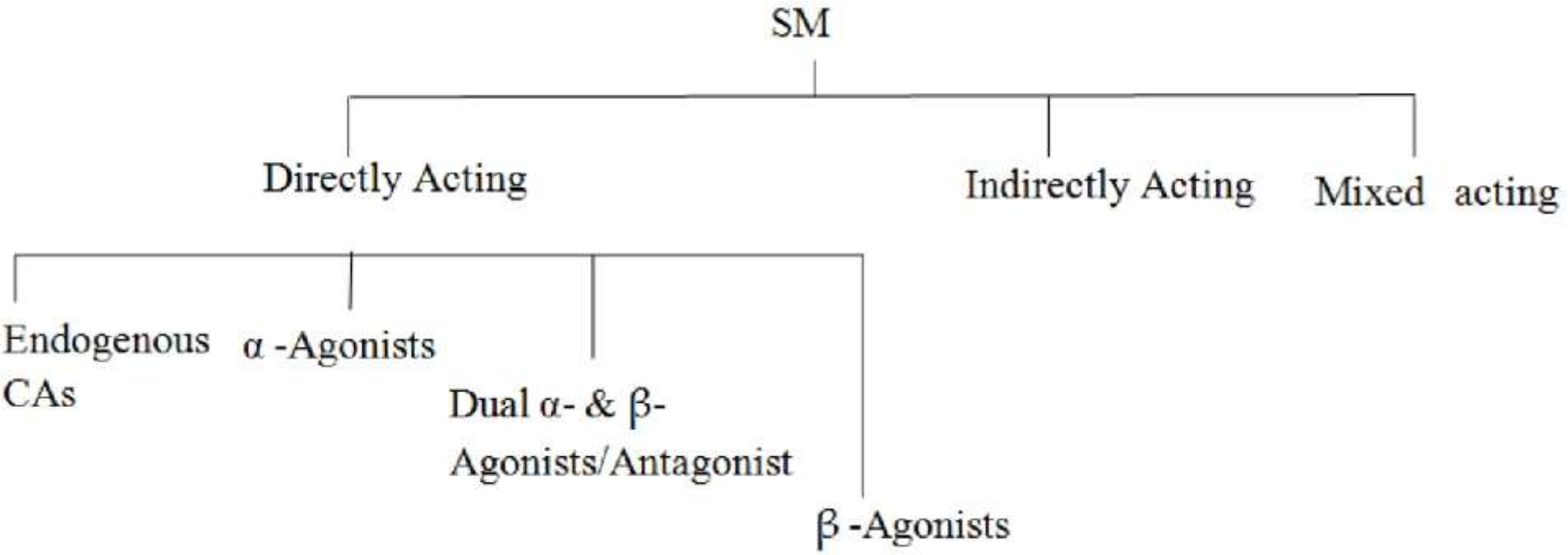
CLASSIFICATION



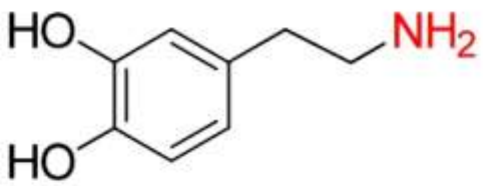
CLASSIFICATION

Endogenous CAs

(1) Dopamine

(2) Norepinephrine

(3) Epinephrine



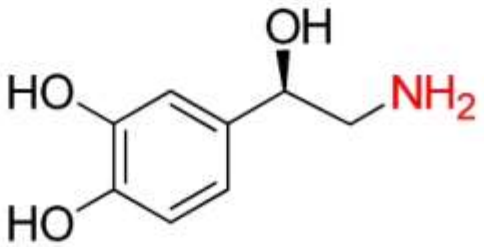
Dopamine

i.v. high dose

Vasoconstriction (α_1 action)

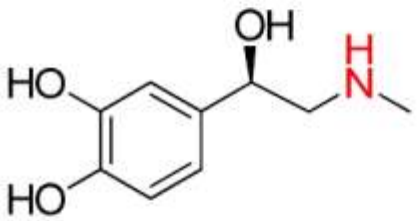
↑ HR (β_1-receptors)

Use: treatment of shock



Norepinephrine

Use: in hypotensive crises



Epinephrine

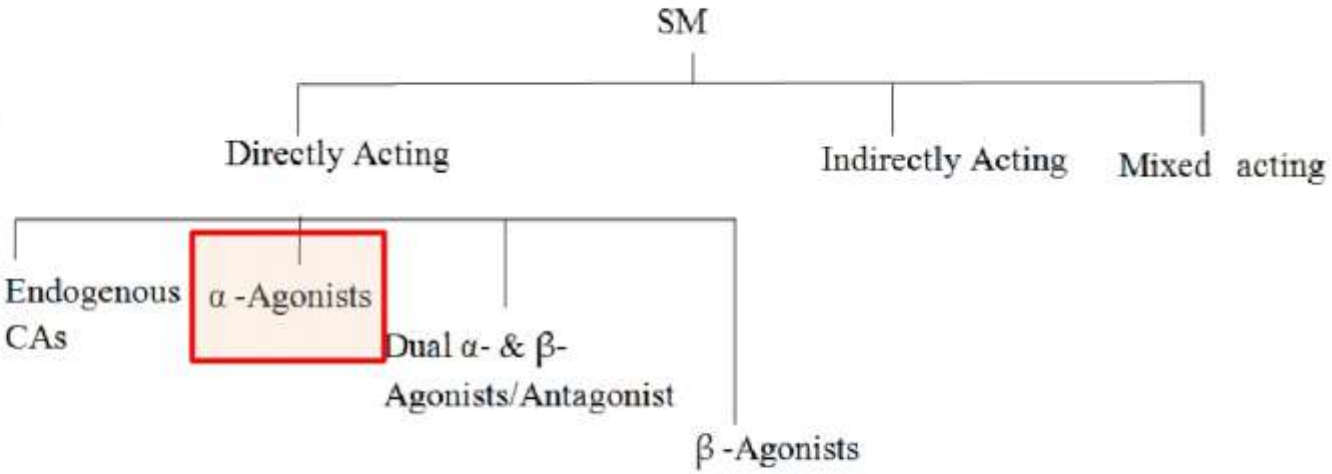
Use: treat hypotensive crises and nasal congestion (α action)

in asthma (β_2 action)

CLASSIFICATION

α -Agonists

- Phenylethanolamines
  1. Phenylephrine
  2. Methoxamine
  3. Midodrine
- 2-Arylimidazoline
  1. Naphazoline
  2. tetrahydrozoline
  3. xylometazoline
  4. oxymetazoline
- 2-Aminoimidazolines
  1. Clonidine
  2. Apraclonidine
  3. Brimonidine
- Open-Ring Imidazolidines
  1. Guanabenz
  2. Guanfacine
- Methyldopa

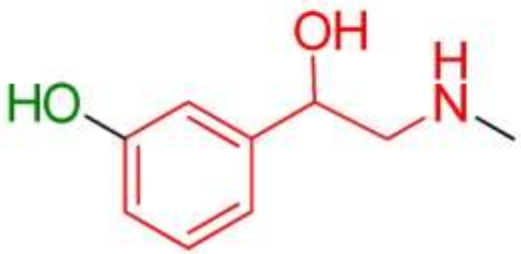


CLASSIFICATION

Phenylethanolamines

- All are α_1-agonists
- lacks the catechol moiety i.e. not metabolized by COMT
- Thus have long duration of action (DOA)

(1) Phenylephrine

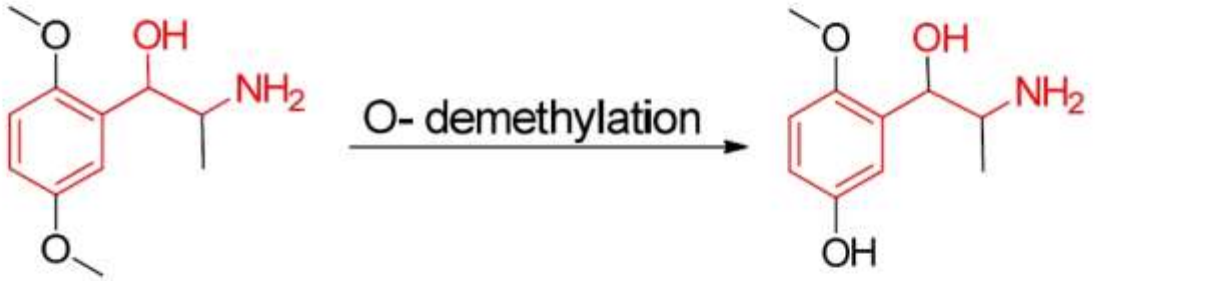


Use:

- severe hypotension, nasal decongestant
- used to dilate the pupil and in open-angle glaucoma

Phenylethanolamines

(2) Methoxamine

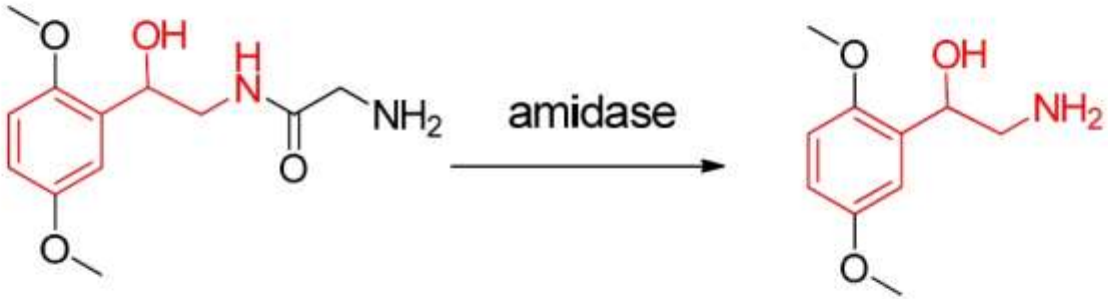


Methoxamine

m-phenolic active metabolite

- during surgery to maintain adequate arterial blood pressure

(3) Midodrine



Midodrine

desglymidodrine

- N-glycyl prodrug of desglymidodrine
- Vasoconstrictor → used for treatment hypotension

CLASSIFICATION

2-Arylimidazoline

- All are α_1-agonists
- Used for their vasoconstrictive effects as nasal decongestant and ophthalmic decongestant

(1) Naphazoline

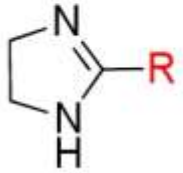
(2) Tetrahydrozoline

(3) Xylometazoline

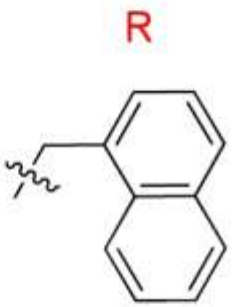
(4) Oxymetazoline

CLASSIFICATION

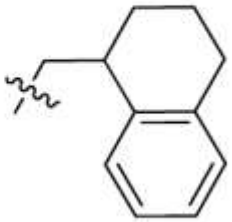
2-Arylimidazoline



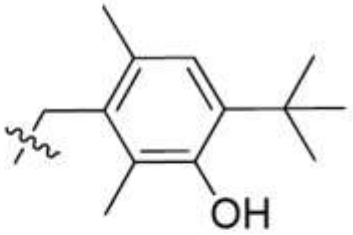
Naphazoline



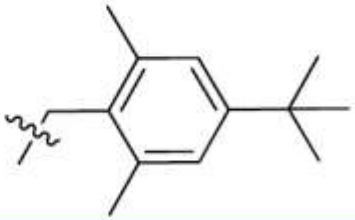
Tetrahydrozoline



Oxymetazoline



xylometazoline



Imidazoline moity
pKa 9-10
Limited access to the CNS

- one-carbon bridge between imidazoline ring and a phenyl ring, and thus has a <u>phenylethylamine structure</u>

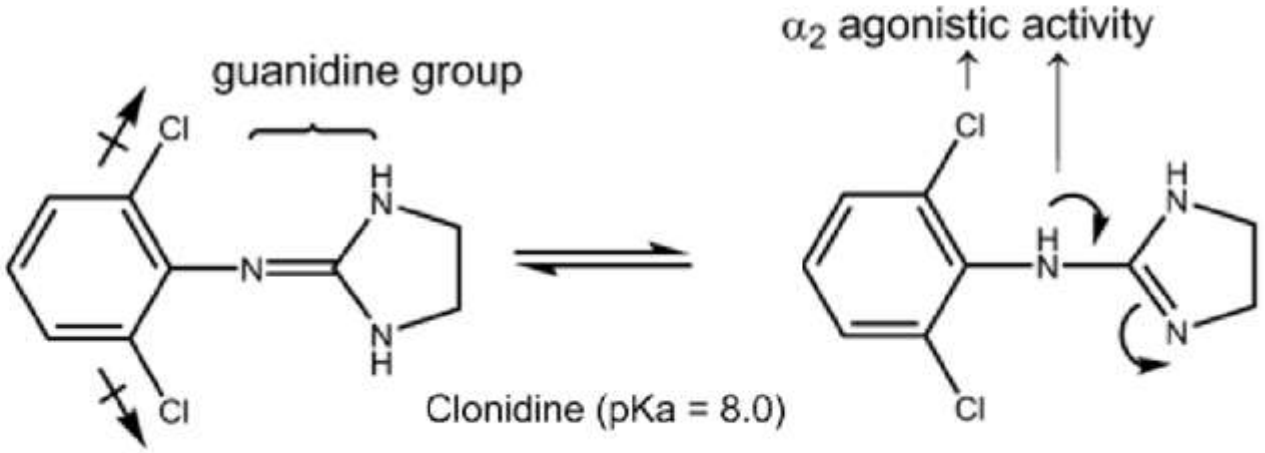
- lipophilic substituents on the phenyl ring may be important for the α_1-selectivity

CLASSIFICATION

2-Aminoimidazolines

- presence of O-chlorine groups and NH bridge.

(1) Clonidine



inductive and resonance effects of the dichlorophenyl ring decrease pKa of clonidine

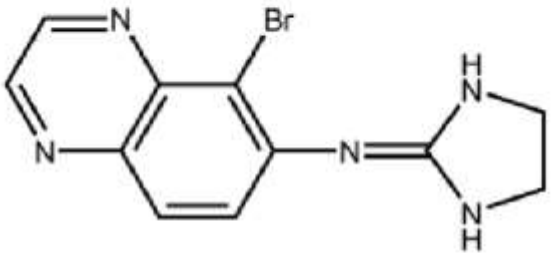
- [nasal decongestant to hypotensive]

- PNS → α_1-agonist → nasal decongestants + hypertension
- Low pKa → remains nonionized → crosses the BBB
- CNS → α_{2A}-adrenergic agonist → causing inhibition of sympathetic output → vasodilation → ↓ HR → hypotension

CLASSIFICATION

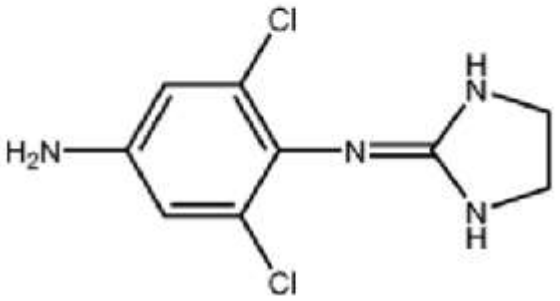
2-Aminoimidazolines

(2) Apraclonidine



- Does not cross the BBB.
- α_1 agonist and α_2 agonist effect in eye
- used specifically to control the intraocular pressure that can increase during laser surgery on the eye

(3) Brimonidine

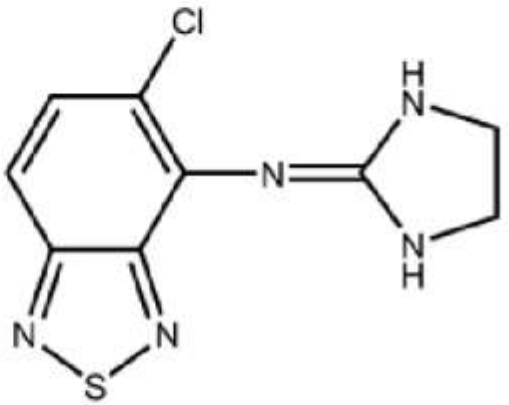


- cross the BBB → produce hypotension like clonidine + and sedation
- First-line agent for treating glaucoma
- reducing aqueous humor production and increasing outflow

CLASSIFICATION

2-Aminoimidazolines

(4) Tizanidine



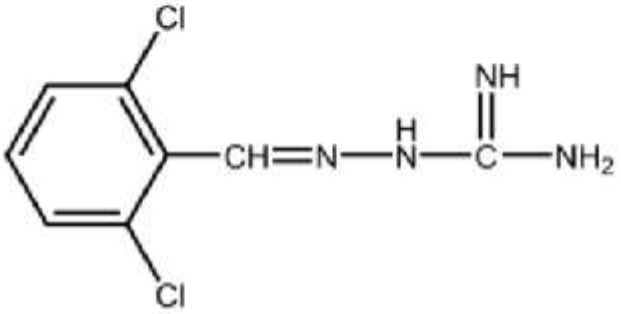
- α_2 -adrenergic agonist spinal interneurons → causing inhibition of sympathetic output → decreased muscle tone and frequency of muscle spasms → reduce spasticity [spasm] associated with cerebral or spinal cord injury.

CLASSIFICATION

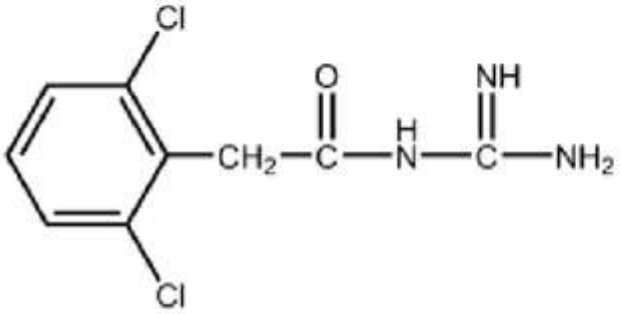
Open-Ring Imidazolidines

- All are α_2-agonists
- Used as antihypertensive drugs
- Mechanism is same as clonidine

(1) Guanabenz and (2) Guanfacine



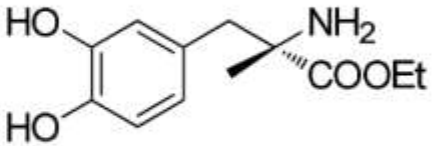
Guanabenz
pKa = 8.1 → mainly nonionized→
penetrate the CNS
oral bioavailability = 70-80%



Guanfacine
pKa = 7 → mainly nonionized→
penetrate the CNS
oral bioavailability = >80%

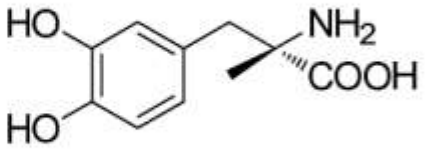
CLASSIFICATION

Methyldopa



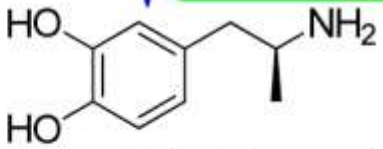
Methyldopate

Esterase



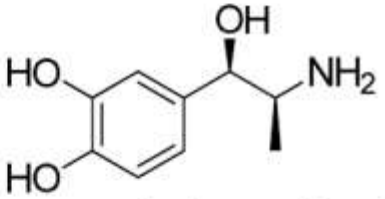
L- α -Methyldopa

Step_2 — DOPA decarboxylase



α -Methyldopamine

Step_3 — dopamine β-hydroxylase



(1*R*,2*S*)- α-methylnorepinephrine
selective α_2-agonist

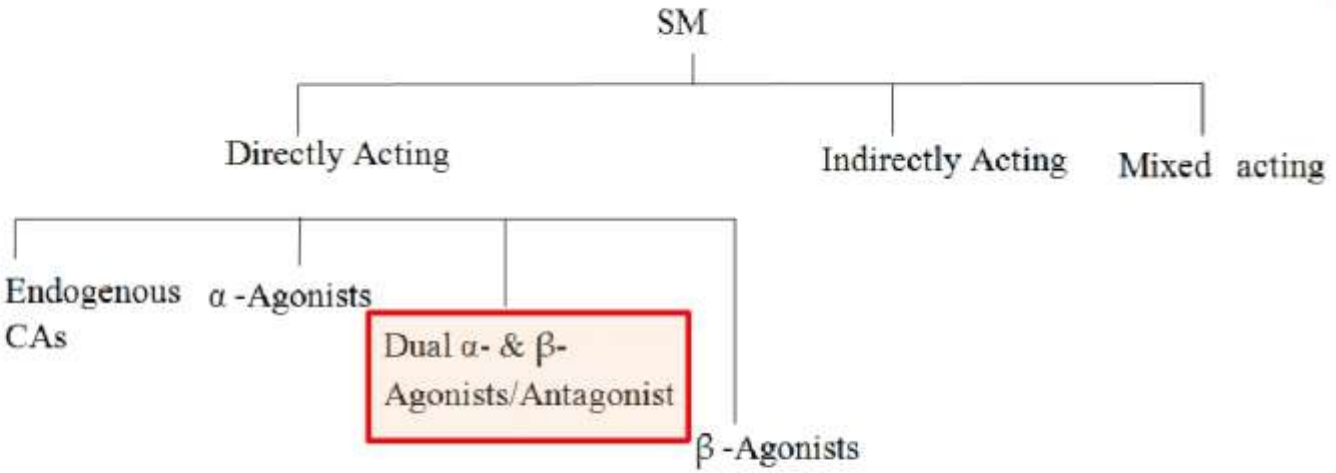
Chemistry : L-α-Methyldopa is a pro-drug
zwitterion

M/A:

- originally designed as DOPA DC inhibitor but it is metabolized by enzymes and gives active metabolite α-methylnorepinephrine which is α_2-agonist acting in the CNS → decrease sympathetic outflow → lower blood pressure.
- only oral dosage from are possible
- Its ester form Methyldopate in i.v. formulation

Use : antihypertensive

CLASSIFICATION

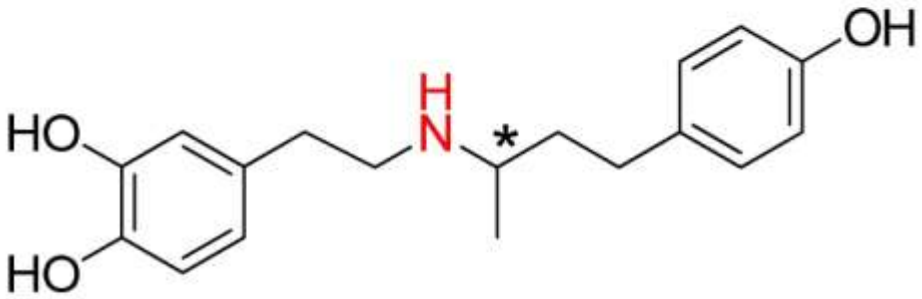


Dual α- & β-Agonists/Antagonists

1. Dobutamine

Dual α- & β-Agonists/Antagonists

(1) Dobutamine

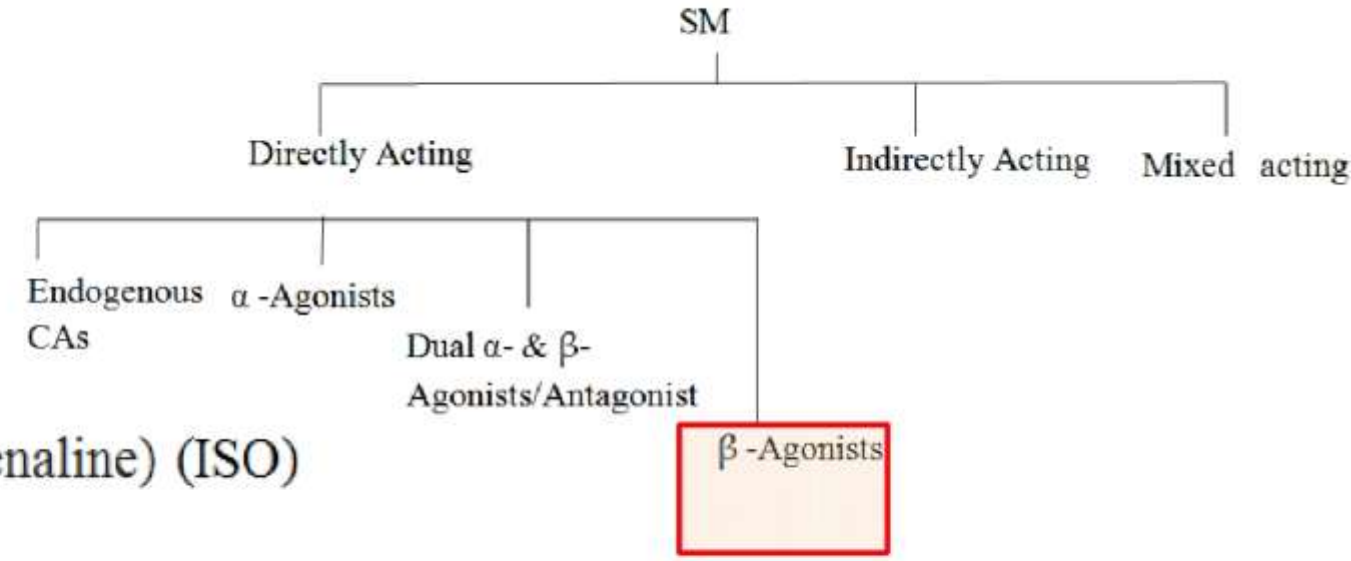


Chemistry:

- (-) isomer is a potent α_1-agonist
- (+) isomer is a potent α_1-antagonist
- isomers are β_1-agonist [(+) > (-)]
- thus, when the racemate is used clinically, the α-effects of the enantiomers cancel each other, leaving primarily the β_1-effects.

Use: used as a cardiac stimulant after surgery or congestive heart failure (CHF)

CLASSIFICATION



β-Agonists

1. Isoproterenol (Isoprenaline) (ISO)
2. Metaproterenol
3. terbutaline

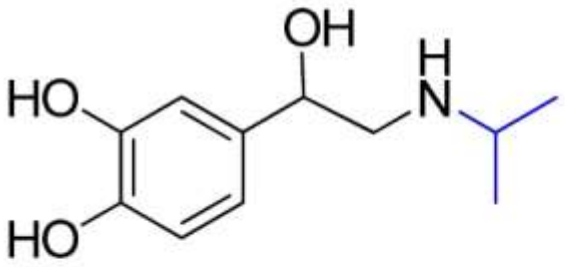
} Resorcinol bronchodilators

4. Albuterol (Salbutamol)
5. pirbuterol
6. salmeterol
7. Formoterol
8. Isoetharine
9. Bitolterol
10. Ritodrine

CLASSIFICATION

resorcinol bronchodilators

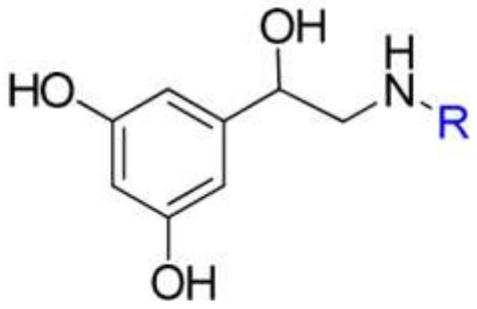
(1) Isoproterenol

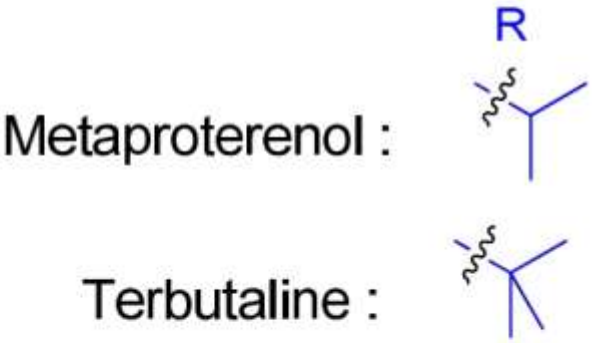


β_1 agonist → ↑ HR → use for treatment of heart block

β_2 agonist → bronchodilation → asthma , COPD

(2) Metaproterenol (3) terbutaline



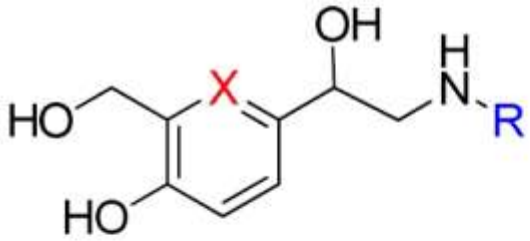


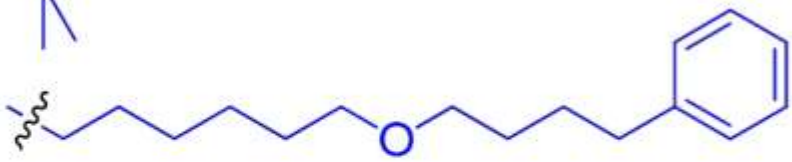
- Resorcinol moiety → selective β2 agonist + not metabolized by COMT

CLASSIFICATION

(4) Albuterol (5) pirbuterol (6) Salmeterol

- 3' Hydroxymethyl moiety → selective β2 agonist + not metabolized by COMT
- Bulky N-substituents → selective β + not metabolized by MAO
- N-phenylbutoxyhexyl substituent in salmeterol → very long acting
- Levalbuterol = *(R)* isomer of racemic albuterol

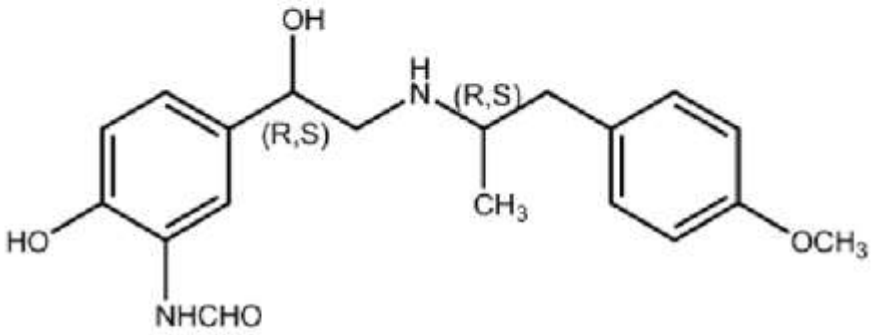


	X	R
Albuterol :	C	
pirbuterol :	N	
salmeterol :	C	

CLASSIFICATION

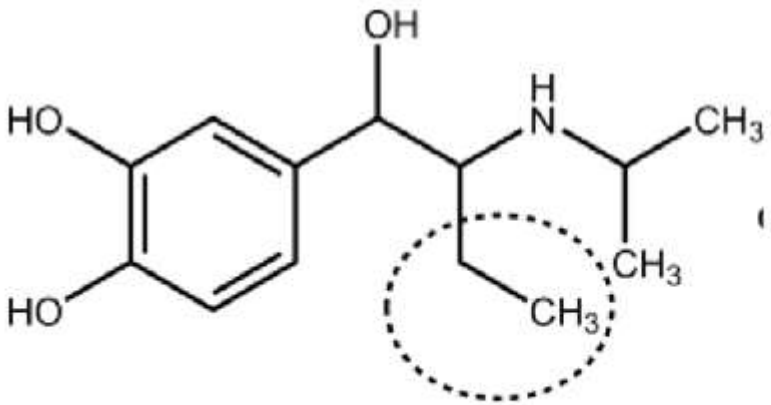
(7) Formoterol

3'-formylamino group (β-directing)

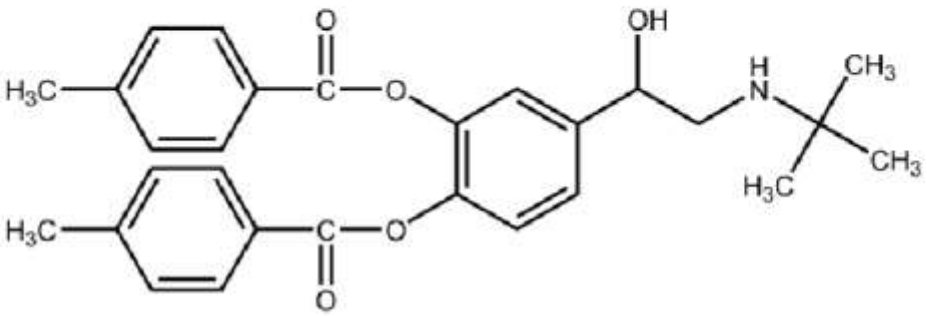


(8) Isoetharine (α-ethyl ISO)

- Because of the presence of the β_2 -directing α-ethyl group and β-directing isopropyl group, isoetharine is a potent β_2 -agonist and is resistant to MAO

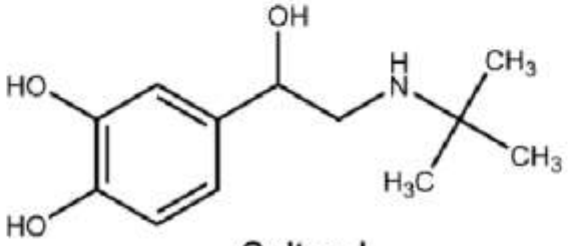


(9) Bitolterol



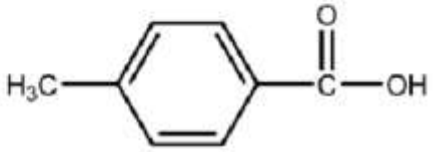
Bitolterol (a prodrug of Colterol)

esterases in the lung and other tissues



Colterol

\+ 2

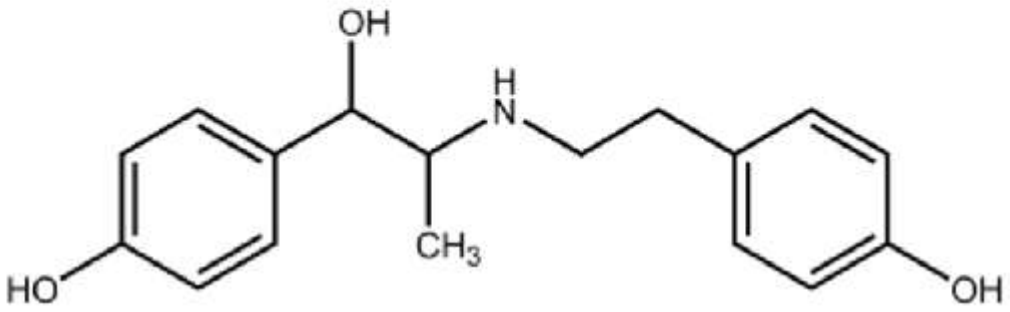


p-Toluic Acid

- N-*tert-butyl* group
  → selective β2 + not metabolized by MAO
- Prodrug resist to metabolism by COMT

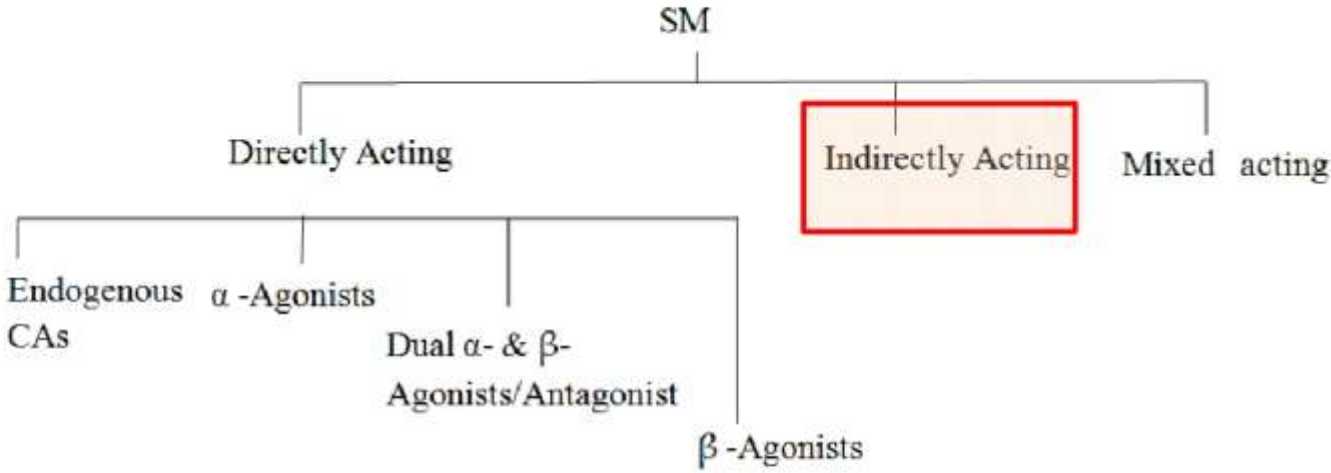
CLASSIFICATION

(10) Ritodrine



- Selective β2 -agonist that was developed specifically for use as a uterine relaxant.

CLASSIFICATION



Indirect-Acting Sympathomimetics

Phenylisopropylamines

1. Amphetamine
2. Methamphetamine
3. Hydroxyamphetamine

Phenylpropanolamines

1. (+)-Pseudoephedrine

M/A

- Act by releasing endogenous NE.
- They enter the nerve ending by way of the active-uptake process and displace NE from its storage granules.

CLASSIFICATION

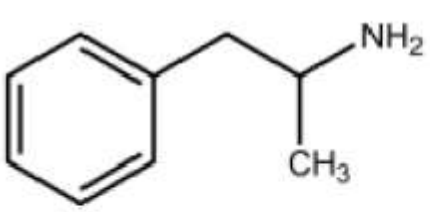
Phenylisopropylamines

(1) Amphetamine (2) methamphetamine

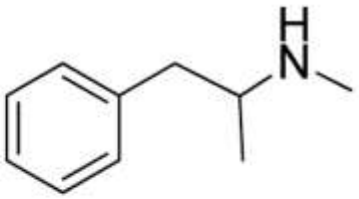
- By mimicking the release of the CAs NTs, NE , DA + serotonin action → CNS stimulant and central appetite suppressant effects

(3) Hydroxyamphetamine

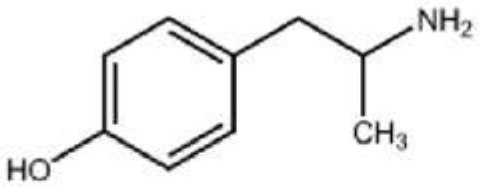
- presence of *p*-OH group → no CNS stimulant action
- used to dilate the pupil diagnosis / surgical procedures on the eye.



Amphetamine
Log P = 2.81



Methamphetamine



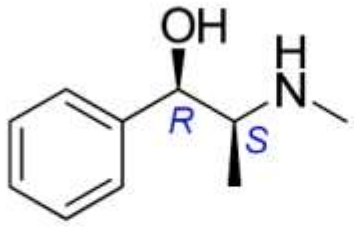
Hydroxyamphetamine
Log P = 1.07
pKa = 10.71

CLASSIFICATION

Phenylpropanolamines

(1) L-(+)-Pseudoephedrine

- β-OH has *S*- stereochemistry ,Thus no directly acting mechanism
- Causes indirect vasoconstriction →Use: nasal decongestant



(-) Ephedrine

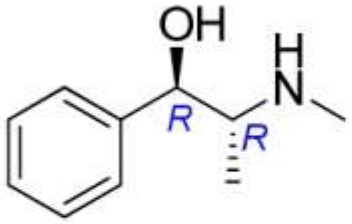
Enantiomers

(+) Ephedrine

Ephedrine
(threo racemate)
Mix acting drug

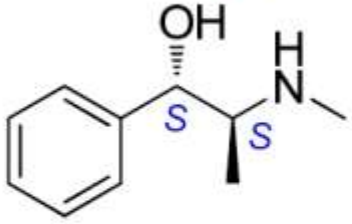
Diastireomers

Diastireomers



(-) Pseudoephedrine

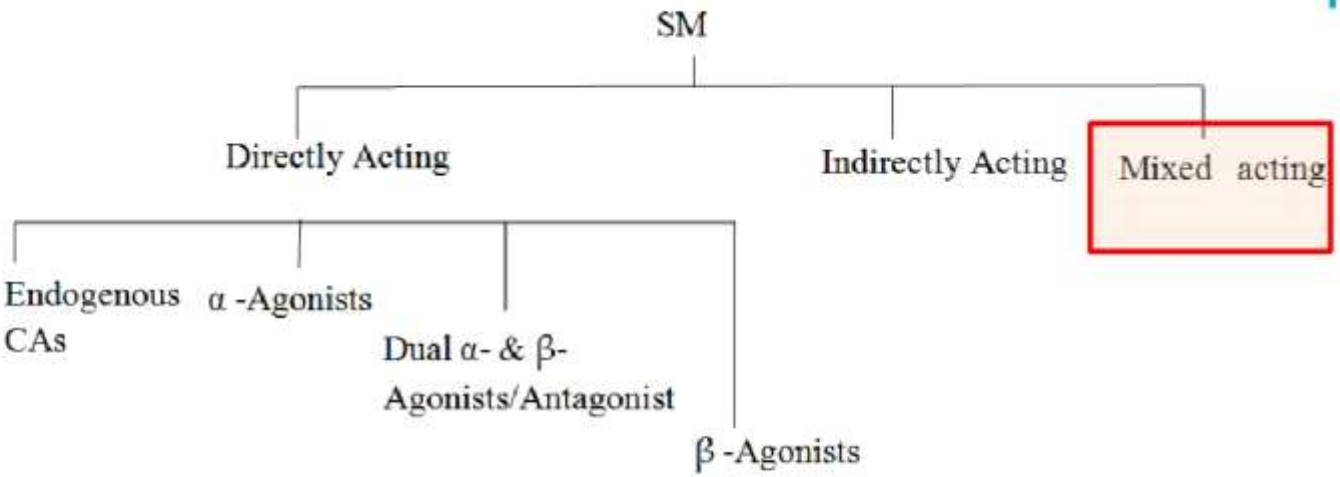
Enantiomers



(+) Pseudoephedrine

Pseudoephedrine
(Erythro racemate)
Indirectly acting drug

CLASSIFICATION



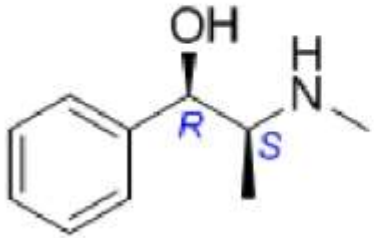
Mixed-Acting Sympathomimetics

1. (-) Ephedrine

CLASSIFICATION

Phenylpropanolamines

(1) D-(-)-Ephedrine



(-) Ephedrine

- *(1R,2S)-D-(-)*-ephedrine is most active from all four isomers

- An α- and β -adrenergic agonist (*β*-OH has *R*- stereochemistry) and also enhance release of NE
- As it is mix acting , it has Ephedrine can be used for a variety of purposes, a bronchodilator, vasopressor, cardiac stimulant, and nasal decongestant

CLASSIFICATION

Phenylpropanolamines

(2) Phenylpropanolamine / β-hydroxyamphetamine

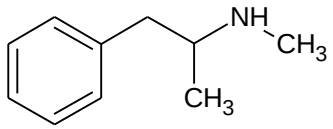
- *N*- desmethyl analog of ephedrine

- lacks *N*-methyl group → more polar →much less stimulation
  → α selective → higher vasopressive action

- Use : appetite suppressants and cough and cold medications
- FDA discontinued

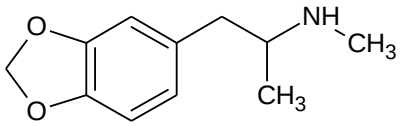
ABUSED SYMPATHOMIMETICS
Central Nervous Stimulants

Metamphetamine :



(***N*-methylamphetamine**) is a potent central nervous system (CNS) stimulant that is mainly used as a recreational drug and less commonly as a second-line treatment for attention deficit hyperactivity disorder and obesity.

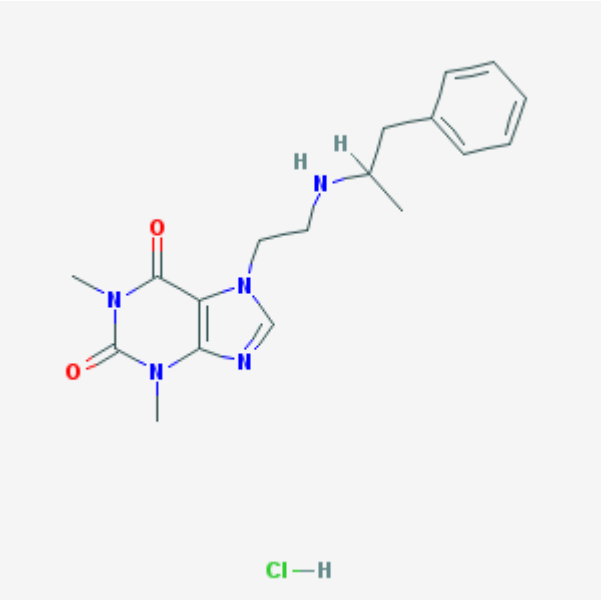
3,4-Methylenedioxymethamphetamine (MDMA)



Commonly known as **ecstasy** (**E**), is also recreational drug. The desired effects include altered sensations and increased energy, empathy, and pleasure. When taken by mouth, effects begin after 30–45 minutes and last 3–6 hours.

Adverse effects include addiction, memory problems, paranoia, difficulty sleeping, teeth grinding, blurred vision, sweating, and a rapid heartbeat. Deaths have been reported due to increased body temperature and dehydration.

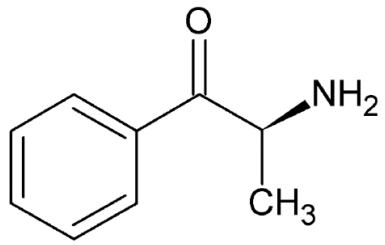
Fenethylline hydrochloride (CAPTAGON)



1,3-dimethyl-7-[2-(1-phenylpropan-2-ylamino)ethyl]purine-2,6-dione; hydrochloride

Fenethylline is a codrug of amphetamine and theophylline which behaves as a prodrug. 12–22 age group in Saudi Arabia are addicted to fenethylline. In 2017 captagon was the most popular narcotic in Saudi Arabia. Fenethylline is a popular drug in Western Asia, and is allegedly used by militant groups in Syria.

Cathinone β-keto-amphetamine

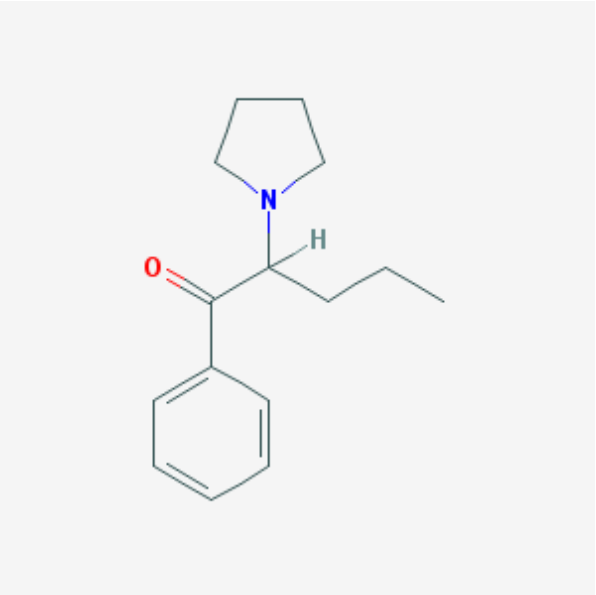


(S)-2-Amino-1-phenyl-1-propanone

Cathinone has been found to stimulate the release of dopamine and inhibit the reuptake of epinephrine, norepinephrine and serotonin in the central nervous system (CNS). Origin is plant, it is used by chewing.

Alpha-pyrrolidinovalerophenone; Alpha-

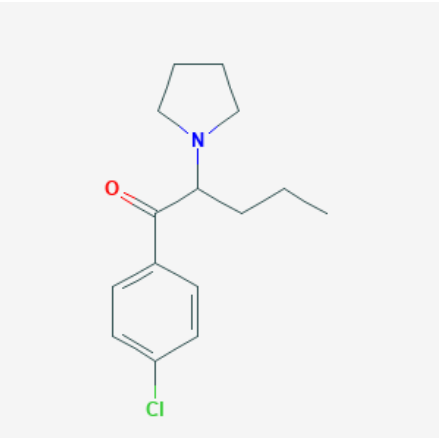
PVP;



1-Phenyl-2-(pyrrolidin-1-yl)pentan-1-one;

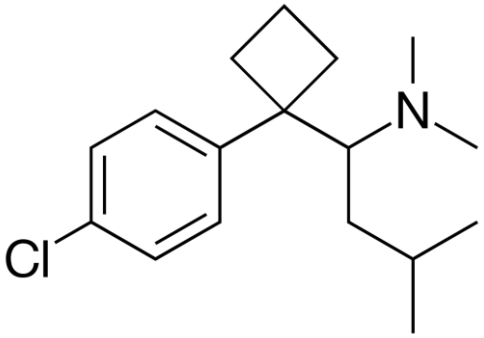
Desmethyl pyrovalerone; Alpha-Pyrrolidinopentiophenone

In 2011, **FLAKKA** was legal with the names of "**Ivory Wave**", "**Vanilla Sky**", "**Bliss**" and "**Purple Rain**".
The heart rate is increasing, the emotions are getting stronger, the person feels like a superhero. It releases high amounts of dopamine and increases body temperature excessively. For this reason, those who use clothes disintegrate. It is named as 'Beath Salt' (bath salt), because it was like a bath salt. It was produced in China and sold for only $ 25 a dose. When the zombie pill dosage was increased, it turned people into zombies.



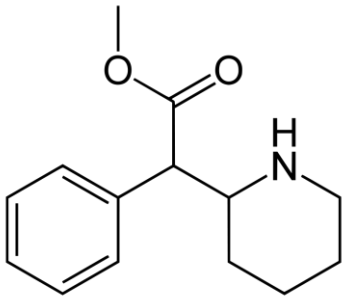
4-Chloro-alpha-PVP

Antiobesity Sympathomimetic amines :



Sibutramine (REDUCTIL), is an appetite suppressant which has been discontinued in many countries. Until 2010, it was widely marketed and prescribed as an adjunct in the treatment of obesity along with diet and exercise. It has been associated with increased cardiovascular events and strokes and has been withdrawn from many countries on the World.

Methylphenidate RITALIN



It is a stimulant medication used to treat attention deficit hyperactivity disorder (ADHD) and narcolepsy.