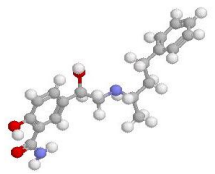
Beta-blockers, WADA S3



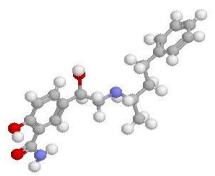
β-agonists:

S3. BETA-2 AGONISTS

All beta-2 agonists, including all optical isomers (e.g. *d*- and *l*-) where relevant, are prohibited except inhaled salbutamol (maximum 1600 micrograms over 24 hours), inhaled formoterol (maximum delivered dose 54 micrograms over 24 hours) and salmeterol when taken by inhalation in accordance with the manufacturers' recommended therapeutic regimen.

The presence in urine of salbutamol in excess of 1000 ng/mL or formoterol in excess of 40 ng/mL is presumed not to be an intended therapeutic use of the substance and will be considered as an *Adverse Analytical Finding* unless the *Athlete* proves, through a controlled pharmacokinetic study, that the abnormal result was the consequence of the use of the therapeutic inhaled dose up to the maximum indicated above.

Beta-blockers, WADA S3

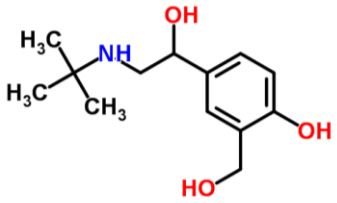


β_2-agonists:

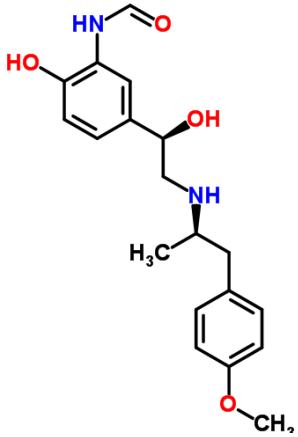
β2 +

Phenylethanolamines: bronchodilators anti-asthma.

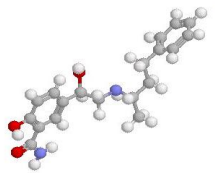
• Short-acting: **SALBUTAMOL**



• Long-acting: **FORMOTEROL**



Beta-blockers, WADA P2



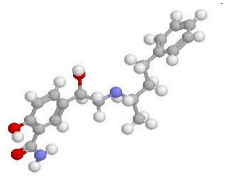
β-antagonists:

P2. BETA-BLOCKERS

Unless otherwise specified, beta-blockers are prohibited *In-Competition* only, in the following sports.

- Archery (WA) (also prohibited *Out-of-Competition*)
- Automobile (FIA)
- Billiards (all disciplines) (WCBS)
- Darts (WDF)
- Golf (IGF)
- Shooting (ISSF, IPC) (also prohibited *Out-of-Competition*)
- Skiing/Snowboarding (FIS) in ski jumping, freestyle aerials/halfpipe and snowboard halfpipe/big air

Beta-blockers, WADA P2



β-blockers: lowers blood pressure by reducing peripheral vascular resistance

Non-selective β-antagonists:

PROPRANOLOL, PINDOLOL, TIMOLOL

cfr adrenergic drugs

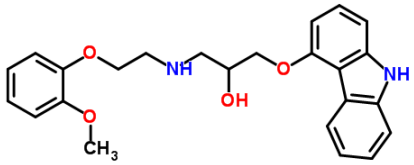
Selective β_1-antagonists:

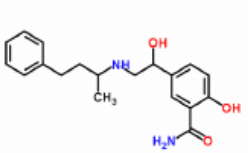
ATENOLOL, METOPROLOL, ACEBUTOLOL

cfr adrenergic drugs

Mixed α_1/β_1-antagonists: α_1: vasodilat.

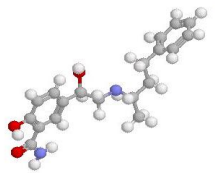
LABETALOL, CARVEDILOL



Name	**LABETALOL**
Structure	
Systematic name	2-hydroxy-5-{1-hydroxy-2-[(4-phenylbutan-2-yl)amino]ethyl}benzamide
Formula	$C_{19}H_{24}N_2O_3$
MW	328.4055
Monoisotopic mass	328.178692644
Mp	189°C
H bond acceptors	5
H bond donors	5
Acid p*Ka*	8.05 (phenol)
Basic p*ka*	9.80 (amine)
ACD Log D pH 5.5	-0.66
ACD Log D pH 7.4	0.56
Solubility	20 mg/mL water (hydrochloride)
LD50	600 mg/Kg mouse p.o.
Therapeutic cat	antihypertensive
ATC	**C07AG01** C CARDIOVASCULAR SYSTEM C07 BETA BLOCKING AGENTS C07A BETA BLOCKING AGENTS C07AG Alpha and beta blocking agents
Receptors	α_1/β_1 (antagonist)

Nomi commerciali (IT)	
IPOLAB, TRANDATE	A, RR, compresse, iniettabile

Stimulants, WADA S6



αβ-agonists:

S6. STIMULANTS

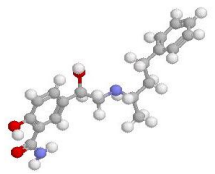
All stimulants, including all optical isomers (e.g. *d*- and *l*-) where relevant, are prohibited, except imidazole derivatives for topical use and those stimulants included in the 2014 Monitoring Program*.

Stimulants include:

a: Non-Specified Stimulants:

Adrafinil; amfepramone; amfetamine; amfetaminil; amiphenazole; benfluorex; benzylpiperazine; bromantan; clobenzorex; cocaine; cropropamide; crotetamide; fencamine; fenetylline; fenfluramine; fenproporex; fonturacetam [4-phenylpiracetam (carphedon)]; furfenorex; mefenorex; mephentermine; mesocarb; metamfetamine(*d*-); p-methylamphetamine; modafinil; norfenfluramine; phendimetrazine; phenmetrazine; phentermine; prenylamine; prolintane.
A stimulant not expressly listed in this section is a Specified Substance.

Stimulants, WADA S6



b: Specified Stimulants (examples):

Benzfetamine; cathine; cathinone and its analogues** (e.g. **mephedrone, methedrone, α- pyrrolidinovalerophenone); dimethylamphetamine; ephedrine***; epinephrine**** (adrenaline); etamivan; etilamfetamine; etilefrine; famprofazone; fenbutrazate; fencamfamin; heptaminol; hydroxyamfetamine (parahydroamphetamine); isometheptene; levmetamfetamine; meclofenoxate; methylenedioxymethamphetamine; methylephedrine***; methylhexaneamine (dimethylpentylamine); methylphenidate; nikethamide; norfenefrine; octopamine; oxilofrine (methylsynephrine); pemoline; pentetrazol; phenpromethamine; propylhexedrine; pseudoephedrine*****; selegiline; sibutramine; strychnine; tenamfetamine (methylenedioxyamphetamine); trimetazidine; tuaminoheptane;** and other substances with a similar chemical structure or similar biological effect(s).

* The following substances included in the 2014 Monitoring Program (bupropion, caffeine, nicotine, phenylephrine, phenylpropanolamine, pipradol, synephrine) are not considered as *Prohibited Substances*.

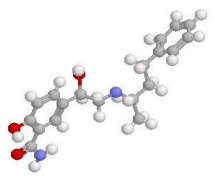
** **Cathine** is prohibited when its concentration in urine is greater than 5 micrograms per milliliter.

*** Each of **ephedrine** and **methylephedrine** is prohibited when its concentration in urine is greater than 10 micrograms per milliliter.

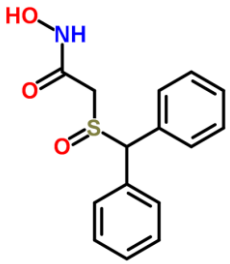
**** Local administration (e.g. nasal, ophthalmologic) of **epinephrine** (**adrenaline**) or co-administration with local anaesthetic agents is not prohibited.

***** **Pseudoephedrine** is prohibited when its concentration in urine is greater than 150 micrograms per milliliter.

Stimulants, WADA S6

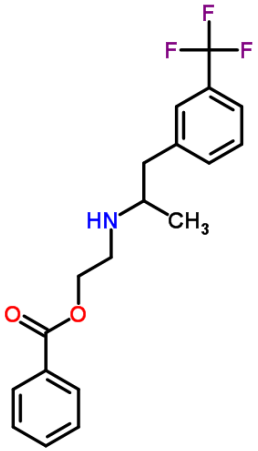


Non-specified stimulants:



ADRAFINIL

off-label anti-fatigue

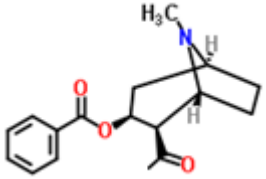


BENFLUOREX

withdrawn drug, cardiovascular toxicity

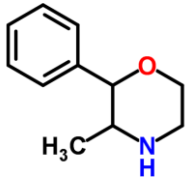
COCAINE

abuse drug,

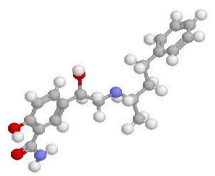


PHENMETRAZINE

appetite suppressant, stimulant

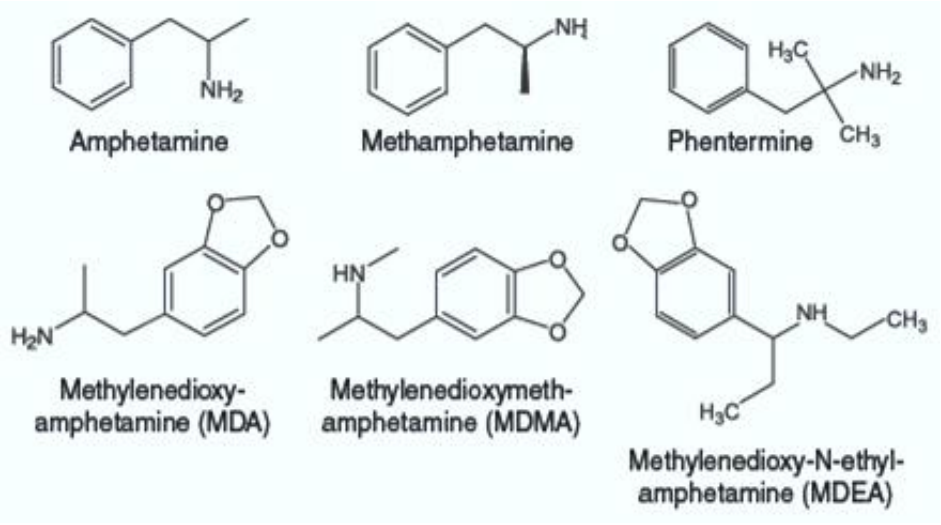


Stimulants, WADA S6

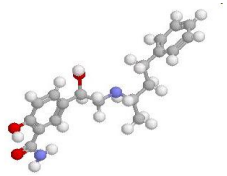


Mixed Simpathomimetics: **αβ +**

Phenylisopropanolamines or Amphetamines: stimulants, anorexigenic, drugs of abuse.



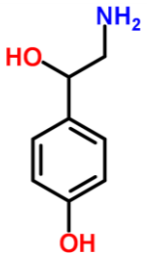
Stimulants, WADA S6



Specified stimulants:

OCTOPAMINE

(NOR-SINEPHRINE)



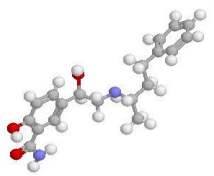
METHYLPHENIDATE

indirect adrenergic (dopamine-norepinephrine reuptake inhibitor)

Name	**METHYLPHENIDATE**
Structure	
Systematic name	methyl phenyl(piperidin-2-yl)acetate
Formula	$C_{14}H_{20}ClNO_2$
MW	269.767 (hydrochloride)
Monoisotopic mass	233.141579
Mp	224-226°C (hydrochloride)
H bond acceptors	3
H bond donors	1
Acid pK*a*	--
Basic pk*a*	9.09
ACD Log D pH 5.5	-0.55
ACD Log D pH 7.4	-0.28
Solubility	water, methanol, ethyl acetate
LD50	190 mg/Kg rat p.o.
Therapeutic cat	anti attention-deficit hyperactivity disorder
ATC	**N06BA04** N NERVOUS SYSTEM N06 PSYCHOANALEPTICS N06B PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS N06BA Centrally acting sympathomimetics
Receptors	adrenergic (indirect)

Nomi commerciali (IT)	
RITALIN	A, stupef. Tab. II, compresse

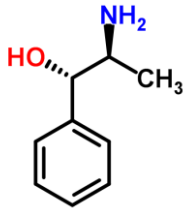
Stimulants, WADA S6



Not prohibited/limited:

CATHINE

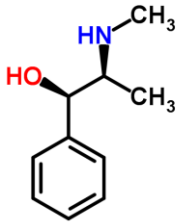
> 5 µg/mL urine



Catha edulis

EPHEDRINE

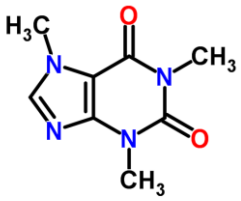
> 10 µg/mL urine



Ephedra sp.pl.

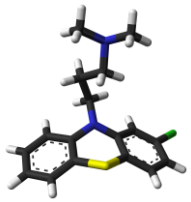
CAFFEINE

not prohibited



Coffea arabica

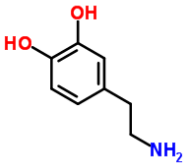
CNS drugs



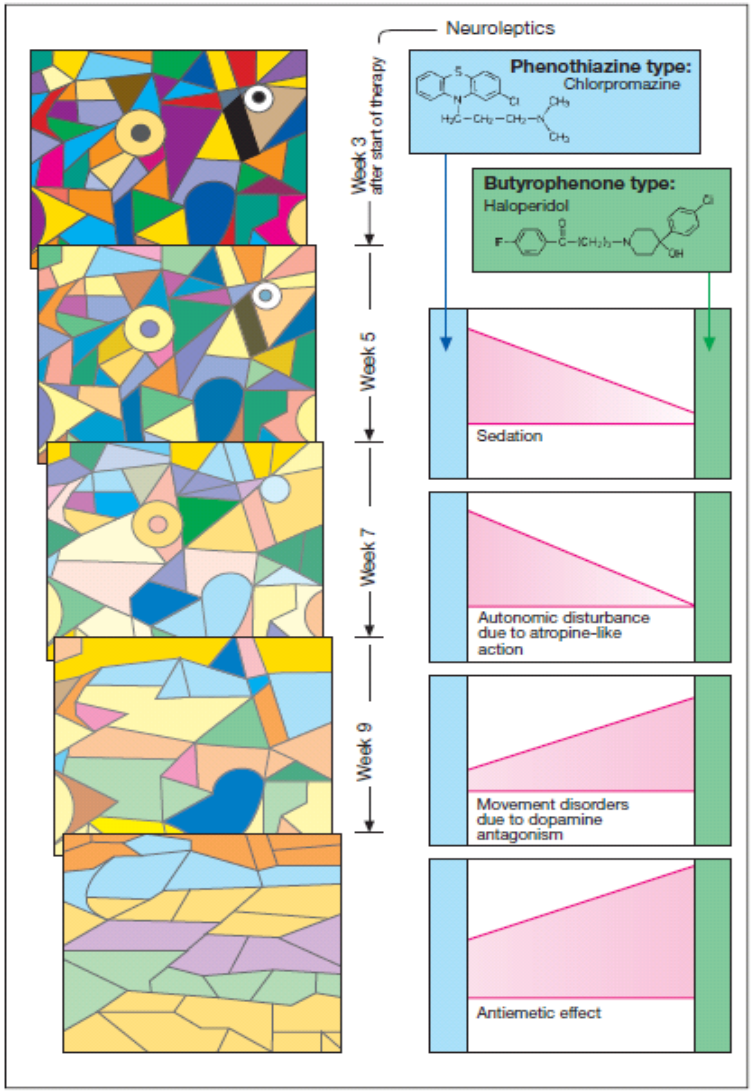
Antipsychotics (neuroleptics):

Psychosis: Mania and sensory hallucination. Schizophrenia: functional impairment of the CNS with hallucinations, manic behavior, thought disorder, incoherence, blunted affect, negativism, stereotyped behavior and lack of initiative.

Changes(↑) in **dopamin**ergic transmission.

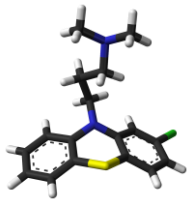


Neurosis: Maintained ability to perceive reality. Anxiety disorders with changes in mood, thought and behavioral dysfunctions.



A. Effects of neuroleptics in schizophrenia

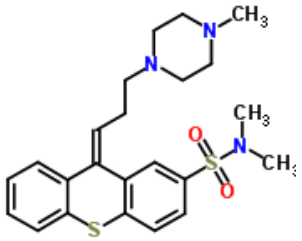
CNS drugs

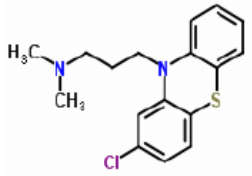


Antipsychotics (neuroleptics):

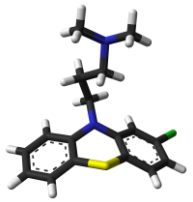
Phenotiazines: D_2 receptor antagonists. **CHLORPROMAZINE.** EW substituent critical for the activity. Lateral chain must be of 3 C. Extrapyramidal toxic effects.

Thioxanthenes: *cis*-THIOTIXENE



Name	**CHLORPROMAZINE**
Structure	
Systematic name	3-(2-chloro-10H-phenothiazin-10-yl)-N,N-dimethylpropan-1-amine
Formula	$C_{17}H_{19}ClN_2S$
MW	318.864
Monoisotopic mass	318.095747015
Mp	60°C
H bond acceptors	2
H bond donors	0
Acid p*Ka*	--
Basic p*ka*	9.20
ACD Log D pH 5.5	2.15
ACD Log D pH 7.4	3.24
Solubility	Diethyl ether, ethanol. Acidic water
LD50	141 mg/Kg rat p.o.
Therapeutic cat	Antipsychotic
ATC	**N05AA01** N NERVOUS SYSTEM N05 PSYCHOLEPTICS N05A ANTIPSYCHOTICS N05AA Phenothiazines with aliphatic side-chain
Receptors	D_2

Nomi commerciali (IT)	
CLORPROMAZINA CLOR, LARGACTIL, PROZIN	C, RR, iniettabile, compresse



Antipsychotics (neuroleptics):

phenotiazine/thioxanthene metabolism:

- demethylation
- sulphoxidation
- hydroxylation
- glucuronidation

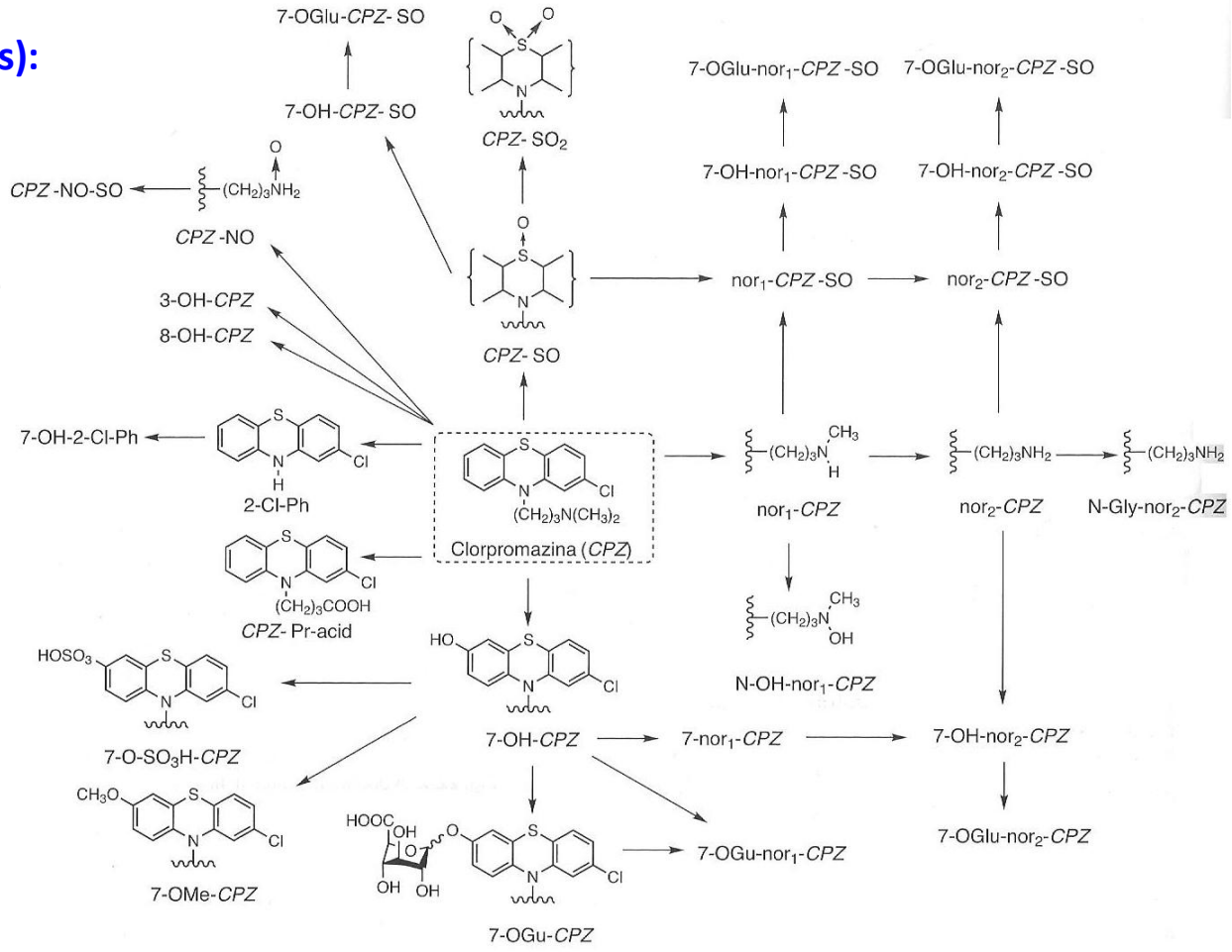
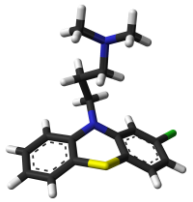


Fig. 22.6. Metabolismo della clorpromazina. Abbreviazioni: CPZ, clorpromazina; NO, N-ossido; SO, solfossido; SO_2, solfone; OGlu, O-glucuronide; Ph, fenotiazina, Pr-acid, acido propionico; O-SO_3H, solfato.

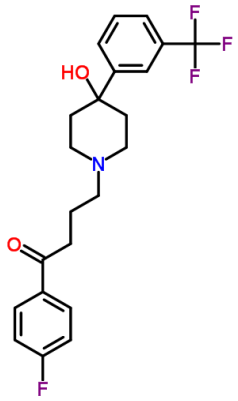
CNS drugs

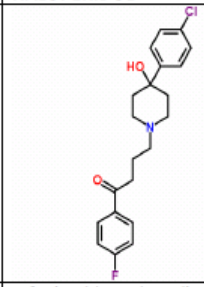


Antipsychotics (neuroleptics):

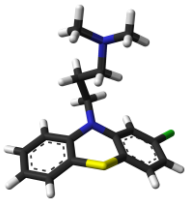
Butyrrophenones: D_2 / 5-HT_2 receptors antagonists. **HALOPERIDOL.** Sedative effect lower than phenotiazines one. Extrapyramidal toxic effects.

TRIFLUPERIDOL:



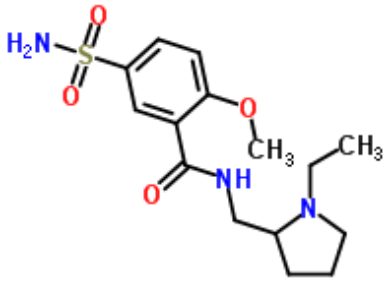
Name	**HALOPERIDOL**
Structure	
Systematic name	4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one
Formula	$C_{21}H_{23}ClFNO_2$
MW	375.864
Monoisotopic mass	375.140134897
Mp	152°C
H bond acceptors	3
H bond donors	1
Acid p*Ka*	--
Basic p*ka*	8.05
ACD Log D pH 5.5	1.23
ACD Log D pH 7.4	2.93
Solubility	chloroform, methanol, acetone, and dilute acids
LD50	850 mg/Kg rat p.o.
Therapeutic cat	Antipsychotic
ATC	**N05AD01** N NERVOUS SYSTEM N05 PSYCHOLEPTICS N05A ANTIPSYCHOTICS N05AD Butyrophenone derivatives
Receptors	D2, 5-HT_2 (antagonist)

Nomi commerciali (IT)	
ALOPERIDOLO, HALDOL, SERENASE	A, RR, iniettabile, compresse, gocce



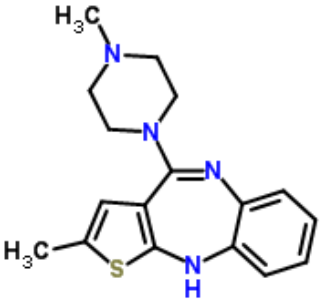
Atypical antipsychotics (2nd generation neuroleptics):

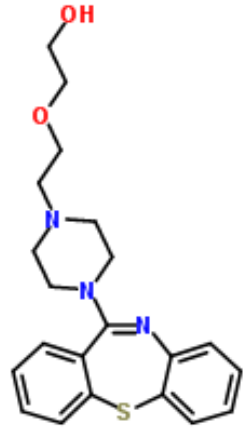
Benzamides: D_2 / D_3 receptors antagonists. **SULPIRIDE.** M_3, 5-HT_{1A}, 5-HT_3 antagonist too. Low absorption because of hydrophilicity. Antipsychotic effect lower than phenotiazines one. Less extrapyramidal toxic effects.



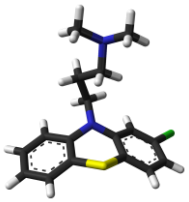
Dibenzo(di)azepines: D_1 / D_2 receptors antagonists.

OLANZAPINE: D_2 / 5-HT_{2A} receptors antagonist.





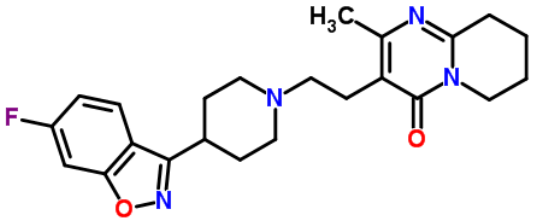
QUETIAPINE: H_1 / α_1 and α_2 / 5-HT_{2A} and D_2 receptors antagonist.



Atypical antipsychotics (2nd generation neuroleptics):

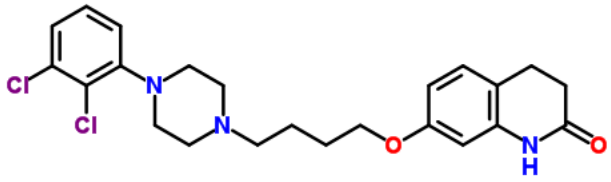
Benzoisoxazoles and benzoisothiazoles: 5-HT_{2A} / D_2 receptors antagonists.

RISPERIDONE

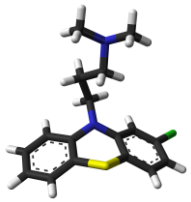


Quinolinones and indolones: 5-$HT_{1A,2A,2C}$ / D_2 receptors antagonists.

ARYLPIPRAZOLE



CNS drugs



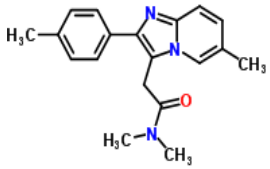
Anxiolytics: neurosis therapy

$GABA_A$ receptors allosteric agonists:

Benzodiazepines (DIAZEPAM, CHLODIAZEPOXIDE)

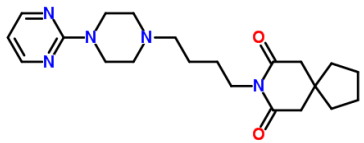
Imidazopyridines, Pyrazolopyridazines, Cyclopyrrolones (ZOPICLONE, ZALEPLON, ZOLPIDEM)

aminoacidergics; sedative-hypnotics



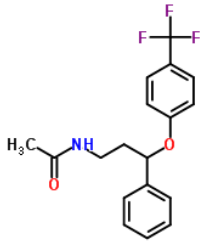
5-HT1A agonists (BUSPIRONE)

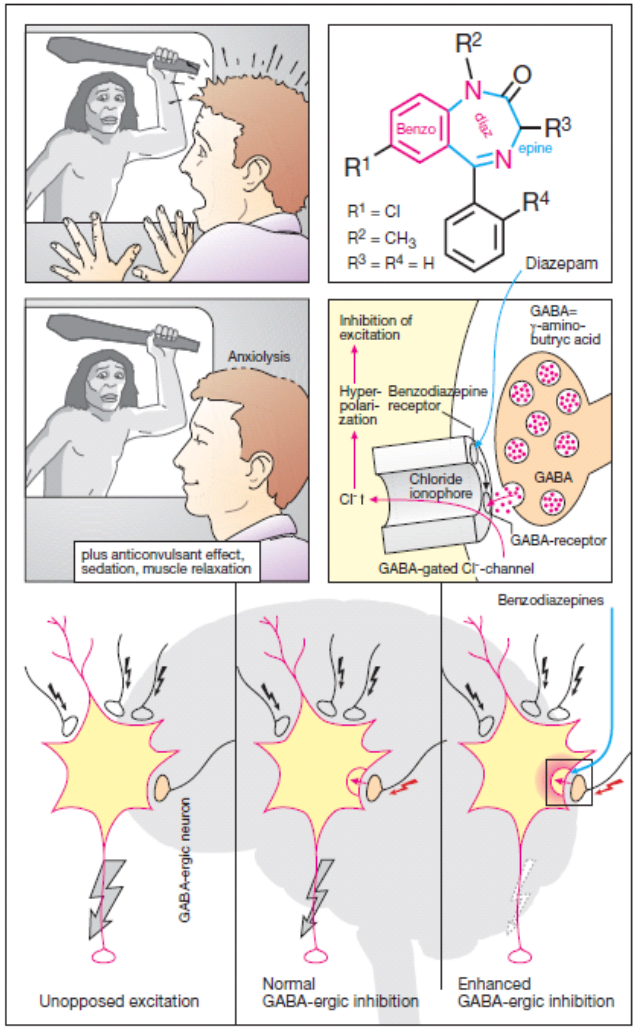
serotoninergic compounds



SSRI (FLUOXETINE, PAROXETINE)

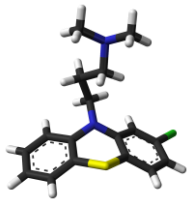
antidepressant drugs



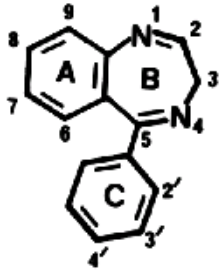


A. Action of benzodiazepines

CNS drugs



Anxiolytics:



Benzodiazepines SAR:

• *A-ring*: should be aromatic / heteroaromatic (π/ π interactions). EW in 7 increases anxiolytic action. 6,8,9-substituents decrease it.

• *B-ring*: A proton acceptor in 2-position is important. 3-OH affects elimination rate, but not the anxiolytic power.

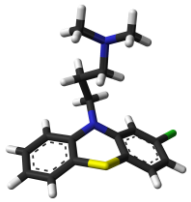
• *C-ring*: not necessary. 4'-substitution: minor agonist activity. 2'-substitution: unchanged potency.

• *Heterocyclic-1,2-condensation*: high receptor affinity.

Name	**DIAZEPAM**
Structure	
Systematic name	7-chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one
Formula	$C_{16}H_{13}ClN_2O$
MW	284.74
Monoisotopic mass	284.071640755
Mp	125°C
H bond acceptors	3
H bond donors	0
Acid pK*a*	--
Basic pk*a*	2.92 (imine)
ACD Log D pH 5.5	2.80
ACD Log D pH 7.4	2.80
Solubility	ethanol, chloroform, (water)
LD50	250 mg/Kg rat p.o.
Therapeutic cat	sedative-hypnotic
ATC	**N05BA01** N NERVOUS SYSTEM N05 PSYCHOLEPTICS N05B ANXIOLYTICS N05BA Benzodiazepine derivatives
Receptors	$GABA_A$

Nomi commerciali (IT)	
ANSIOLIN, DIAZEMULS, DIAZEPAM, MICROPAM, NOAM, TRANQUIRIT, VALIUM, VATRAN,	C, RR, compresse, gocce, clismi, iniettabili

CNS drugs



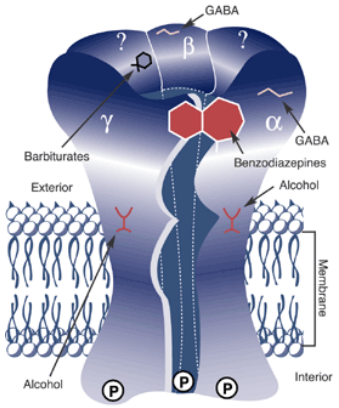
Sedative-hypnotics

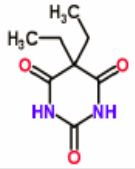
Allosteric modifiers (agonists):

BARBITURATES

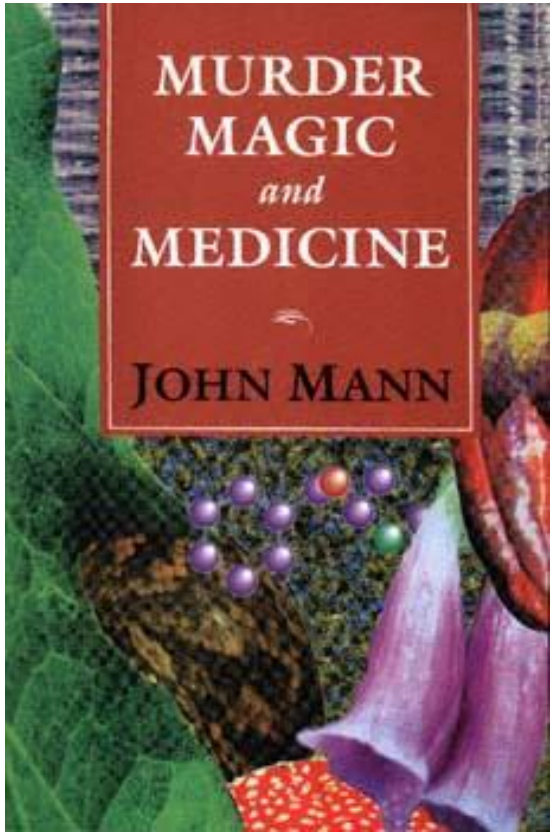
sedative effect / low terapeutic index

increase the time of the opening of the associated chloride ion channel



Name	**BARBITAL**
Structure	
Systematic name	5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione
Formula	$C_8H_{12}N_2O_3$
MW	184.1925
Monoisotopic mass	184.08479226
Mp	188-192°C
H bond acceptors	5
H bond donors	2
Acid p*Kα*	8.4; 12.15
Basic p*kα*	--
ACD Log D pH 5.5	0.80
ACD Log D pH 7.4	0.69
Solubility	Acetone, ethyl acetate, water (sodium salt)
LD50	600 mg/Kg mouse p.o.
Therapeutic cat	sedative-hypnotic
ATC	**N05CA04** N NERVOUS SYSTEM N05 PSYCHOLEPTICS N05C HYPNOTICS AND SEDATIVES N05CA Barbiturates, plain
Receptors	$GABA_A$ (allosteric)

CNS drugs



Contents

Psychotomimetics

Hallucinogens: produce, after administration of a single active dose, a significant shift in thinking, mood and perception without affecting significantly the memory.

Do not produce stupor, narcosis and overstimulation;

produce little effect autonomic and do not cause addiction.

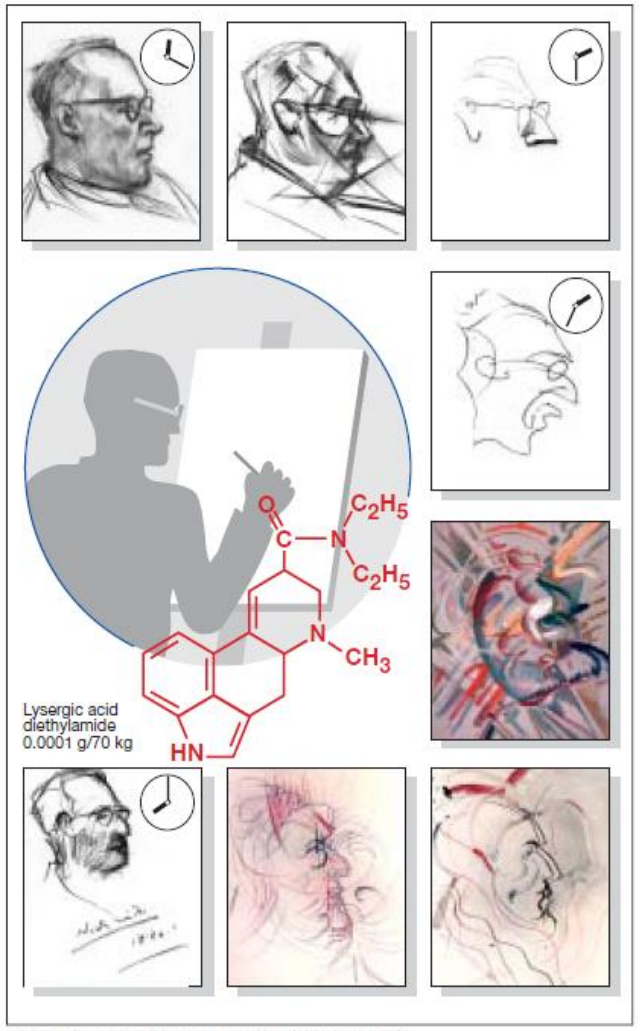
Different mechanisms of action:

CB receptors agonists (cannabinols)

NMDA (Glu) receptor antagonists

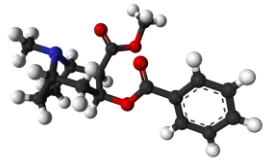
5-HT_{2A} receptor partial agonists

K opioid receptor agonists



A. Psychotomimetic effect of LSD in a portrait artist

Cannabinoids, WADA S8

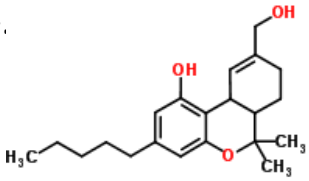


Psychotomimetics

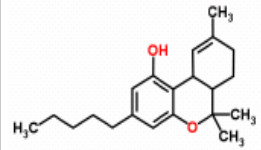
Cannabinoids:

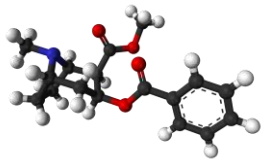
Δ^9-TETRAHYDROCANNABINOL

From *Cannabis sativa, indica e ruderalis*. Taken by inhalation (volatile). Main metabolite: 11-hydroxy-.



Action on CB-1 e CB-2 receptors (transmembrane, G-protein coupled).

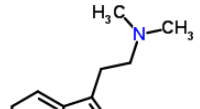
Name	**Δ^9-TETRAHYDROCANNABINOL**
Structure	
Systematic name	6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol
Formula	$C_{21}H_{30}O_2$
MW	314.4617
Monoisotopic mass	314.224580204
Mp	--
H bond acceptors	2
H bond donors	1
Acid pK*a*	9.34 (phenol)
Basic pk*a*	--
ACD Log D pH 5.5	7.68
ACD Log D pH 7.4	7.68
Solubility	ethanol, chloroform, 2.8 mg/mL water
LD50	1270 mg/Kg rat p.o.
Therapeutic cat	
ATC	**A04AD10** A ALIMENTARY TRACT AND METABOLISM A04 ANTIEMETICS AND ANTINAUSEANTS A04A ANTIEMETICS AND ANTINAUSEANTS A04AD Other antiemetics
Receptors	CB-1, CB-2



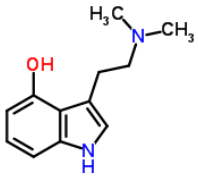
Psychotomimetics Ar-C-C-N

Indolalkylamines:

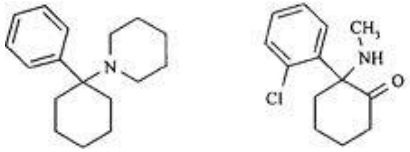
DIMETHYLTRYPTAMINE (DMT)



PSILOCYN



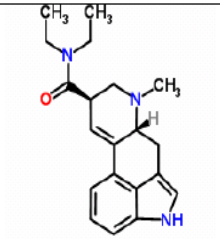
Glutamatergics:



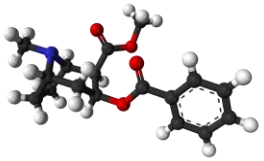
NMDA-antagonists: **PCP / KETAMINE**

Ergolines:

LSD, 5-HT, DA, H, NA agonist, antagonist and partial agonist.

Name	**LSD**
Structure	
Systematic name	(8β)-N,N-diethyl-6-methyl-9,10-didehydroergoline-8-carboxamide
Formula	$C_{20}H_{25}N_3O$
MW	323.432
Monoisotopic mass	323.199762437
Mp	85°C
H bond acceptors	4
H bond donors	1
Acid p*Ka*	--
Basic p*ka*	7.98
ACD Log D pH 5.5	0.76
ACD Log D pH 7.4	2.37
Solubility	water, benzene
LD50	50 mg/Kg mouse i.v.
Therapeutic cat	psychotomimetic
ATC	--
Receptors	$5\text{-}HT_{2A}$

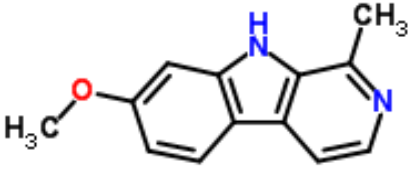
CNS drugs



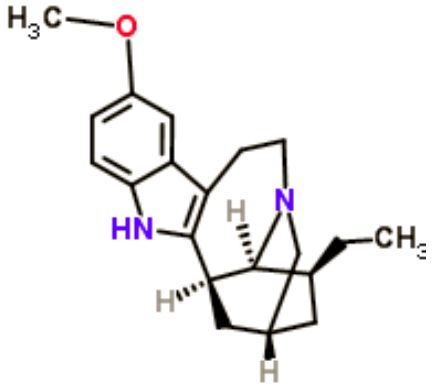
Psychotomimetics Ar-C-C-N

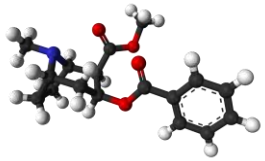
Betacarbolines:

HARMINE (*Malpighiaceae*) south america



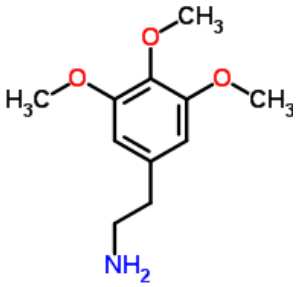
IBOGAINE (*Apocynaceae*) africa





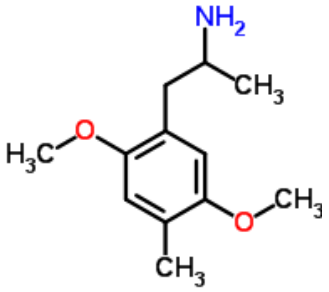
Psychotomimetics Ar-C-C-N

Phenylalkylamines:

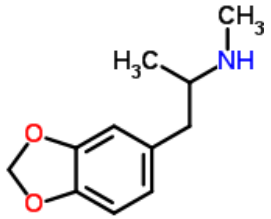


MESCALINE

(*Lophophora williamsii*)

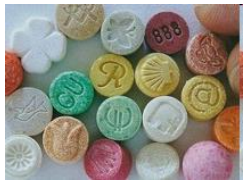


DOM

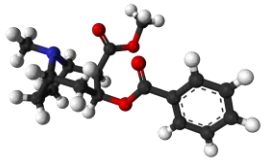


MDMA

(*designer drugs)*



Stimulants, WADA S6



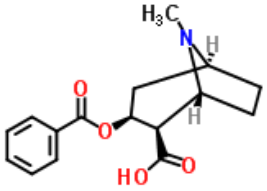
Psychotomimetics

Catecholamines re-uptake inhibitors:

COCAINE

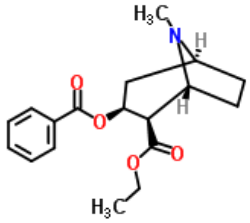
Metabolism**:**

BENZOYLECGONINE



Alcohol co-metabolism:

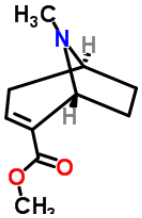
COCAETHYLENE

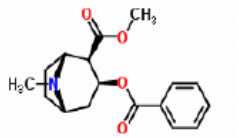


Thermal pyrolysis:

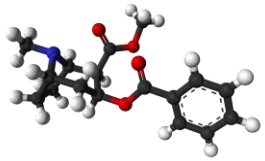
ANHYDROECGONINE-

METHYL ESTER



Name	**COCAINE**
Structure	
Systematic name	methyl (1R,2R,3S,5S)-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate
Formula	$C_{17}H_{21}NO_4$
MW	303.3529
Monoisotopic mass	303.147058165
Mp	195°C
H bond acceptors	5
H bond donors	0
Acid p*Ka*	--
Basic p*ka*	8.85
ACD Log D pH 5.5	-0.81
ACD Log D pH 7.4	0.52
Solubility	ethanol, chloroform, acidic water
LD50	93 mg/Kg mouse p.o.
Therapeutic cat	Anesthetics
ATC **N01BC01** N NERVOUS SYSTEM N01 ANESTHETICS N01B ANESTHETICS, LOCAL N01BC Esters of benzoic acid **R02AD03** R RESPIRATORY SYSTEM R02 THROAT PREPARATIONS R02A THROAT PREPARATIONS R02AD Anesthetics, local	 **S01HA01** S SENSORY ORGANS S01 OPHTHALMOLOGICALS S01H LOCAL ANESTHETICS S01HA Local anesthetics **S02DA02** S SENSORY ORGANS S02 OTOLOGICALS S02D OTHER OTOLOGICALS S02DA Analgesics and anesthetics
Receptors	NE/DA (re-uptake)

Stimulants, Narcotics, Cannabinoids, WADA S6, S7, S8



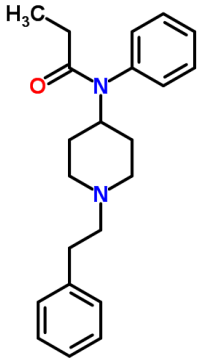
Drugs of abuse

NIDA NATIONAL INSTITUTE ON DRUG ABUSE
The Science of Drug Abuse & Addiction

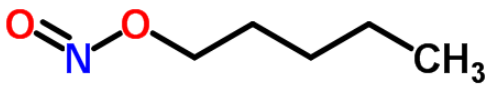
- Alcohol
- Club Drugs
- Cocaine
- Fentanyl
- Heroin
- Inhalants
- LSD (Acid)
- Marijuana
- MDMA (Ecstasy)
- Methamphetamine
- PCP/Phencyclidine
- Prescription Drugs
- Steroids (Anabolic)
- Tobacco Addiction (Nicotine)

http://www.drugabuse.gov/drugs-abuse

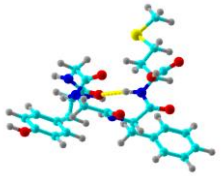
FENTANYL



AMYL NITRITE



Narcotics, WADA S7



Opioids

Analgesics o antinociceptives: painkillers for chronic or acute pain.

Opiate (*Opiaceo*): morphime-related derivative.

Opioid (*Opioide*): active on $OP_{1,2,3,4}$ receptors:

δ receptors (OP_1)

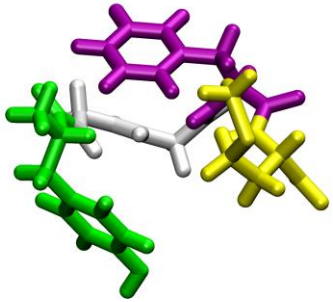
κ receptors (OP_2)

μ receptors (OP_3)

nociceptine receptors [orphan opioid] (OP_4)

Endogenous ligands: **ENKEPHALINS/ENDORPHINS**

Opium alkaloyd: **(-)-MORPHINE**



Met-enkephalin = Tyr-Gly-Gly-Phe-Met

Leu-Enkephalin = Tyr-Gly-Gly-Phe-Leu

β-Endorphin = Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser ^{10}-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys- Asn^{20}-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu^{31}

Dynorphin(dyn$^{1\text{-}17}$) = Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln

Dynorphin(dyn$^{1\text{-}8}$) = Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile

Dynorphin(dyn$^{1\text{-}13}$) = Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys

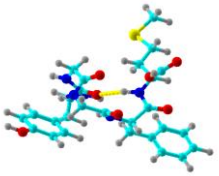
α-Neoendorphin = Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys

β-Neoendorphin = Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro

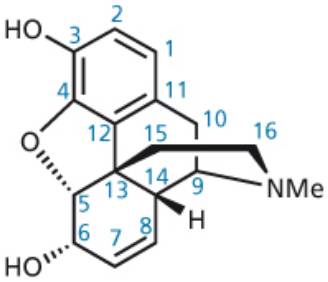
Nociceptin = Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln

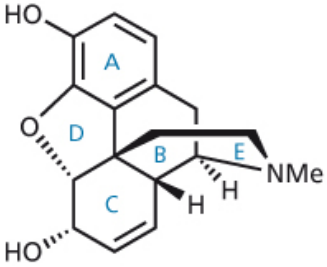
Fig. 24.1. Proteine che fungono da precursori per i peptidi oppioidi endogeni.

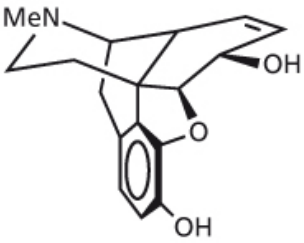
Narcotics, WADA S7

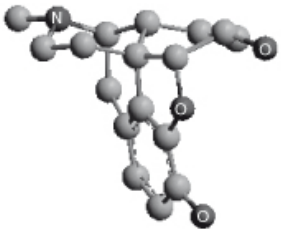


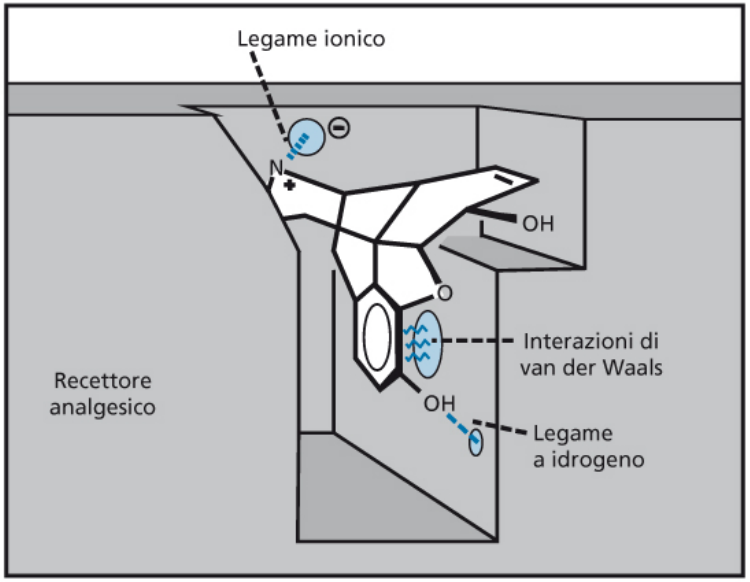
Opioids



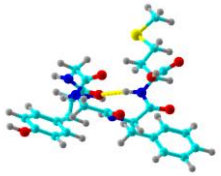


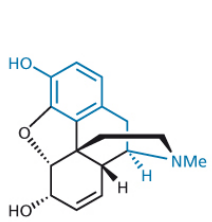




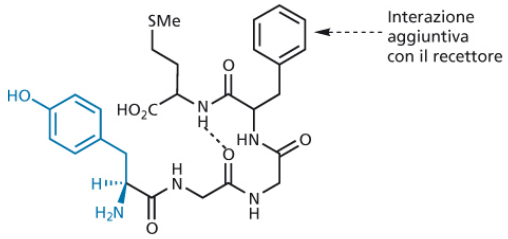


Narcotics, WADA S7

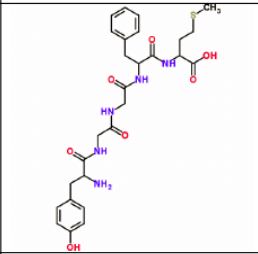


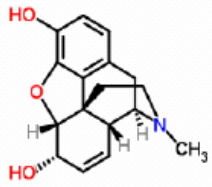


Morfina



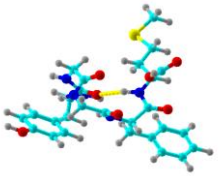
Met-encefalina

Name	**MET-ENKEPHALIN**
Structure	
Systematic name	*Tyrosylglycylglycylphenylalanylmethionine*. 2-(2-(2-(2-(2-amino-3-(4-hydroxyphenyl)propanamido)acetamido)acetamido)-3-phenylpropanamido)-4-(methylthio)butanoic acid
Formula	$C_{27}H_{35}N_5O_7S$
MW	573.661
Monoisotopic mass	573.225719189
Mp	--
H bond acceptors	12
H bond donors	8
Acid pK*a*	3.81
Basic pk*a*	7.73
ACD Log D pH 5.5	-0.97
ACD Log D pH 7.4	-1.16
Solubility	water
LD50	--
Therapeutic cat	opioid
ATC	--
Receptors	OP
Notes	endogenous ligand

Name	**MORPHINE**
Structure	
Systematic name	1S,5R,13R,14S,17R)-4-Methyl-12-oxa-4-azapentacyclo[9.6.1.01,13.05,17.07,18]octadeca-7(18),8,10,15-tetraene-10,14-diol
Formula	$C_{17}H_{19}NO_3$
MW	285.3377
Monoisotopic mass	285.136493479
Mp	253-254°C dec
H bond acceptors	4
H bond donors	2
Acid pK*a*	10.26 (phenol)
Basic pk*a*	9.12
ACD Log D pH 5.5	-1.80
ACD Log D pH 7.4	0.043
Solubility	50 mg/ml in water (hydrochloride)
LD50	461 mg/Kg rat p.o.
Therapeutic cat	opioid analgesic
ATC	**N02AA01** N NERVOUS SYSTEM N02 ANALGESICS N02A OPIOIDS N02AA Natural opium alkaloids
Receptors	OP_3

Nomi commerciali (IT)	
MORFINA CL, MORFINA CLORIDR, MORFINA SOLFATO	A, RNR, iniettabile, compresse, sciroppo

Narcotics, WADA S7



Opioids

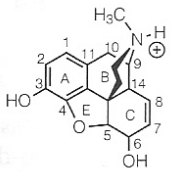
Tolerance and withdrawal: Caused respectively by inhibition and by up-regulation of adenylate cyclase (overproduction of cAMP). Decreases with δ agonists / antagonists.

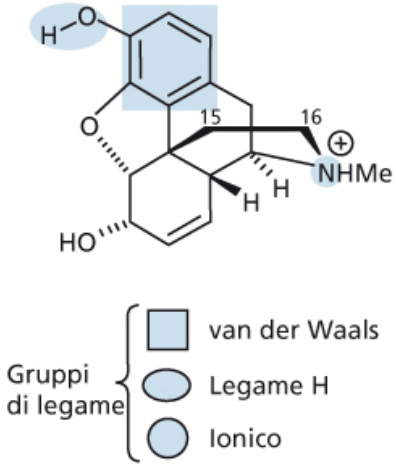
Other side effects: respiratory depression, constipation, excitement, euphoria, nausea, miosis.

SAR: 5R, 6S, 9R, 13S, 14R. Tertiary amine and OH in 3 position are critical.

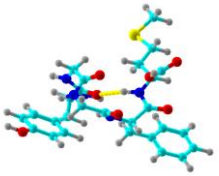
3-5 atoms N-substituents cause antagonism; with larger N-substituents back to agonists.

Struttura, numerazione e SAR per la (−)-morfina

	Sostituzioni	Attività analgesica
 (−)-Morfina	3-H per -OH	Diminuzione di 10 volte
	chetone invece di -OH in 6	Diminuzione, ma aumento in caso di 7,8-diidro
	6-H per 6-OH	Aumento
	7,8-diidro	Aumento
	14 β-OH	Aumento
	3-OCH_3 per OH	Diminuzione
	Estere acetico in 3	Diminuzione
	Estere acetico in 6	Aumento
	NCH_2CH_2Ph per NCH_3	Aumento di 10 volte
	$NCH_2CH{=}CH_2$ per NCH_3	Diventa antagonista μ



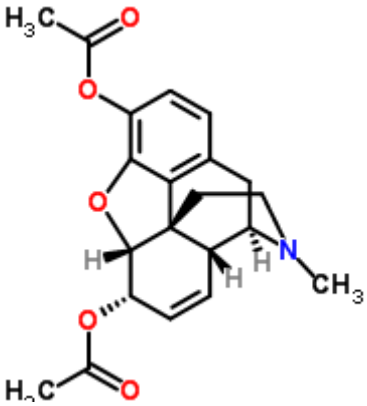
Narcotics, WADA S7



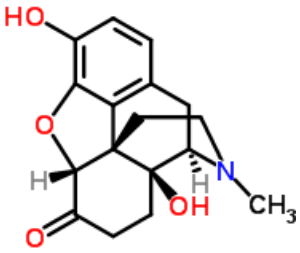
Opioids

μ-agonists: Prodrugs/ 6-ketoderivatives

HEROIN:

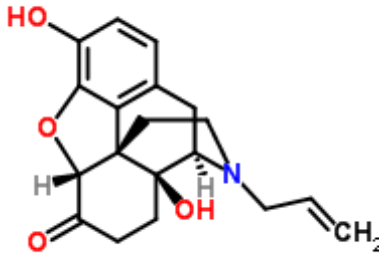


OXYMORPHONE: 10 times more powerful than morphine

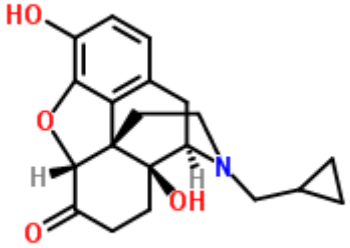


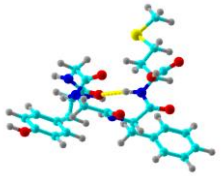
μ-antagonists: induce receptor conformational change, preventing the activation of G-protein.

NALOXONE:



NALTREXONE:





K-opioid psychotomimetics

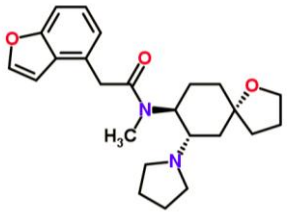
K-opioid agonists:

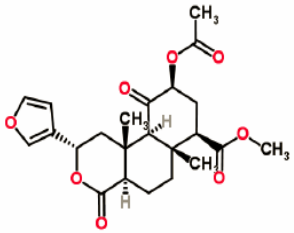
SALVINORIN A: neoclerodane diterpenoid.

Most potent psychotomimetic. No nitrogen!

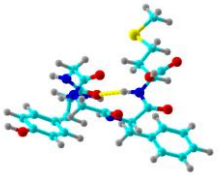
From *Salvia divinorum.*

Share mechanism with **ENADOLINE,** synthesized as analgesic.



Name	**SALVINORIN A**
Structure	
Systematic name	methyl (2S,4aR,6aR,7R,9S,10aS,10bR)-9-(acetyloxy)-2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxododecahydro-2H-benzo[f]isochromene-7-carboxylate
Formula	$C_{23}H_{28}O_8$
MW	432.4636
Monoisotopic mass	432.178417872
Mp	244°C
H bond acceptors	8
H bond donors	0
Acid p*Ka*	--
Basic p*ka*	--
ACD Log D pH 5.5	1.82
ACD Log D pH 7.4	1.82
Solubility	Ethanol, acetone
LD50	280 mg/Kg rat i.v.
Therapeutic cat	psychotomimetic
ATC	--
Receptors	K opioid / D_2 (agonist)

Narcotics, WADA S7

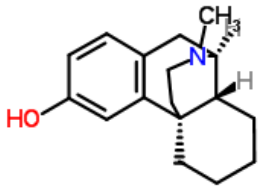


Opioids

Simplification and breakdown:

Morphinans: removal of epoxy bridge.

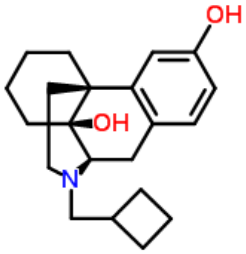
LEVORPHANOL: 6 times more powerful than morphine. Better lipofilicity and better μ-receptor affinity.

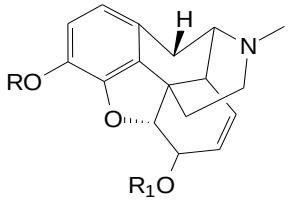


BUTORPHANOL: μ-antagonist and κ-agonist. Analgesic power 5-fold larger with respect to morphine.

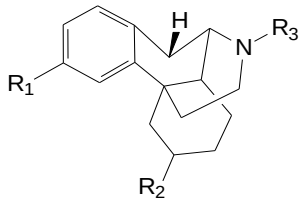
Various side effects.

Not used as narcotic.

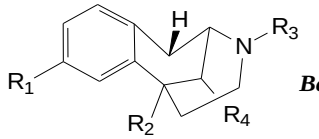




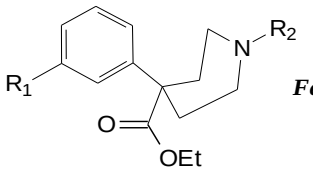
Morfinici



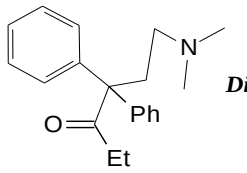
Morfinani



Benzomorfani

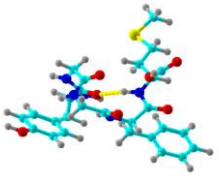


Fenilpiperidine



Difenilpropilamine

Narcotics, WADA S7

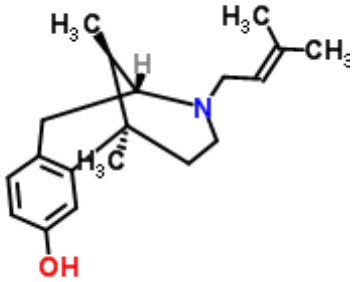


Opioids

Simplification and breakdown:

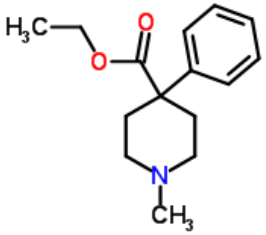
***Benzomorphans*:** removal of epoxy bridge and of C-ring

PENTAZOCINE: weak μ-antagonist and κ-agonist. Analgesic power 6-fold smaller with respect to morphine. Can induce disphoria.

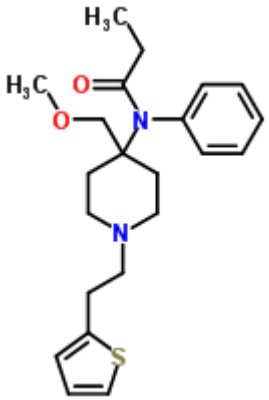


4-phenil(anilido)piperidines:

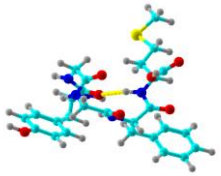
MEPERIDINE: Analgesic power 10-fold smaller with respect to morphine. Used in obstetrics.



SUFENTANYL: Analgesic power 800-fold larger with respect to morphine. It's an anesthetic and causes poor respiratory depression.



Narcotics, WADA S7



Opioids

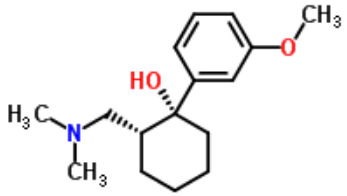
Simplification and breakdown:

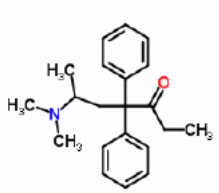
***Diphenylpropylamines*:**

METHADONE: Eutomer: R(-). Analgesic used in drug addiction recovery. Half-life 19 h.

***Phenylpropylamines* :**

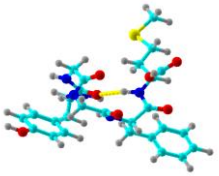
TRAMADOL: Opioid power 3800-fold smaller with respect to morphine. Active on δ, κ receptors, NET and SERT. Painkiller.



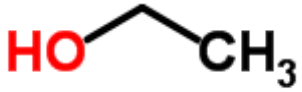
Name	**METHADONE**
Structure	
Systematic name	6-(dimethylamino)-4,4-diphenylheptan-3-one
Formula	$C_{21}H_{27}NO$
MW	309.4452
Monoisotopic mass	309.209264491
Mp	100°C
H bond acceptors	2
H bond donors	0
Acid pK*a*	--
Basic pk*a*	9.12
ACD Log D pH 5.5	0.96
ACD Log D pH 7.4	2.29
Solubility	water (hydrochloride) ethanol, chloroform
LD50	30 mg/Kg rat p.o.
Therapeutic cat	analgesic/opioid detoxification adjunct
ATC	**N07BC02** N NERVOUS SYSTEM N07 OTHER NERVOUS SYSTEM DRUGS N07B DRUGS USED IN ADDICTIVE DISORDERS N07BC Drugs used in opioid dependence
Receptors	OP_3

Nomi commerciali (IT)	
EPTADONE, METADONE CLORIDR	H, OSP1, iniettabile, compresse, sciroppo

Alcohol, WADA P1



Ethanol



P1. ALCOHOL

Alcohol (**ethanol**) is prohibited *In-Competition* only, in the following sports. Detection will be conducted by analysis of breath and/or blood. The doping violation threshold is equivalent to a blood alcohol concentration of 0.10 g/L.

- Air Sports (FAI)
- Archery (WA)
- Automobile (FIA)
- Karate (WKF)
- Motorcycling (FIM)
- Powerboating (UIM)