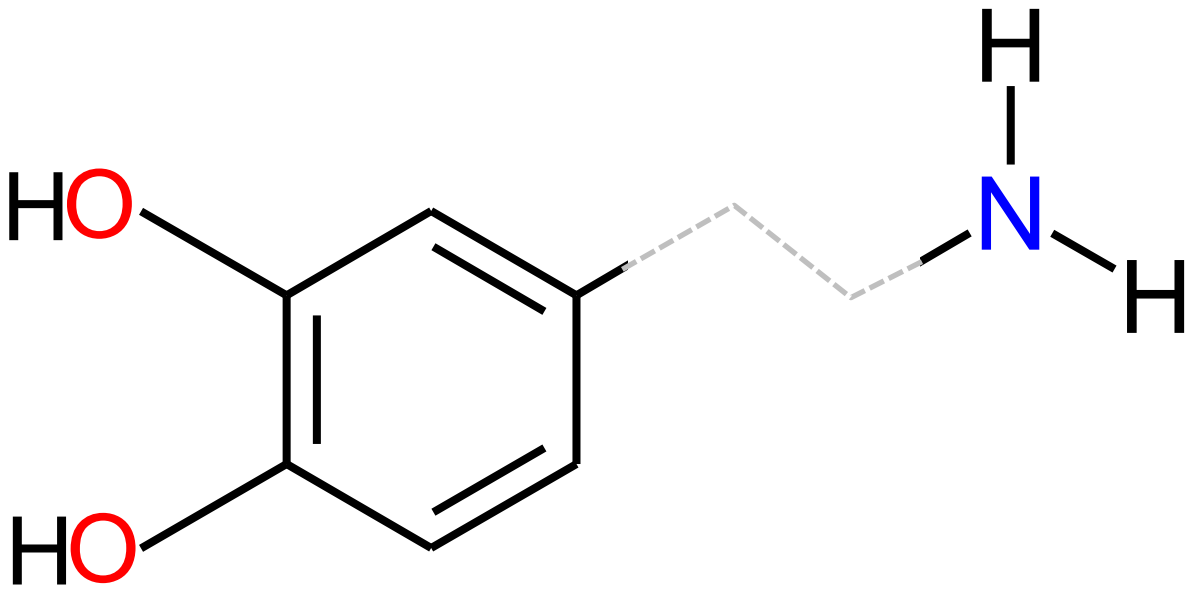
FIGHT OR FLIGHT RESPONSE	RESULTING SYMPTOMS
Mind and body set on high alert watching out for signs of danger.	*Sense of danger, impending doom, Agitation - uneasiness - can't relax*
Rapid breathing helps to divert blood to vital organs	*Dizziness - Lightheadedness - Hyperventilation*
'Tunnel Vision' - Peripheral vision is diminished so that sight is centrally focused (on any danger) Pupils of the eyes widen to let in more light.	*Eye strain - Fear of going blind Blurred vision / spots in front of eyes - Sensitivity to light Feelings of unreality*
Adrenaline increases heart rate sending blood to major muscle groups - to prepare for action.	*Rapid heart beat - Palpitations - Flutters - Feeling of 'skipped' or 'missed' beats. Tight chest - Choking sensation*
Increase in sweat so that the body does not overheat.	*Sweating (even in cold) Hot and cold flushes*
Stomach produces extra acid and digestive juices. Muscle action increases to quickly digest and eliminate food	*Frequently needing toilet Nausea 'Butterflies' Churning stomach Acidity Indigestion - Diarrhoea*
Muscles tense to prepare you for a quick departure and to make the body more resilient to attack.	*Muscle tension - Shaking Stiffness Trembling - ' Jelly legs' - Twitching Even severe pain at times.*
Blood vessels to skin constricted reducing any potential blood loss especially in hands and feet.	*Cold clammy hands - 'Pins and needles' - Tingling sensations or numbness in hands and feet*



credits: https://cbt4panic.org/the-fight-or-flight-response-symptoms/

2. Neurotransmitters

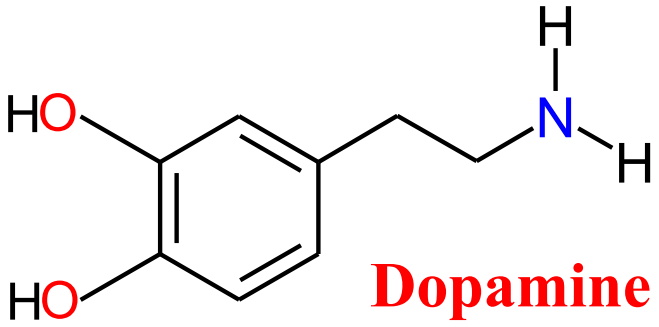
Catecholamines: before starting...



cathecol **amine**

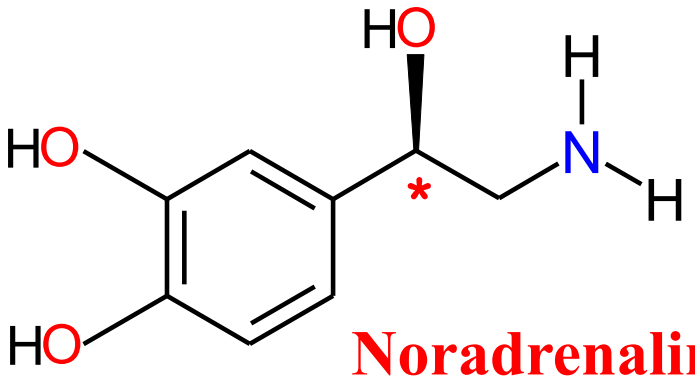
2. Neurotransmitters

Dopamine, Noradrenaline (Norepinephrine) and Adrenaline (Epinephrine) :



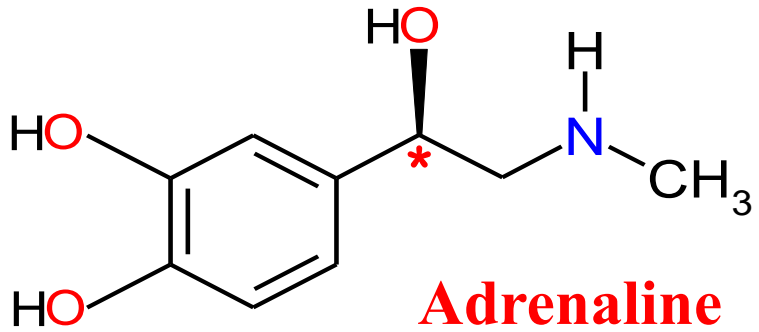
Dopamine

4-(2-aminoethyl)benzene-1,2-diol



Noradrenaline

4-[(1R)-2-amino-1-hydroxyethyl]benzene-1,2-diol



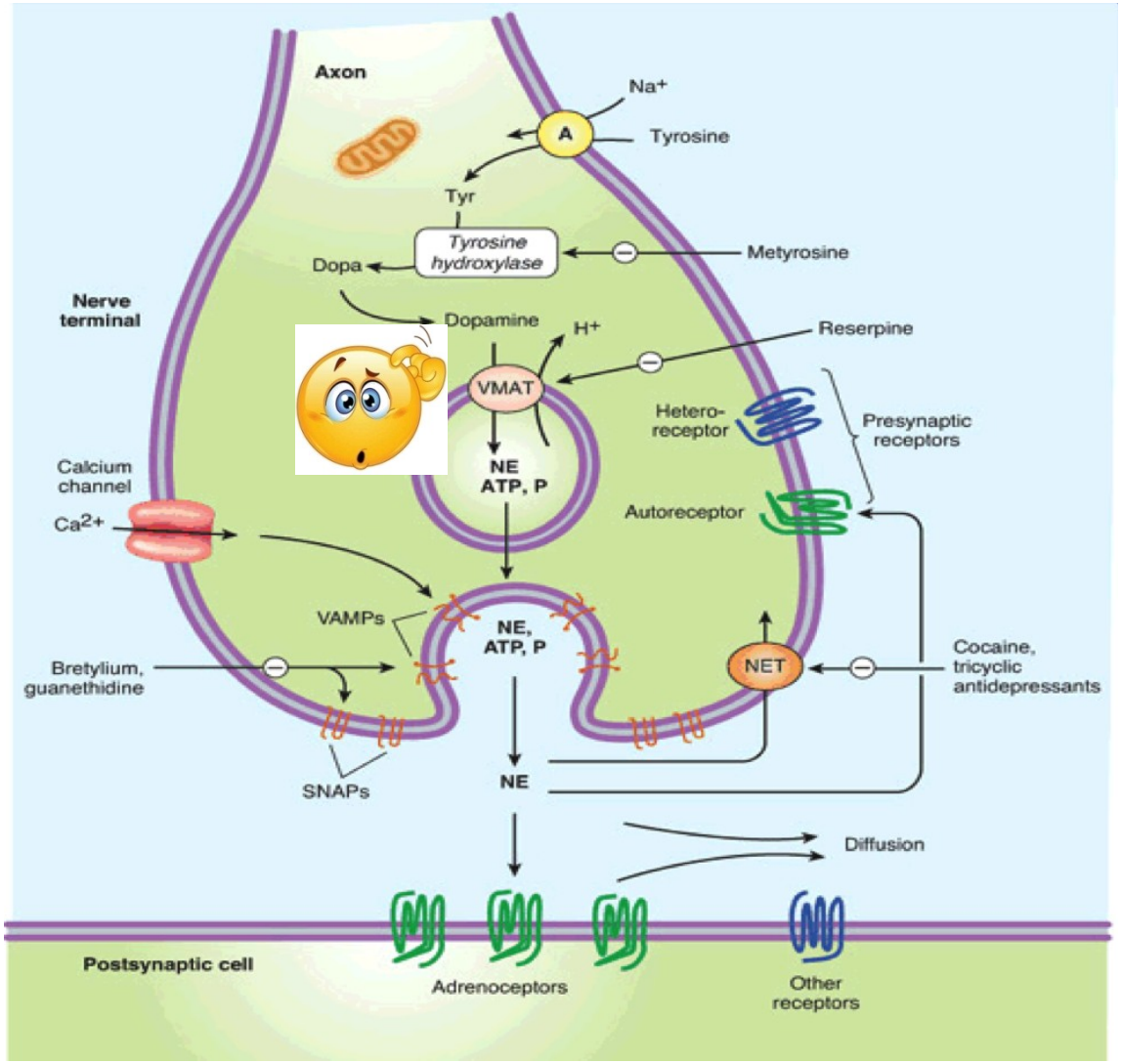
Adrenaline

(R)-4-(1-hydroxy-2-(methylamino)ethyl)benzene-1,2-diol

(nor : normal, no R)

3. Transmission process

Dopaminergic and Noradrenergic Synapses



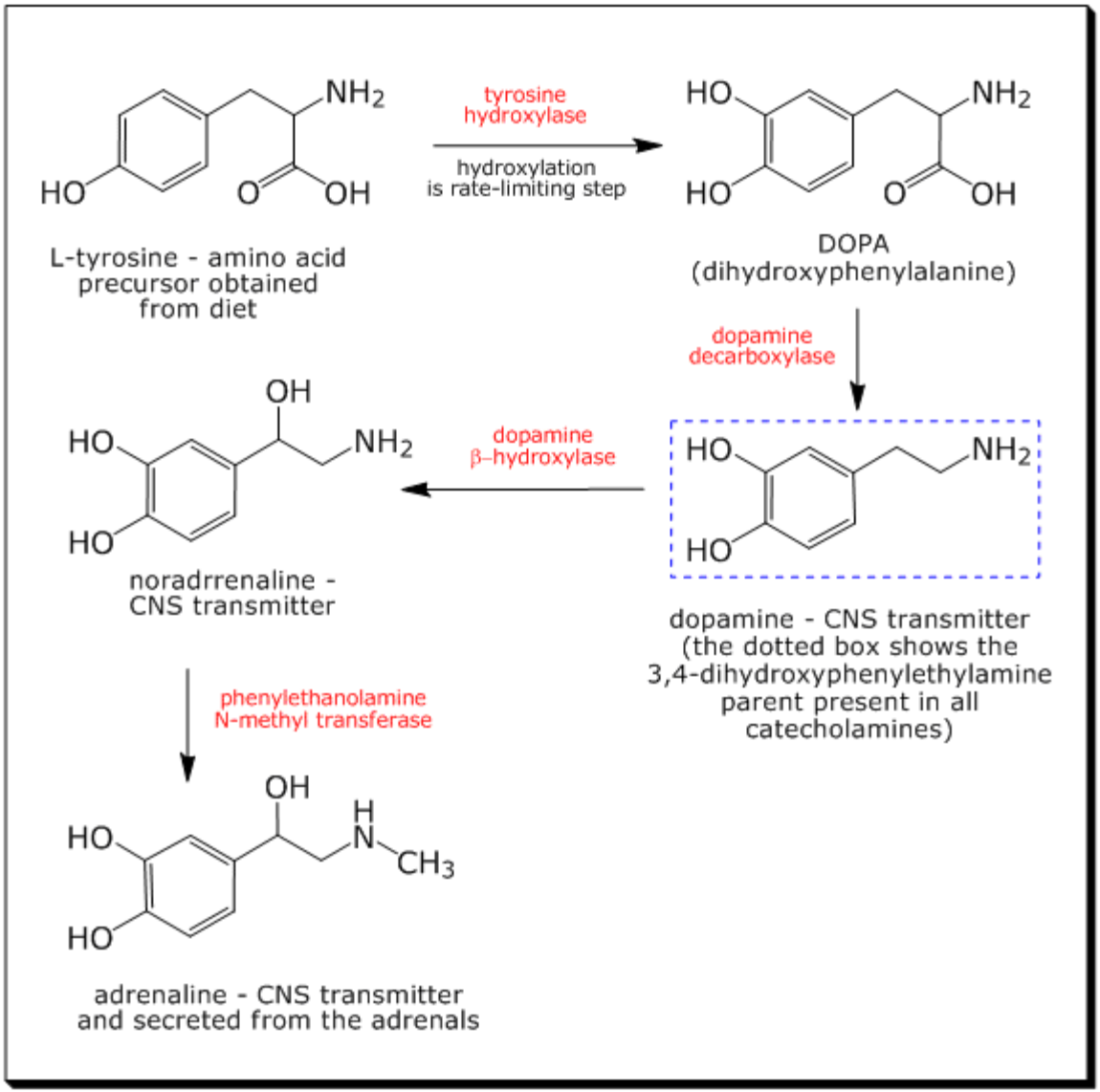
3. Transmission process

Synthesis and Release

1. The amino acid tyrosine is transported into the sympathetic nerve axon.
2. Tyrosine (Tyr) is converted to DOPA by tyrosine hydroxylase (***rate-limiting step for NE synthesis***).
3. DOPA is converted to dopamine (DA) by DOPA decarboxylase.
4. Dopamine is transported into vesicles then converted to norepinephrine (NE) by dopamine β-hydroxylase (DBH); transport into the vesicle can by blocked by the drug ***reserpine***.
5. An action potential traveling down the axon depolarizes the membrane and causes calcium to enter the axon.
6. Increased intracellular calcium causes the vesicles to migrate to the axonal membrane and fuse with the membrane, which permits the NE to diffuse out of the vesicle into the extracellular (junctional) space. DBH, and depending on the nerve other secondary neurotransmitters (e.g., ATP), is released along with the NE.
7. The NE binds to the postjunctional receptor and stimulates the effector organ response.

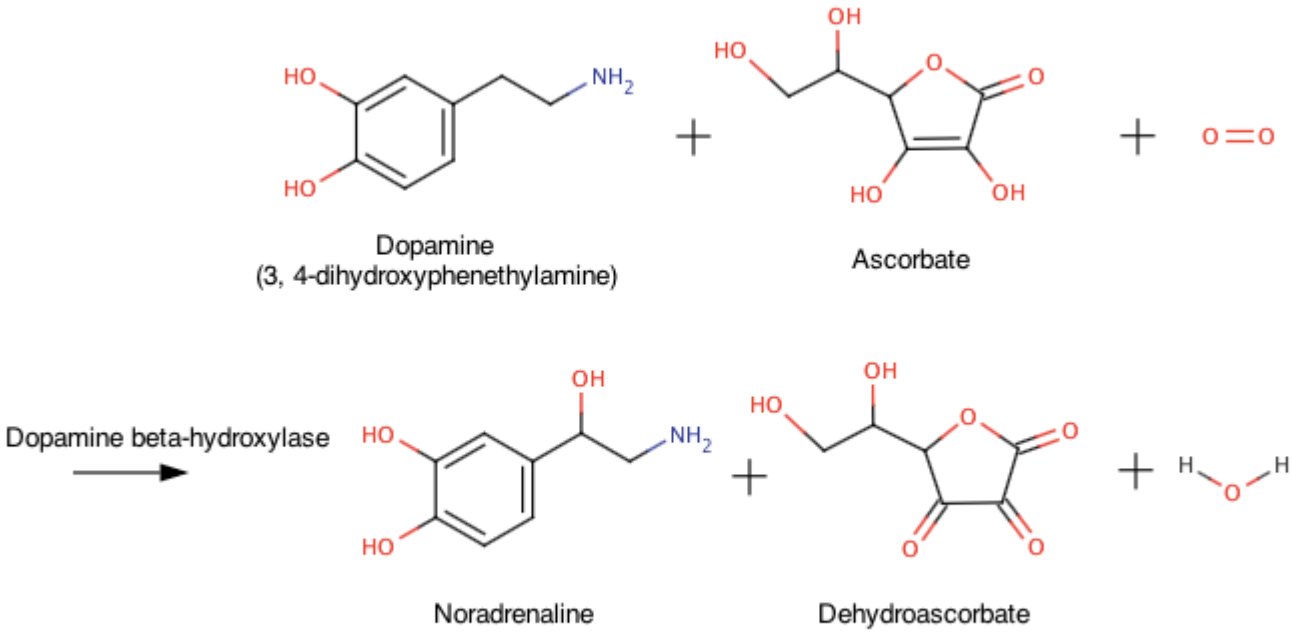
3. Transmission process

Biosynthesis:



3. Transmission process

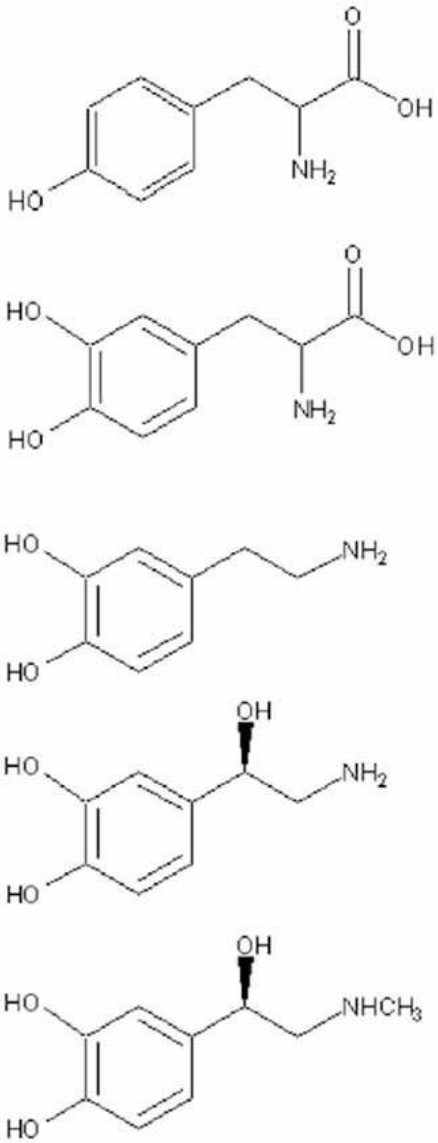
Dop



It is t -molecule neurotransmitters that is membrane-bound, making norepinephrine the only known transmitter synthesized inside vesicles. It is expressed in noradrenergic nerve terminals of the central and peripheral nervous systems, as well as in chromaffin cells of the adrenal medulla.

3. Transmission process

Biosynthesis:

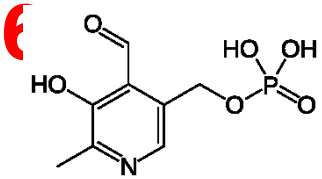


Tyrosine

↓ tyrosine-3-monooxygenase (tyrosine hydroxylase) — *tetrahydrobiopterin* **BH4**

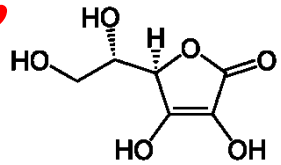
L-Dopa

↓ aromatic L-amino acid decarboxylase — *pyridoxal phosphate* **Vit.B6**



Dopamine

↓ dopamine beta-hydroxylase — *ascorbate* **Vit.C**



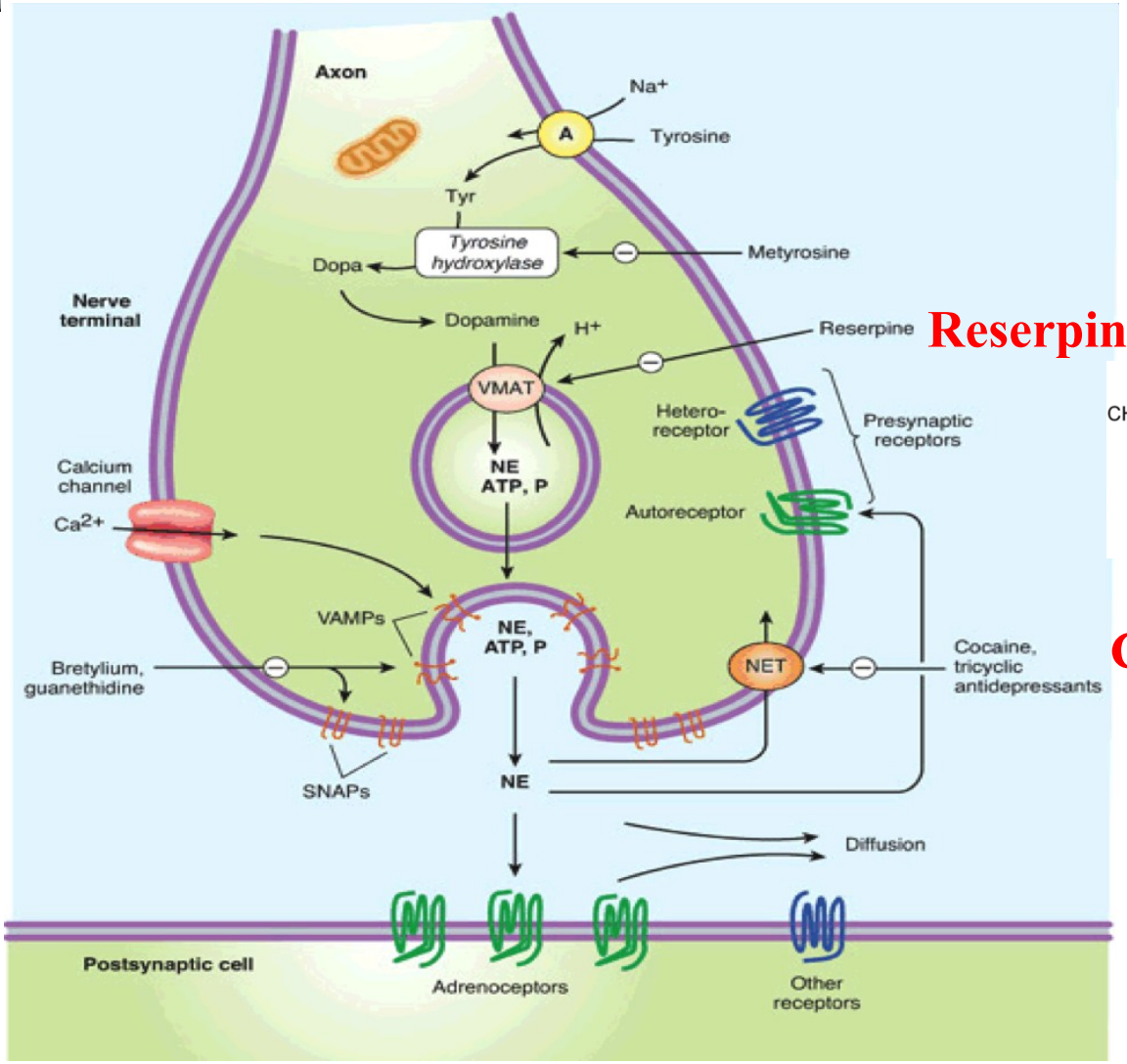
Noradrenaline

↓ phenylethanolamine-N-methyltransferase — *S-adenosylmethionine*

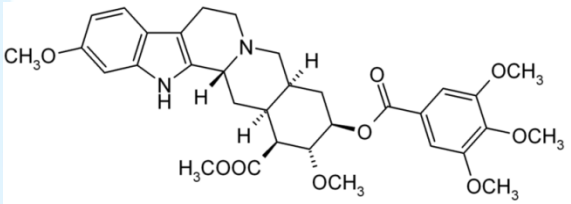
Adrenaline

Now it is clear why…

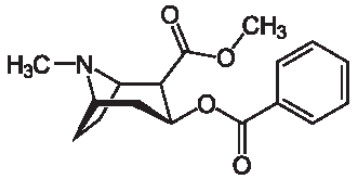
I open a small parenthesis … on the transporters!!



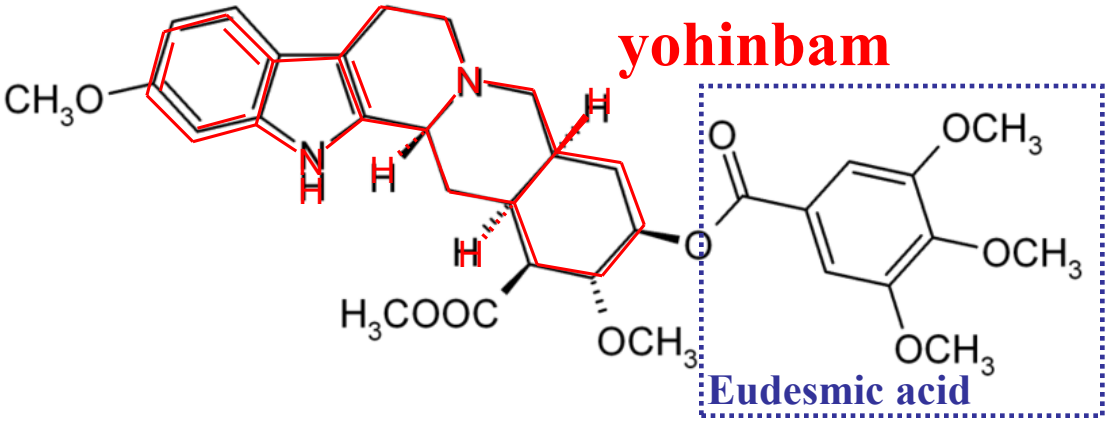
Reserpine



Cocaine



Reserpine…



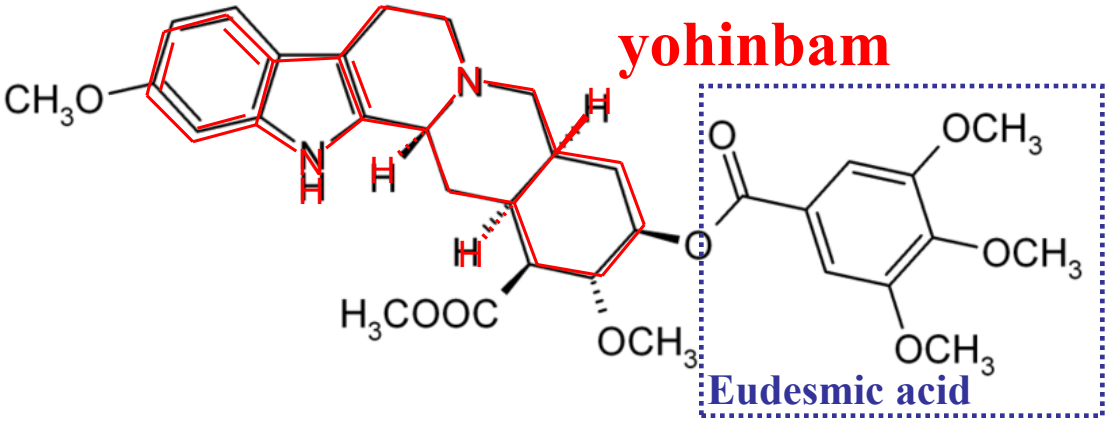
Rauwolfia serpentina

Bernard Brodie

In 1955, *Bernard Brodie*, a researcher at the NIMH, reported that ***reserpine***, an herb used to treat mental illness in India, depleted serotonin in the brain. *Reserpine* also made the laboratory rabbits sluggish, and thus it appeared that lowering serotonin in the brain could affect mood.

Reserpine is an indole alkaloid that is able to deplete catecholamine (NA, DA, AD) and serotonin (5-HT) in both central and peripheral nervous system and some other sites.

Reserpine…



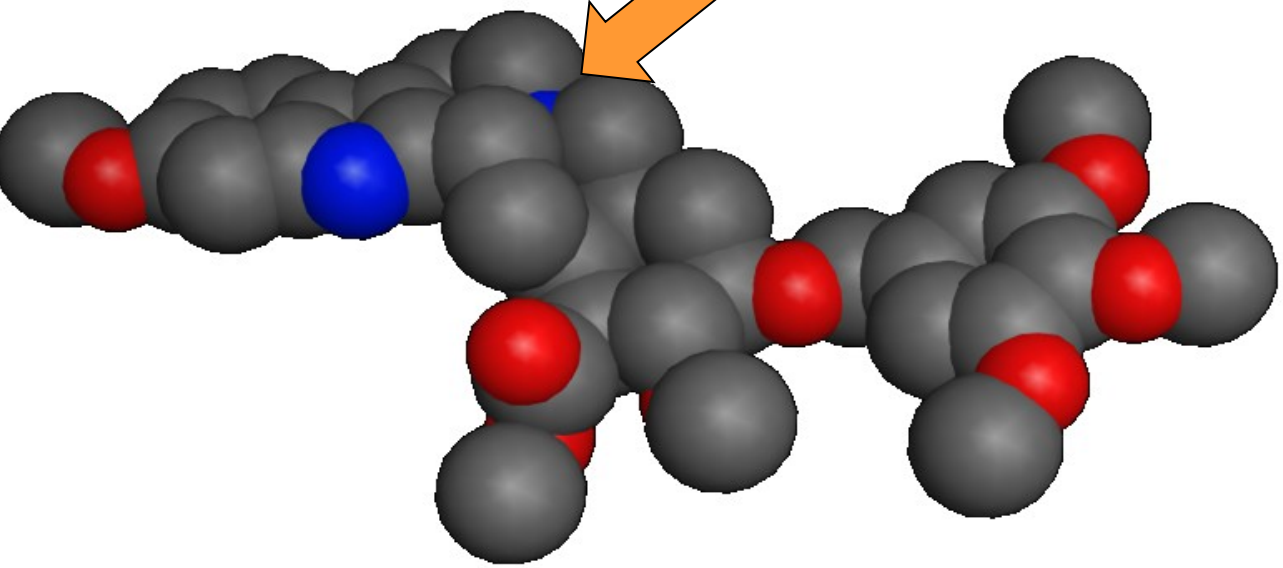
Rauwolfia serpentina

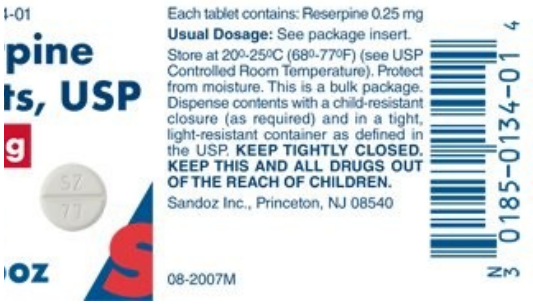
Reserpine is an indole alkaloid ***antihypertensive*** and ***antipsychotic*** drug that has been used for the control of high blood pressure and for the relief of psychotic symptoms, although because of the development of better drugs for these purposes and because of its numerous side-effects, ***it is rarely used today.***

Reserpine is an ***reversible inhibitor of vesicular monoamine transporter*** (VMAT). This normally transports free norepinephrine, serotonin, and dopamine from the cytoplasm of the presynaptic nerve terminal into storage vesicles for subsequent release into the synaptic cleft ("exocytosis"); unprotected neurotransmitters are metabolized by MAO (as well as by COMT) in the cytoplasm and therefore never reach the synapse.

Reserpine…

This N is sterically hindered
and inserted in a hydrophobic skeleton!!!

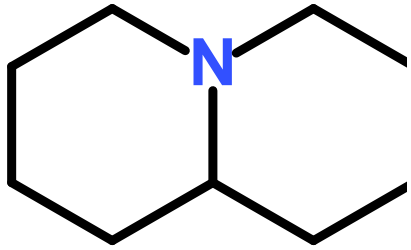


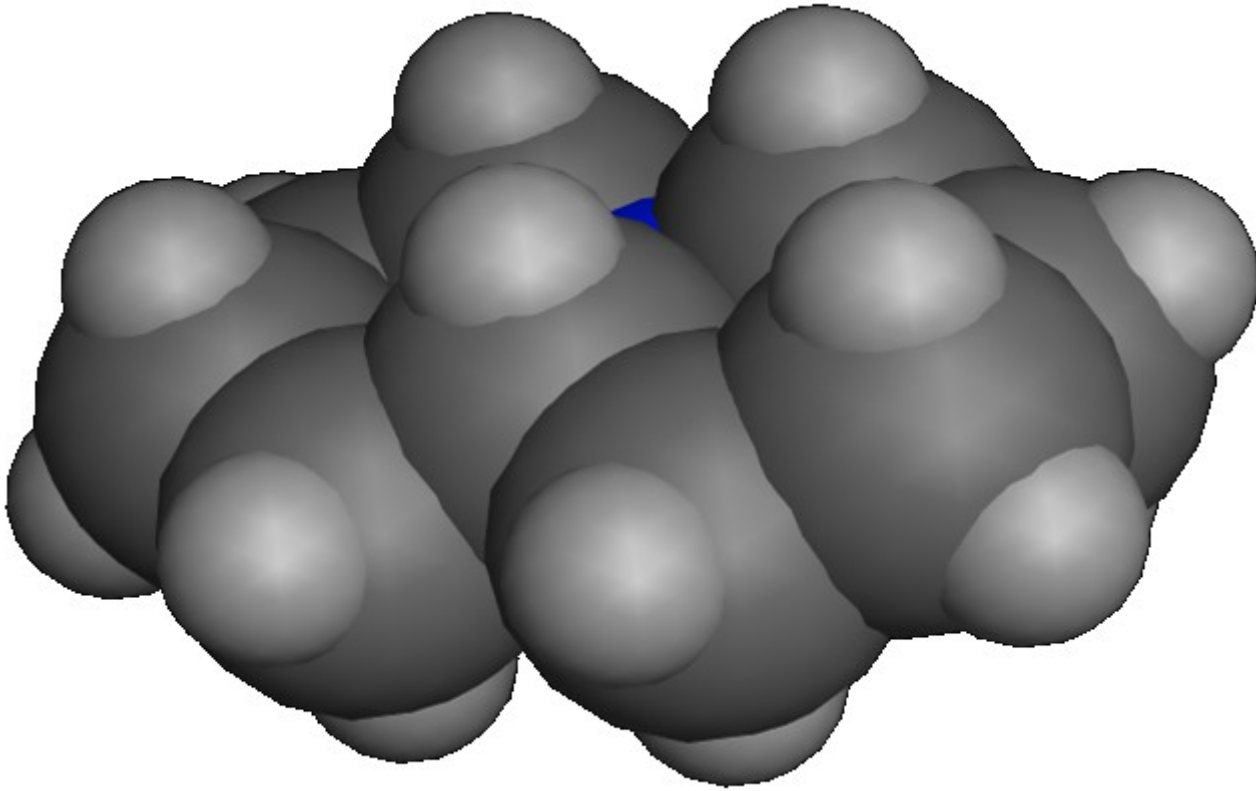


log P = 3.2
pKa = 6.6
PSA = 118 Å^2

Just for organic chemist nerds!!!

This N is sterically hindered





Quinolizidine

log P = 2.0

pKa = 7.0

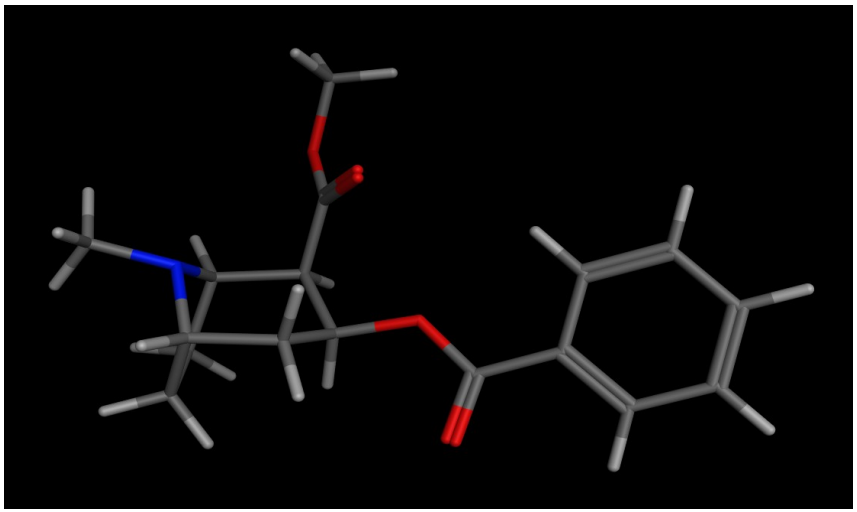
Solubility: C

3. Transmission process

Removal and Metabolism

1. Most (~90%) of the NE is transported back into the nerve terminal by a neuronal reuptake transport system. This transporter is blocked by ***cocaine***; therefore, cocaine increases junctional NE concentrations by blocking its reuptake and subsequent metabolism. (*This is a major mechanism by which cocaine stimulates cardiac function and raises blood pressure.*)
2. Some of the junctional NE diffuses into capillaries and is carried out of the tissue by the circulation. Therefore, high levels of sympathetic activation in the body increase the plasma concentration of NE and its metabolites.
3. Some of the junctional NE is metabolized within the extracellular space before reaching the capillaries.
4. A small amount of NE (~5%) is taken up by the postjunctional tissue (termed "extraneuronal uptake") and metabolized.

Cocaine…



Erythroxylum coca

Lipophilicity: *logP = 2.3*

Molecular weight: *303.3*

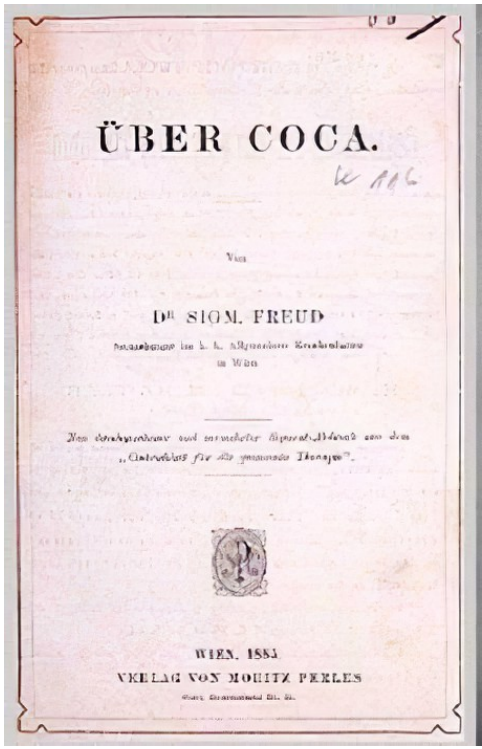
Polar surface area (PSA): ≅ *56 Å²*

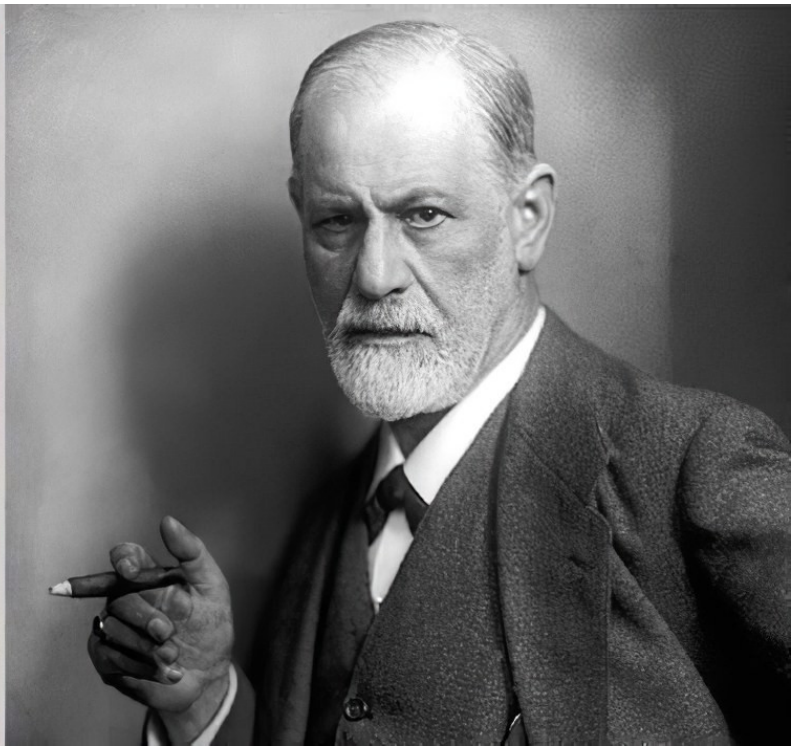
Hydrogen bonding (O + N): *5*

Charge: *pKa = 8.6*

Cocaine (coca) is a stimulant of the central nervous system, an appetite suppressant, and a topical anesthetic. Specifically, it is a ***serotonin–norepinephrine–dopamine reuptake inhibitor*** (also known as a triple reuptake inhibitor (TRI) in rats with ratios of about: serotonin:dopamine = 2:3, serotonin:norepinephrine = 2:5), which mediates functionality of these neurotransmitters as an exogenous catecholamine transporter ligand. It is ***addicting*** because of the way it affects the ***mesolimbic reward pathway***.

Sigmund Freud and Uber Coca…

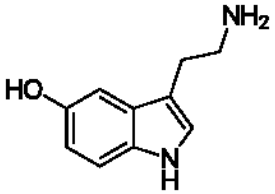


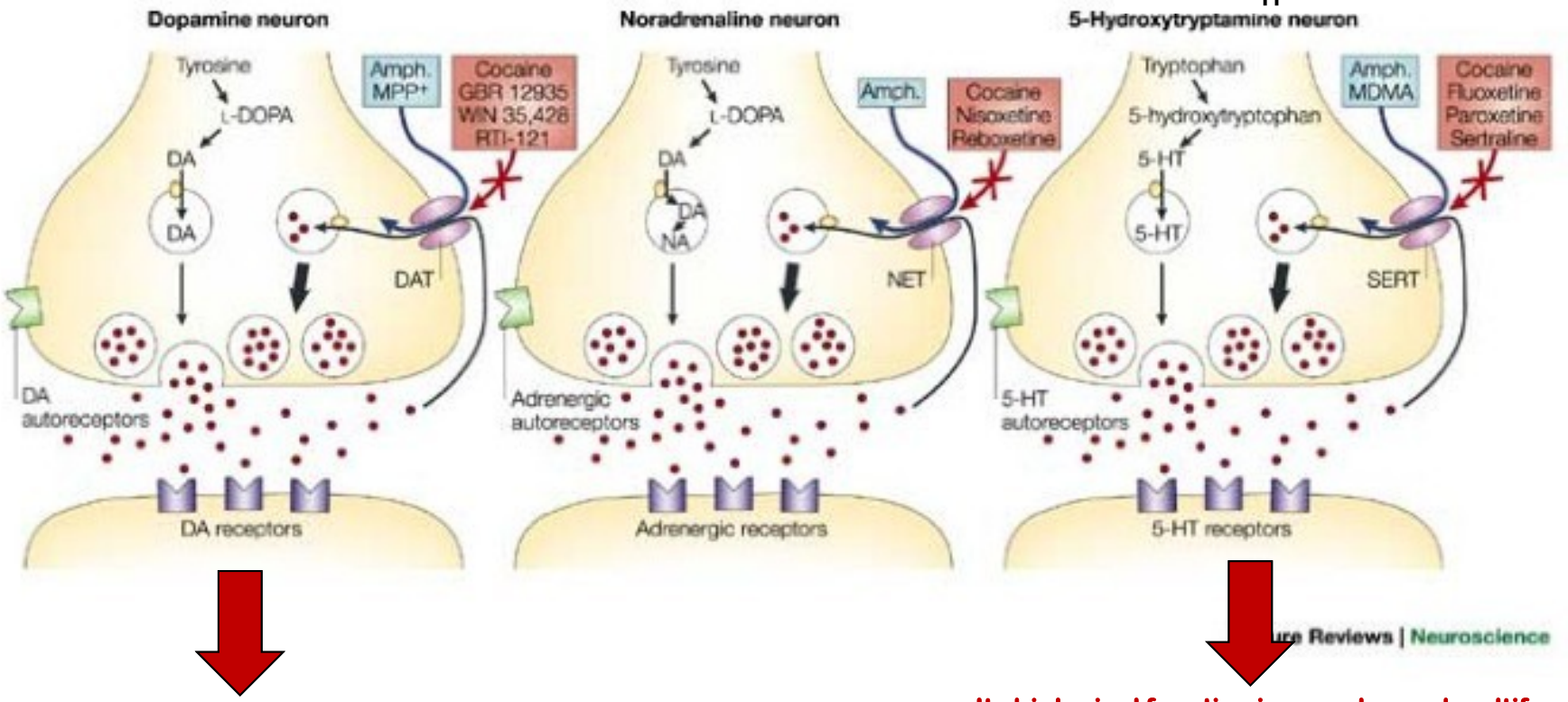


The effects of cocaine are described by Freud as follows:

cheerfulness, stable euphoria, which is no different from that experienced by a person in good health… There is an increase in self-control and greater vitality, ability to work… Physical and mental work is done without feeling tired… And this without having the undesirable effects that, for example, alcohol causes…

Dopamine, Noradrenaline and Serotonine transporters: lights and shadows in medchem





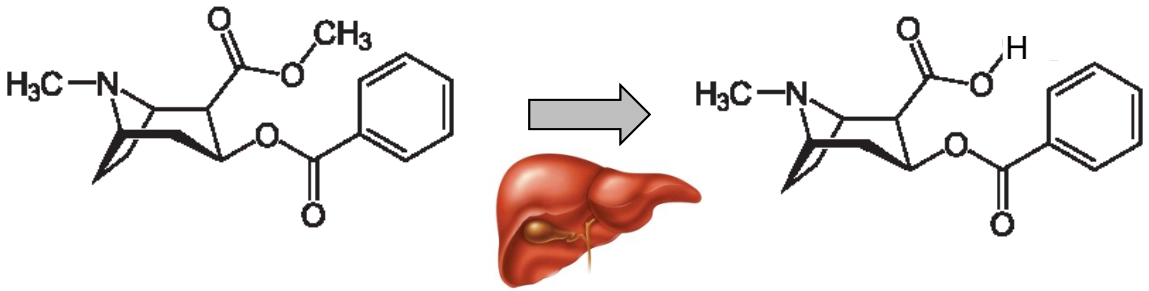
activation of reward circuits and psychological addiction

Its biological function is complex and multifaceted, modulating mood, cognition, reward, learning, memory, and numerous physiological processes such as vomiting and vasoconstriction.

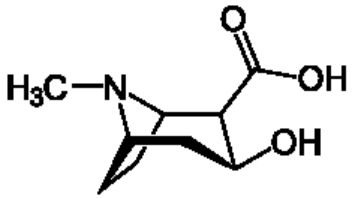
Credits: Torres, G., Gainetdinov, R. & Caron, M. Plasma membrane monoamine transporters: structure, regulation and function. *Nat Rev Neurosci* 4, 13–25 (2003).

Cocaine…

Cocaine is metabolized, primarily in the liver, with only about 1% excreted unchanged in the urine. The metabolism is dominated by hydrolytic ester cleavage, so the eliminated metabolites consist mostly of ***benzoylecgonine***, the major metabolite, and other significant metabolites in lesser amounts such as ***ecgonine methyl ester*** and ***ecgonine***.

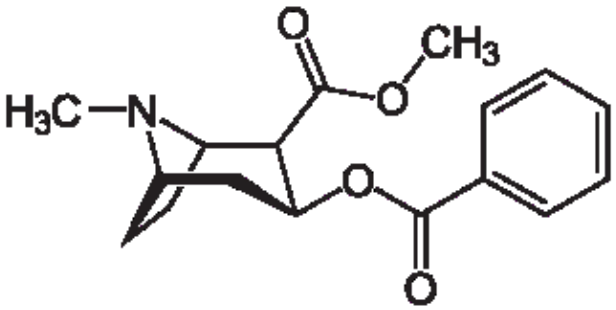


benzoylecgonine



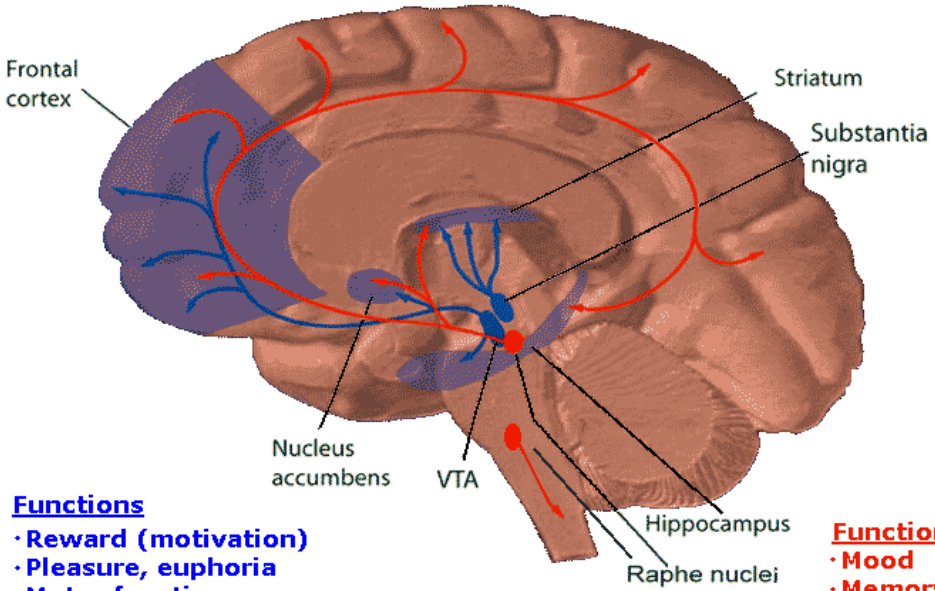
ecgonine

Cocaine…



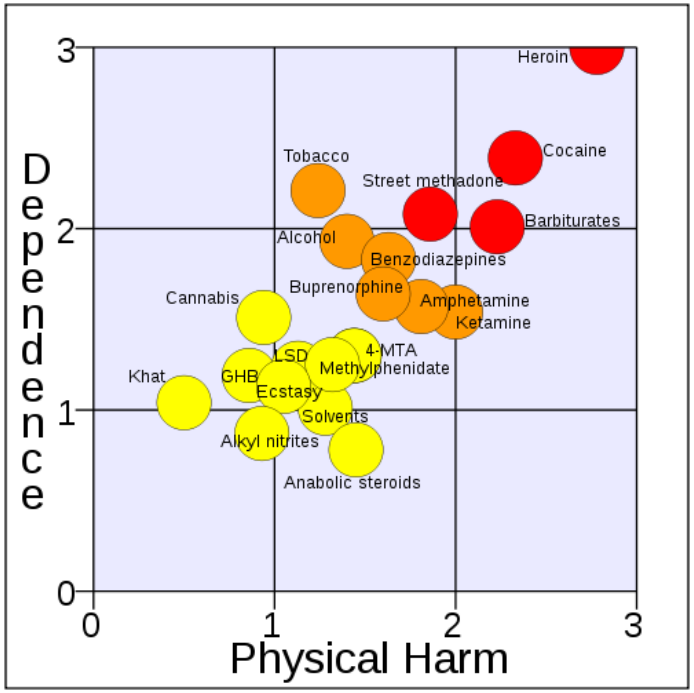
Cocaine (coca) is ***addicting*** because of the way it affects the ***mesolimbic reward pathway***.

Dopamine Pathways **Serotonin Pathways**



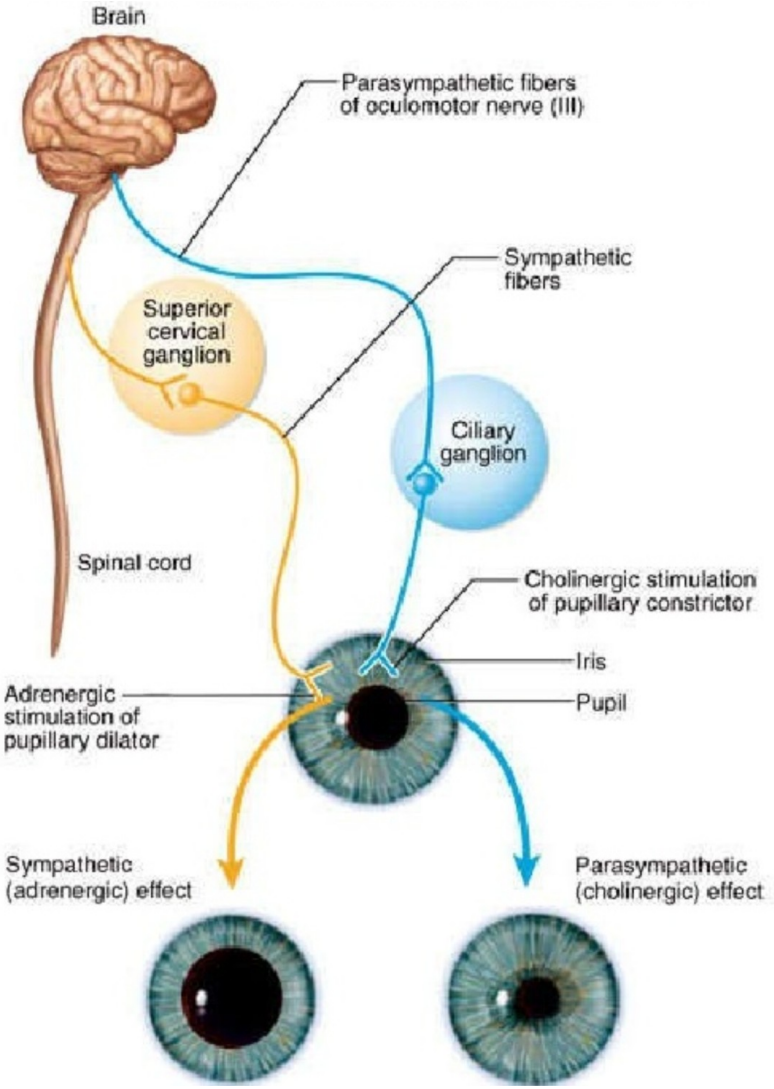
Functions
- **Reward (motivation)**
- **Pleasure, euphoria**
- **Motor function (fine tuning)**
- **Compulsion**
- **Perseveration**

Functions
- **Mood**
- **Memory processing**
- **Sleep**
- **Cognition**



The Lancet **369, 1047–1053, 2007**

The eyes don't lie!!!



Pinned Out Pupils

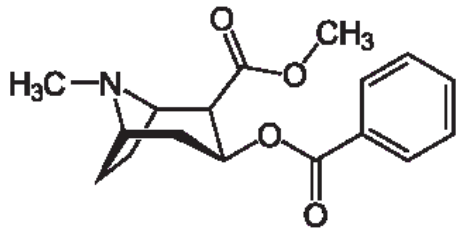
Opiods, Benzodiazapines, and Barbiturates cause pupil constriction.

Opioids: Percocet, vicodin, oxycodone, heroin.
Benzodiazepines alleviate anxiety. [Xanax, valium]
Barbiturates also called tranquilizers or sedatives.

Dilated Pupils

Hallucinogens & Stimulants are known to cause pupil dilation.

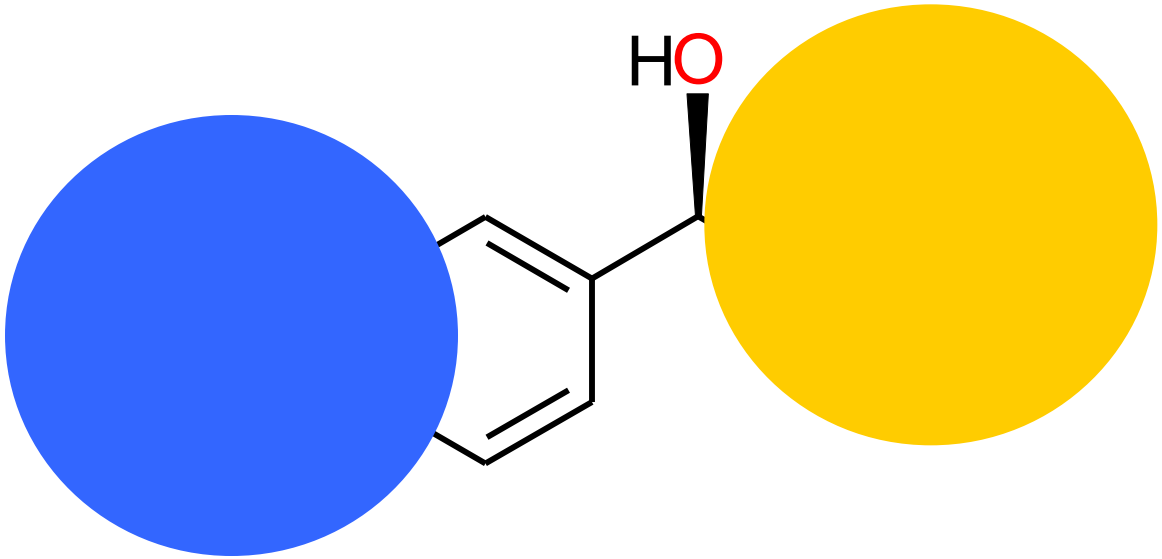
Hallucinogens: Pot, LSD [Mushrooms, Acid]
Stimulants: Cocaine, crack, crystal meth.
Antidepressants can also cause dilation.



3. Transmission process

Removal and Metabolism

MAO: monoamino oxidase

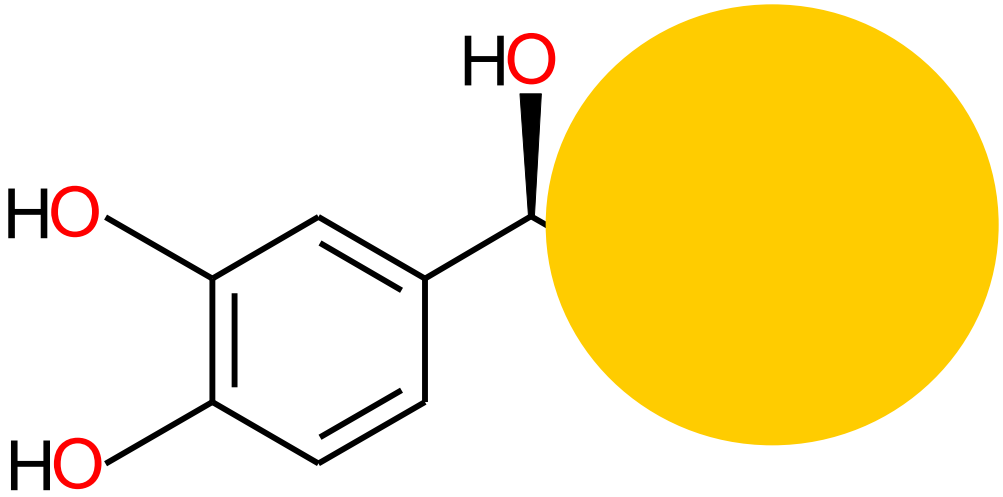


COMT: catechol-O-methyl-transferase

3. Transmission process

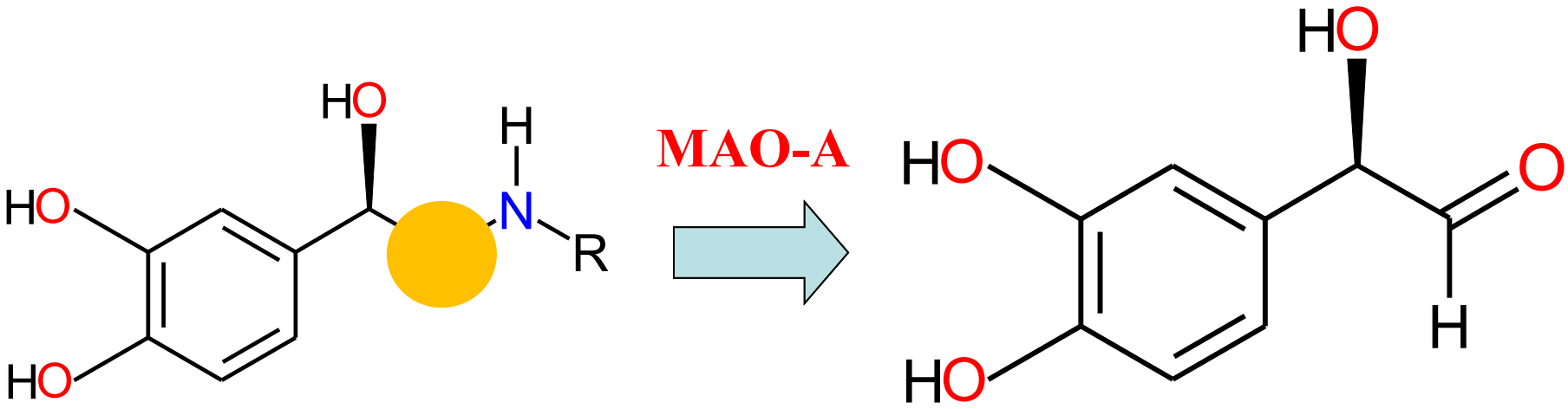
Removal and Metabolism

MAO: monoamino oxidase



3. Transmission process

MAO: monoamino oxidase



3,4-didydroxyphenylglycoaldehyde (DOPGAL)

3. Transmission process

MAO: monoamino oxidase

In humans there are two types of MAO: MAO-A and MAO-B.

Both are found in neurons and astroglia.

Outside the central nervous system:

MAO-A is also found in the liver, gastrointestinal tract, and placenta.

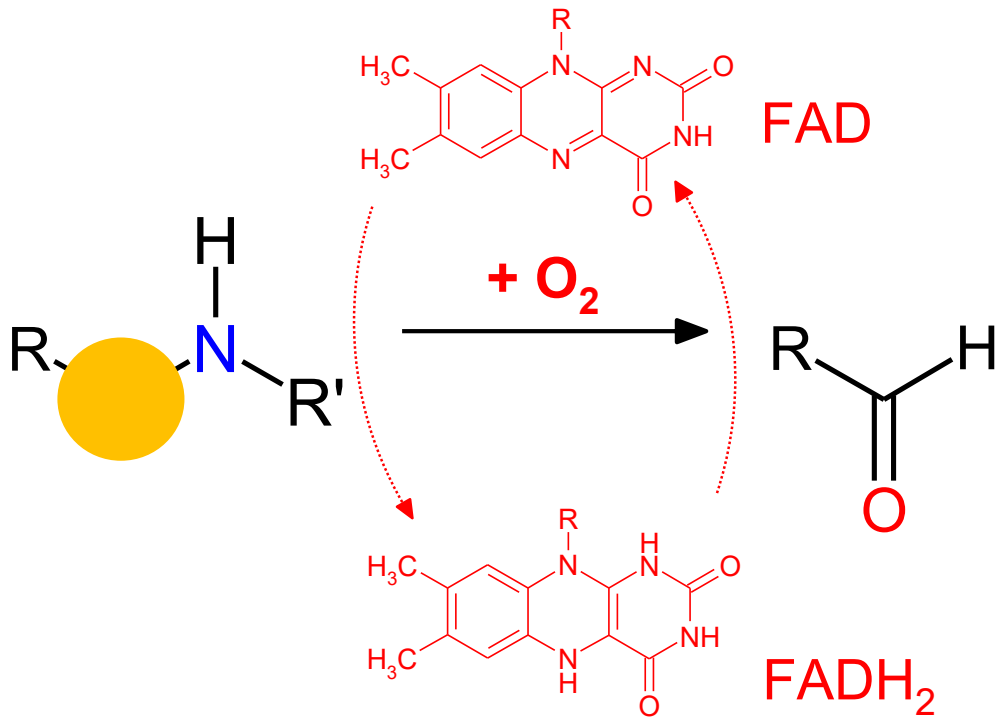
MAO-B is mostly found in blood platelets.

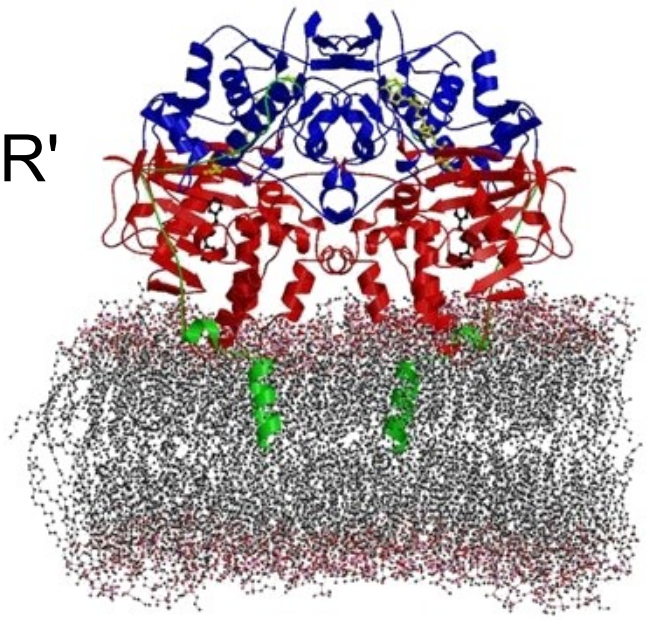
MAO-A preferentially deaminates norepinephrine (noradrenaline), epinephrine (adrenaline), serotonin, and dopamine (dopamine is equally deaminated by MAO-A and MAO-B).

3. Transmission process

MAO: monoamino oxidase

Monoamine oxidases (MAO) are a family of enzymes that catalyze the oxidation of monoamines.



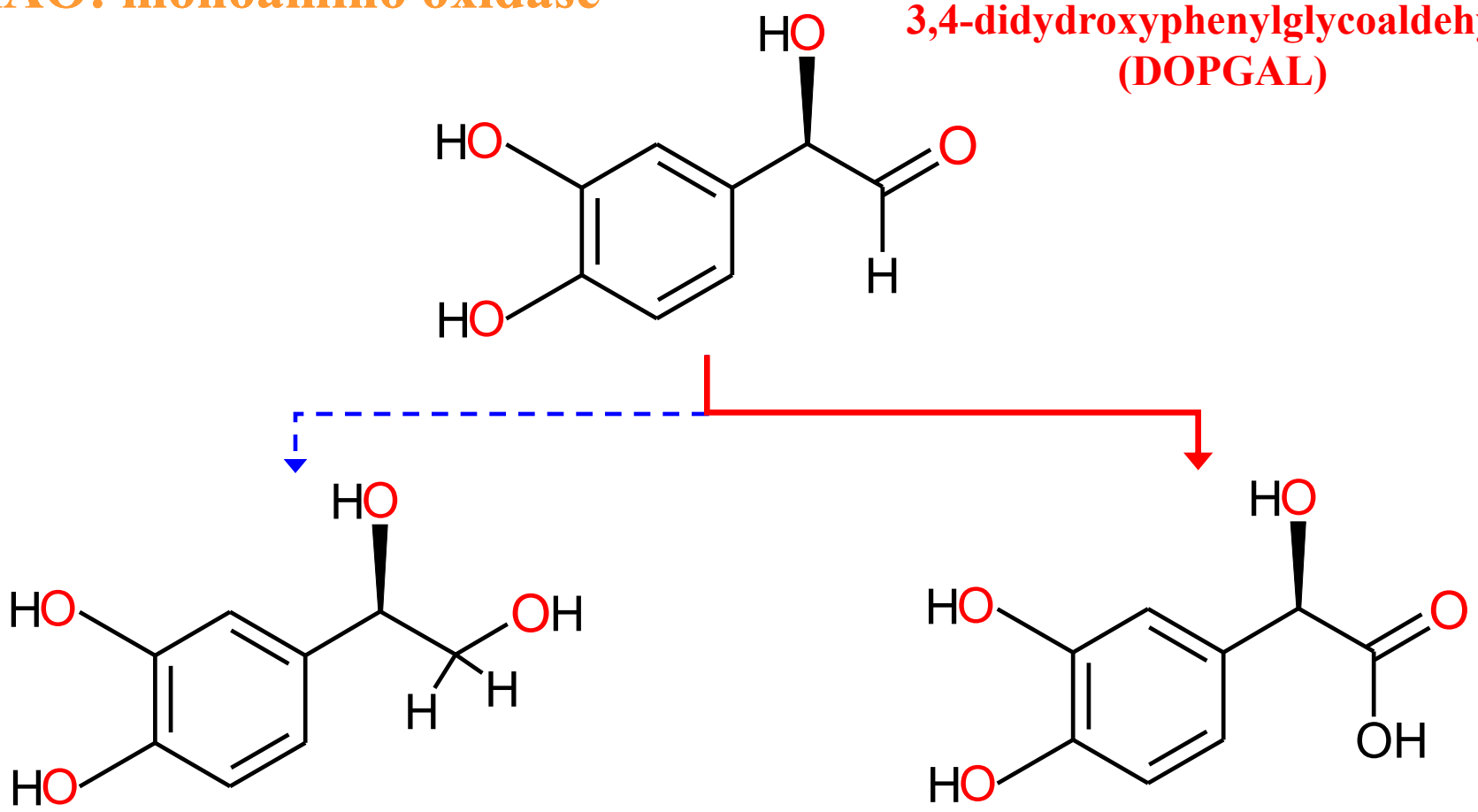


Human MAO-A: PDB code 2BXS

They are found bound to the outer membrane of mitochondria.

3. Transmission process

MAO: monoamino oxidase



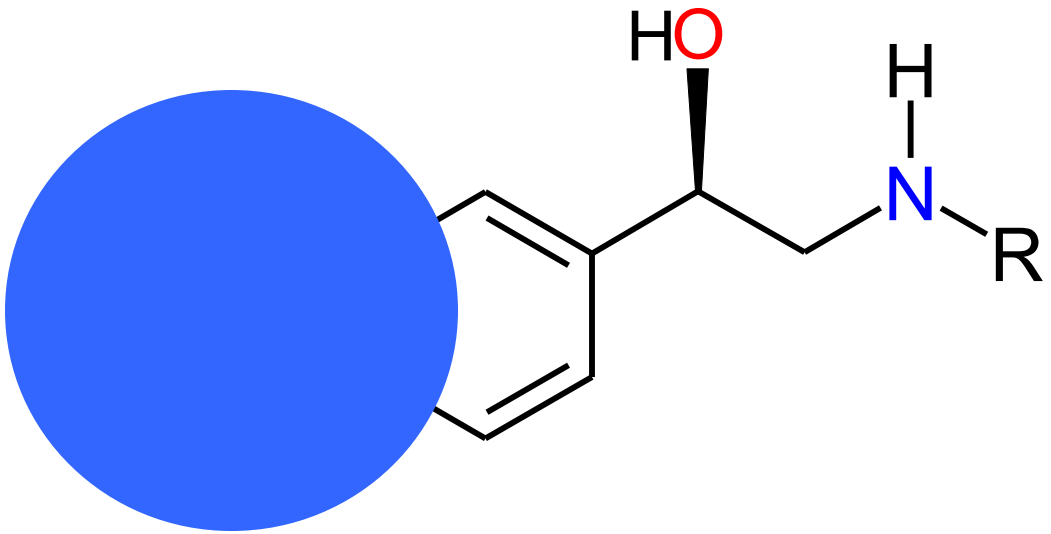
3,4-didydroxyphenylglycoaldehyde (DOPGAL)

3,4-dihydroxyphenylethylene glycol (DOPEG)

3,4-dihydroxymandelic acid (DOMA)

3. Transmission process

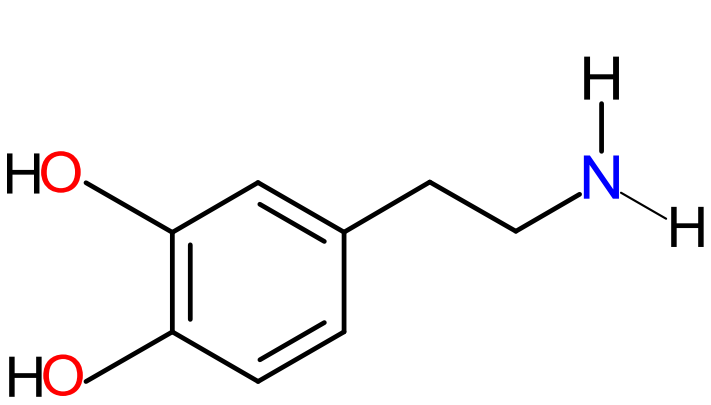
Removal and Metabolism

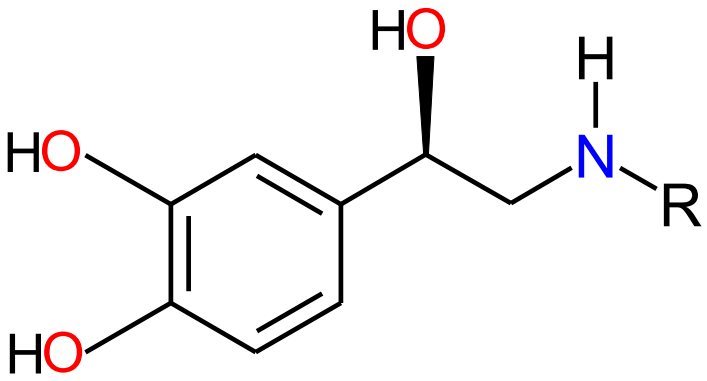


COMT: catechol-O-methyl-transferase

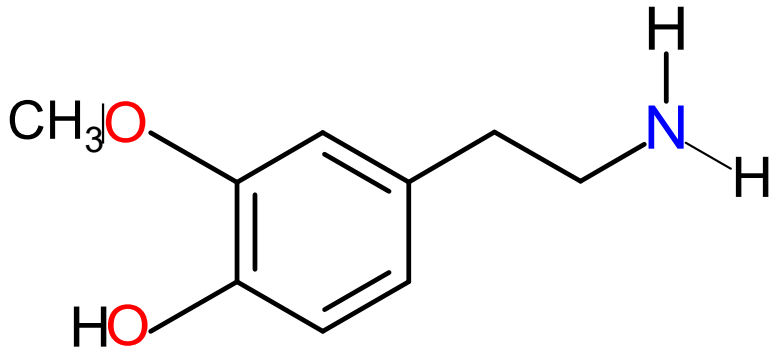
3. Transmission process

COMT: catechol-O-methyltranferase

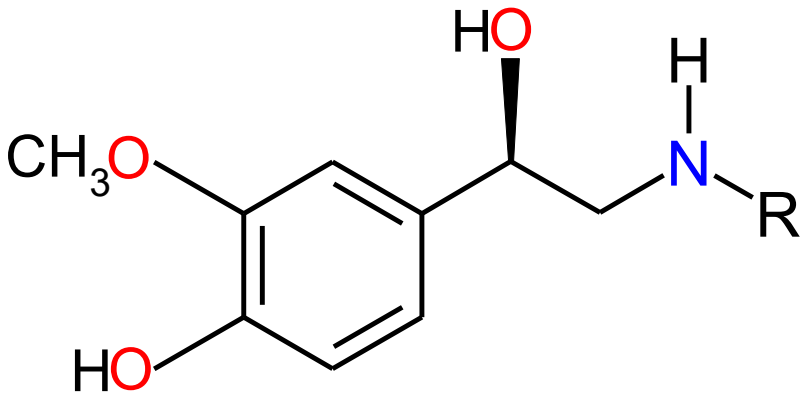




COMT



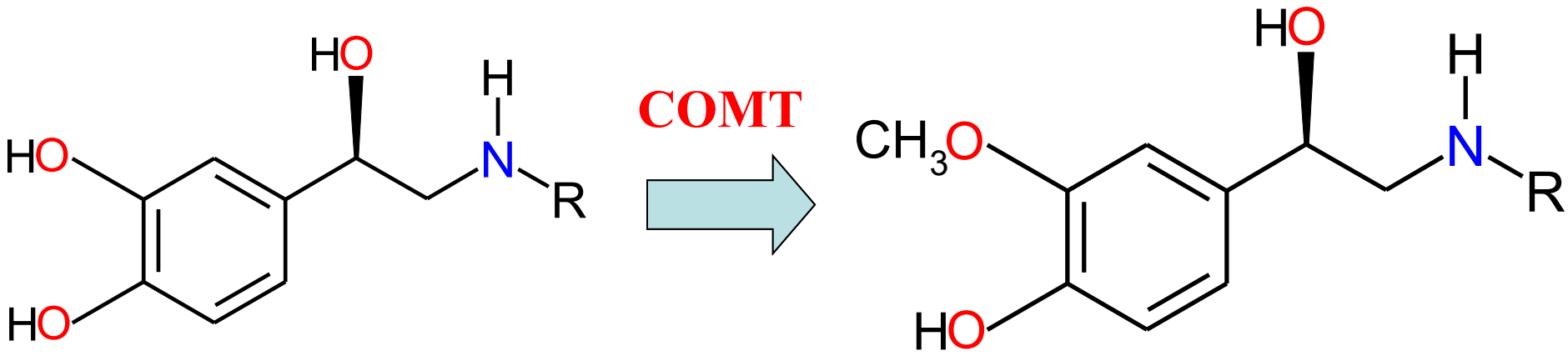
Normetanephrine



Metanephrine

3. Transmission process

COMT: catechol-O-methyltranferase



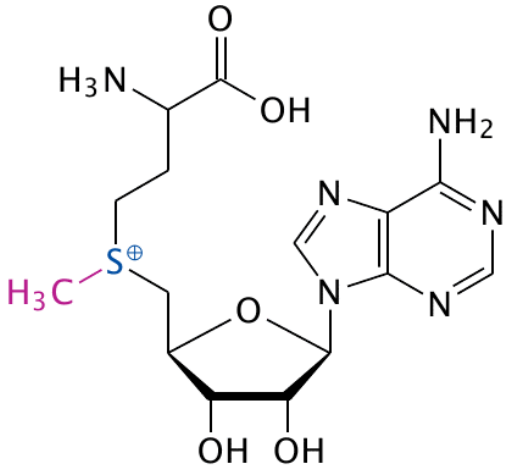
COMT is primarily an extra-neuronal enzyme, but some of the enzyme may also be localized intra-neuronally. Vice versa COMT resides predominately in glia cells.

Adrenal chromaffin cells express abundant COMT, which explains why all plasma metanephrine derives from *O*-methylation of CA within the adrenal medulla. This fact is used in the detection of pheochromocytoma, the tumor that synthesizes CA and expresses COMT. The enzyme utilizes *S*-adenosylmethionine as a cofactor. COMT metabolizes circulating catechols mainly in the liver and kidney.

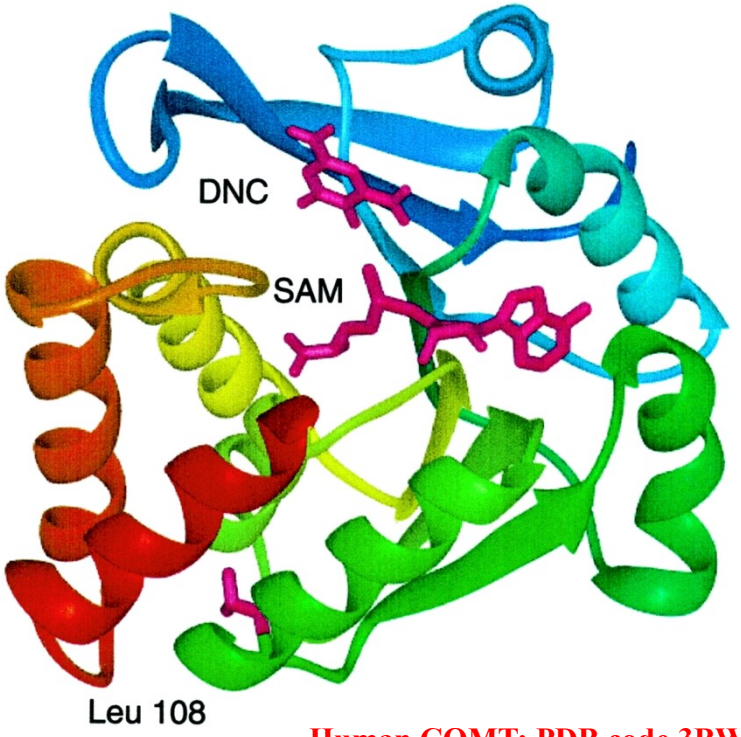
3. Transmission process

COMT: catechol-O-methyltranferase

Catechol-O-methyl transferase introduces a methyl group to the catecholamine, which is donated by S-adenosyl methionine (SAM).



SAM

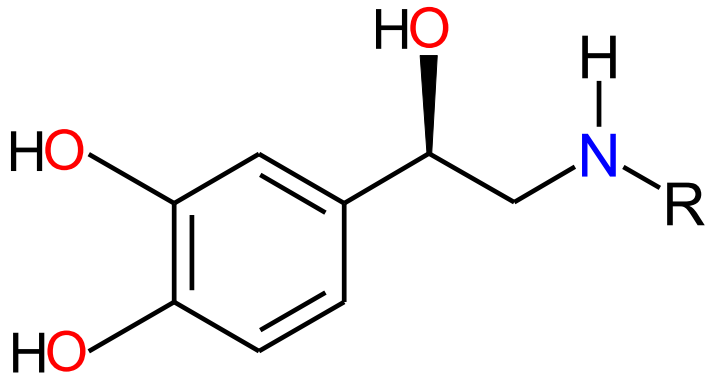


Human COMT: PDB code 3BWY

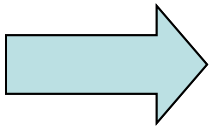
Any compound having a catechol structure, like catecholestrogens and catechol- containing flavonoids, are substrates of COMT.

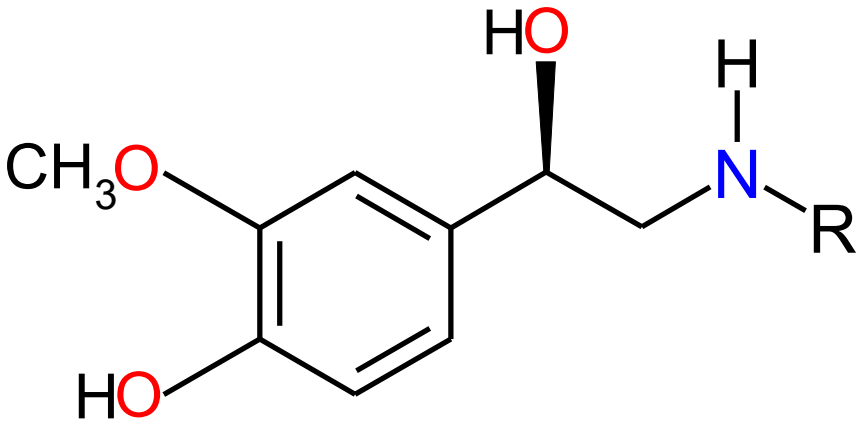
***Levodopa*, the precursor of catecholamines, is an important substrate of COMT.**

Do you have any great pharmaceutical intuition?



COMT





ACTIVE

INACTIVE

4. Adrenergic receptors

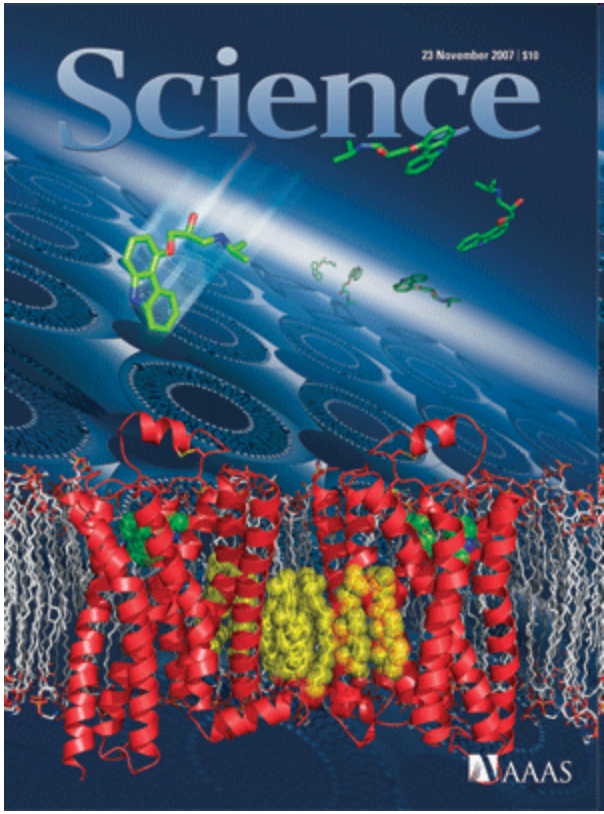
Receptor types

The **adrenergic receptors (or adrenoceptors)** are a class of G protein-coupled receptors **(Family A).**

There are two main groups of adrenergic receptors, α and β, with several subtypes:

α receptors have the subtypes α1 (a Gq coupled receptor) and α2 (a Gi coupled receptor).

β receptors have the subtypes β1, β2 and β3. All three are linked to Gs proteins (although β2 also couples to Gi)



4. Adrenergic receptors

α adrenergic receptors

- They are subdivided into two types:

α_1, found in smooth muscle, heart, and liver, with effects including vasoconstriction, intestinal relaxation, uterine contraction and pupillary dilation;

α_2, found in platelets, vascular smooth muscle, nerve termini, and pancreatic islets, with effects including platelet aggregation, vasoconstriction, and ***inhibition of norepinephrine release*** and of insulin secretion.

4. Adrenergic receptors

β adrenergic receptors

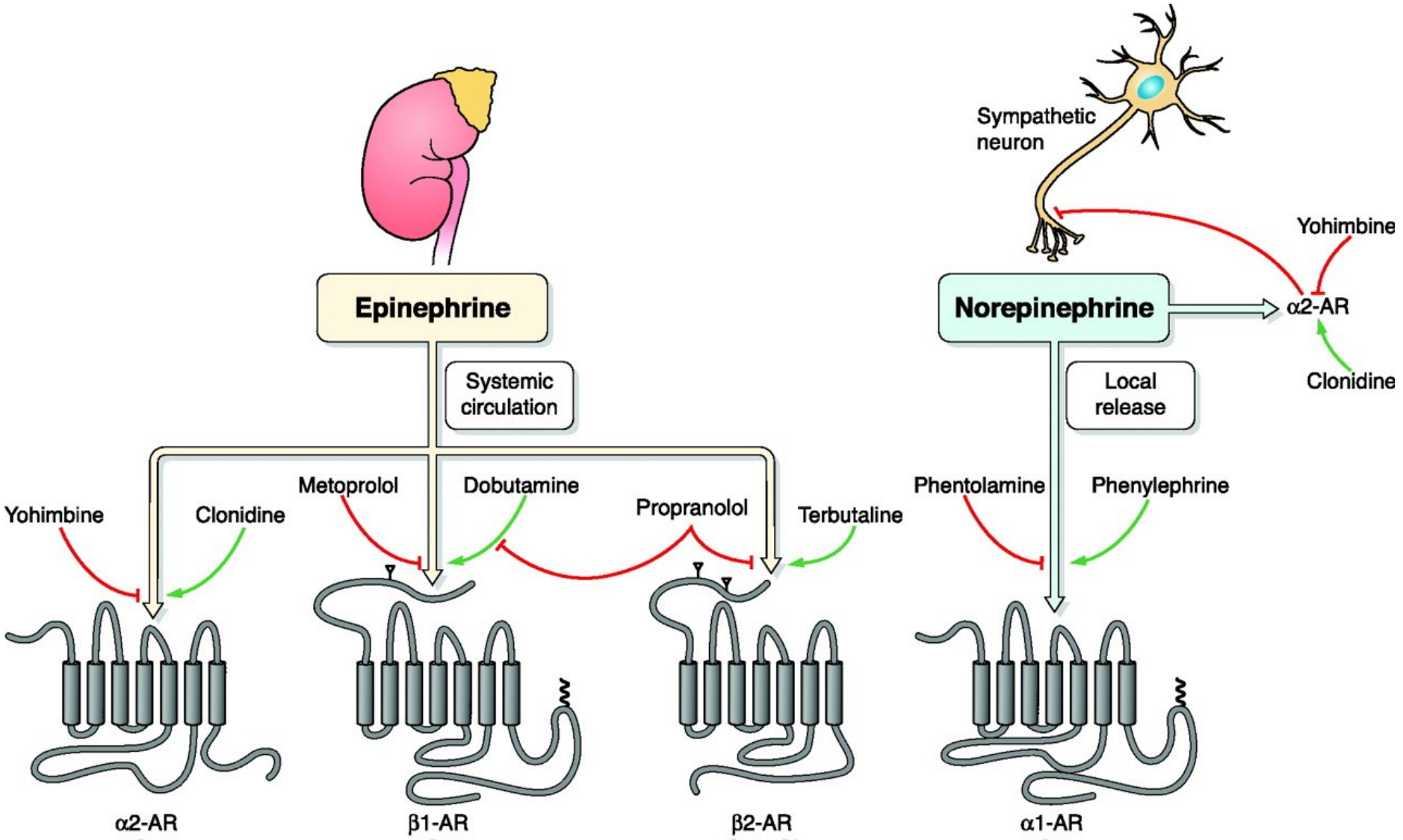
- There are three known types of beta receptor, designated β_1, β_2 and β_3.

β_1-Adrenergic receptors are located mainly in the ***heart***;

β_2-Adrenergic receptors are located mainly in the lungs, gastrointestinal tract, liver, uterus, ***vascular smooth muscle***, and skeletal muscle;

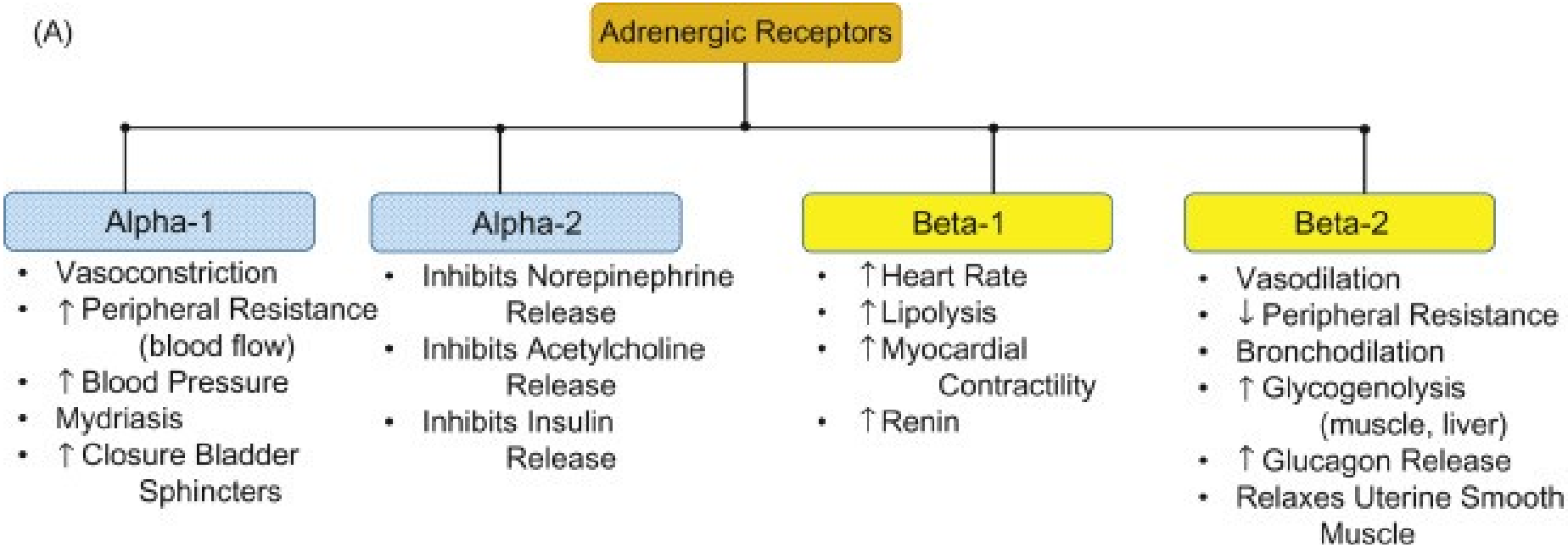
β_3-receptors are located in ***fat cells***.

4. Adrenergic receptors



4. adrenergic receptors (classification)

(A)

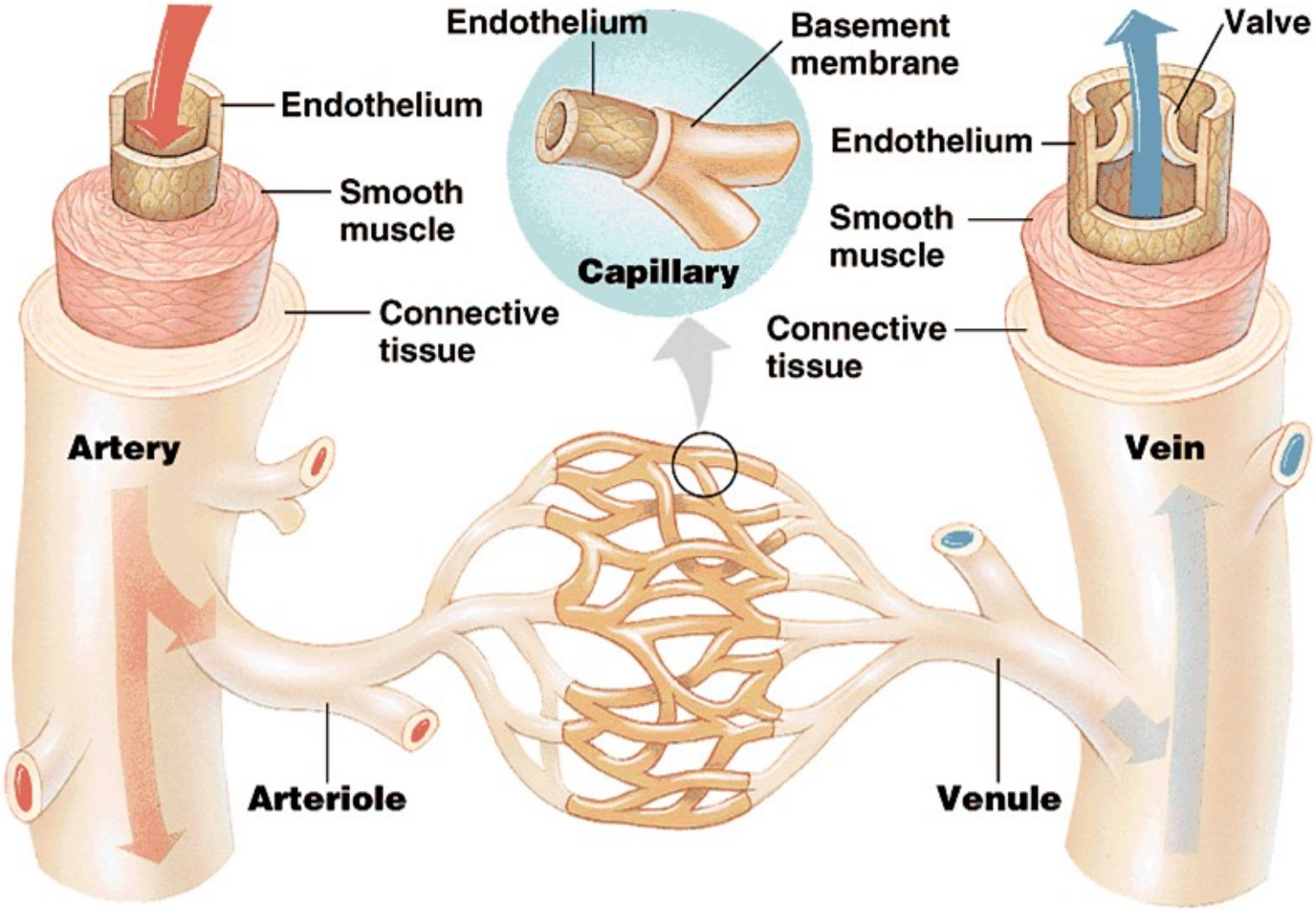


(B)

Alpha-1	Alpha-2	Beta-1	Beta-2
NE > E	E > NE	E = NE	E >> NE
NE = Norepinephrine; E = Epinephrine			

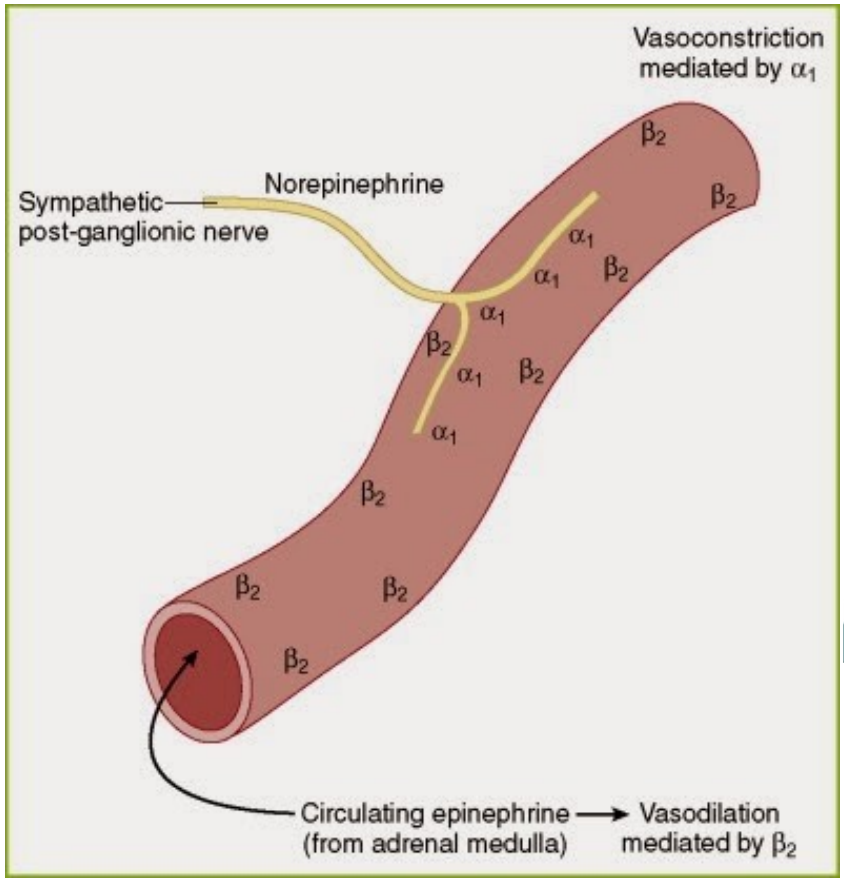
4. Adrenergic receptors

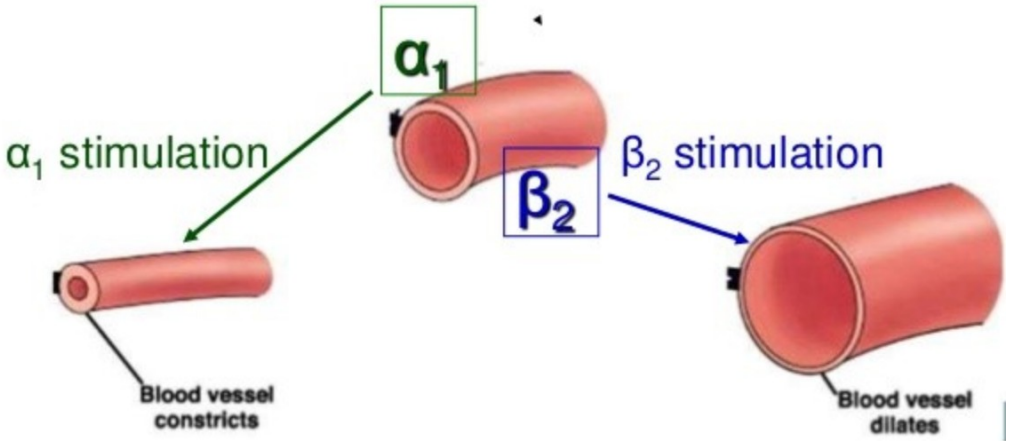
Anatomy of artery, vein and capillary vessels:



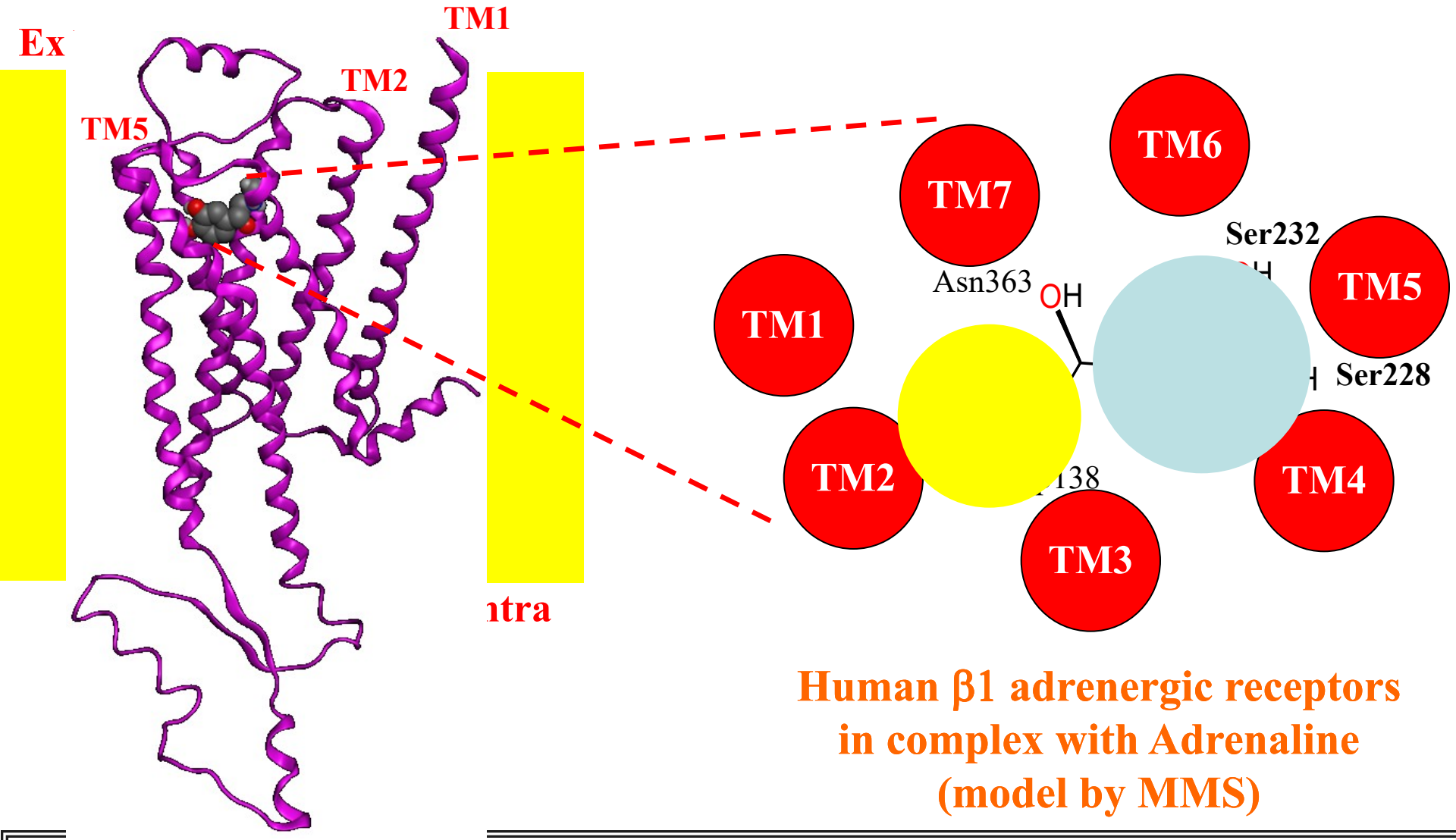
4. Adrenergic receptors

Adrenergic vascular control:



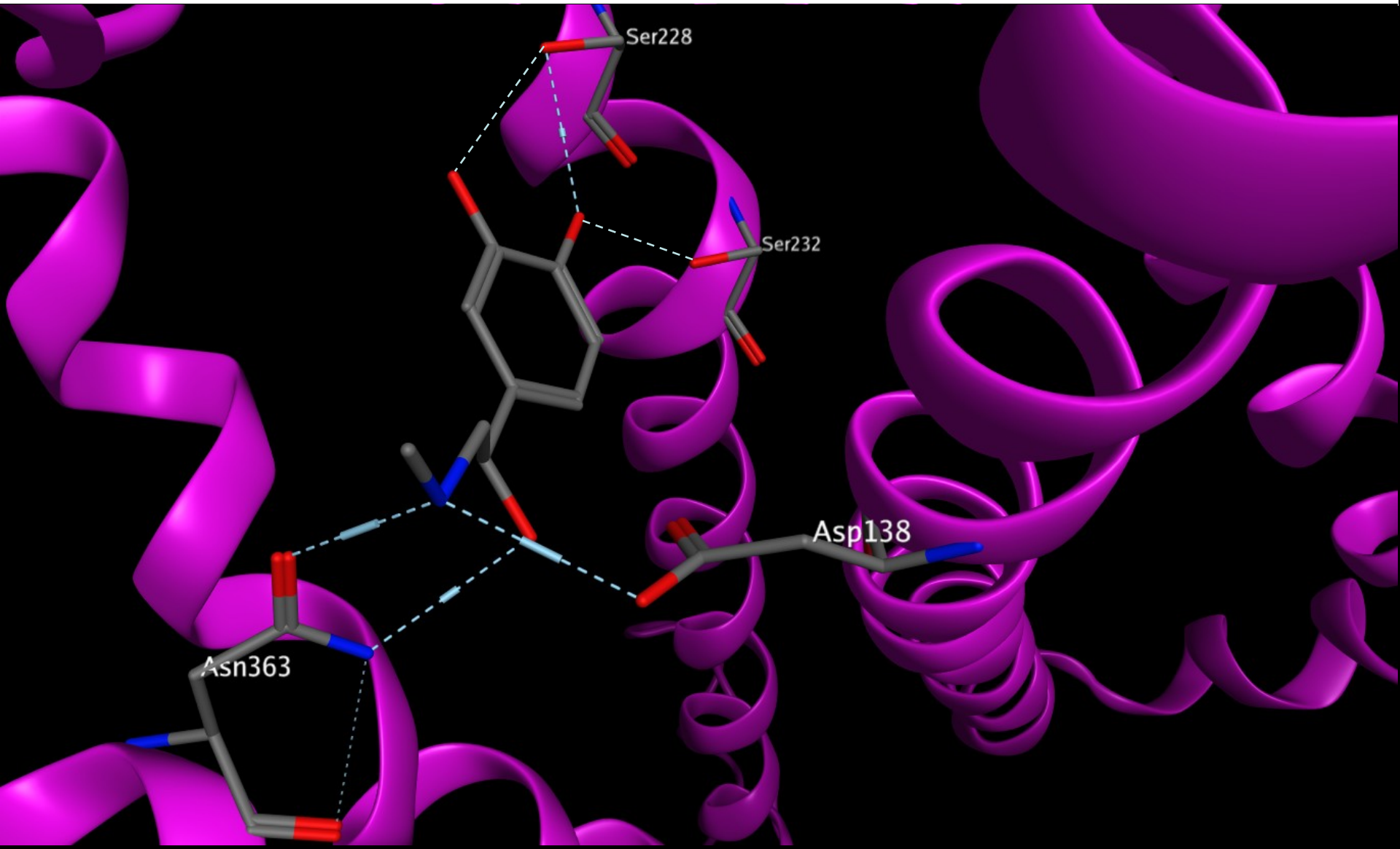


4. Adrenergic receptors



Human β1 adrenergic receptors in complex with Adrenaline (model by MMS)

View from the extracellular environment:

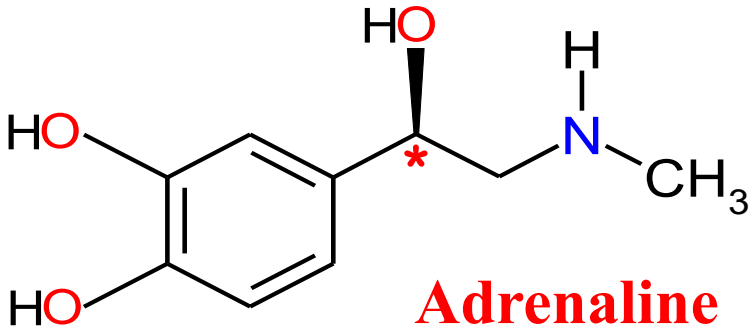


5. Adrenergic agonists

5.1 Adrenaline as an agonist... as a drug!

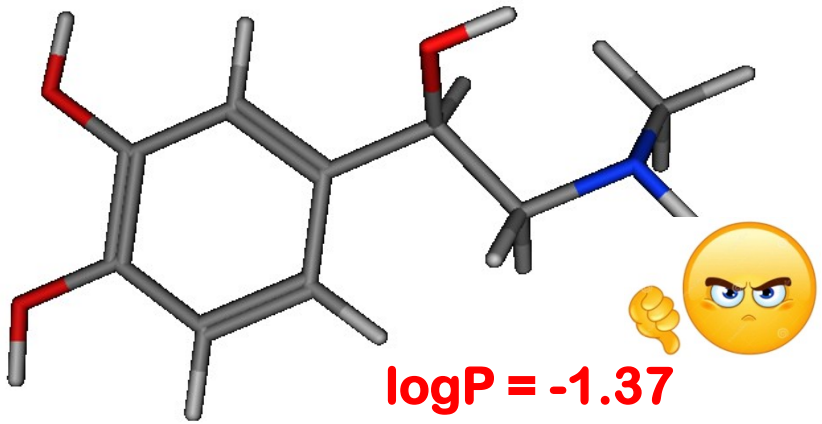
Advantages

- **Natural messenger**



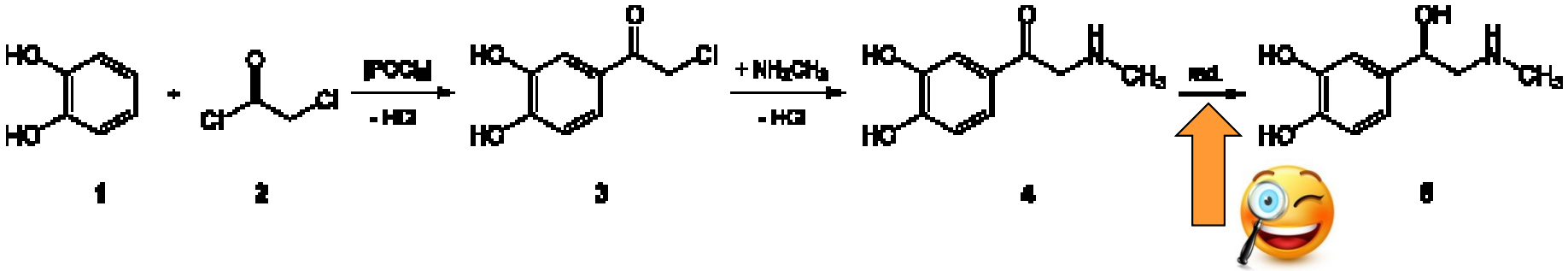
Adrenaline

(R)-4-(1-hydroxy-2-(methylamino)ethyl)benzene-1,2-diol



logP = -1.37
pKa = 8.6

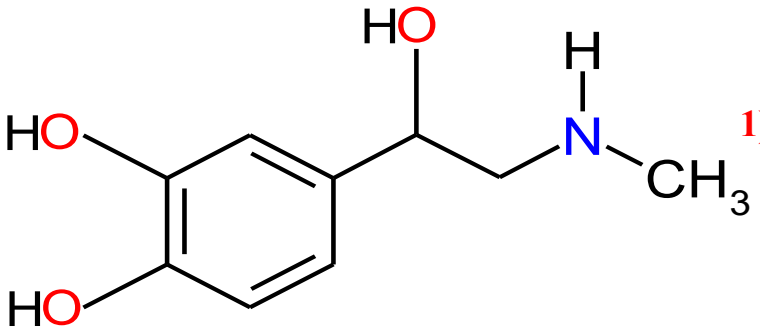
- **Easily synthesised**



Do you remember?

Thanks, Zorro96!!

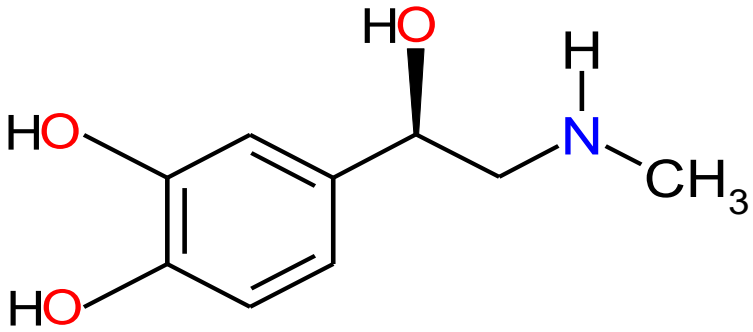
Resolution of the enantiomers:



(*R*,*S*)-Adrenaline

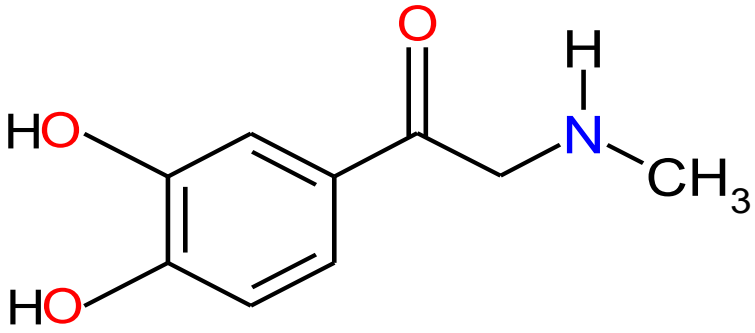
1) L(+)-Tartaric acid

2) NH_4OH, aq



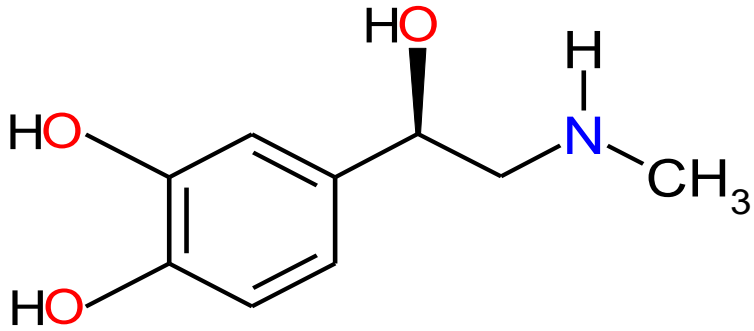
R(-)-Adrenaline

Enantioselective reduction:



H_2 (10-40 atm)

chiral cat



R(-)-Adrenaline

92–99% yield

97–99.9% ee

TON up to 100,000

5. Adrenergic agonists

5.1 Epinephrine as an agonist: therapeutic uses

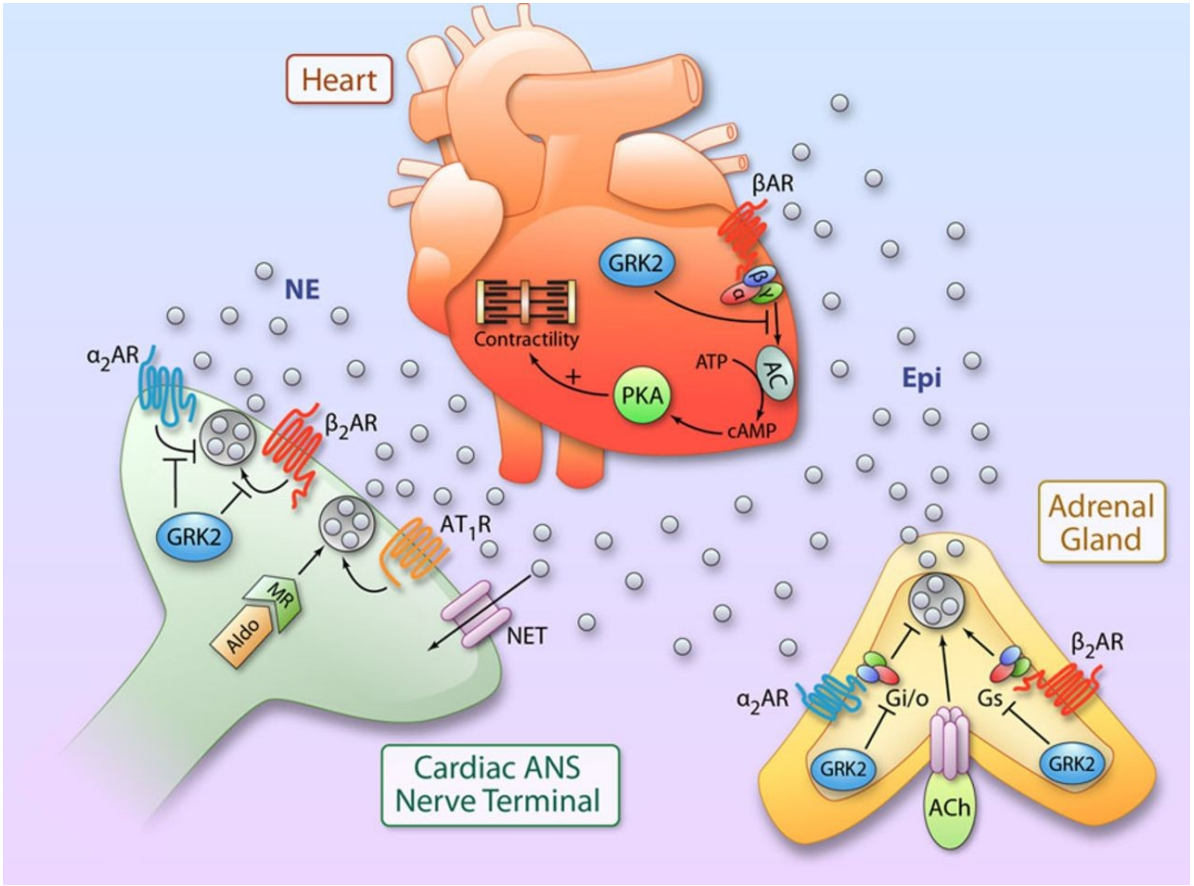
Cardiac arrest: resuscitation!!

This is the first drug given in all causes of cardiac arrest and should be readily available in all clinical areas. Adrenaline concentrates the blood around the vital organs, specifically the brain and the heart, by peripheral vasoconstriction. These are the organs that must continue to receive blood to increase the chances of survival following cardiac arrest. Adrenaline also strengthens cardiac contractions as it stimulates the cardiac muscle. This further increases the amount of blood circulating to the vital organs, and also increases the chance of the heart returning to a normal rhythm.

5. Adrenergic agonists

5.1 Epinephrine as an agonist: therapeutic uses

Cardiac arrest: resuscitation!!



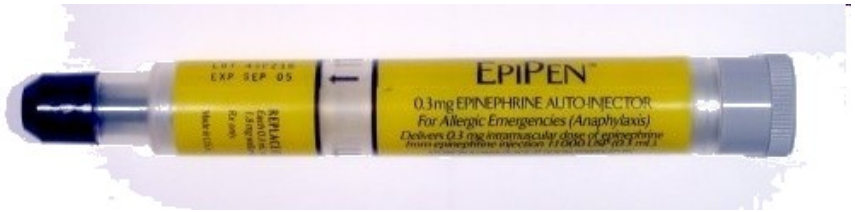
Adrenergic nervous system (ANS) input to the heart and its regulation (see text for details). ACh, acetylcholine; Aldo, aldosterone; AR, adrenergic receptor; $G_{i/o}$, inhibitory or other G protein; G_s, stimulatory G protein; MR, mineralocorticoid receptor; NE, norepinephrine; Epi, epinephrine; NET, norepinephrine transporter (illustration credit: Ben Smith - https://www.ahajournals.org/doi/full/10.1161/circresaha.113.300308).

5. Adrenergic agonists

5.1 Epinephrine as an agonist: therapeutic uses

Shock and anaphylaxis

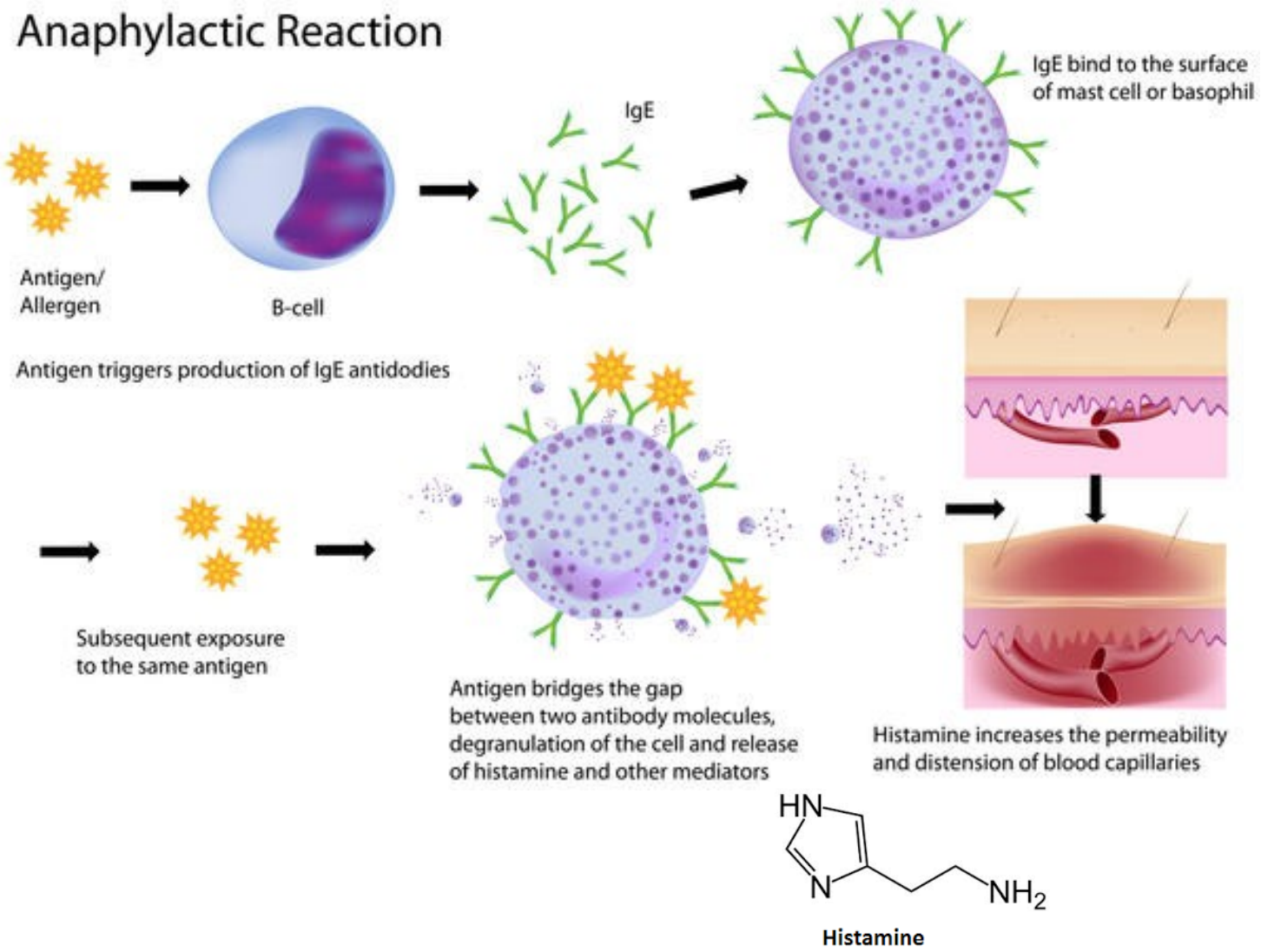
Due to its vasoconstrictive effects, adrenaline is the drug of choice for treating ***anaphylaxis***. It is also useful in treating sepsis. Allergy patients undergoing immunotherapy may receive an adrenaline rinse before the allergen extract is administered, thus reducing the immune response to the administered allergen. It is also used as a bronchodilator for asthma if specific $\beta_2$agonists are unavailable or ineffective. In cases of shock, epinephrine has been used to restore and maintain sufficient blood pressure and ensure adequate blood flow to vital organs.



EpiPen ® autoinjector

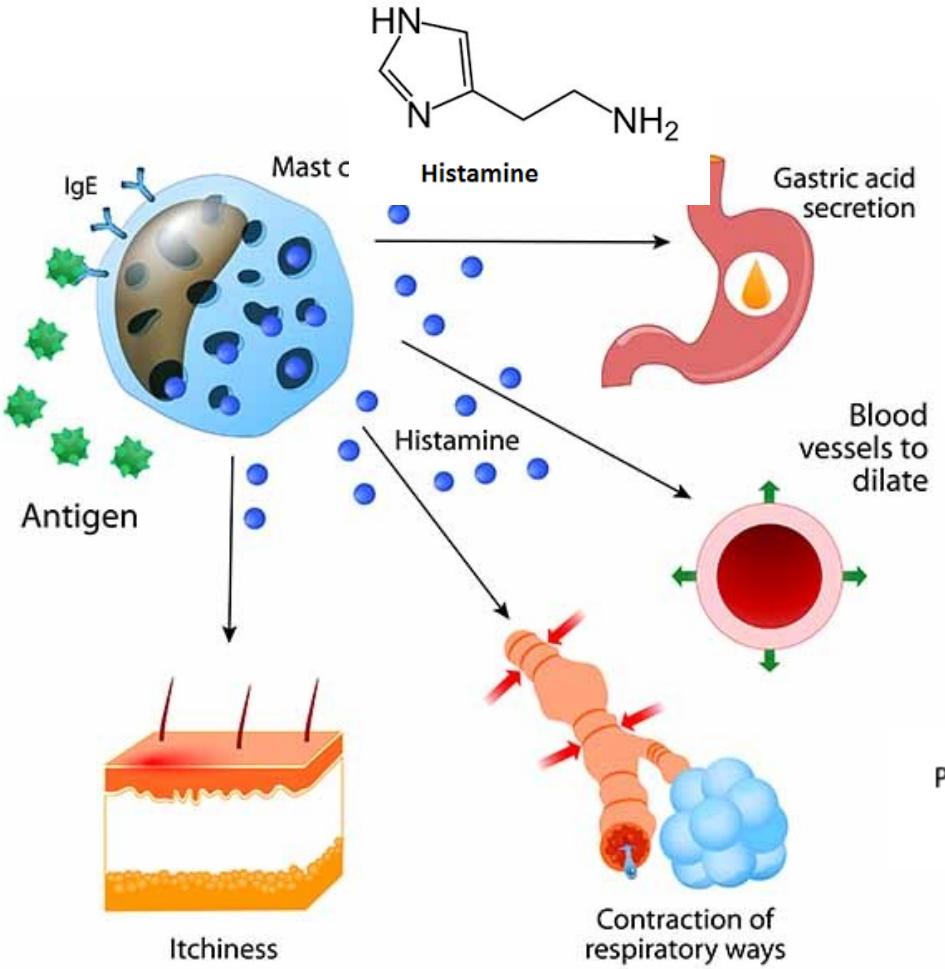
5. Adrenergic agonists

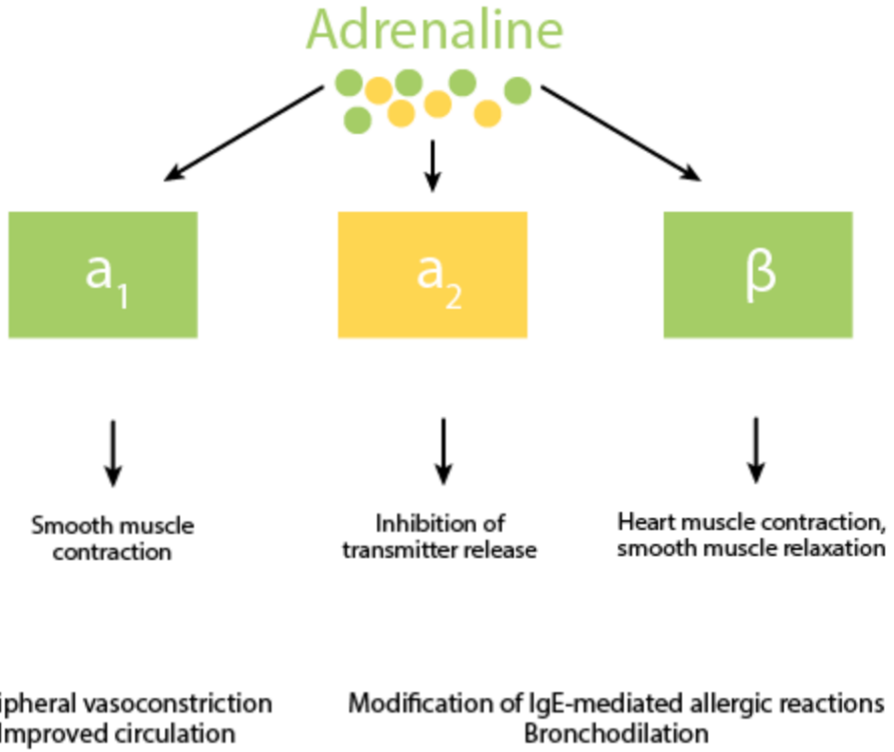
5.1 Epinephrine as an agonist: therapeutic uses



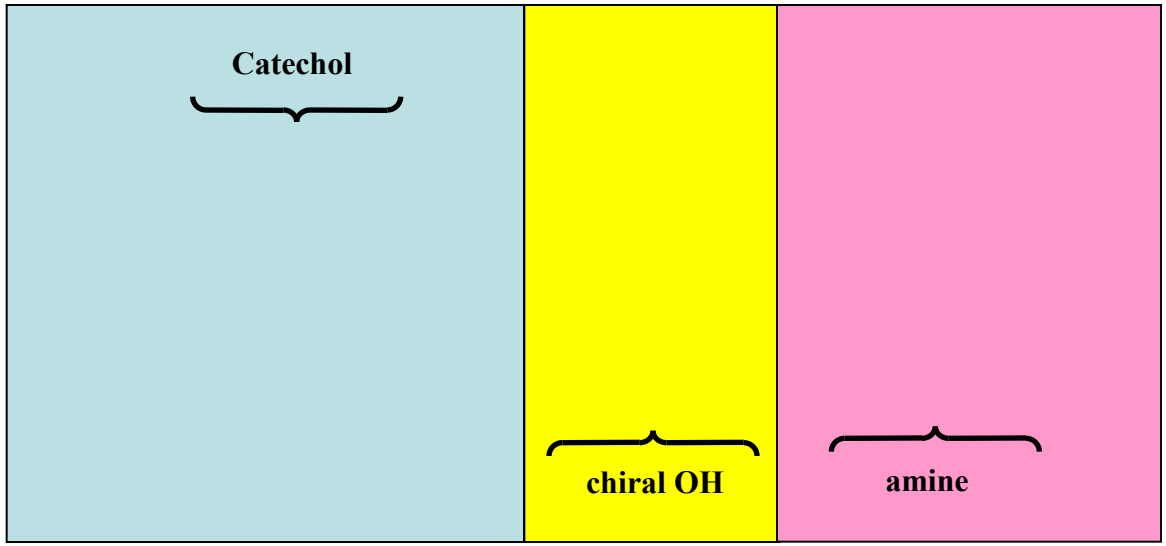
5. Adrenergic agonists

5.1 Epinephrine as an agonist: therapeutic uses



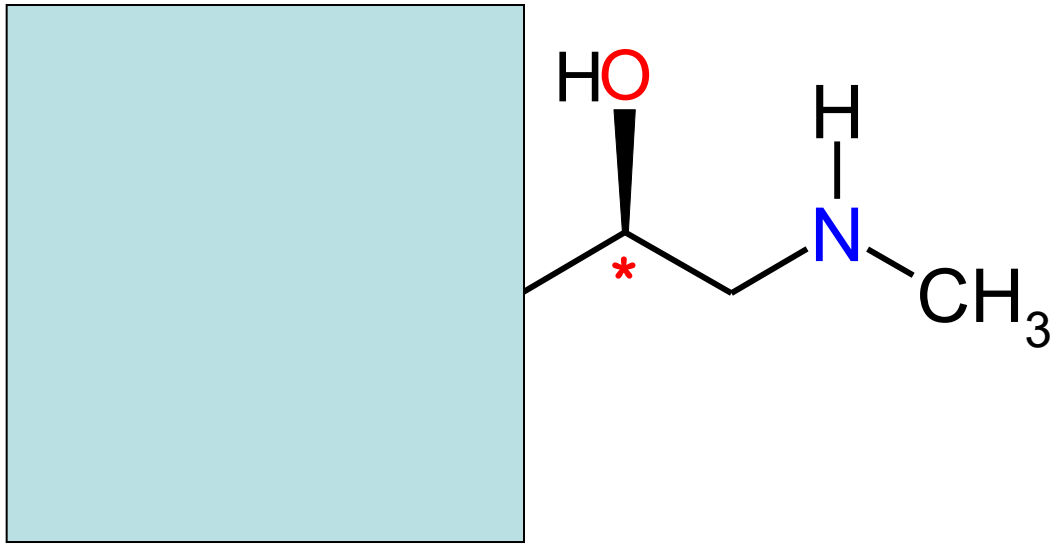


6. SAR for epinephrine



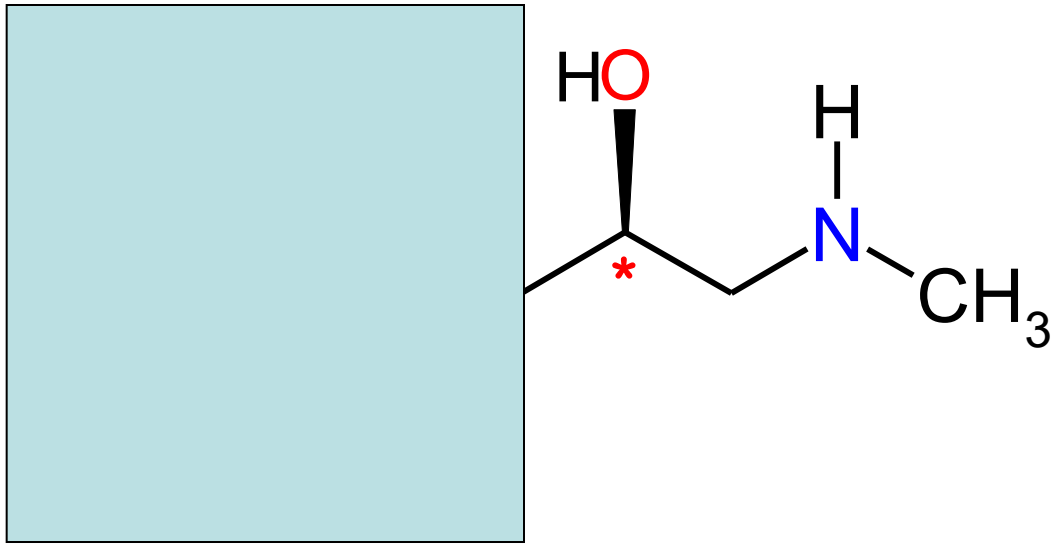
Structure-activity relationships in the α1-ARs had their birthplace in the hypothesis of Easson and Stedman.

6. SAR for epinephrine



Initially in the β_2-AR, *meta*- and *para*-hydroxyl substitutions that mimic norepinephrine and epinephrine seemed essential for full agonism, but the α1-ARs were shown to be quite tolerant of the position and chemical group so long as hydrogen-bonding was capable at the *meta*-position of the ring. In addition, fluorine substitutions in the *ortho*-positions 2- and 6- in epinephrine can confer selectivity between α– and β-ARs.

6. SAR for epinephrine

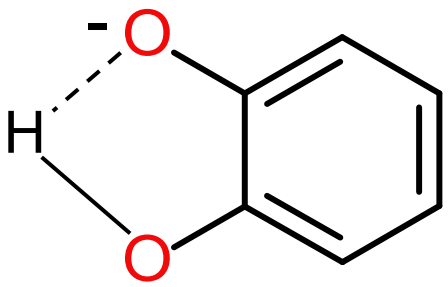


Further investigation and analysis of the properties of the 3-hydroxyl group identified the following parameters as important:

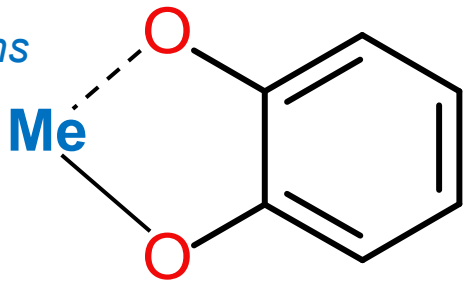
1. *Size*
2. *Electronic effects on the aromatic system (resonance and inductive)*
3. *Capacity to form hydrogen bonds*
4. *Acidity*
5. *Ability to chelate with metals*
6. *Capacity to form a redox system*

A little summary…

Intramolecular H-bonding

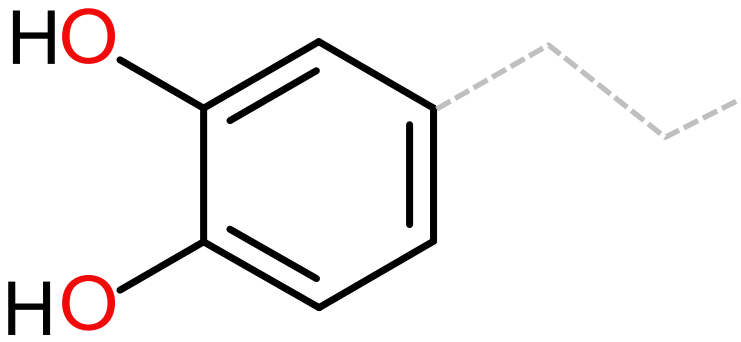


Metal-coordinations

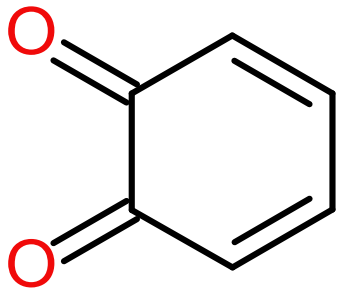


$Me^{+/2+}$

pKa = 9.45

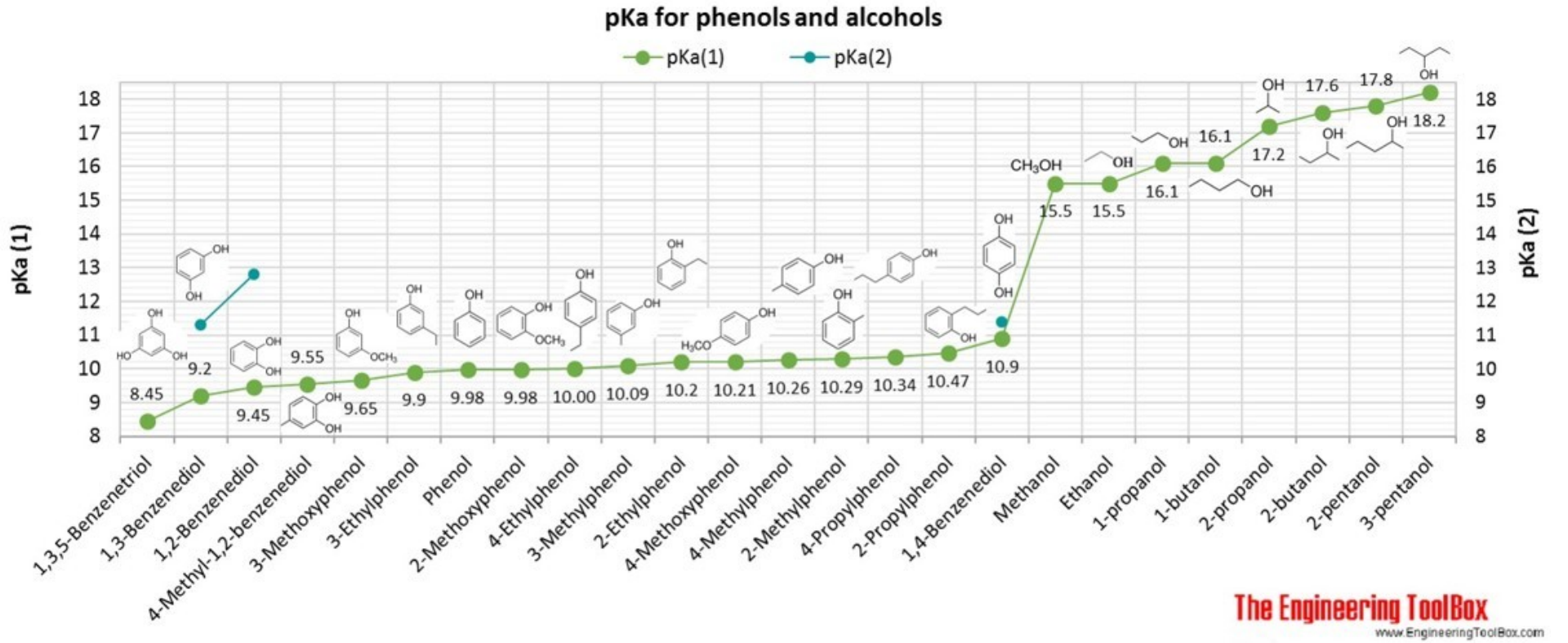


Oxidation



Ortho-quinone

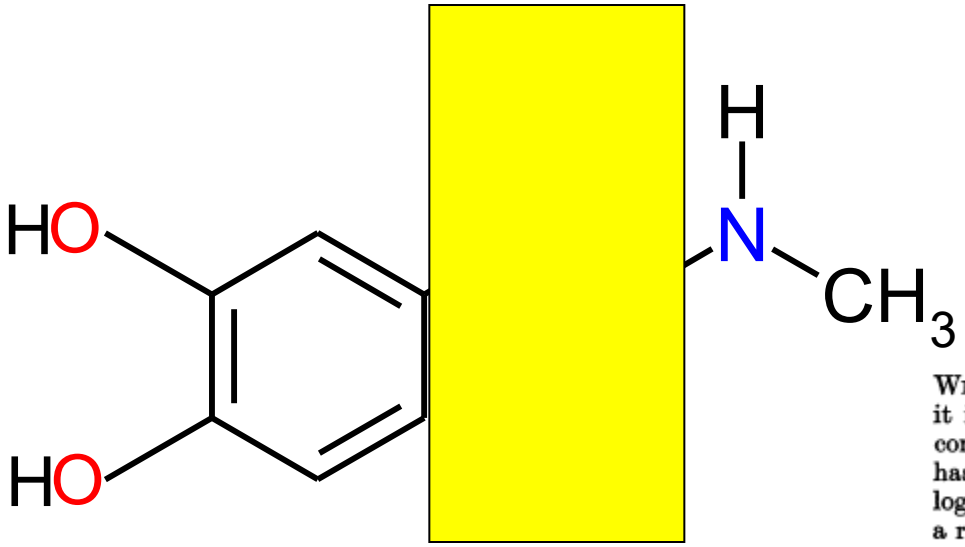
A little memory about pKa for phenols and alcohols…



The Engineering ToolBox
www.EngineeringToolBox.com

Thanks, Zorro96!!

6. SAR for epinephrine



CLXX. STUDIES ON THE RELATIONSHIP BETWEEN CHEMICAL CONSTITUTION AND PHYSIOLOGICAL ACTION.

V. MOLECULAR DISSYMMETRY AND PHYSIOLOGICAL ACTIVITY.

By LESLIE HILTON EASSON and EDGAR STEDMAN.

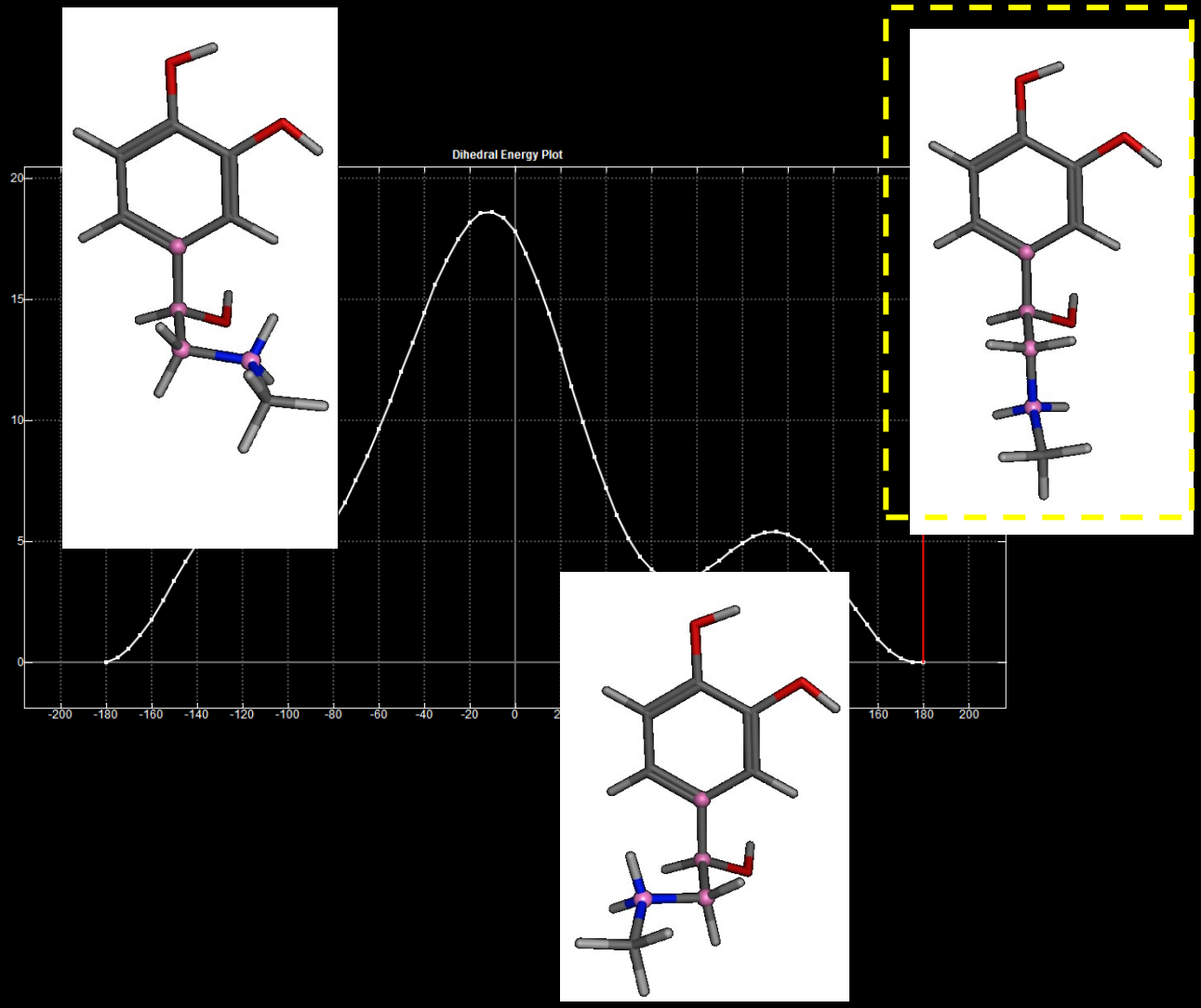
From the Department of Medical Chemistry, University of Edinburgh.

(*Received June 30th, 1933.*)

When a molecularly dissymmetric substance possesses pharmacological activity it is frequently, although not invariably, found that one optical isomeride is considerably more potent than the other. The work carried out on this subject has been reviewed by Cushny [1926], who himself made a detailed pharmacological comparison of the antimeric adrenalines and hyoscyamines. Largely as a result of his studies on these substances, Cushny regarded optical activity as a factor which is quite distinct from general structure in determining the magnitude of the specific pharmacological activity of a molecule, and this view is, we believe, the one which is currently held.

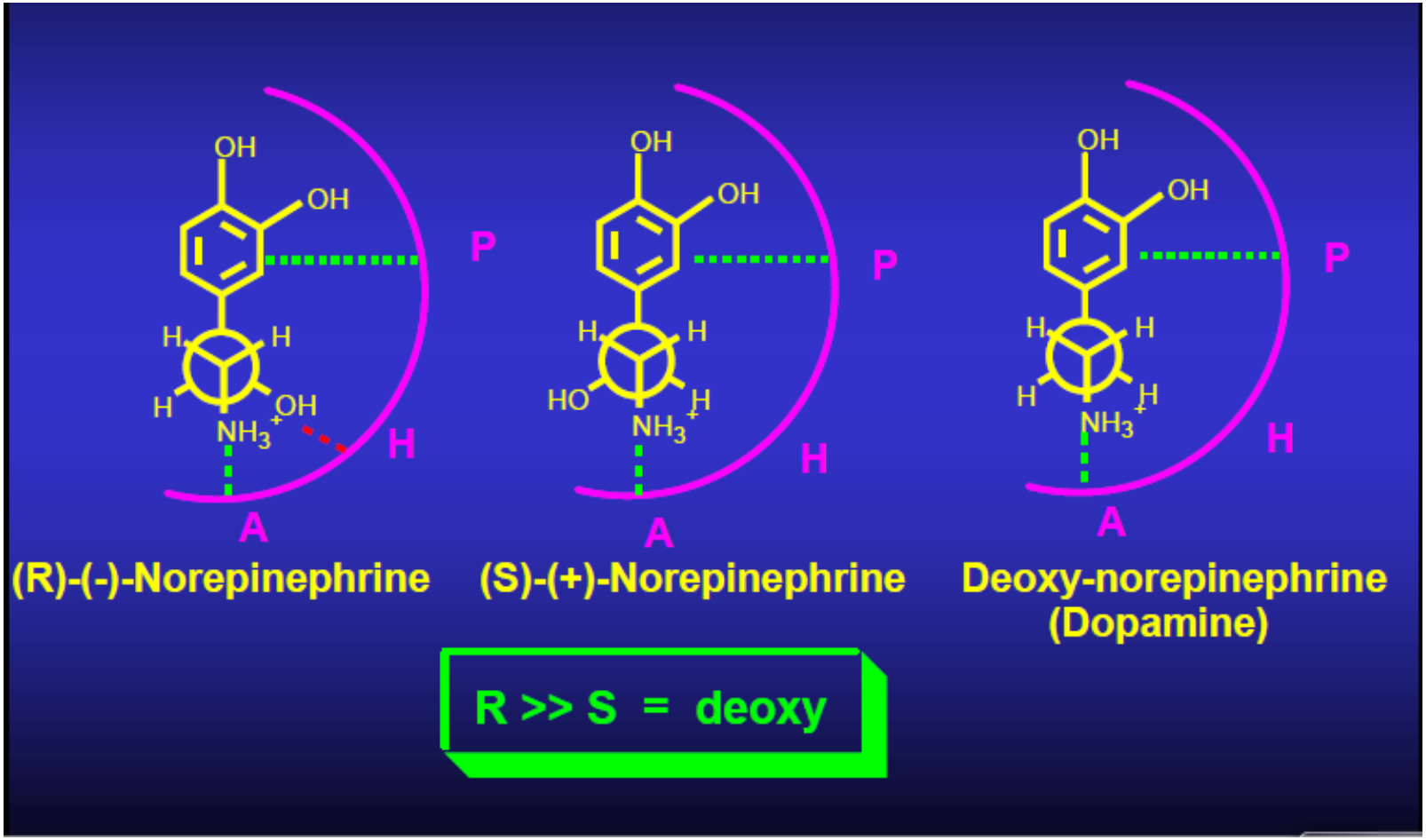
According to the Easson-Stedman hypothesis, potency is enhanced by the β-hydroxyl on the chiral carbon, and this has been confirmed to contribute about a 10–100 fold increased potency for the *R*(−) enantiomers.

What about adrenaline's conformation?



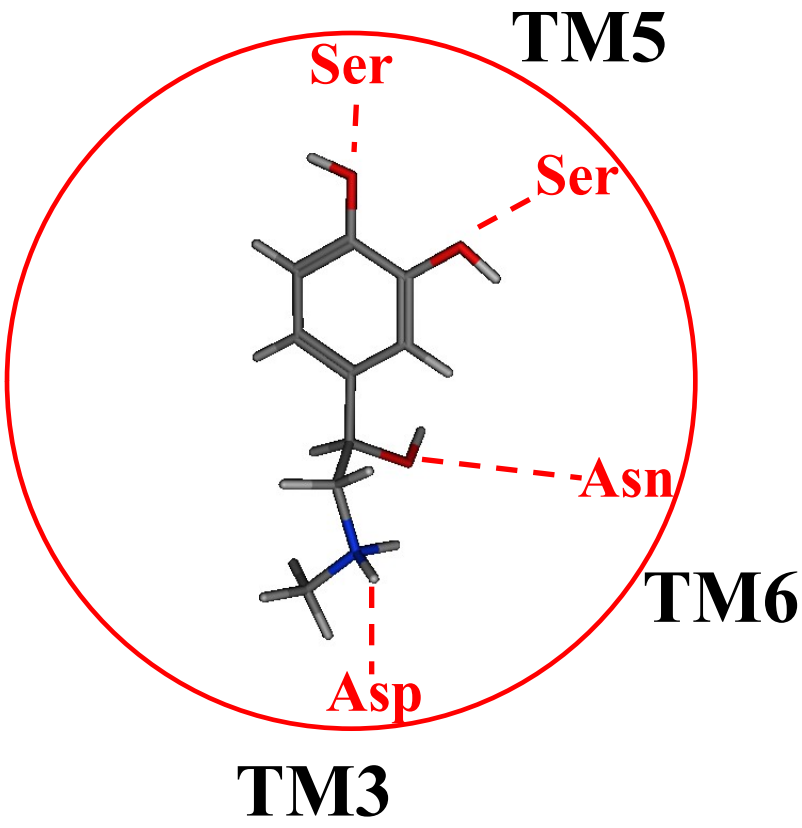
in water

6. SAR for epinephrine

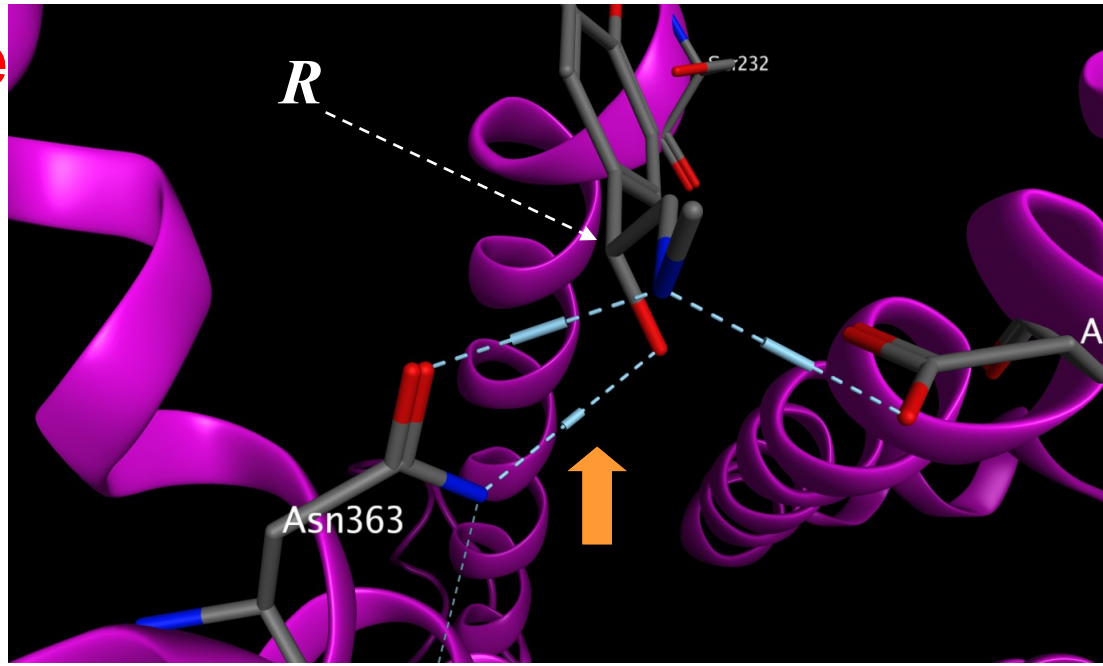


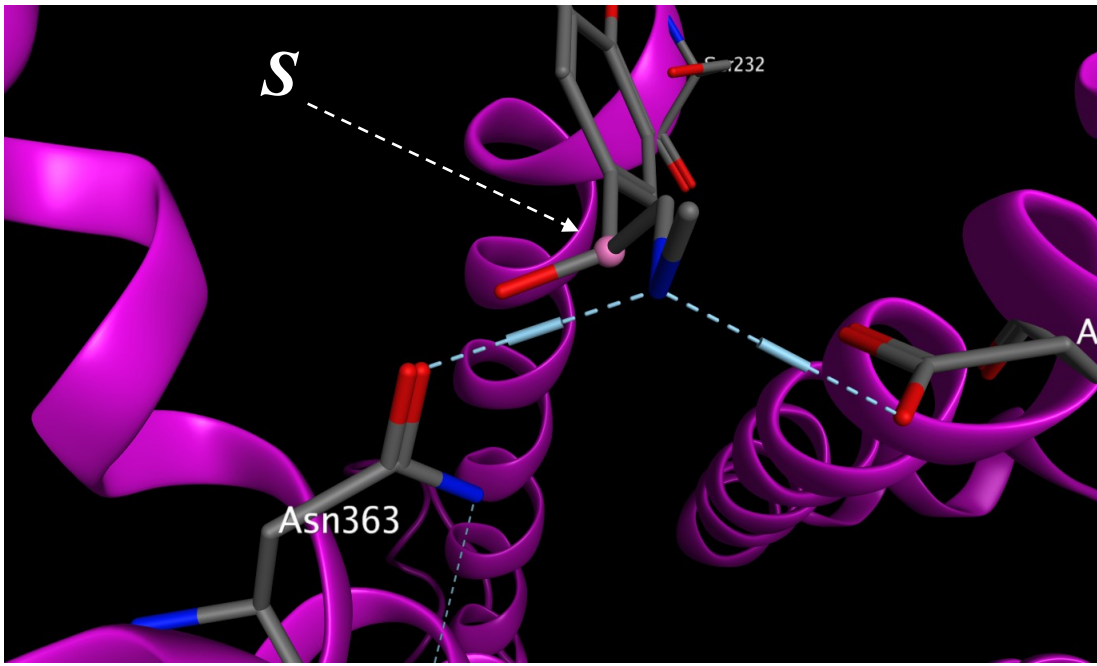
Eutomer: the more pharmacologically active of the enantiomers of a drug.

6. SAR for epinephrine

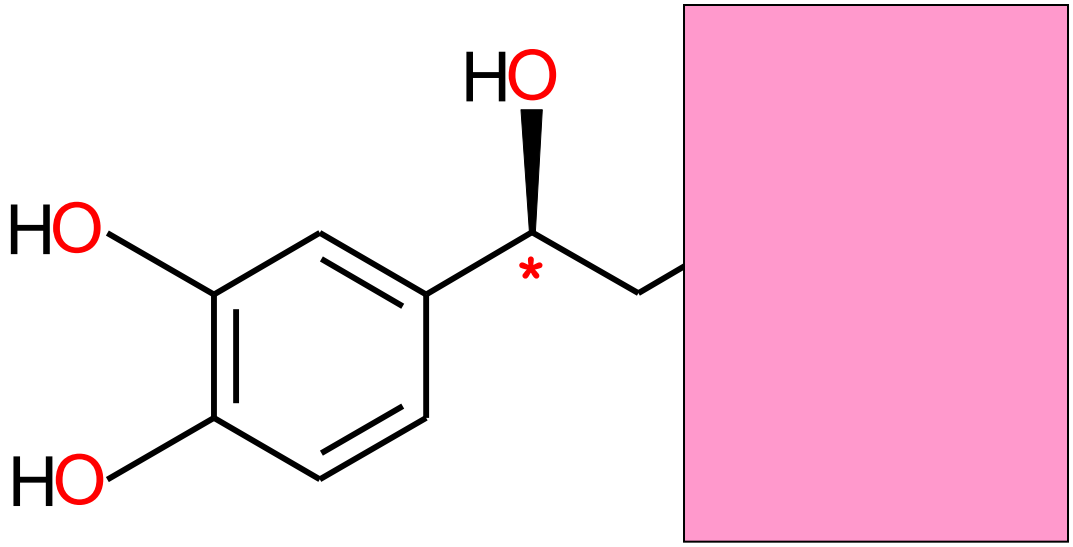


Human β1 adrenergic receptors
in complex with Adrenaline
(homology model by MMS)





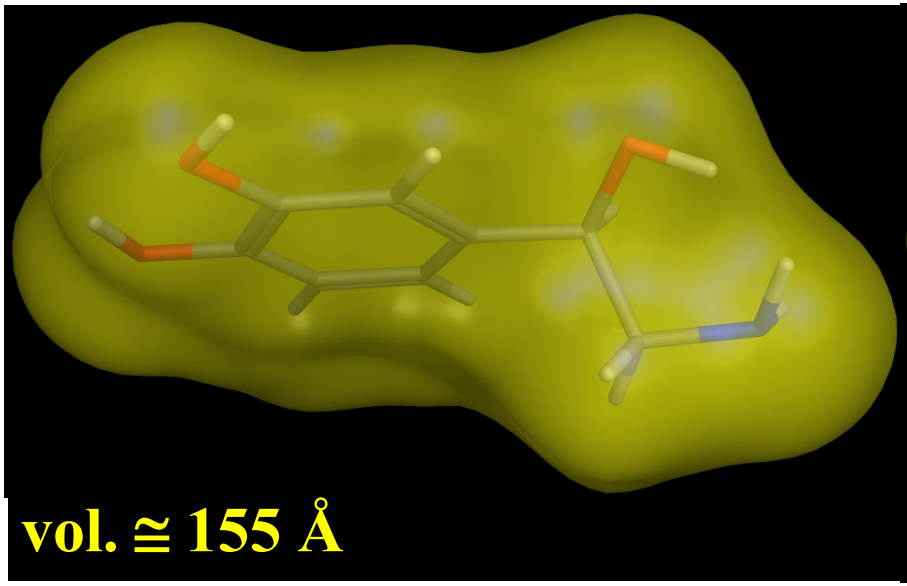
6. SAR for epinephrine

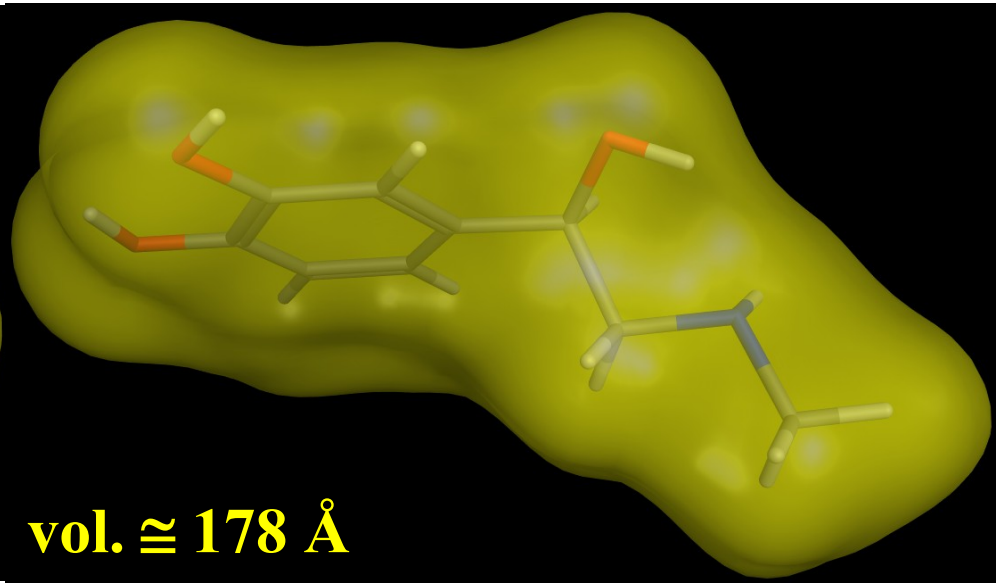


Quaternization of the nitrogen atom, or its replacement by a neutral atom such as oxygen, dramatically reduces its potency and intrinsic activity. In addition, substituents on the basic nitrogen are poorly tolerated in α-ARs for either agonists or antagonists, usually being limited to one carbon length.

However, they are well tolerated in β-ARs, with increasing steric bulk adjacent to the nitrogen being associated with increased antagonist potency or increased agonist selectivity .

6. SAR for epinephrine





Greater selectivity for α–receptors

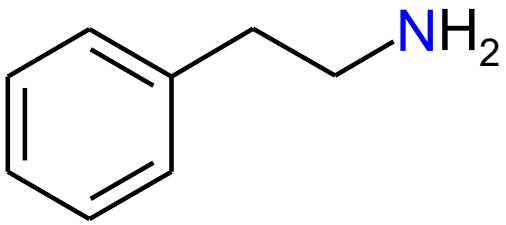
Equal selectivity for both α and β-receptors

7. Design of α-adrenergic agonists

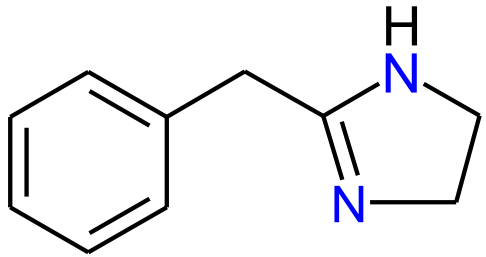
Direct and Indirect α-agonists

Direct Acting Drugs

These are drugs which directly active the α_1-adrenergic receptor. They are less potent than the endogenous agonists epinephrine or nor-epinephrine. However, because of structural modifications they are orally active and have longer plasma half-lives. There are two structural classes of α_1 agonists: the ***phenylethylamines*** which are close structural analogs of epinephrine and nor-epinephrine and the structurally unrelated ***imidazolines***. The major action of these agents is to produce α_1-adrenergic receptor mediated vasoconstriction.



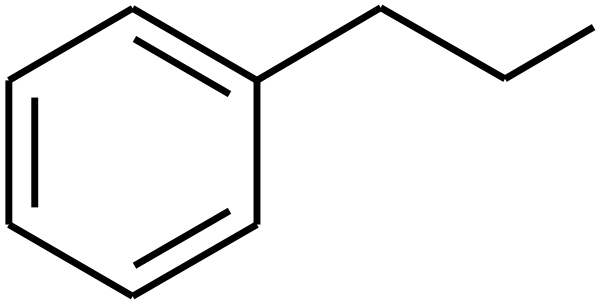
Phenylethylamine derivatives



Imidazoline derivatives

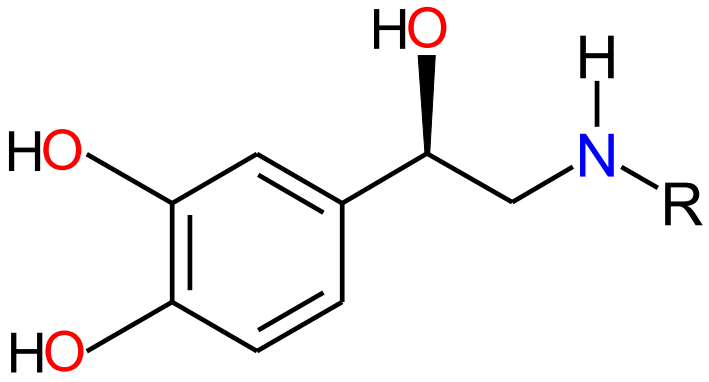
7. Design of α-adrenergic agonists

Direct Acting Drugs

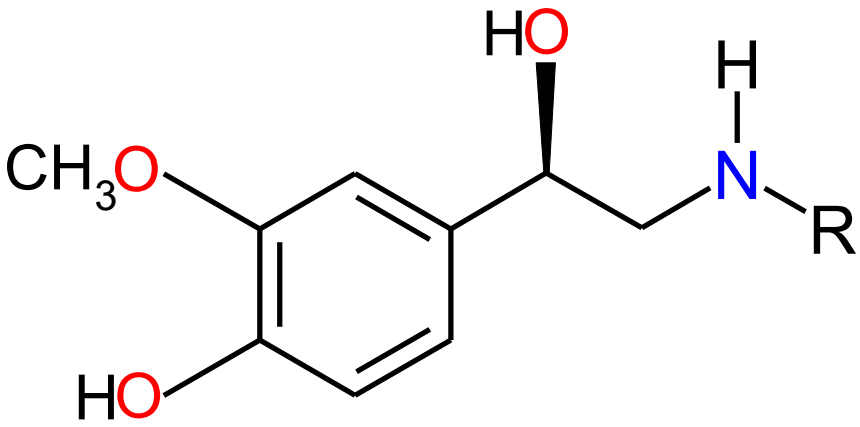


derivatives

Do you have any great pharmaceutical intuition



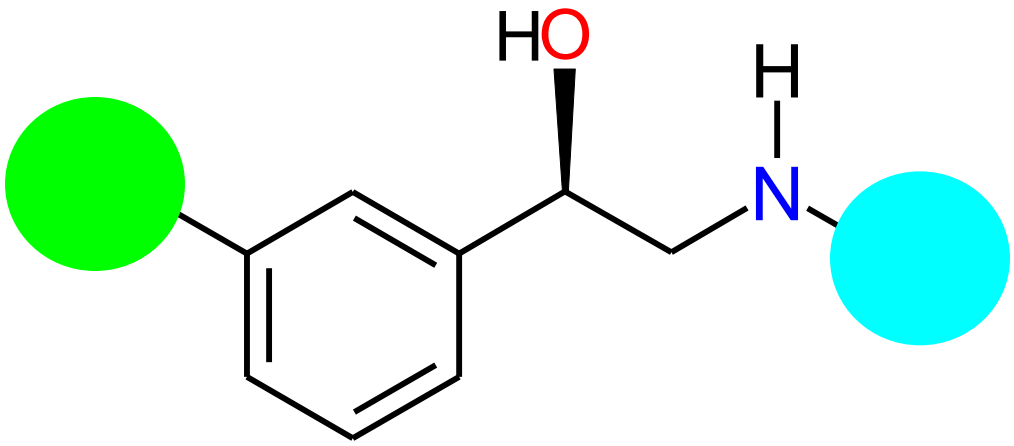
COMT

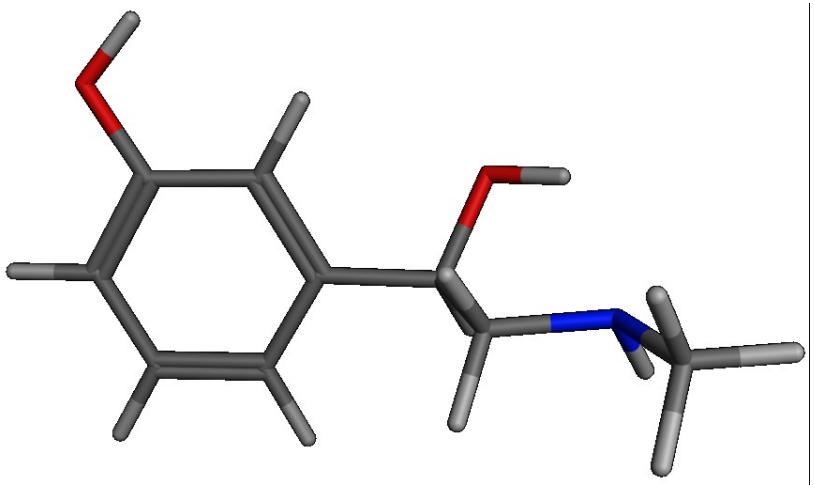


ACTIVE

INACTIVE

7. Design of α-adrenergic agonists





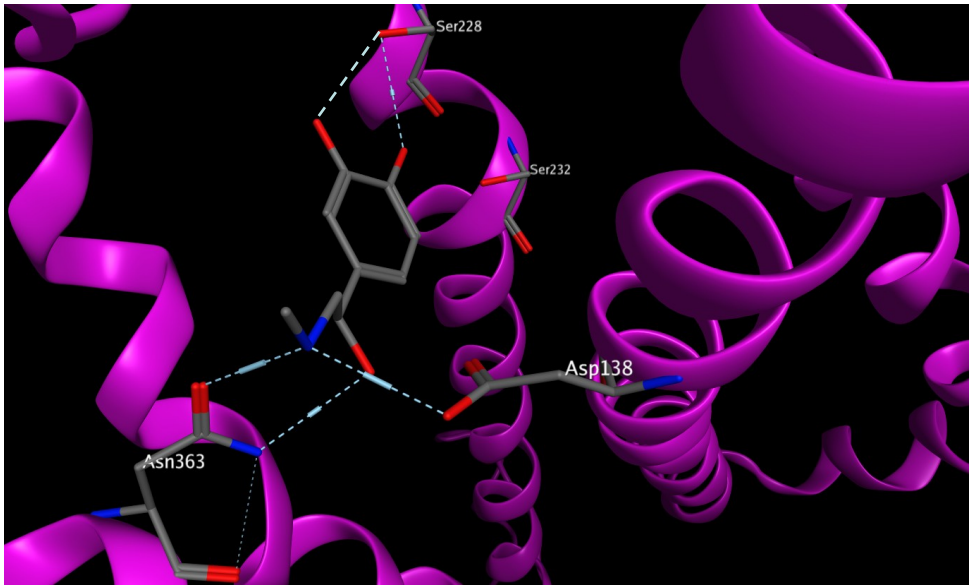
Phenylephrine
(m-Synephrine)

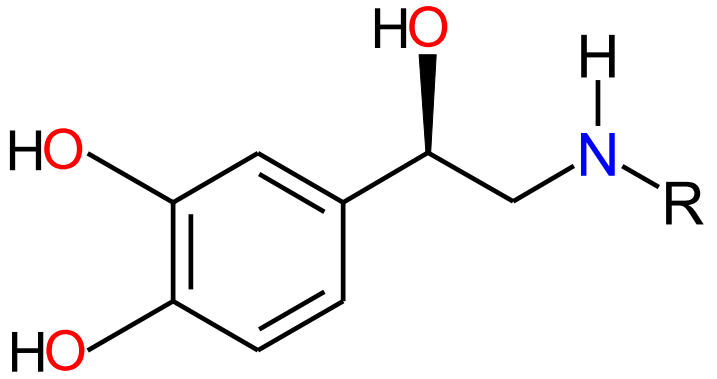
(*R*)-l-(3-Hydroxyphenyl)-N-methylethanolamine

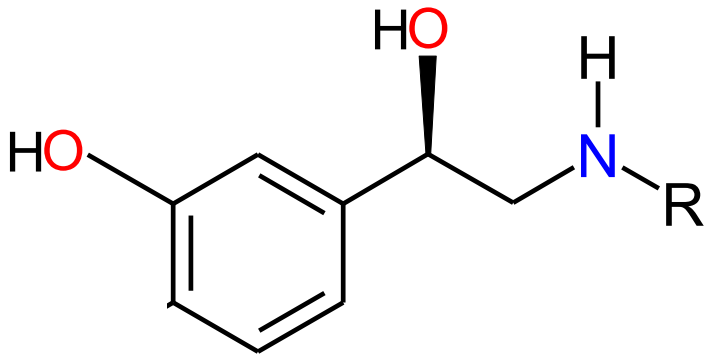
logP = - 0.3
pKa = 9.0

Phenylephrine is a sympathomimetic amine that acts **as** α-adrenergic receptors. Phenylephrine is a **postsynaptic α_1-receptor agonist** with effect also on β-receptors of the heart. Phenylephrine is a powerful vasoconstrictor. It is used as a **nasal decongestant** but may also be useful in treating **hypotension** and shock, symptomatic relief of external or internal **hemorrhoids**.

Could you comment about receptor affinities?

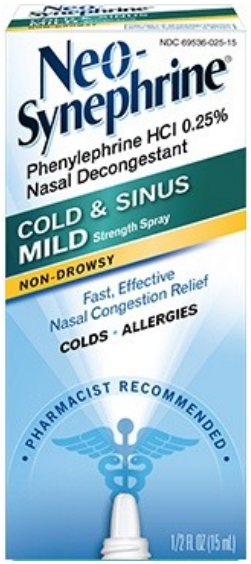






7. Design of α-adrenergic agonists

Famous formulations containing Phenylephrine:

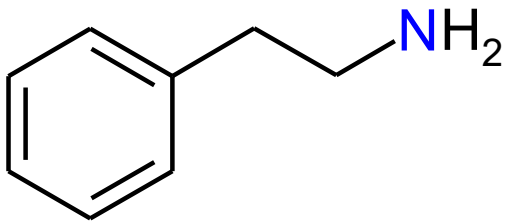


Remember: the effectiveness of Phenylephrine as nasal decongestant is still questionable. Several clinical studies were not able to distinguish between the effects of phenylephrine or a placebo.

Horak, F.; Zieglmayer, P.; Zieglmayer, R. ; Lemell, P.; Yao, R.; Staudinger, H.; Danzig, M. (2009). "A placebo-controlled study of the nasal decongestant effect of phenylephrine and pseudoephedrine in the Vienna Challenge Chamber". *Annals of Allergy, Asthma & Immunology* 102 (2): 116–20.

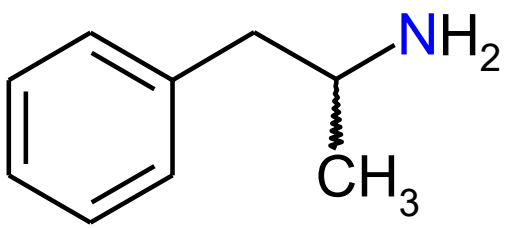
7. Design of α-adrenergic agonists

Famous Phenylephrine Analogs:



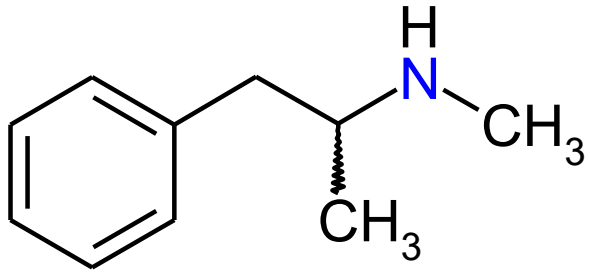
Phenylethylamine (PEA)

logP = 1.4
pKa = 9.8



(*R*,*S*)-Amphetamina

logP = 1.8
pKa = 10.0



(*R*,*S*)-Metamphetamina

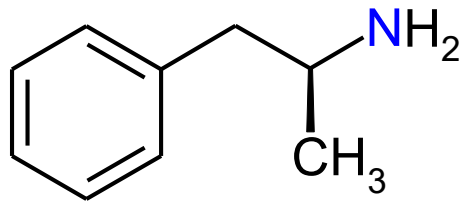
logP = 2.1
pKa = 9.9

These compounds don't act *directly* as adrenergic agonists (we will see in a few minutes their mechanism of action) but you can immediately discover three *direct* adrenergic agonists!!!

7. Design of α-adrenergic agonists

Famous Phenylephrine Analogs:

Appetrol: meprobamate 300 mg. + *dextroamphetamine sulfate* 15 mg

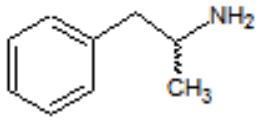


(*S*) (+) Amphetamina

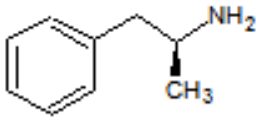
Dextroamphetamine is a potent central nervous system stimulant and amphetamine enantiomer that is prescribed for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. It is also used as an athletic performance and cognitive enhancer, and recreationally as an aphrodisiac and euphoriant. Dextroamphetamine is also widely used by military air forces as a 'go-pill' during fatigue-inducing mission profiles such as night-time bombing missions. Preparations containing dextroamphetamine were also used in World War II as a treatment against fatigue.

7. Design of α-adrenergic agonists

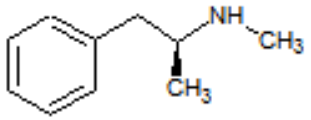
Indirect Acting Drugs



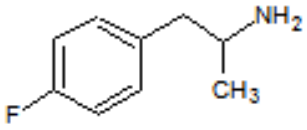
Amphetamine/Benzedrine
[1-phenylpropan-2-amine]



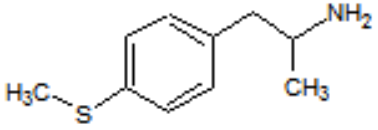
Dextroamphetamine
[(2*S*)-1-phenylpropan-2-amine]



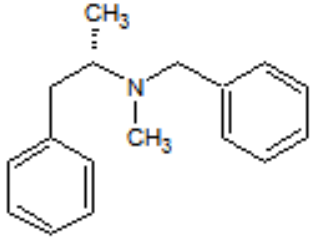
Methamphetamine (crystal meth)
[(2*S*)-*N*-methyl-1-phenylpropan-2-amine]



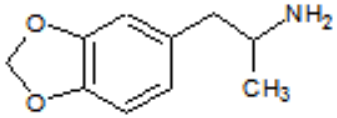
4-FMP
[1-(4-fluorophenyl)propan-2-amine]



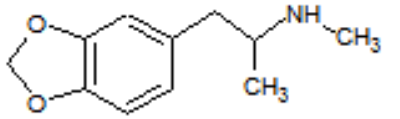
4-MTA
[1-[4-(methylthio)phenyl]propan-2-amine]



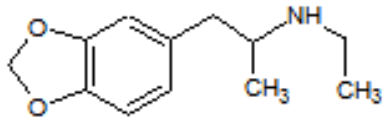
Benzphetamine
[(2*S*)-*N*-benzyl-*N*-methyl-1-phenylpropan-2-amine]



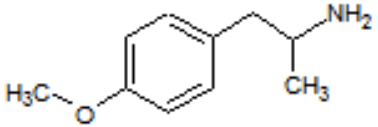
MDA
[1-(1,3-benzodioxol-5-yl)propan-2-amine]



MDMA (Ecstasy)
[1-(1,3-benzodioxol-5-yl)-*N*-methylpropan-2-amine]



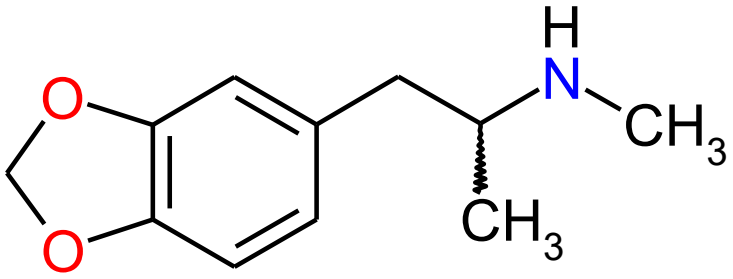
MDEA
[1-(1,3-benzodioxol-5-yl)-*N*-ethylpropan-2-amine]

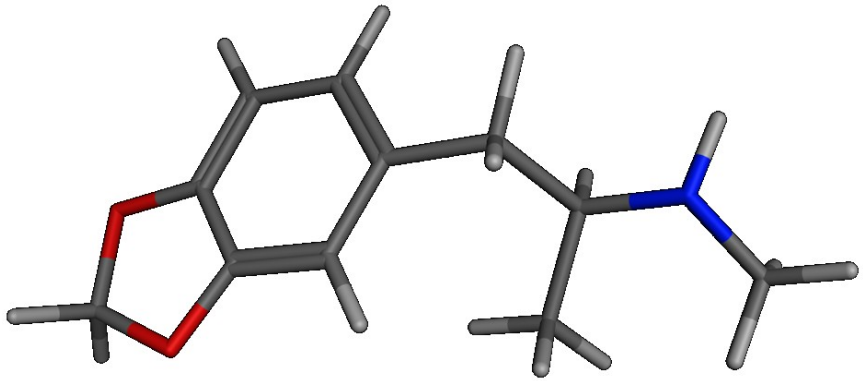


PMA
[1-(4-methoxyphenyl)propan-2-amine]

7. Design of α-adrenergic agonists

MDMA (Ecstasy)





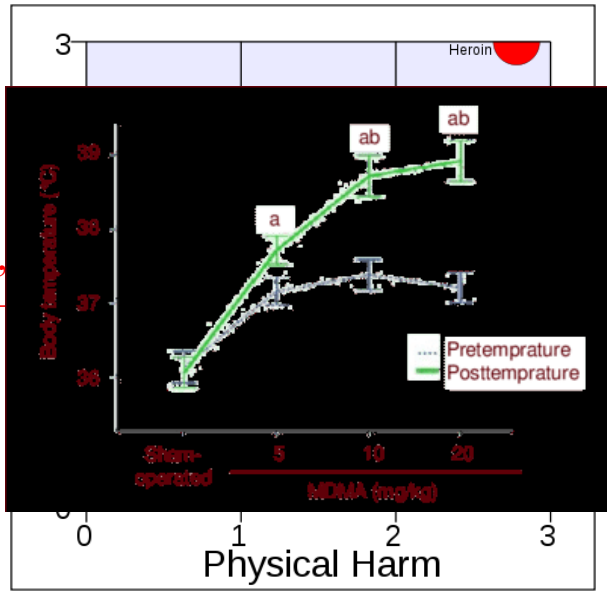
3,4-**M**ethyleneDioxy-**M**eth**A**mphetamine

logP = 1.8

In general, MDMA users begin reporting subjective effects within 30 to 60 minutes of consumption, hitting a peak at about 75 to 120 minutes which plateaus for about 3.5 hours.

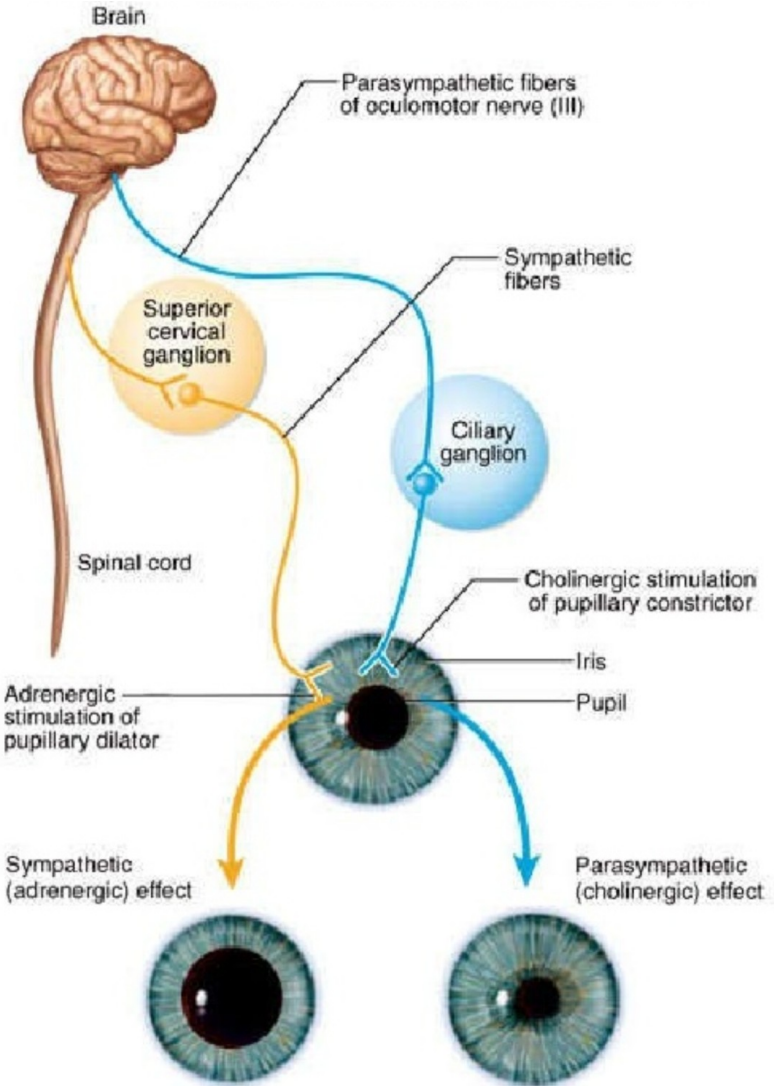
The average ecstasy tablet contains 60–70 mg (base equivalent) of MDMA, usually as the hydrochloride salt. Powdered MDMA is typically 30–40% pure, due to bulking agents (e.g., lactose) and binding agents.

The club drug MDMA **suppresses the body's temperature-regulating system**, occasionally with fatal consequences. Abusers have developed temperatures as high as 40°C, suffered multiple organ failure, and died. Treatment in these emergencies has been limited mainly to cooling the victim with ice or refrigerating blankets.



The Lancet **369, 1047–1053, 2007**

The eyes don't lie!!!



Pinned Out Pupils

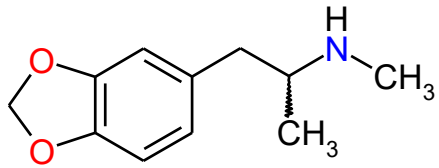
Opiods, Benzodiazapines, and Barbiturates cause pupil constriction.

Opioids: Percocet, vicodin, oxycodone, heroin.
Benzodiazepines alleviate anxiety. [Xanax, valium]
Barbiturates also called tranquilizers or sedatives.

Dilated Pupils

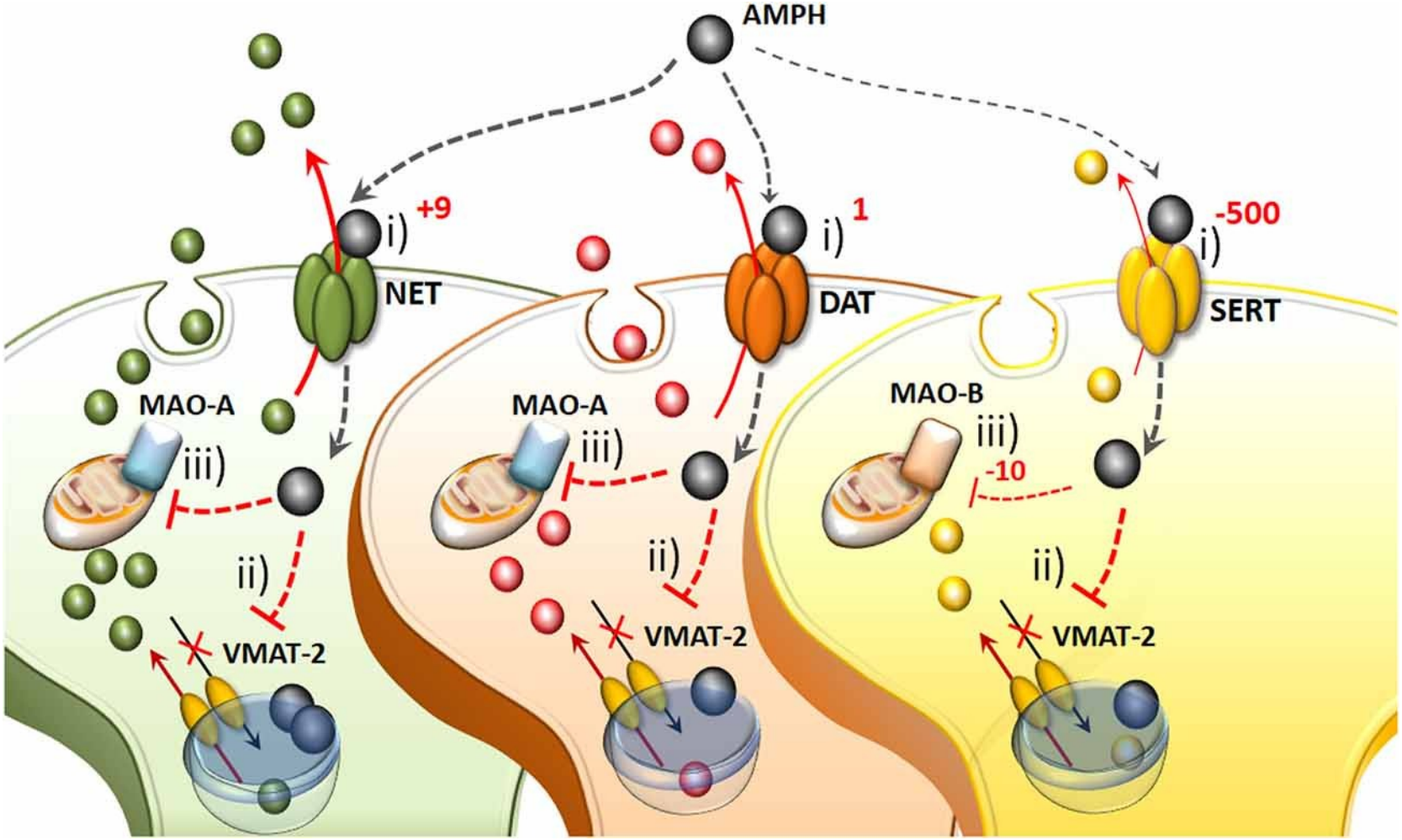
Hallucinogens & Stimulants are known to cause pupil dilation.

Hallucinogens: Pot, LSD [Mushrooms, Acid]
Stimulants: Cocaine, crack, crystal meth.
Antidepressants can also cause dilation.



7. Design of α-adrenergic agonists

Model of the actions of amphetamine at adrenergic/dopaminergic/serotoninergic-containing nerve terminals.



Credits: https://www.frontiersin.org/articles/10.3389/fnana.2019.00048

7. Design of α-adrenergic agonists

The molecular mechanisms of amphetamine(s) (AMPHs) in monoamine-containing neurons. (i) The primary molecular target, which provides neuronal selectivity for AMPHs, consists in the plasma membrane transporter. In fact, AMPHs behave as competitive substrates for the re-uptake through the NE transporter (NET), dopamine (DA) transporter (DAT) and 5-HT transporter (SERT; Rothman and Baumann, 2003; Fleckenstein et al., 2007). These transporters normally work by taking up extracellular monoamines to the axoplasm, which is the main mechanism to terminate their activity (Iversen et al., 1965; Axelrod and Kopin, 1969; Coyle and Axelrod, 1971; Aggarwal and Mortensen, 2017). Cross-affinity between AMPHs and neurotransmitters contributes to generate the quite selective storage of AMPHs within specific neurons. Once bound to the plasma membrane transporter, AMPHs enter the axoplasm while reverting the transport direction (Sulzer et al., 1993). This occurs mostly for catecholamine neurons since AMPHs strongly discriminate between SERT, to which they bind with much lower affinity (500-fold less) compared with DAT and NET (Rothman and Baumann, 2003). In particular, AMPHs bind to the NET with five-to-nine-fold higher affinity compared with the DAT (Rothman and Baumann, 2003). This is the main reason why AMPHs release NE more potently than DA and much more than 5-HT (Rothman et al., 2001). (ii) Within monoamine axons, AMPHs encounter a second specific target called vesicular monoamine transporter type-2 (VMAT-2), which is also shared with monoamines. In this way, AMPHs enter the synaptic vesicles. At this level, AMPHs impair the acidification of the vesicle, which generates an acidic pH (Sulzer and Rayport, 1990; Sulzer et al., 1993, 1995). This acidic environment is erased by AMPHs, which rise the vesicular pH value from 4 up to 7, which corresponds to a 1,000-fold increase in the concentration of H^+ ions. Thus, monoamines, which are weak bases, are charged at low pH, while at a neutral pH lose their charge, and diffuse through the vesicle membrane, thus massively invading the axoplasm (Brown et al., 2000, 2002; Pothos et al., 2000). In this way, axonal monoamines either passively or *via* a reverted plasma membrane transporter fill extracellular space where they reach a massive concentration (Sulzer et al., 1995, 2005). (iii) The third molecular target, which is impaired by AMPHs, is the mitochondrial-bound enzyme monoamine oxidase (MAO). Both MAO-A/-B iso-enzymes oxidatively deaminate DA, NE and 5-HT. Nonetheless, MAO-A/-B isoforms differ in substrate preference, inhibitor affinity and regional distribution within either single neurons or different animal species (Robinson et al., 1977; Youdim, 1980; Sourkes, 1983; Gesi et al., 2001; Youdim et al., 2006; Bortolato et al., 2008). These differences are seminal to explain the specific effects of AMPHs within various monoamine neurons. In fact, MAO-A, are competitively inhibited by methamphetamine (METH) with a 10-fold higher affinity compared with MAO-B. MAO-A is placed within synaptic terminals of DA and NE neurons, while MAO-B are the only isoform operating within 5-HT terminals and non-catecholamine neurons. Thus, apart from rats and a few animal species, the effect of AMPHs on the amount of extracellular monoamines is remarkable concerning NE and DA, being less pronounced for 5-HT.

7. Design of α-adrenergic agonists

Transporter reversal is the action of reversing a membrane transporter via a process known as *phosphorylation*. Neurotransmitter transporters normally function as part of the reuptake process, by carrying neurotransmitter chemicals from the extracellular space into the cytoplasm of a presynaptic neuron. When they operate in reverse, they instead carry the neurotransmitter from the cytoplasm into the extracellular space, where it may become capable of binding to postsynaptic receptors. Transporter reversal is utilized by drugs that act as *releasing agents*, e.g., *amphetamine*.

Amphetamine and other similar substances colloquially termed "releasing agents" reverse the transport direction of monoamine transporters through the activation of a presynaptic intracellular receptor called **trace amine-associated receptor 1 (TAAR1)**. TAAR1 signals through *protein kinase A* and *protein kinase C* to phosphorylate monoamine transporters, which subsequently either reverse transport direction or withdrawal into the cytoplasm, resulting in non-competitive reuptake inhibition.

Miller GM (January 2011). "The emerging role of trace amine-associated receptor 1 in the functional regulation of monoamine transporters and dopaminergic activity". *J. Neurochem.* **116 (2): 164–176**

Imidazoline receptors… a new fascinating communication pathway!

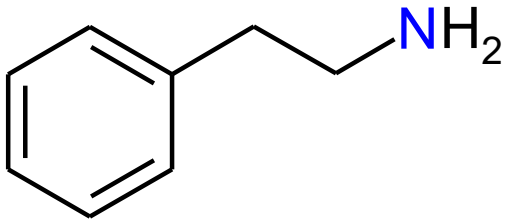
The observed structure-activity relationship for imidazoline-derivatives showed that activation of alpha-adrenergic receptors was not the prime mechanism of this action.

On the basis of this, the existence of a *non-adrenergic receptor* specifically acted upon by imidazolines was suggested. The identification and biochemical characterization of these receptors were delayed by the fact that all the available ligands were "hybrid", i.e. they bound not only to 2-adrenergic receptors and sometimes 1-adrenergic receptors but also to specific, non-adrenergic imidazoline receptors. This was particularly true in the case of clonidine.

There are at least three classes of imidazoline receptors.

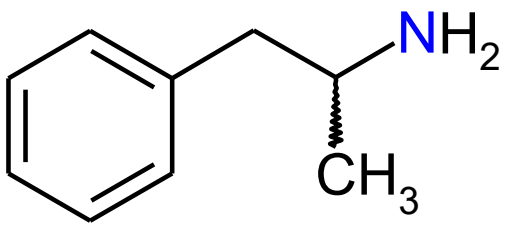
Do you have a smart idea to transform these in a novel adrenergic agosnists?

Famous Phenylephrine Analogs:



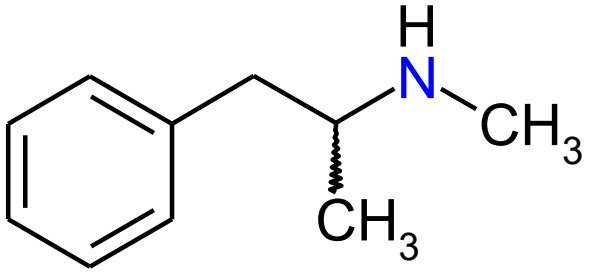
Phenylethylamine (PEA)

logP = 1.4
pKa = 9.8



(*R*,*S*)-Amphetamina

logP = 1.8
pKa = 10.0

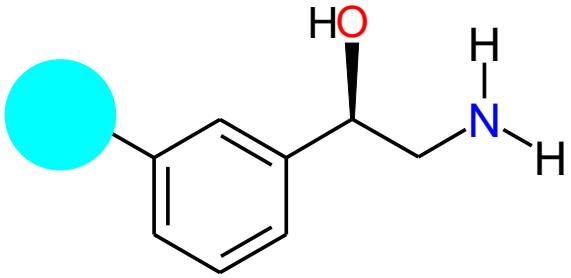


(*R*,*S*)-Metamphetamina

logP = 2.1
pKa = 9.9

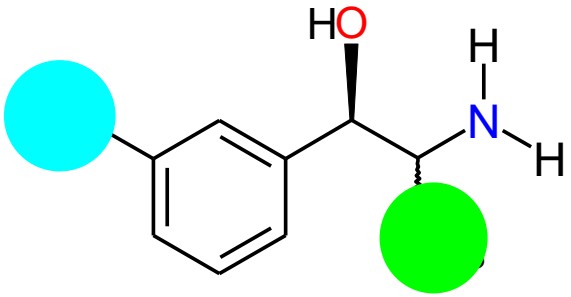
7. Design of α-adrenergic agonists

Other direct phenylethylamino α-adrenergic agonists:



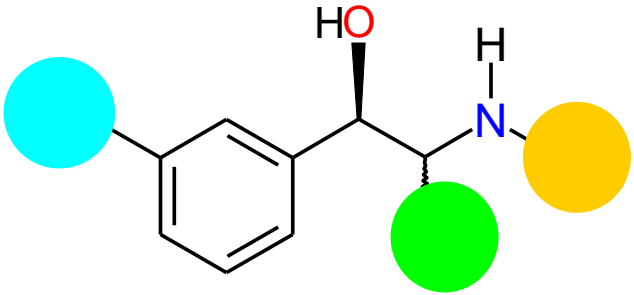
Norphenylephrine

logP = -0.7
pKa = 9.0



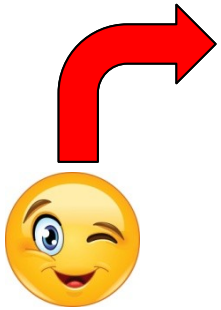
Metaraminol

logP = -0.3
pKa = 8.8



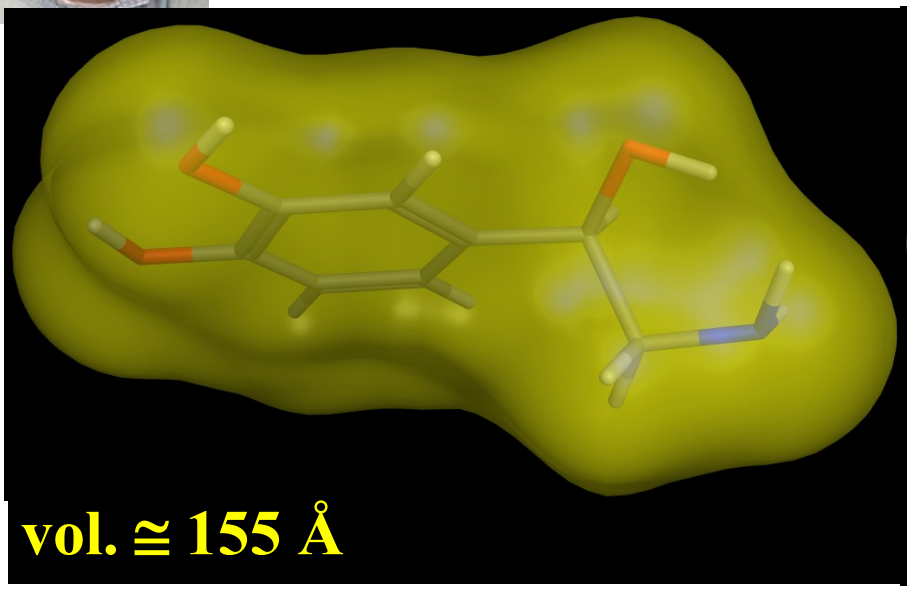
3-Hydroxyephedrine

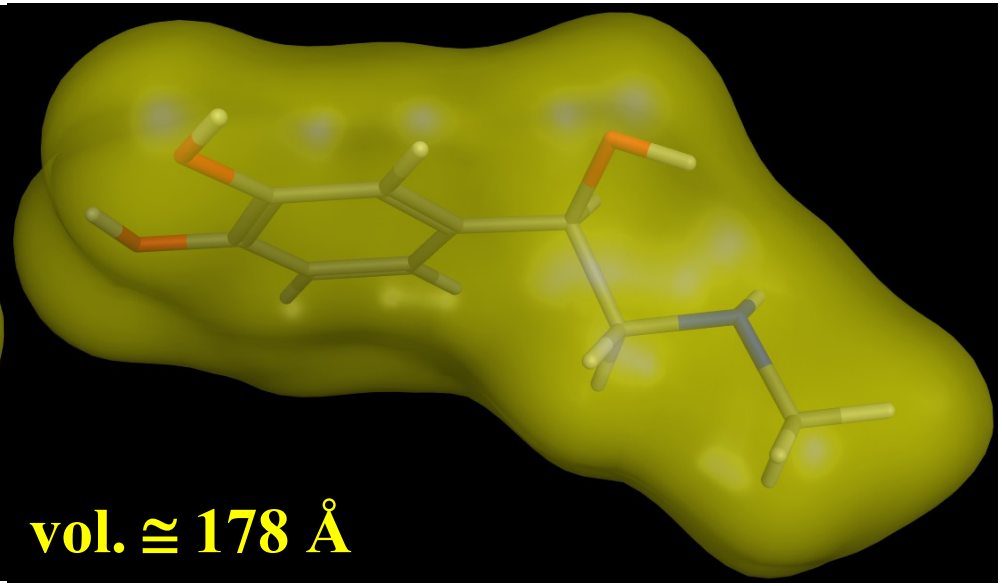
logP = 0.3
pKa = 8.9



They are sympathomimetic agent that acts predominantly at alpha-1 adrenergic receptors. It has been used primarily as a vasoconstrictor in the treatment of HYPOTENSION. They can be internalized by nor-adrenaline transporter (NET) and restored in the synaptic vescicoles by VMAT2 transporter. Finally, they also stimulates the release of norepinephrine (*indirect agonists*).

From alpha to beta... remember?



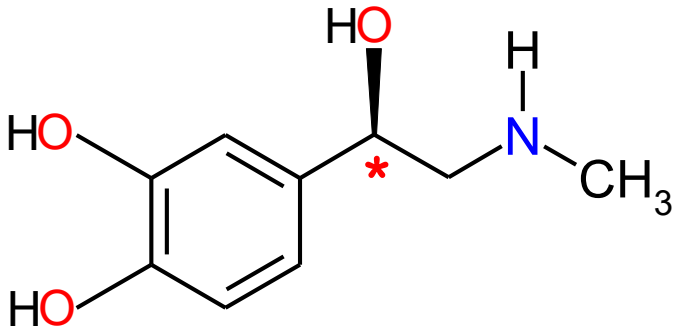


Greater selectivity for α–receptors

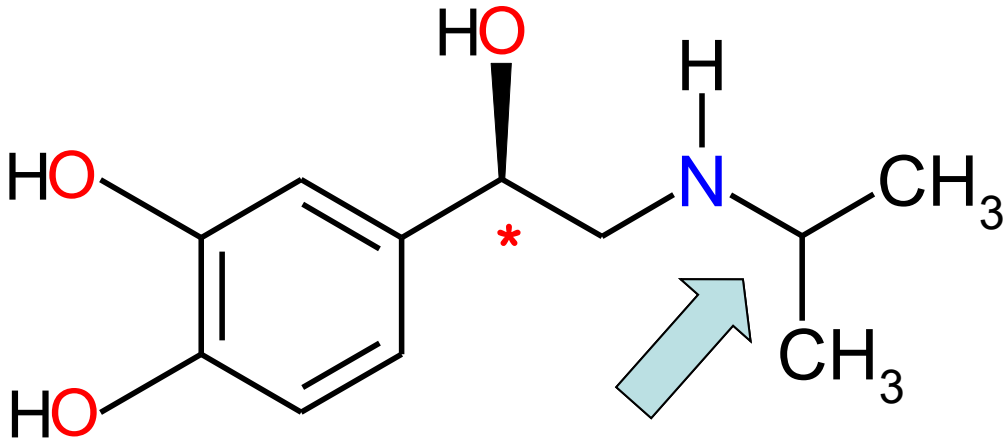
Equal selectivity for both α and β-receptors

Perhaps, still greater selectivity for β-receptors could be generated by appending larger alkyl substituent on nitrogen!

9. Design of β-adrenergic agonists



Equal selectivity for both α and β-receptors



Greater selectivity for β–receptors

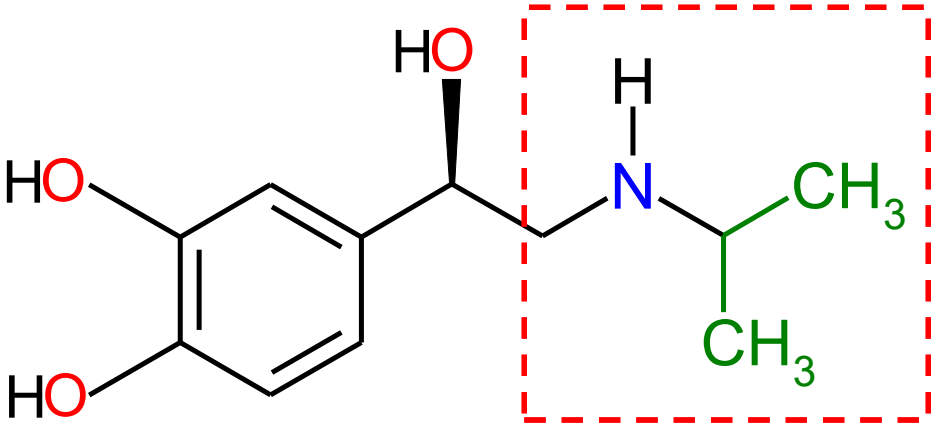
Isoprenaline

Unfortunately, isoprenaline acts as agonist selectively on all beta receptors, activating β1 and β2 receptors equally.

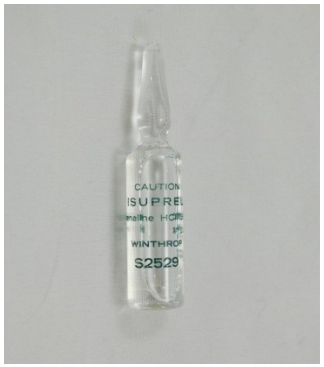
Became the most widely used inhaled treatment for asthma for at least 20 years. The adverse effects of isoprenaline are also related to the drug's cardiovascular effects. Isoprenaline can produce an elevated heart rate (tachycardia), which predisposes patients to cardiac dysrhythmias.

9. Design of β-adrenergic agonists

From β1 to β2-agonists:

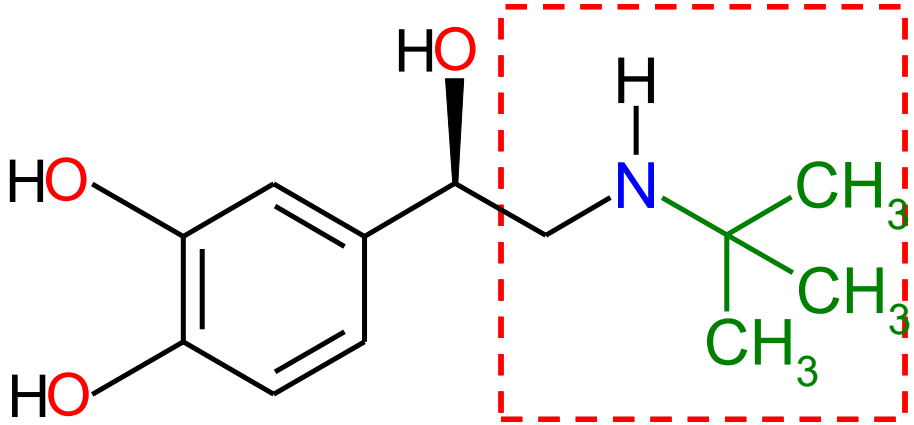


log P = -0.2



Isoprenaline

β1 ≅ β2



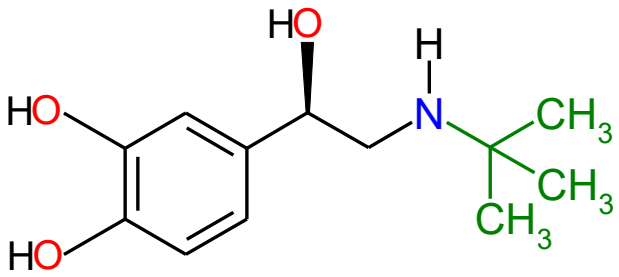
log P = 0.2

***t*-butil-adrenaline (Colterol)**

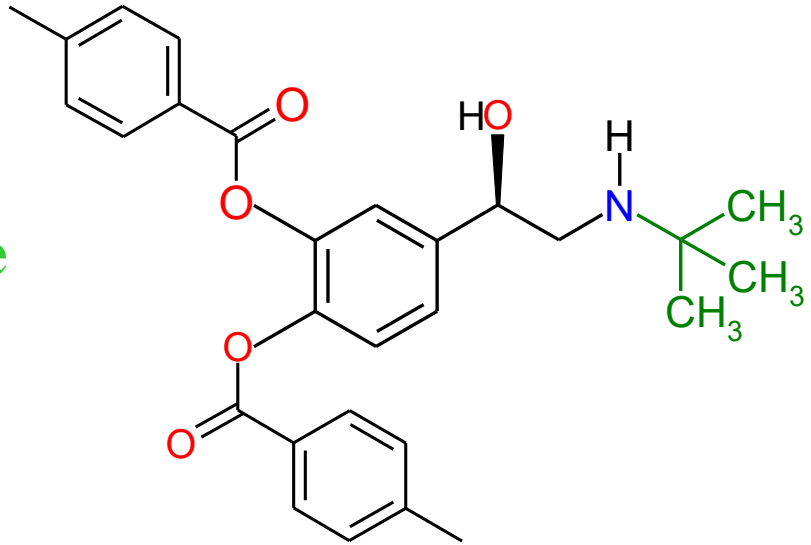
β2 > β1

9. Design of β-adrenergic agonists

From a drug to a prodrug!



Esterase



***t*-butil-adrenaline**
(Colterol)

Bitolterol

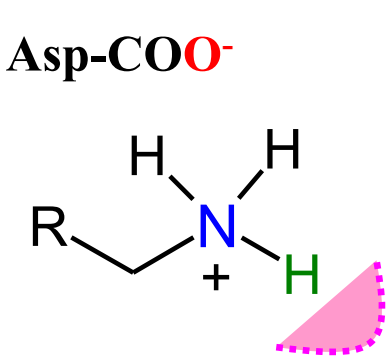
(*RS*)-[4-(1-Hydrossi-2-*tert*-butilammino-etil)-2-(4-metilbenzoil)ossi-fenil] 4-metilbenzoato

(logP = 5.8)

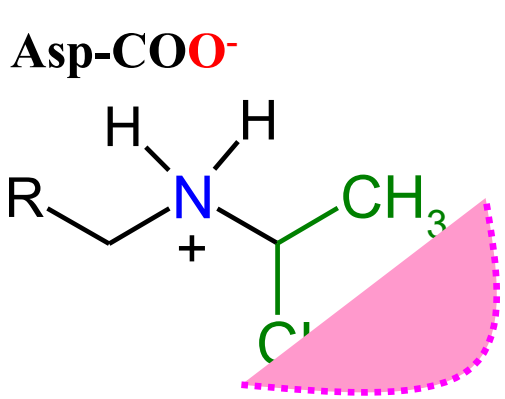
Bitolterol is a prodrug deposits in pulmonary tissue and is hydrolyzed over time (5-8 hours).

9. Design of β-adrenergic agonists

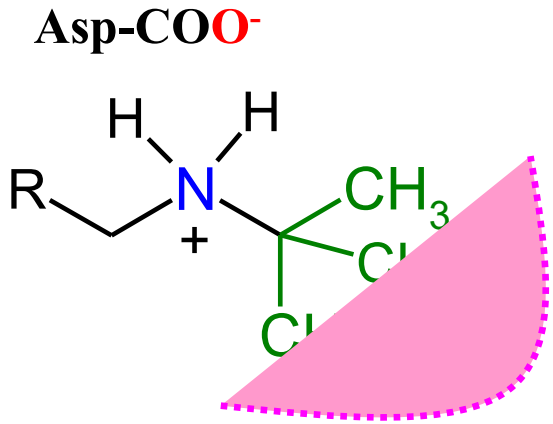
A plausible explanation of selectivity receptors profile:



α1 ≅ α2



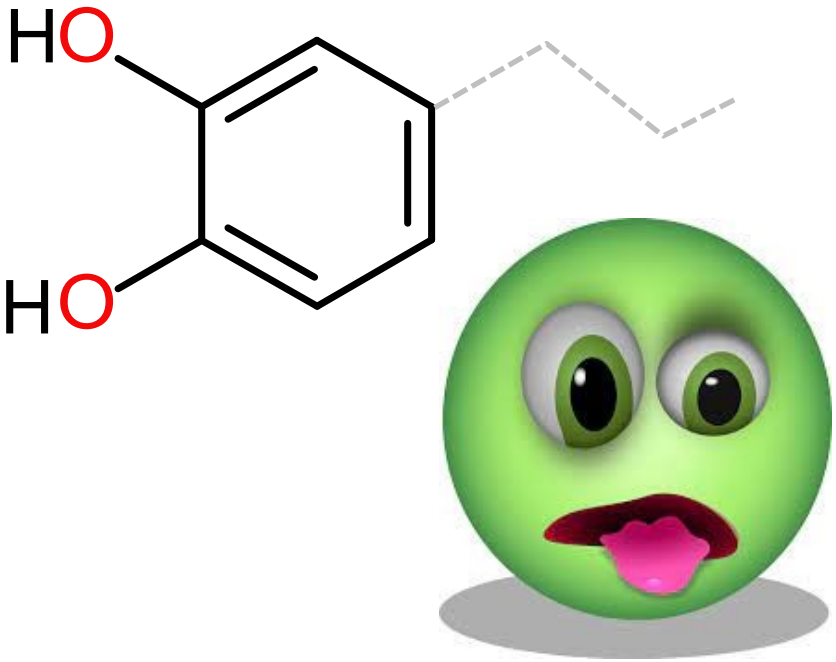
β1



β2

Hydrophobic pocket in proximity of the protonated ammonium salt

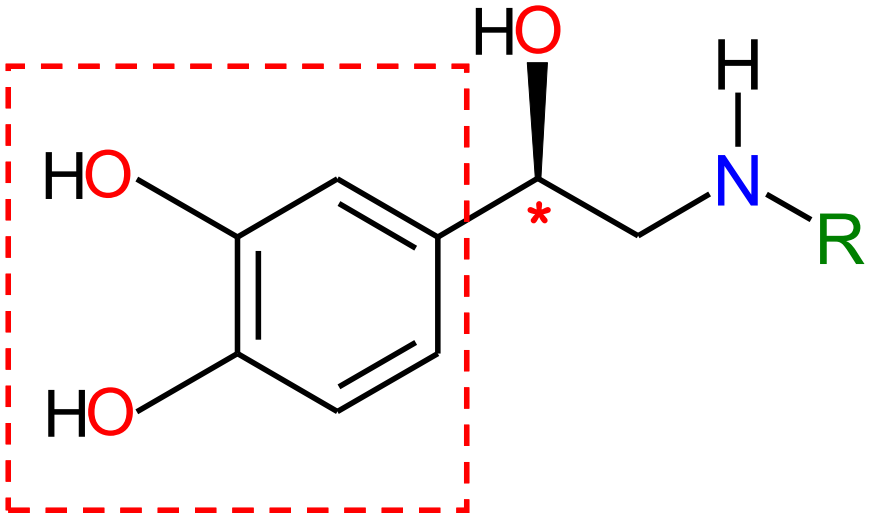
Do you remember catechol urticaria?

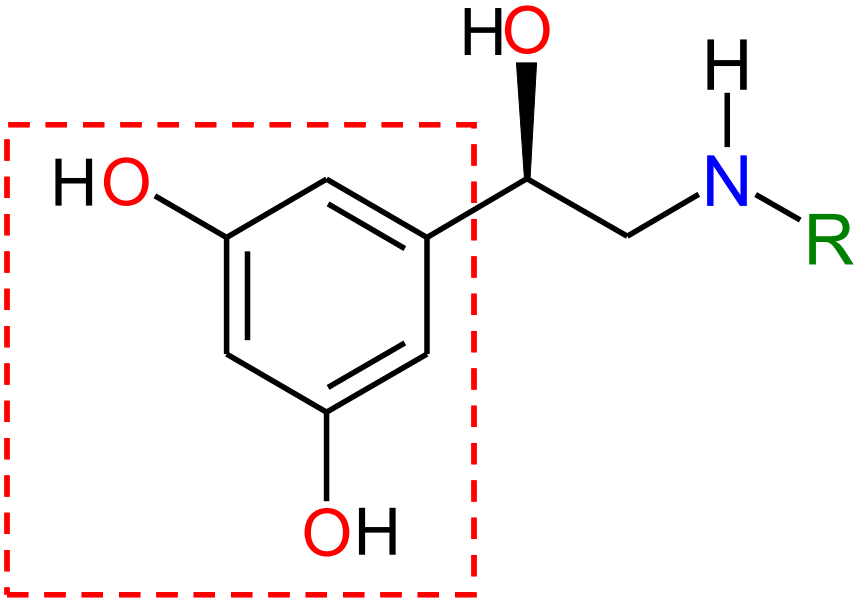


Bioisosters, please help us!

9. Design of β-adrenergic agonists

The first nice example of catechol bioisosterism:

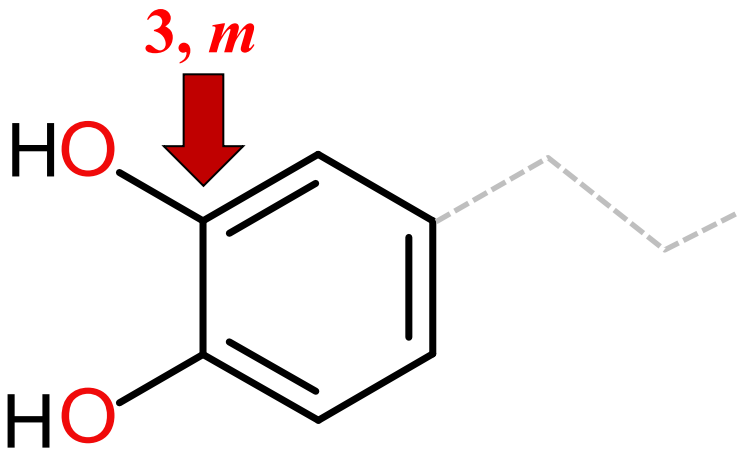


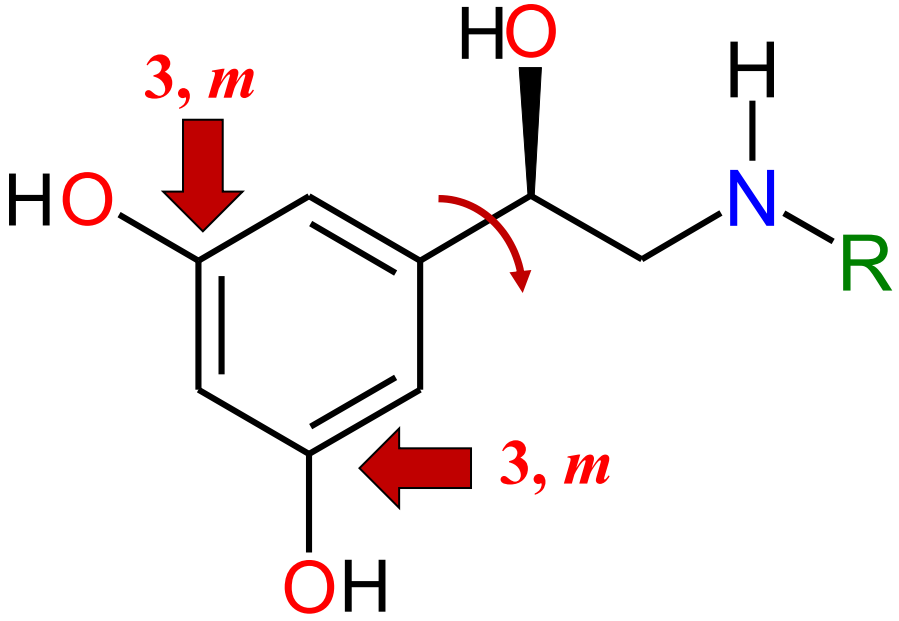


Two interesting advantages:

1. **maintaining the interaction scheme**
2. **abolishing COMT metabolism**

Could you explain this bioisosterim?

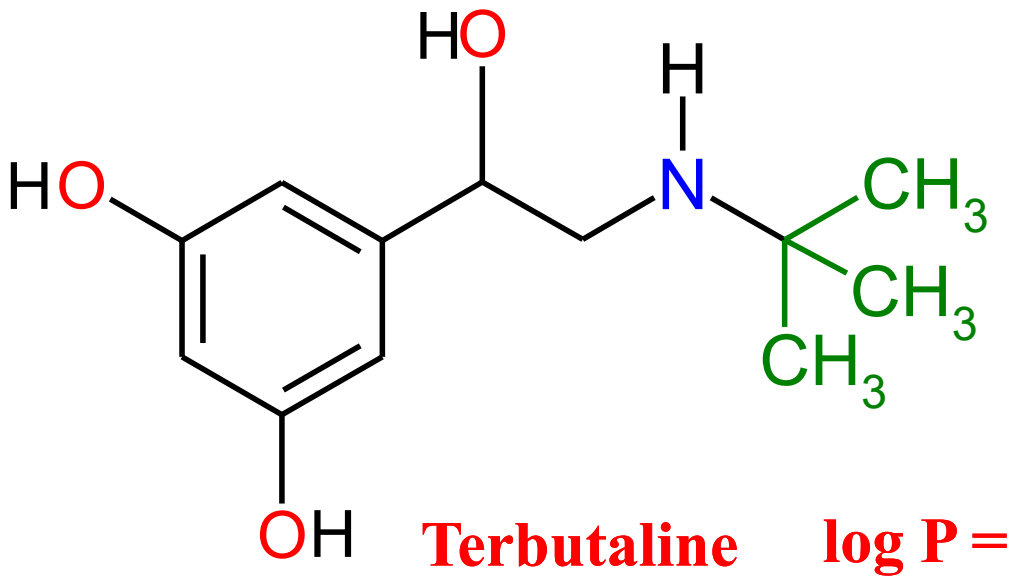




even during the rotation of the dihedral angle the resorcin always allows to position a phenolic hydroxyl at a position 3, *m*

9. Design of β-adrenergic agonists

Selective β2-agonists:



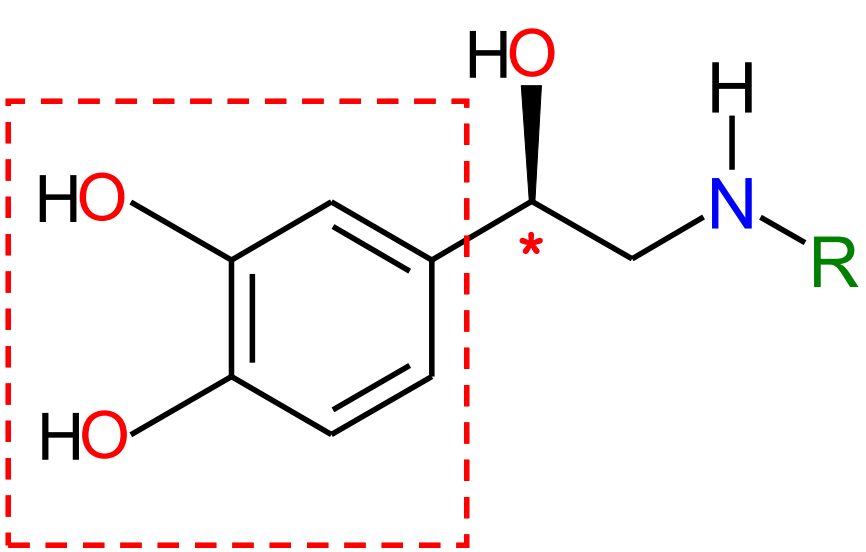
Terbutaline **log P = 0.9**

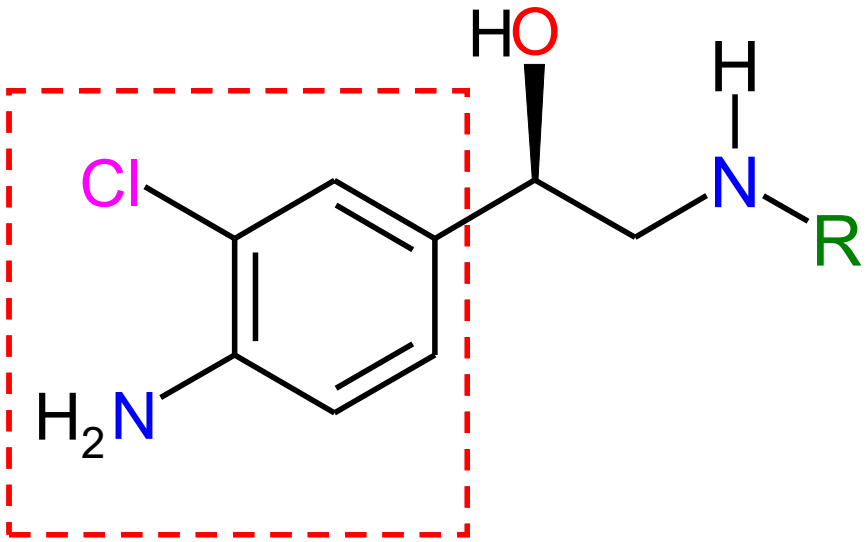
(*RS*)-5-[2-(*tert*-butylamino)-1-hydroxyethyl]benzene-1,3-diol

Terbutaline is a relatively selective beta2-adrenergic ***bronchodilator*** that has little or no effect on alpha-adrenergic receptors. Terbutaline appears to have a greater stimulating effect on beta-receptors of the bronchial, vascular, and uterine smooth muscles (beta2 receptors) than on the beta-receptors of the heart (beta1 receptors). This drug relaxes smooth muscle and inhibits uterine contractions, but may also cause some cardiostimulatory effects and CNS stimulation.

9. Design of β-adrenergic agonists

A unexpected example of catechol bioisosterism:

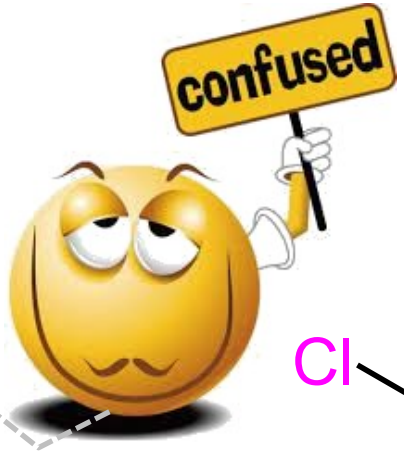


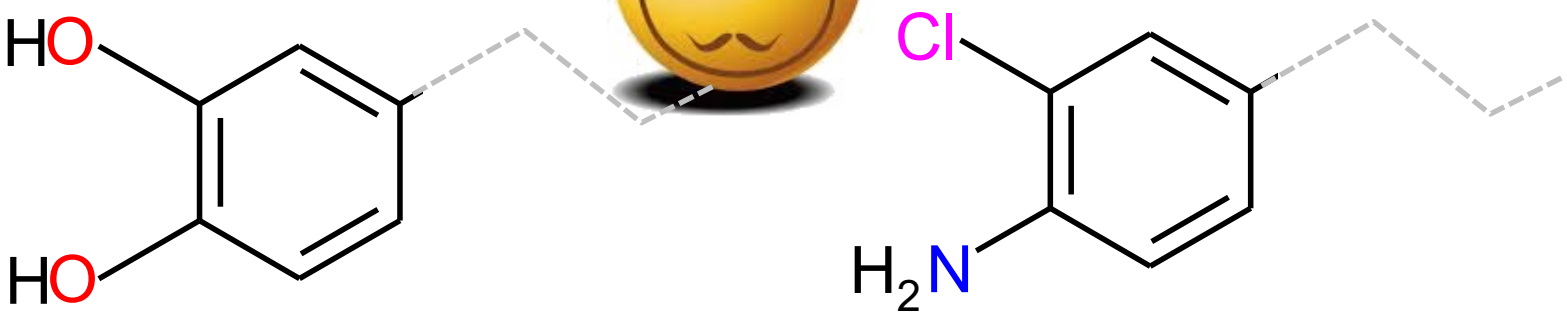


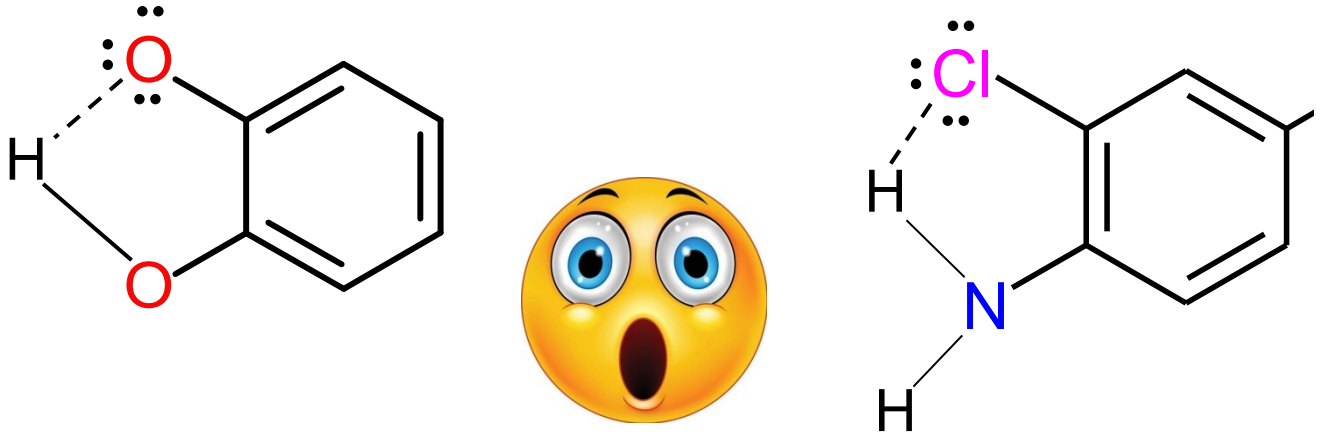
Two interesting advantages:

1. **maintaining the interaction scheme**
2. **abolishing COMT metabolism**

Could you explain this bioisosterim?



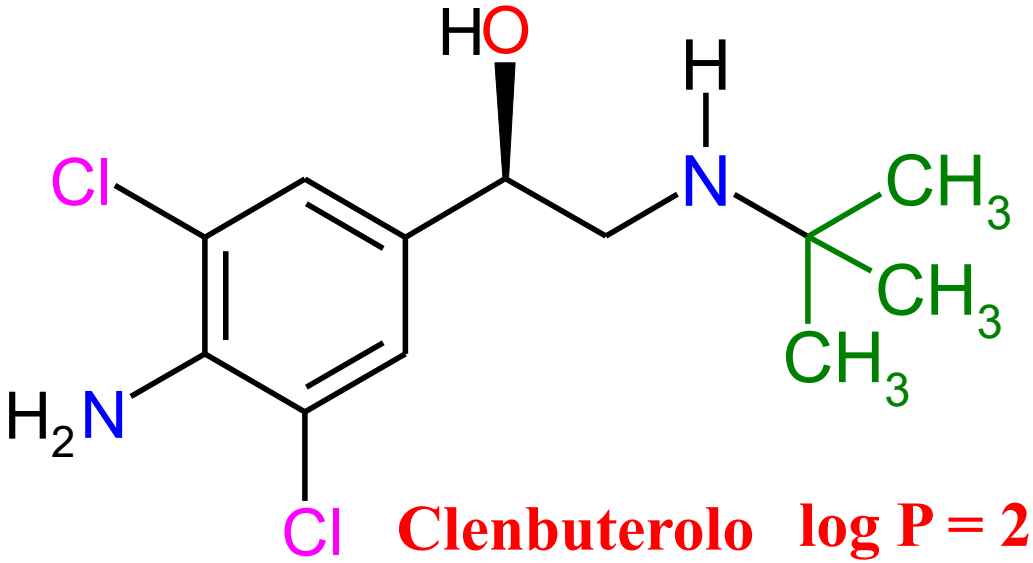




Intramolecular H-bonding

9. Design of β-adrenergic agonists

Selective β2-agonists:



Clenbuterolo **log P = 2.3**

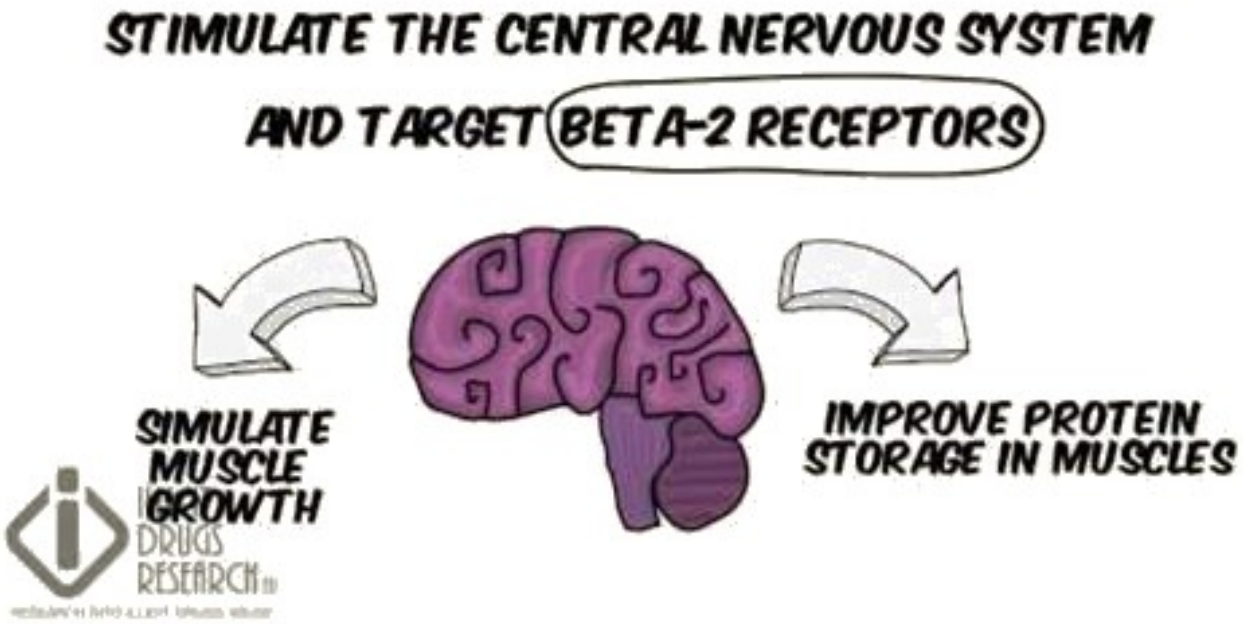
(*RS*)-1-(4-Amino-3,5-dichlorophenyl)-2-(*tert*-butylamino)ethanol

Clenbuterol is a substituted phenylaminoethanol that has beta-2 adrenomimetic properties at very low doses. It is used as a ***bronchodilator in asthma***. Considering its logP, Clenbuterol is a central nervous system (CNS) stimulant.

9. Design of β-adrenergic agonists

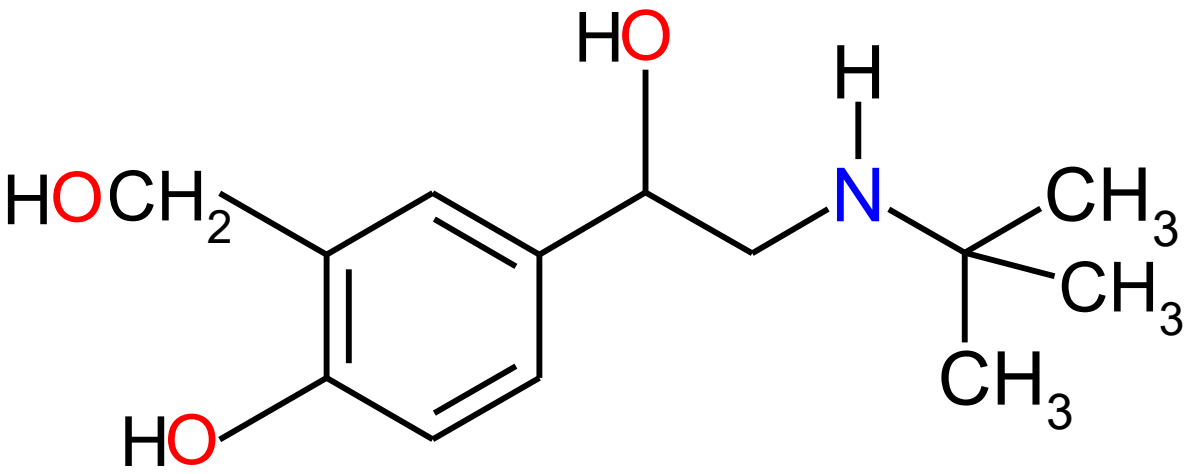
Notable cases of use as performance-enhancing drug

Lean mass builders, which drive or amplify the growth of muscle and lean body mass, are also used to reduce body fat.



9. Design of β-adrenergic agonists

Selective β2-agonists:

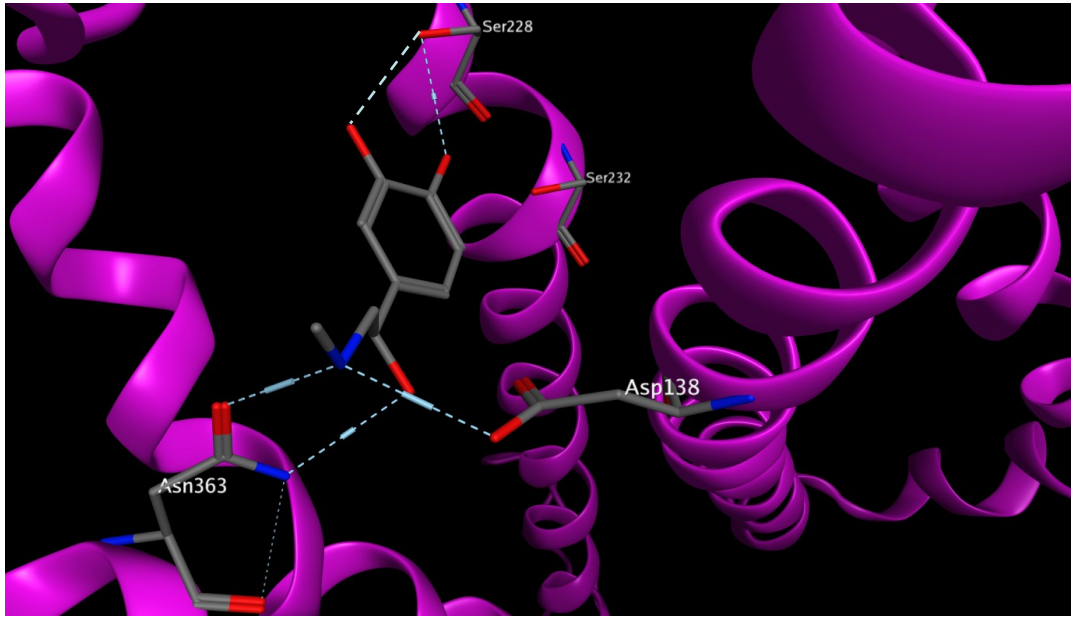


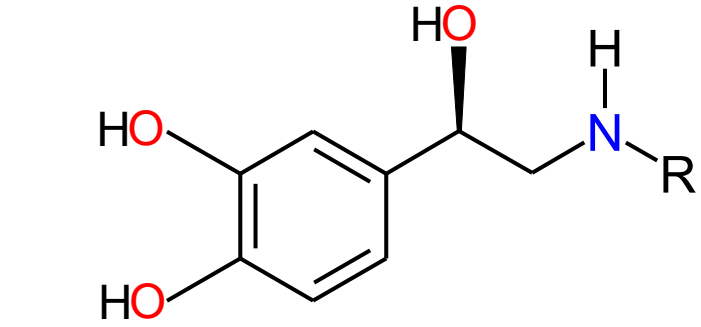
Salbutamol **log P = 1.4**

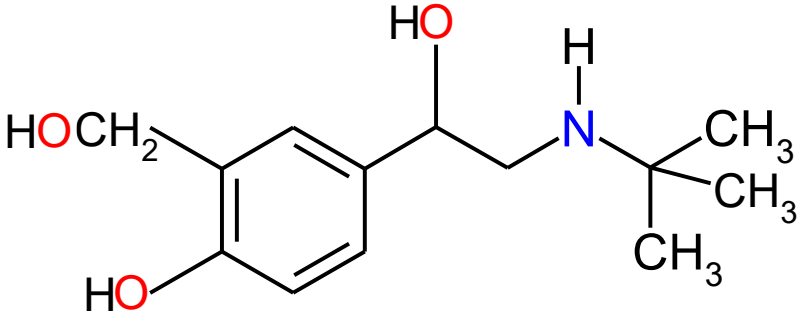
(*RS*)-4-[2-(*tert*-butylamino)-1-hydroxyethyl]-
-2-(hydroxymethyl)phenol

Salbutamol is a short-acting (4 hours) β2-adrenergic receptor "**partial**" agonist used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease. It was launched in 1969 as Ventolin® and has become the world's most widely prescribed bronchodilator drug.

Could you comment why *partial agonist*?

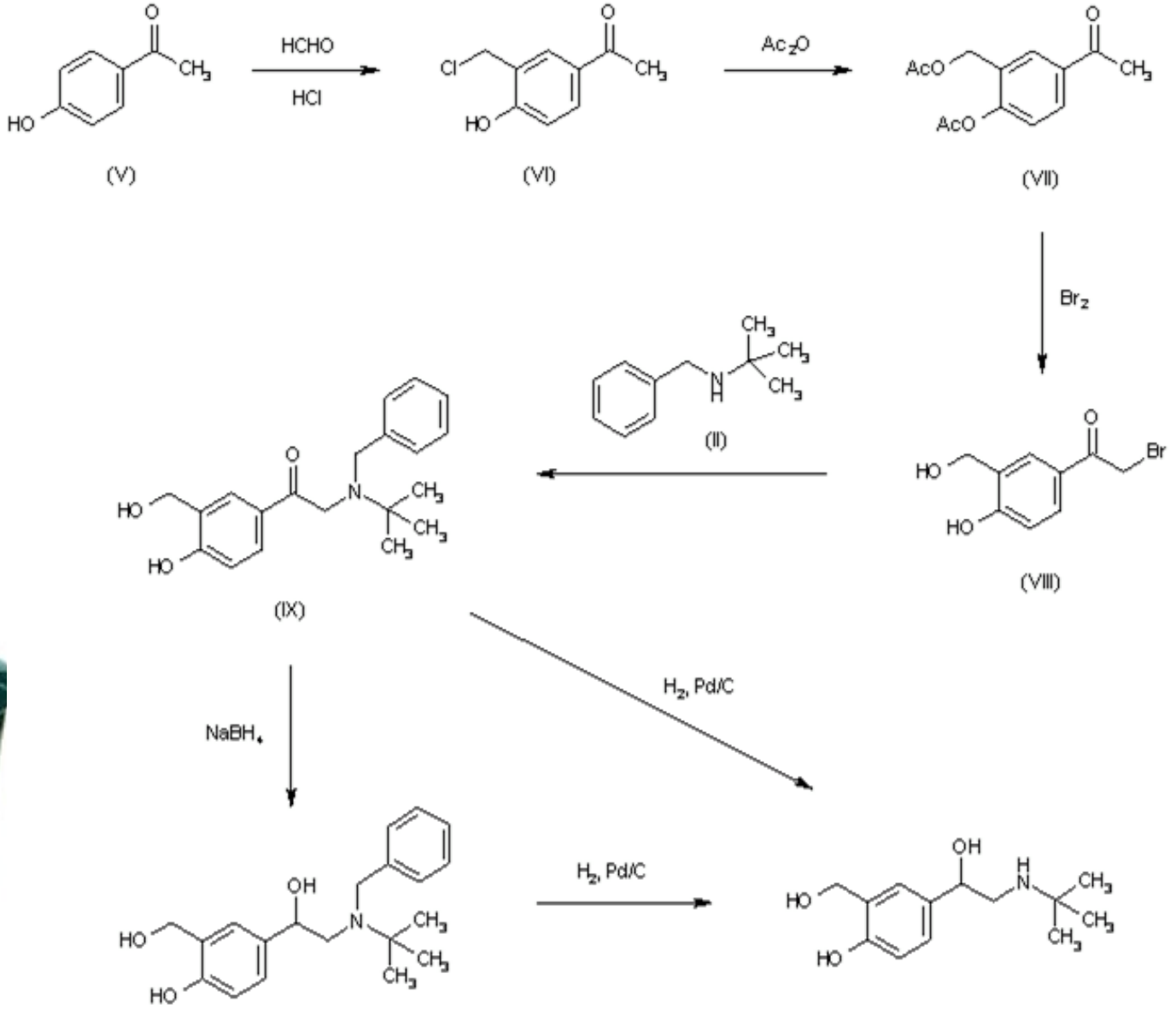






9. Design of β-adrenergic agonists

Synthesis Path

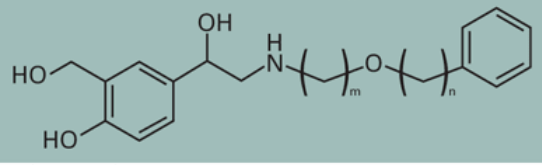


9. Design of β-adrenergic agonists

With the aim of discovering a longer acting β2-agonist, the researchers at GlaxoSmithKline used salbutamol as the starting point in place of adrenaline. From a medicinal chemistry viewpoint, the strategy was to incorporate some lipophilicity into the N-substituent of Salbutamol.

It was found that the best potency was obtained when m equals 5 or 6 carbon atoms and n equals 2 - 4 carbon atoms. Salmeterol (II 10), the molecule that would ultimately be selected from this series, has an 11-atom chain (m=6 and n=4). It was also observed that to maintain a long duration of action, it was as important to have potent compounds as to maintain the calculated logP value within the 3.3 - 4.5 range. LogP values <3.3 invariably lead to short acting compounds in vitro.

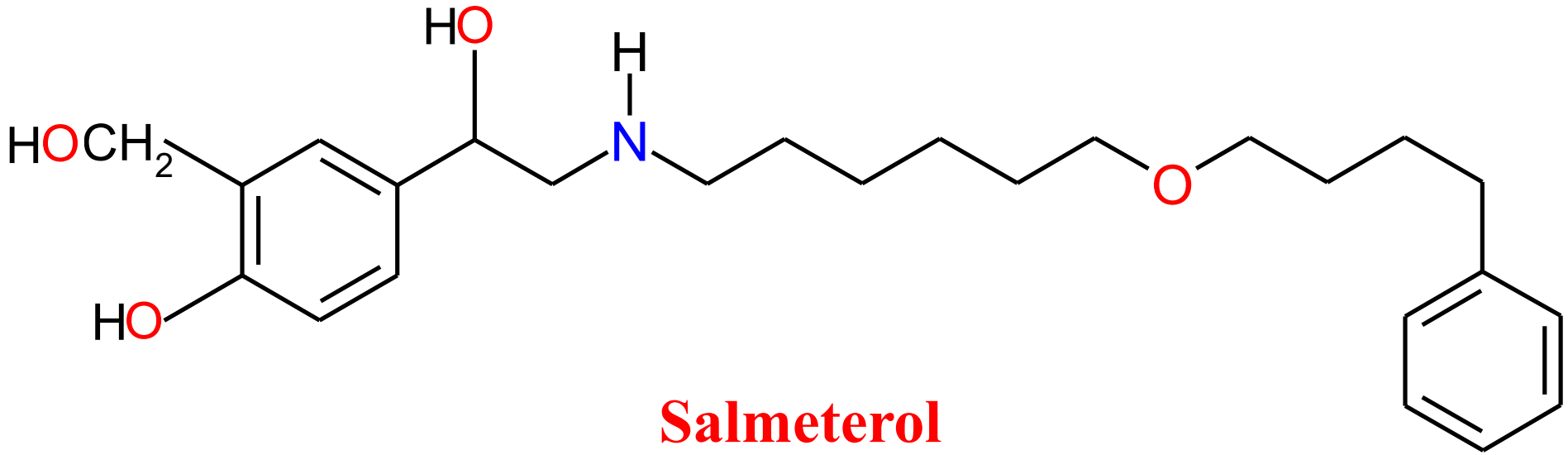
Table II: Modification of the length of the N-alkyl chain



Entry	m	n	GUINEA-PIG TRACHEA		LOG P
			β_2 POTENCY * EPC (ISO=1)	DURATION** Rt_{50} (min)	
II 1	4	3	100	6.8	2.30
II 2	4	4	17.1	20.5	2.83
II 3	4	6	6.5	>60	3.88
II 4	5	2	12	5.0	2.30
II 5	5	3	3.6	>14	2.83
II 6	5	4	0.5	>30	3.35
II 7	6	1	10.5	6.5	2.30
II 8	6	2	11	10.7	2.83
II 9	6	3	2.4	>35	3.35
II 10	6	4	0.90	>30	3.88
II 11	6	5	5.6	>30	4.41
II 12	7	3	8.8	>30	3.88

* potency values shown are equipotent concentrations (EPC) (isoprenaline = 1)
** duration values (Rt_{50}) are for a 50% recovery from a response of 50% of the maximum produced by isoprenaline

9. Design of β-adrenergic agonists



Salmeterol

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

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). Salmeterol, marketed and manufactured by GlaxoSmithKline, in the 1980s.

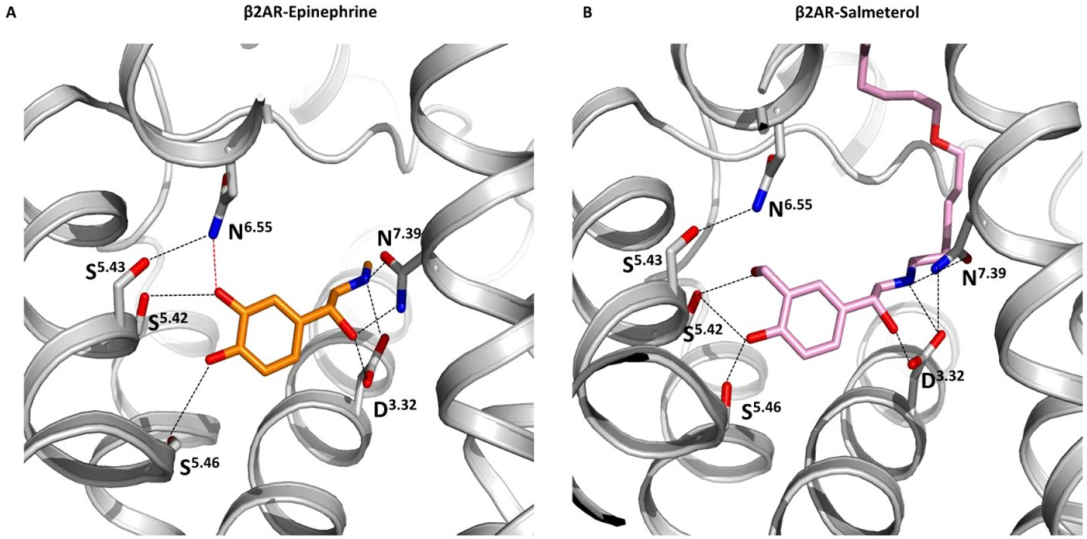
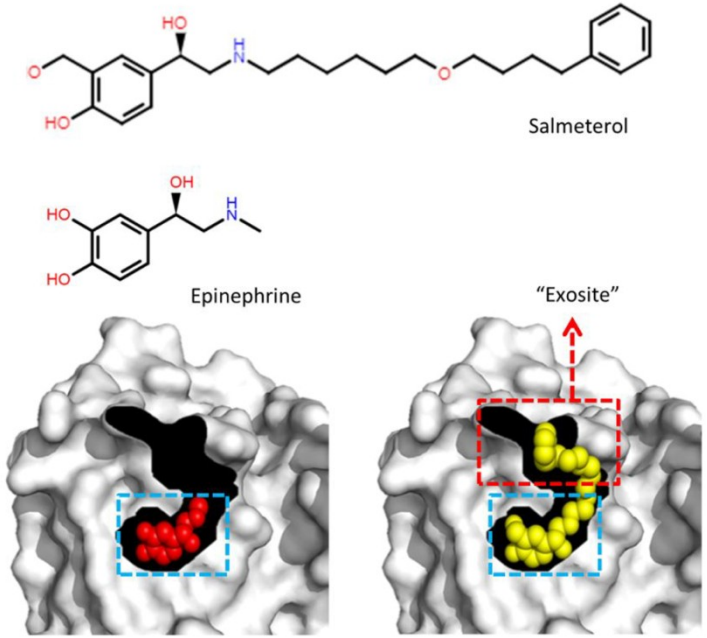


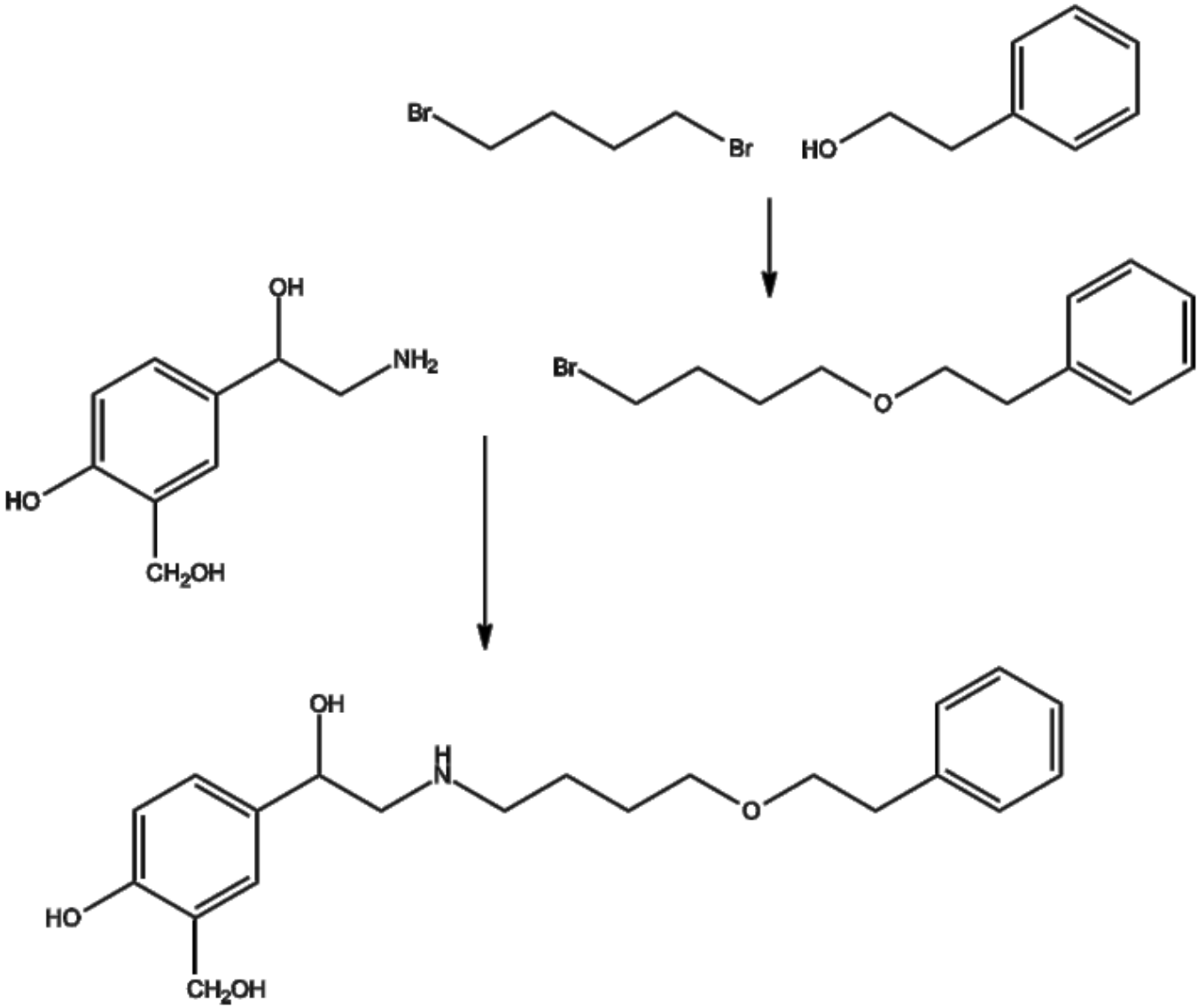
Figure 2. Key structural differences between the binding of epinephrine and salmeterol. (A) Interaction of epinephrine and (B) salmeterol in the orthosteric binding pocket of the β2AR derived from their respective crystal structures. A key difference in the salmeterol-bound structure is the lack of a hydrogen bond between the ligand and Asn293$^{6.55}$ that leads to a disrupted polar network involving Ser204$^{5.43}$, Asn293$^{6.55}$, and the ligand.



credits: https://pubs.acs.org/doi/pdf/10.1021/acs.biochem.8b01237

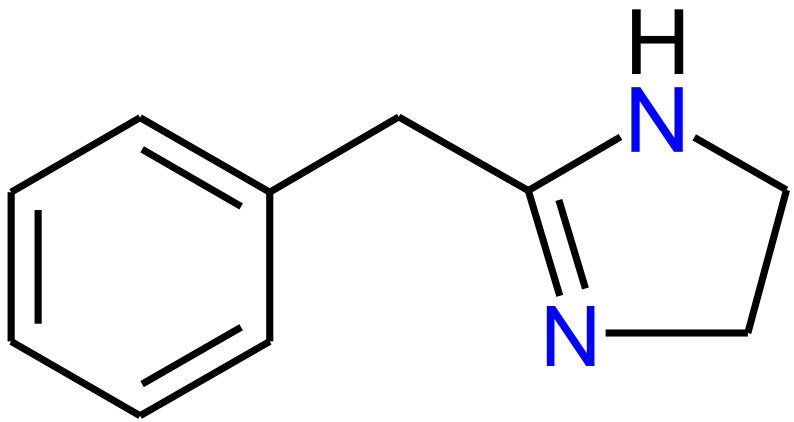
9. Design of β-adrenergic agonists

Synthesis Path



7. Design of α-adrenergic agonists

Direct Acting Drugs

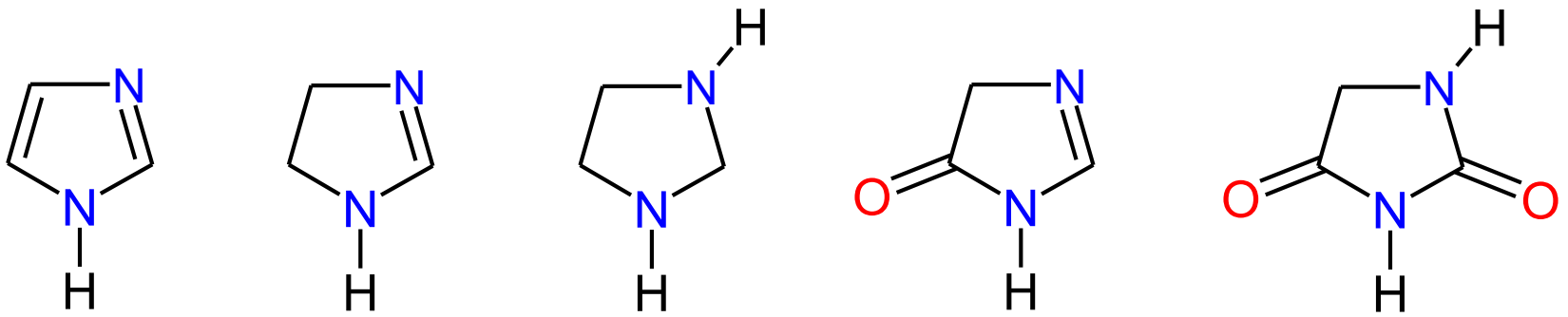


derivatives

7. Design of α-adrenergic agonists

Looks this strange story…

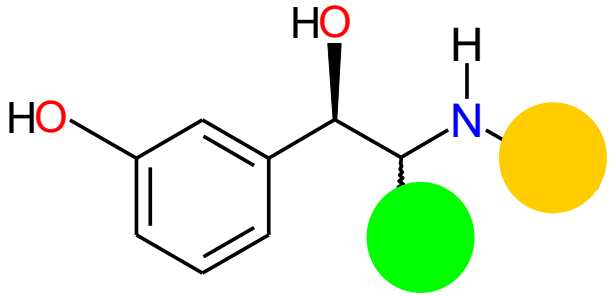
but before starting:



Imidazole Imidazoline Imidazolidine Imidazolinone Imidazolidinedione

7. Design of α-adrenergic agonists

Remember…

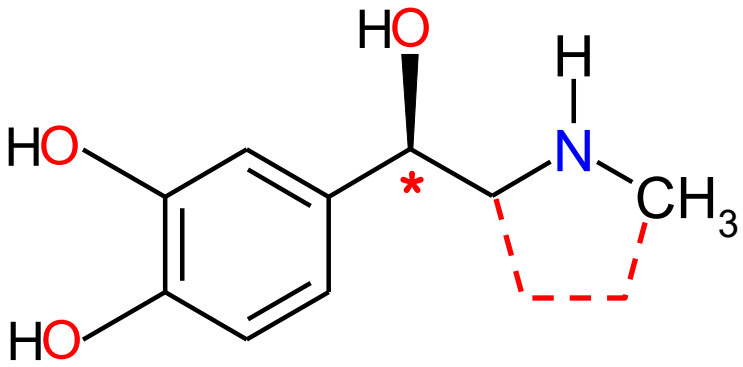


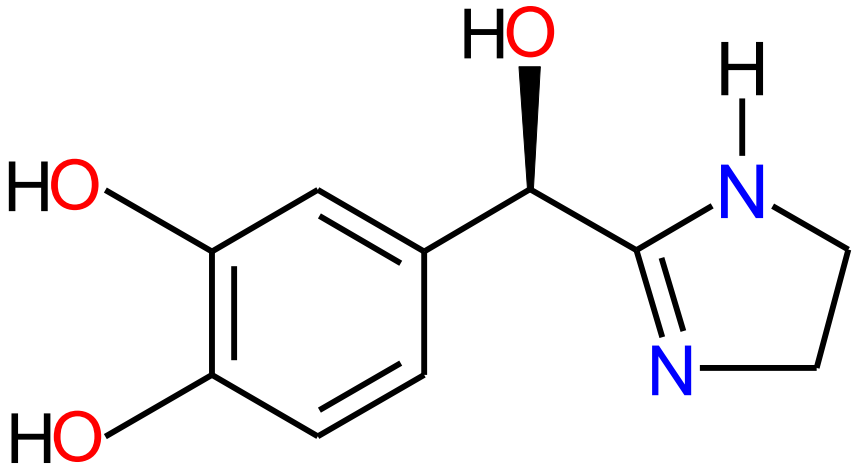
3-Hydroxyephedrine

logP = 0.3

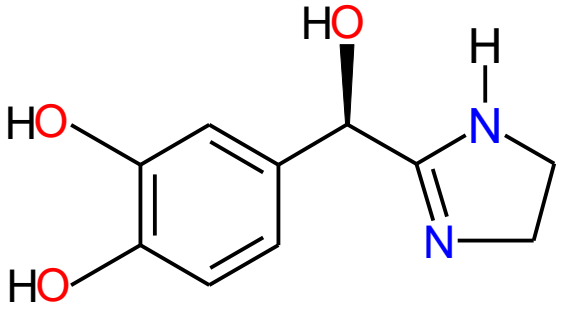
pKa = 8.9

7. Design of α-adrenergic agonists

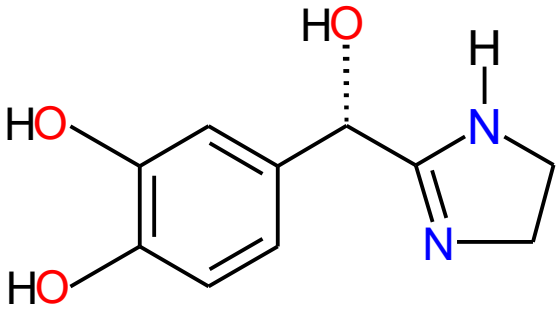




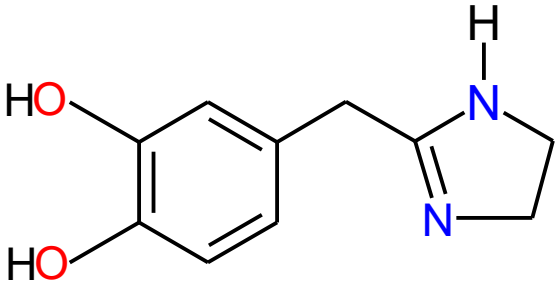
Imidazoline derivatives



R



S

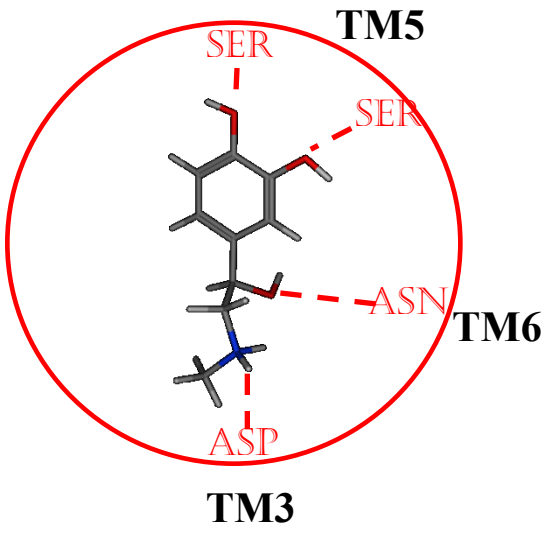


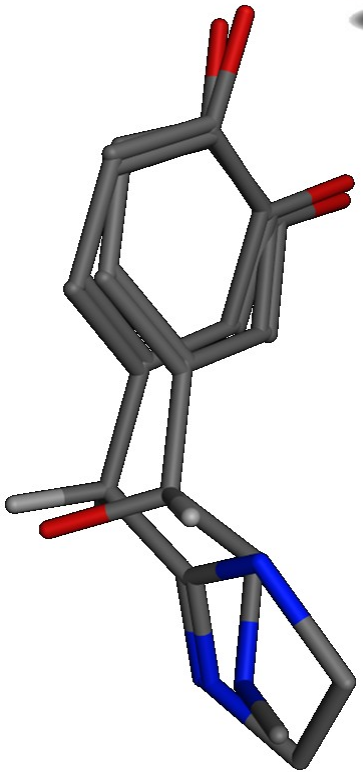
deoxy

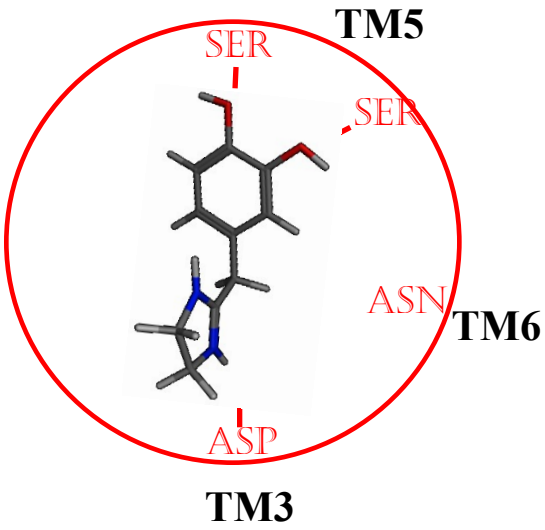
Please… guess the activity profile order!

7. Design of α-adrenergic agonists

deoxy > R > S

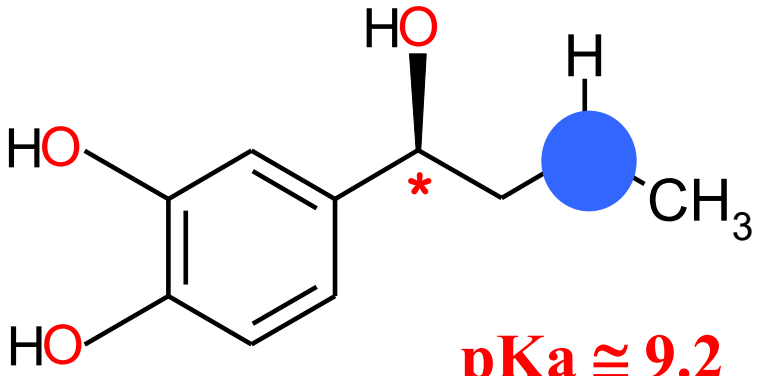




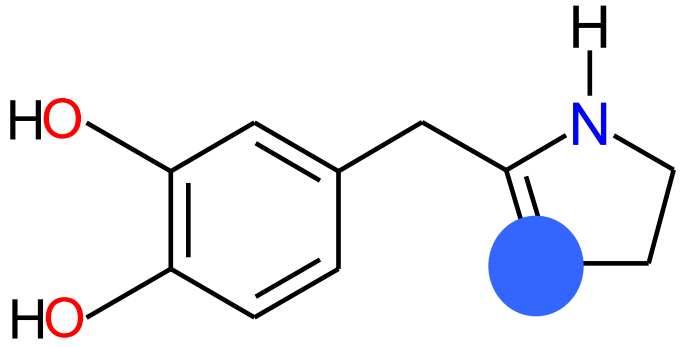


This is very strange!

7. Design of α-adrenergic agonists



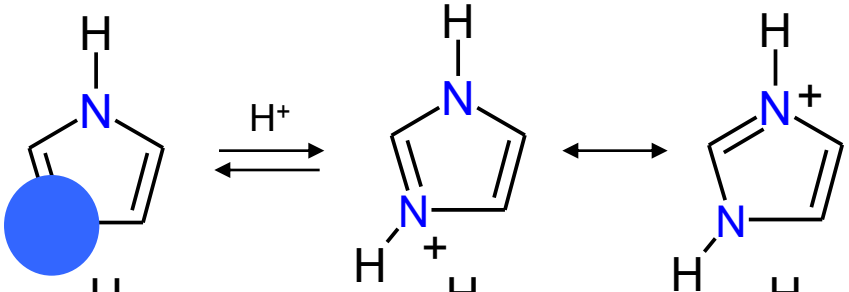
pKa ≅ 9.2



pKa ≅ 9.6

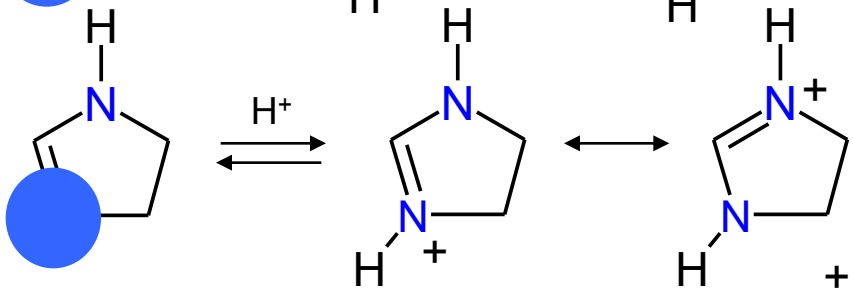
Remember:

Imidazole



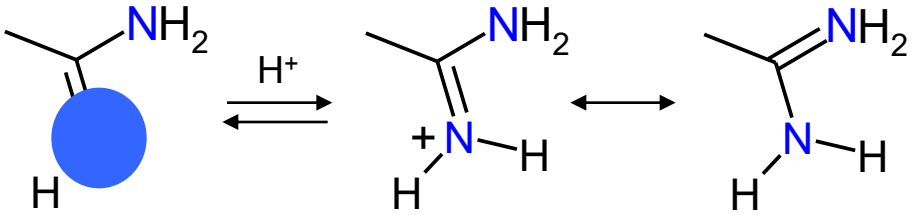
pKa ≅ 7.0

Imidazoline



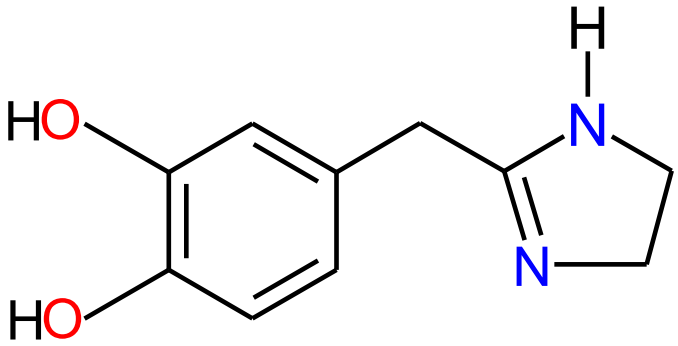
pKa ≅ 10.0

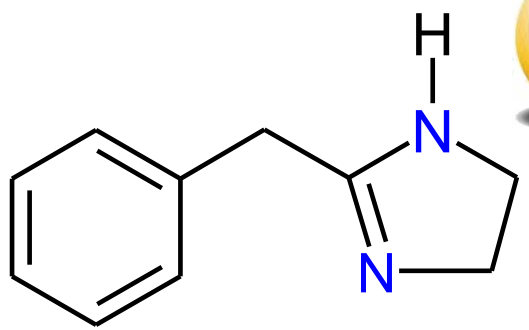
Amidine



pKa ≅ 12.0

7. Design of α-adrenergic agonists



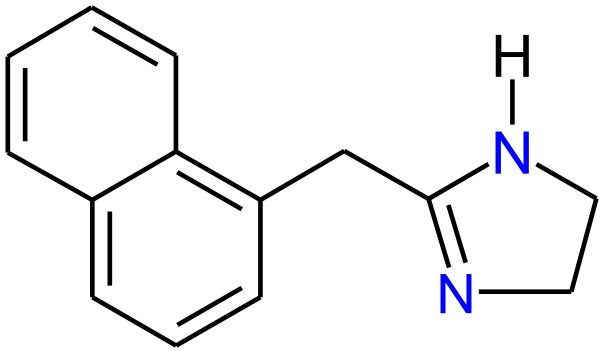


Tolazolina logP = 2.6

2-benzyl-2-imidazoline pKa ≅ 10.3

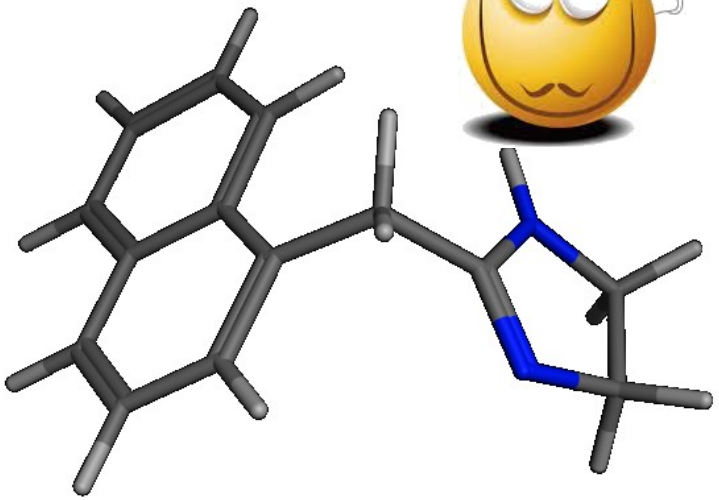
Tolazoline is a vasodilator that ***apparently*** has direct actions on blood vessels (alpha1 antagonist????) and also increases cardiac output (beta1 agonist????). Tolazoline can interact to some degree with histamine, adrenergic, and cholinergic receptors, but the mechanisms of its therapeutic effects are not clear. It is used in treatment of persistent pulmonary hypertension of the newborn.

7. Design of α-adrenergic agonists



Naphazoline

2-(1-naphthylmethyl)-2-imidazoline

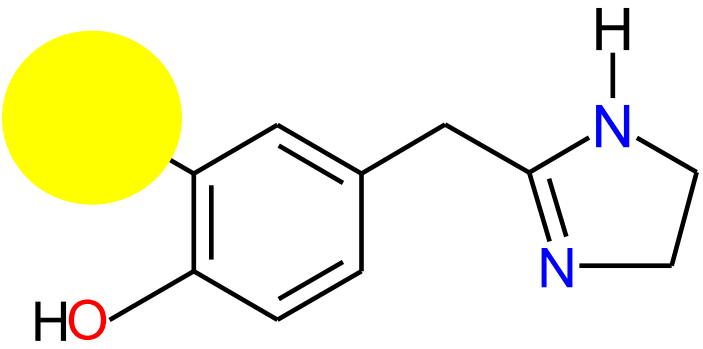


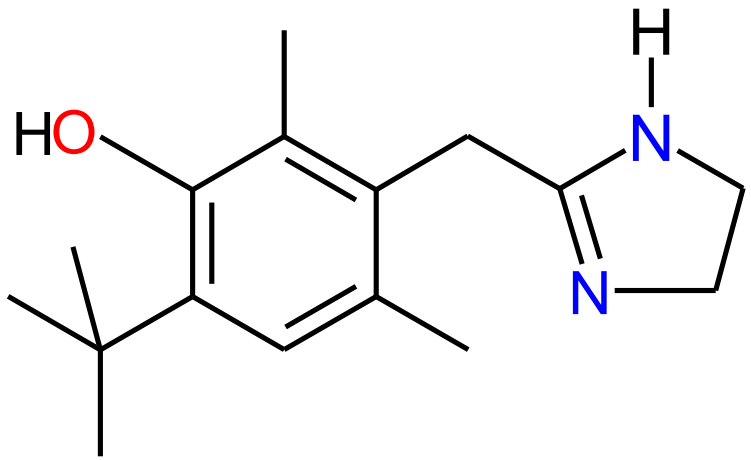
logP = 3.4

pKa ≅ 10.1

Naphazoline is, ***apparently***, a direct acting sympathomimetic drug, which acts on alpha-adrenergic receptors in the arterioles of the nasal mucosa (alpha1 agonist???). This activates the adrenal system to yield systemic vasoconstriction. In producing vasoconstriction, the result is a decrease in blood flow in the nasal passages and consequently decreased nasal congestion. The vasoconstriction means that there is less pressure in the capillaries and less water can filter out, thus less discharge is made.

7. Design of α-adrenergic agonists





Oxymetazoline

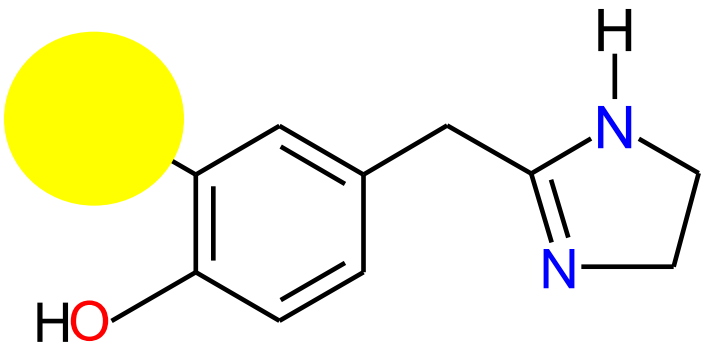
6-tert-butyl-3-(4,5-dihydro-1H-imidazol-2-ylmethyl)
-2,4-dimethylphenol

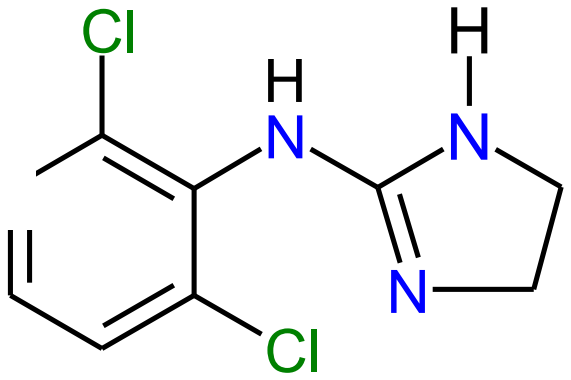
logP = 3.4

Oxymetazoline is indicated for treatment of nasal congestion and redness associated with minor irritations of the eye. Oxymetazoline, ***apparently***, non-selectively agonizes α1 and α2 adrenergic receptors (???). Since vascular beds widely express α1 receptors, the action of oxymetazoline results in vasoconstriction.

7. Design of α-adrenergic agonists

From α1 to α2-agonists:





Clonidine

2-[(2,6-Dichlorophenyl)imino]imidazoline

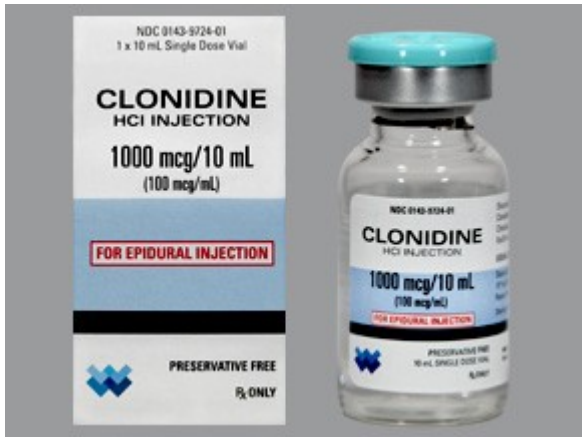
logP = 1.59

pKa = 8.0

Clonidine, an imidazoline-derivative hypotensive agent is a centrally-acting α2-adrenergic agonist, ***apparently***. It crosses the blood-brain barrier and acts in the hypothalamus to induce a decrease in blood pressure. It may also be administered as an epidural infusion as an adjunct treatment in the management of severe cancer pain that is not relieved by opiate analgesics alone.

7. Design of α-adrenergic agonists

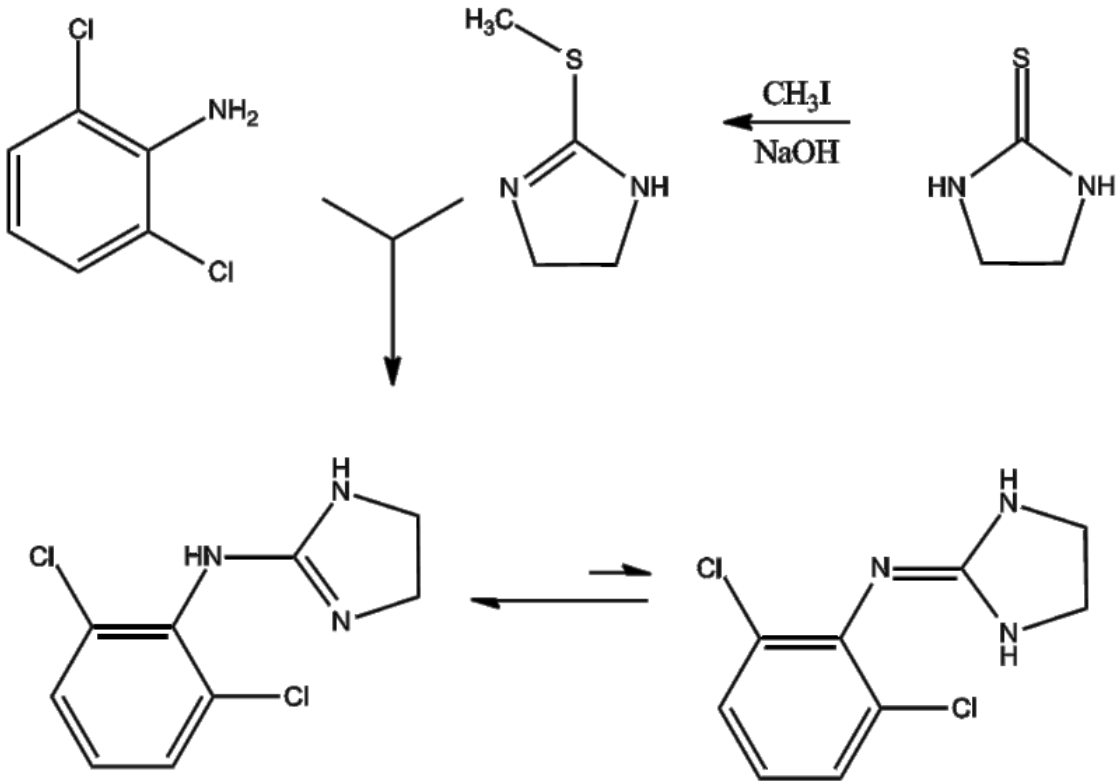
Clonidine most popular formulations:



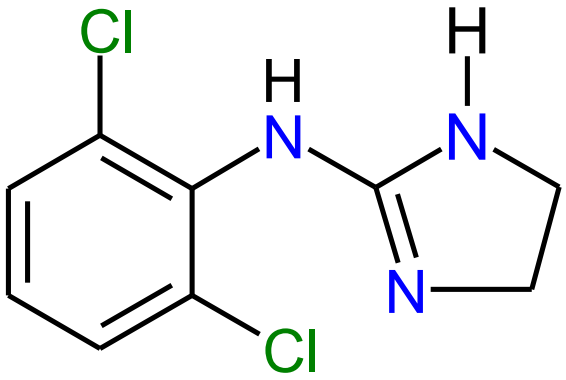
transdermal pach

7. Design of α-adrenergic agonists

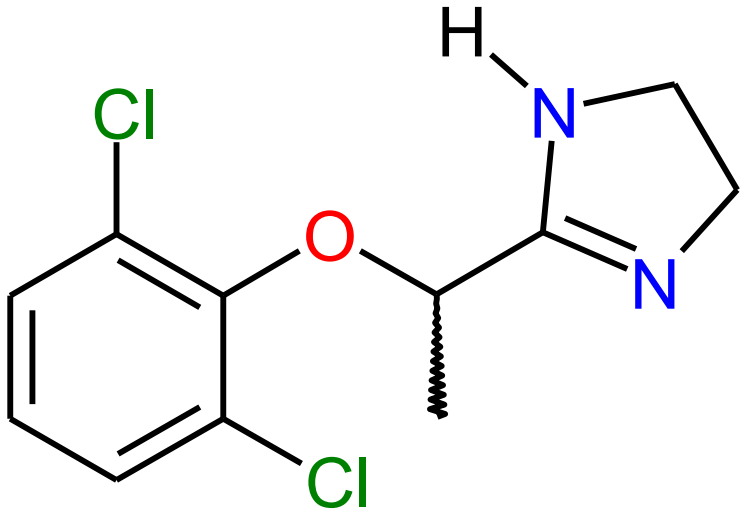
Synthesis Path



7. Design of α-adrenergic agonists



Clonidine, logP = 3.4



Lofexidine, logP = 3.6

(*RS*)-2-[1-(2,6-dichlorophenoxy)ethyl]-
-4,5-dihydro-1*H*-imidazole

Lofexidine is also commonly used in conjunction with the opioid receptor antagonist naltrexone in rapid detoxification cases. When these two drugs are paired, naltrexone is administered to induce an opioid-receptor blockade which attenuates the withdrawal symptoms and accelerate the detoxification process, while lofexidine is given to relieve physical withdrawal symptoms including chills, sweating, stomach cramps, muscle pain, and runny nose.

Imidazoline receptors?!

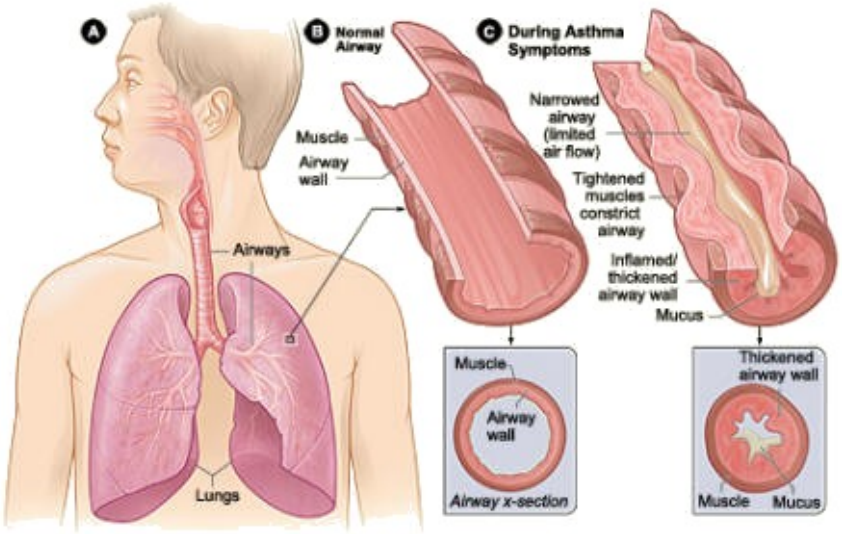
Imidazoline receptors historically referred to a family of nonadrenergic binding sites that recognize compounds with an imidazoline moiety, although this has proven to be an oversimplification. For example, none of the proposed endogenous ligands for imidazoline receptors contain an imidazoline moiety but they are diverse in their chemical structure.

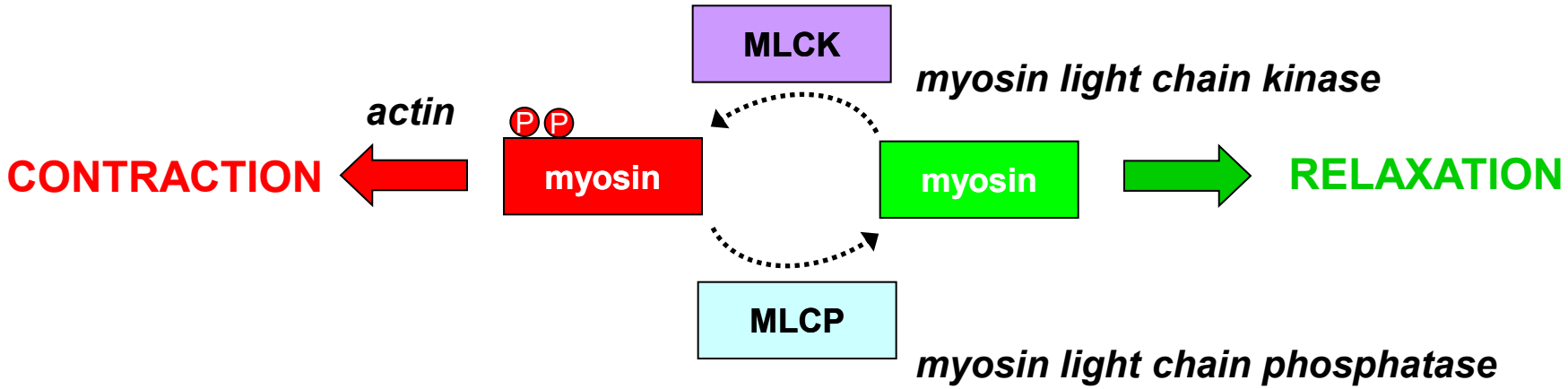
Three receptor subtypes (I_1, I_2, and I_3) have been proposed and the understanding of each has seen differing progress over the decades. I_1 receptors partially mediate the central hypotensive effects of clonidine-like drugs.


TITLE
"CHIMICA FARMACEUTICA E TOSSICOLOGICA II"
DIRECTOR
Stefano Moro
CAMERA
Chimica e Tecnologia Farmaceutiche
DATE
SCENE
TAKE

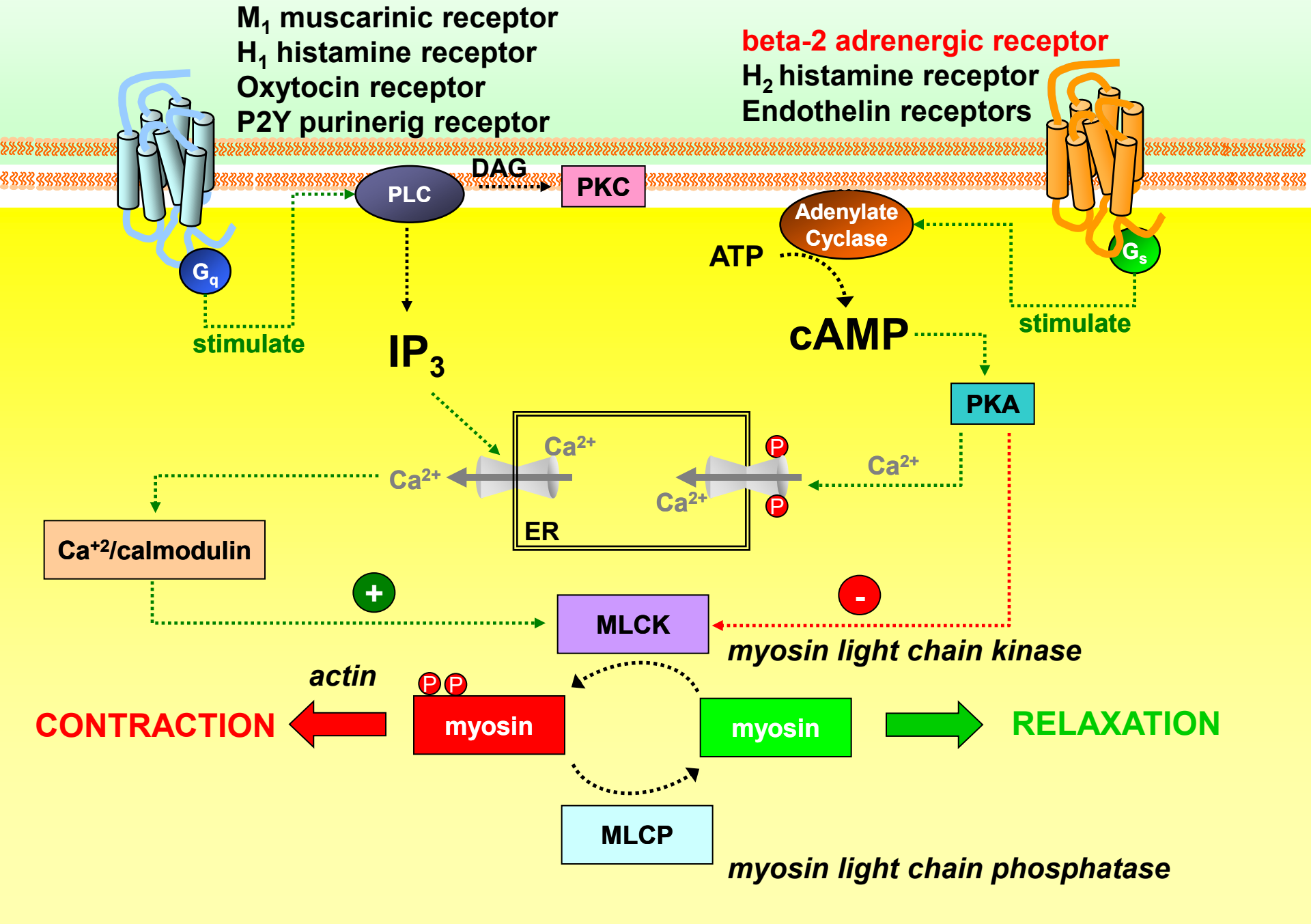
9. Mode of action of β2-adrenergic agonists

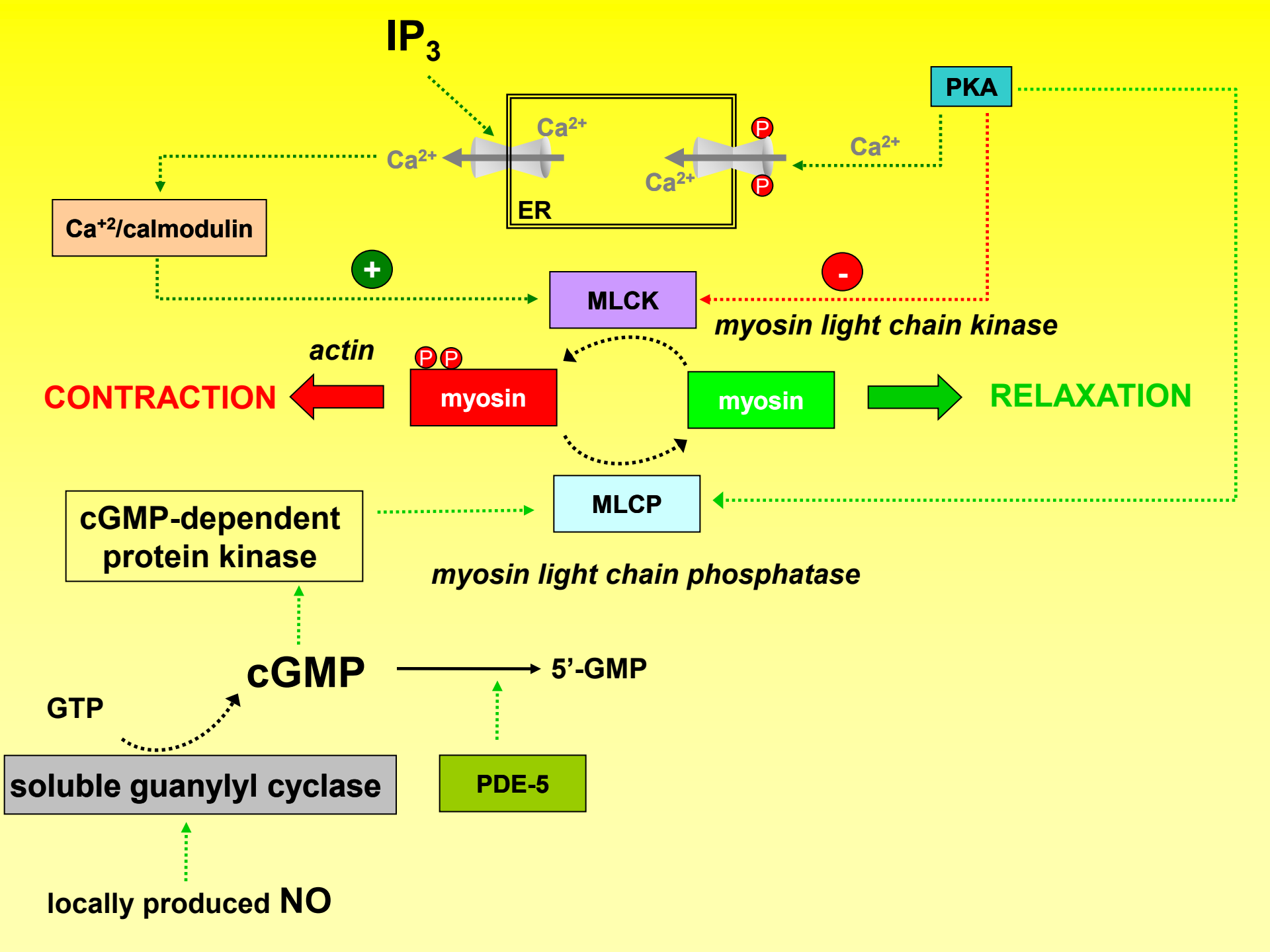
Do you remember myosin phosphorylation control?





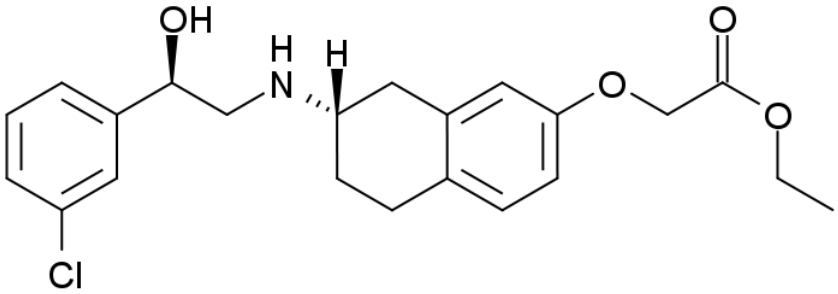
Smooth muscle signal trasduction:

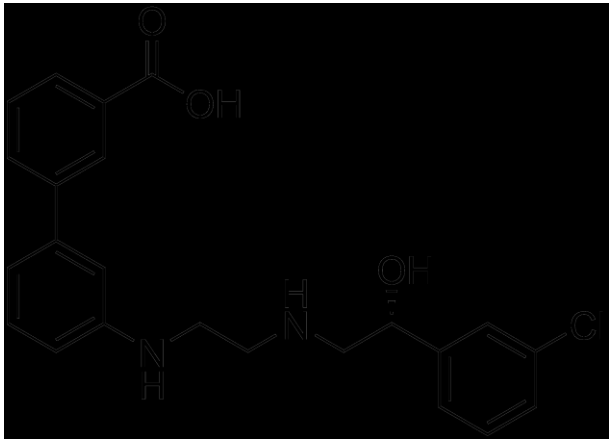



IP3
PKA
Ca2+
Ca2+
Ca2+
Ca2+
P
P
ER
Ca+2/calmodulin
+
-
MLCK
myosin light chain kinase
actin
P P
CONTRACTION
myosin
myosin
RELAXATION
MLCP
cGMP-dependent protein kinase
myosin light chain phosphatase
cGMP
5'-GMP
GTP
soluble guanylyl cyclase
PDE-5
locally produced NO

10. Design of β3-adrenergic agonists

A selective β3 agonist has potential weight loss effects through modulation of lipolysis.





Amibegron (SR-58,611A) is a drug developed by Sanofi-Aventis. On July 31, 2008, Sanofi-Aventis announced that it has decided to discontinue development of amibegron.

Solabegron (GW-427,353) is a drug which acts as a selective agonist for the β3 adrenergic receptor. It is being developed for the treatment of overactive bladder and irritable bowel syndrome. It has been shown to produce visceral analgesia by releasing somatostatin from adipocytes.