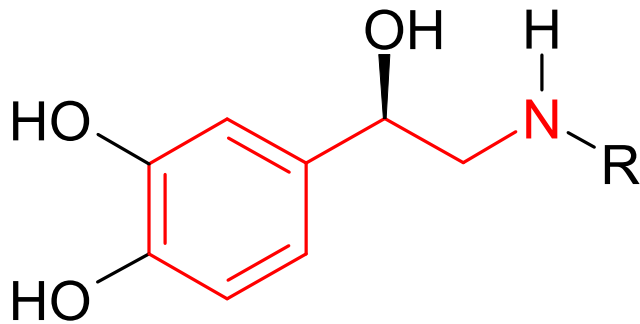


Central nervous system stimulants

- compounds stimulating mental functions and physical performance
 1. Phenylethylamine and phenylisopropylamine derivatives
 2. Modafinil
 3. Purine alkaloids
 4. Compounds with tropane scaffold

1. Phenylethylamine and phenylisopropylamine derivatives

- natural catecholamines analogues

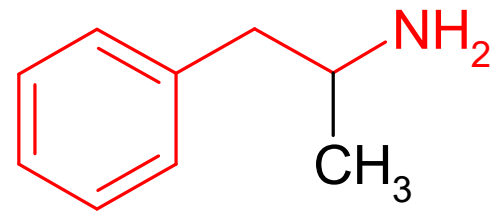


R = H

noradrenaline

R = CH₃

adrenaline



amphetamine

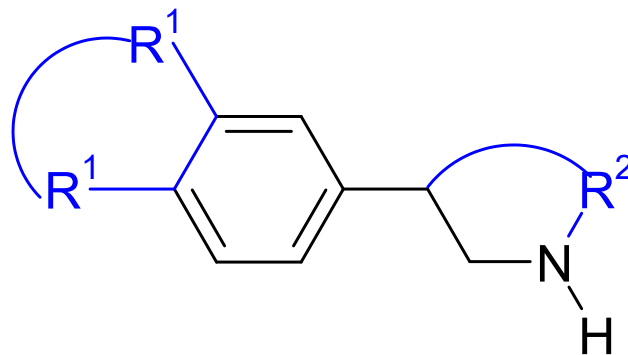
Phenylethylamine and phenylisopropylamine derivatives

= indirect adrenergics – do not interact directly with adrenergic receptors in the brain but inhibit reuptake of catecholamines or increase their release from synapses; some of them act similarly also in serotonergic system

- centrally stimulating and anorectic effects

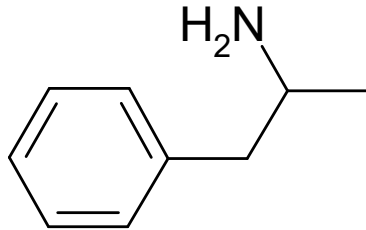
-OH group in α -position toward the aromatic ring is missing or O is the part of a cycle (morpholine)

-OH group on the benzene ring are missing or etherified
phenylethylamine moiety can also be a part of a cycle

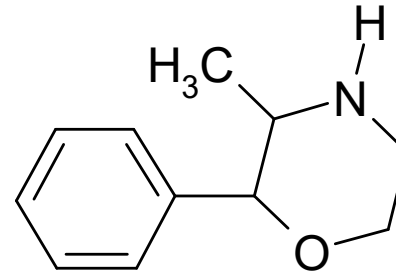


1. Phenylethylamine and phenylisopropylamine derivatives

Compounds used as therapeutics



(*R,S*)-1-phenyl-2-aminopropane
amphetamine

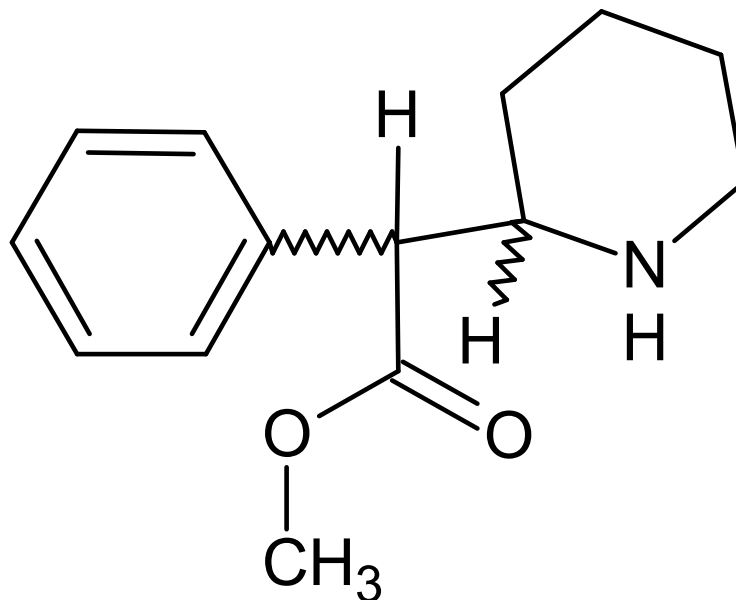


2-phenyl-3-
methylmorpholine
phenmethrazine

- supression of fatigue, feelings of hunger and thirst, increase of performance
- mobilization of energy reserves of organism
- indications: narcolepsy, obesity (obsolete)
- overdosage: total exhausting, dehydration, circulation breakdown
- see further centrally acting anobesics (anorectics)

1. Phenylethylamine and phenylisopropylamine derivatives

Compounds used as therapeutics



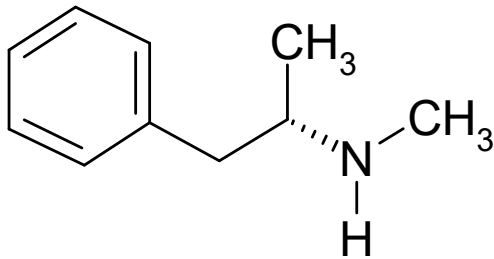
methylphenidate

- for better concentration e.g. in children with some form of autistic disorder
- kinetic disorder

Concerta ® , Ritalin ® , Medikinet ®

Phenylethylamine and phenylisopropylamine derivatives
Psychotropic compounds of amphetamine type

- belong among „hard drugs“
- physical addiction



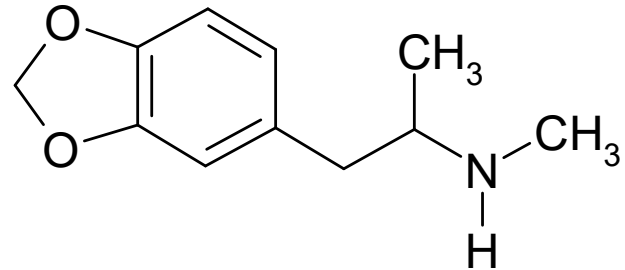
(S)-2-methylamino-1-phenylpropane

N-methylamphetamine

(S)-methamphetamine

syn. **pervitine** (as hydrochloride for *i.v.* application); speed, crank, crystal, crystal meth (base for *i.nas.* administration – also racemate)

- USA, CZ



2-(methylamino)-1-(3,4-methylenedioxyphenyl)propane

3,4-methylenedioxymetamphetamine

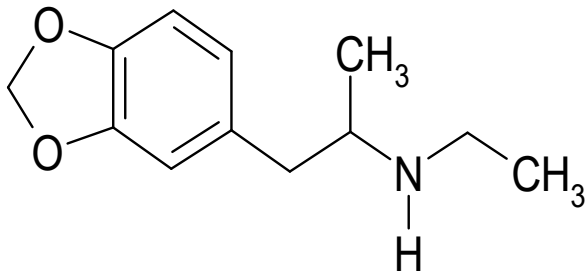
ecstasy

syn. midomafetamine (USAN), MDMA,

Adam, XTC, „E“

- so called dancing drug
- hallucinogenic effect (5HT_{2A} rp.)
- Europe

Phenylethylamine and phenylisopropylamine derivatives
Psychotropic compounds of amphetamine type

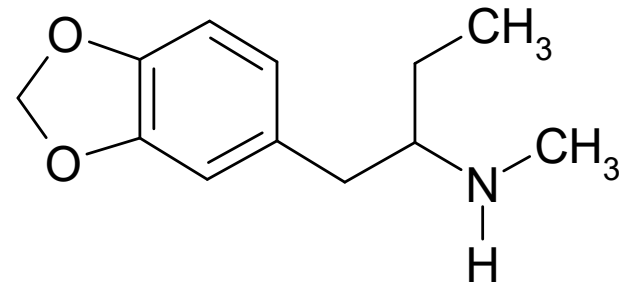


2-(ethylamino)-1-(3,4-
methylenedioxyphenyl)propane

3,4-
methylenedioxyamphetamine

MDEA

syn. MDE, Eve



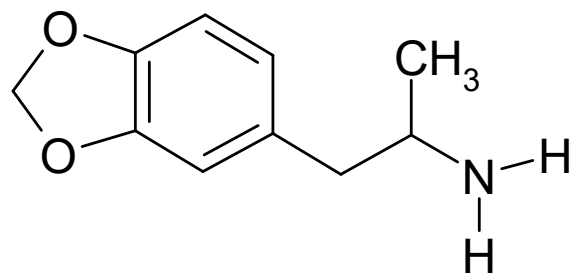
2-(methylamino)-1-(3,4-
methylenedioxyphenyl)butane

MBDB

syn. Eden, methyl J, MDP₂B

•Sweden

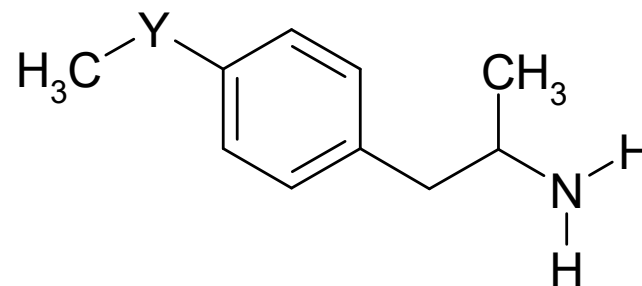
Phenylethylamine and phenylisopropylamine derivatives
Psychotropic compounds of amphetamine type



2-amino-1-(3,4-methylenedioxyphenyl)propane

tenamphetamine

syn. MDA, love drug, love pill



Y = O

2-amino-1-(4-methoxyphenyl)propane

paramethoxyamphetamine

syn. PMA, 4-MA

Y = S

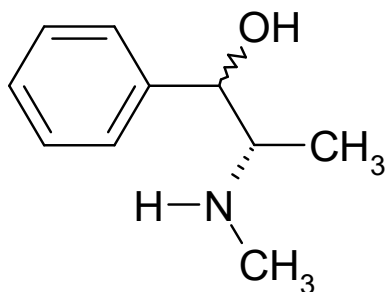
2-amino-1-(4-methylsulphanylphenyl)propane

4-methylthioamphetamine

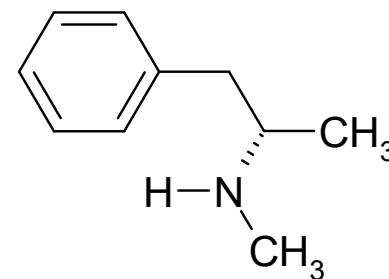
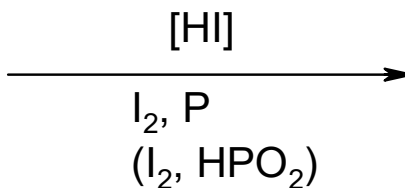
syn. 4-MTA

•NL, UK, D, AU since the end of 1990th

Synthesis of methamphetamine



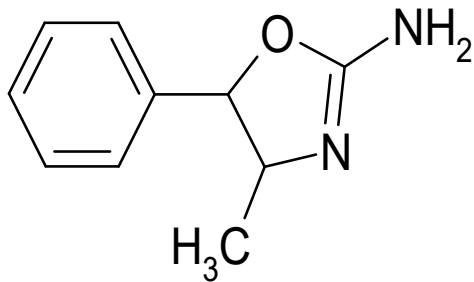
(1*R* or
1*S*,2*S*)-1-phenyl-2-methylaminopropane-
1-ol
(-)-ephedrine, (+)-pseudoephedrine



(*S*)-1-phenyl-2-methylaminopropane
(*S*)-methamphetamine

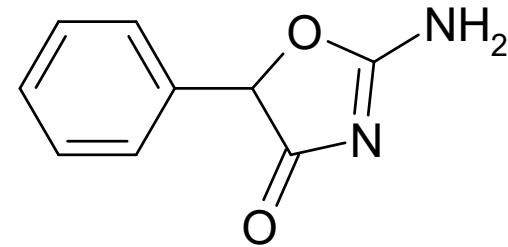
Phenylethylamine and phenylisopropylamine derivatives

Psychotropic compounds – 3,4-dihydrooxazole (2-oxazoline) derivatives



2-amino-5-phenyl-4-methyl-4,5-dihydro-1,3-oxazole

4-methylaminorex

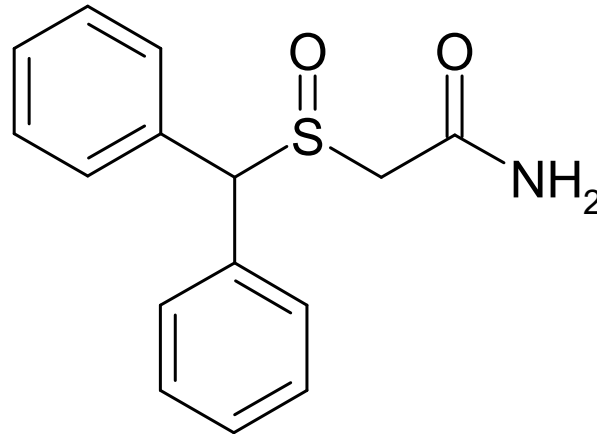


2-amino-5-phenyl-1,3-oxazole-4(5H)-one

pemolin

•formerly circulation and respiration stimulant

2. Modafinil



2-[(diphenylmethyl)sulphonyl]acetamide

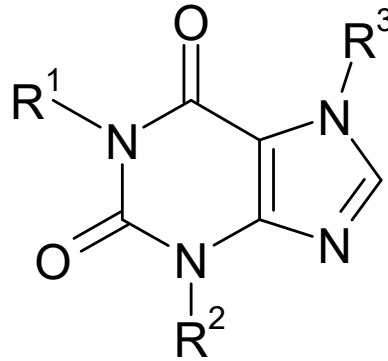
modafinil

↑ vigily and mental acuity during the day

- treatment of narkolepsy and hypersomnia
- mode of action unclear

Vigil® tbl.

3. Purine alkaloids = „methylxanthins“



$R^1 = R^2 = R^3 = -CH_3$

caffeine

$R^1 = R^2 = -CH_3, R^3 = -H$

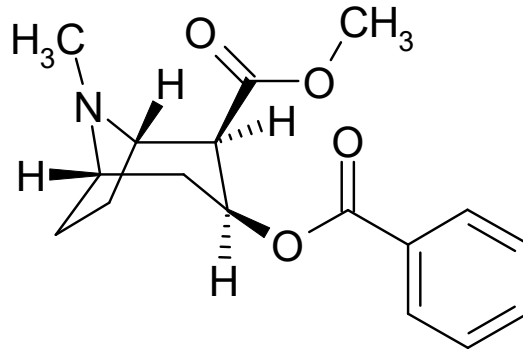
theophylline

$R^1 = -H, R^2 = R^3 = -CH_3$

theobromine

- occurrence in plants (*Coffea, Camelia, Paulinia, Theobroma ...*)
- produced in most synthetically
- CNS stimulant (most caffeine), diuretic, bronchodilatatory (most theophylline) effects
- mode of action: adenosine receptors A_1 inhibition, phosphodiesterase inhibition, catecholamines release

4. Compounds with tropane scaffold



methyl-(1S,2R,3S,5S)-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octan-2-carboxylate
cocaine

Cocaini hydrochloridum PhEur

- semisynthetic preparation from *Erythroxylon coca* leaves extract
- inhibits reuptake of catecholamines \Rightarrow indirect α_1 -sympathomimetic
- CNS stimulation, euphoria; constriction of peripheral vessels, \uparrow blood pressure
- strong psychical addiction
- local-anaesthetic activity, sometimes used in ophthalmology
- a standard for determination of superficial anaesthetic activity of potential local anaesthetics

Cognitive functions enhancers

≈nootropics, neuroanabolics

Cognitive functions: learning, comprehension, speech, judgement

- improve also attention and vigility of consciousness
- used in decrease of these functions due to brain ischemia in injuries and dementias
- structurally heterogenic group, many modes of action possible
- in contrary to previous group the effect begins slowly after several weeks of administration

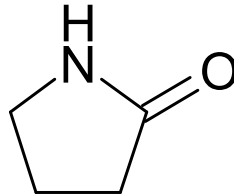
Cognitive functions enhancers classification

1. Racetams
2. Cholinergics acting in CNS
3. Phenoxyalkanoic acids derivatives
4. Compounds of other structures or modes of action

Cognitive functions enhancers

1. Racetams

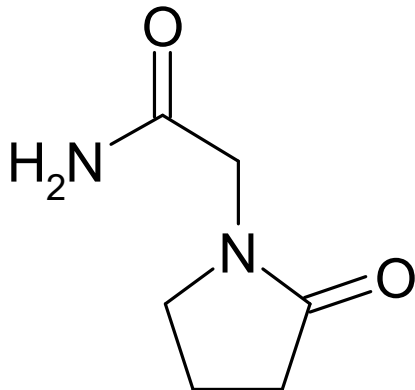
- contain pyrrolidin-2-one (γ -butyrolactame) fragment



- influence glutamate neurotransmission
- increase glucose utilization by brain tissue

Cognitive functions enhancers

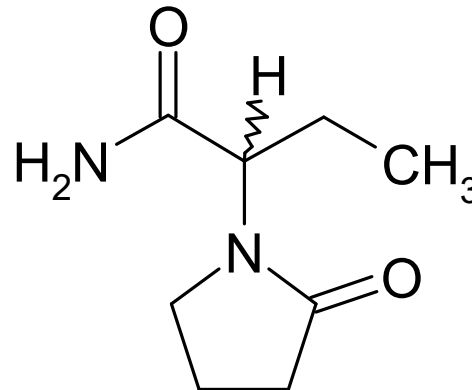
1. Racetams



2-(2-oxopyrrolidin-1-yl)acetamide
piracetam

Geratam[®] tbl., Nootropil[®] tbl.,
Oikamid[®] cps., Kalicor[®] cps. ...

- low hydrophobicity ⇒ low penetration into brain ⇒ high doses necessary (1200 mg single dose)
- low toxicity

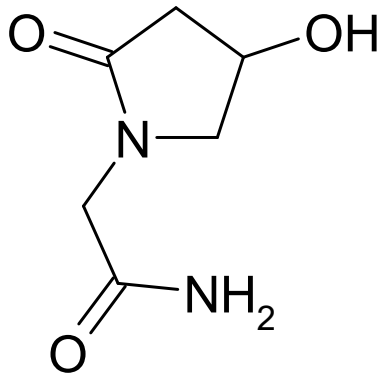


(*R,S*)-2-(2-oxopyrrolidin-1-yl)butanamide

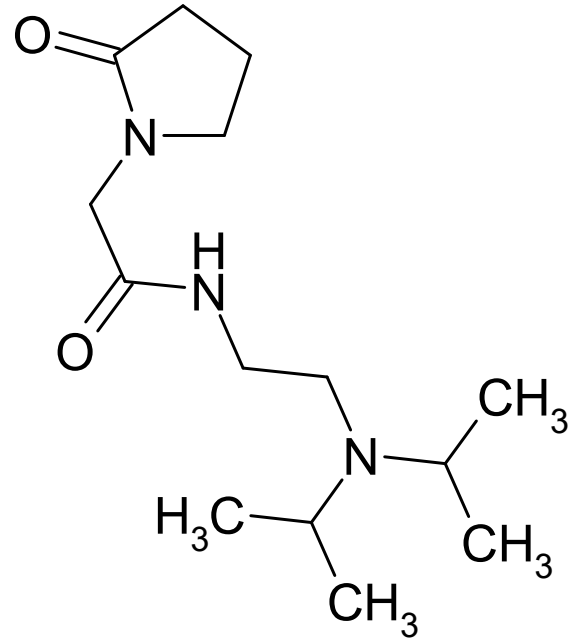
etiracetam – cognitive function enhancer

pure (*S*)-(-)-isomer – **levetiracetam**
antiepileptic of novel mode of action
and a lead compound of a whole novel group
Keppra[®] tbl.

Cognitive functions enhancers Racetams

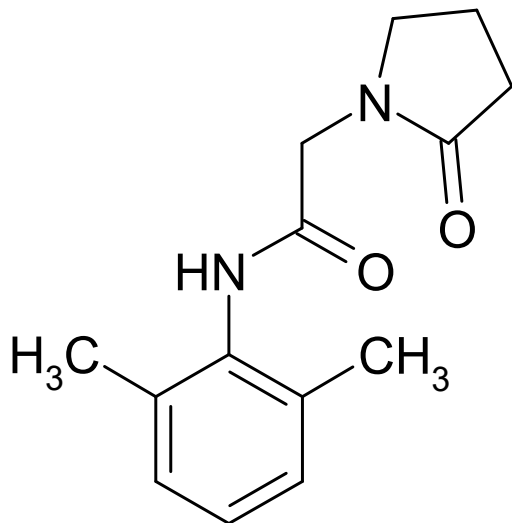


2-(4-hydroxy-2-oxopyrrolidin-1-yl)acetamide
oxiracetam



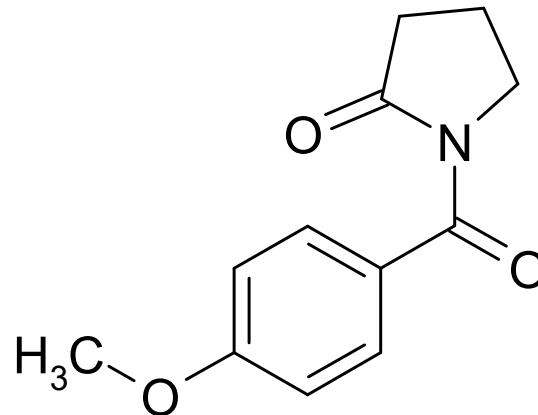
N-[2-(diisopropylamino)ethyl]-2-(2-oxopyrrolidin-1-yl)acetamide
pramiracetam

Cognitive functions enhancers Racetams



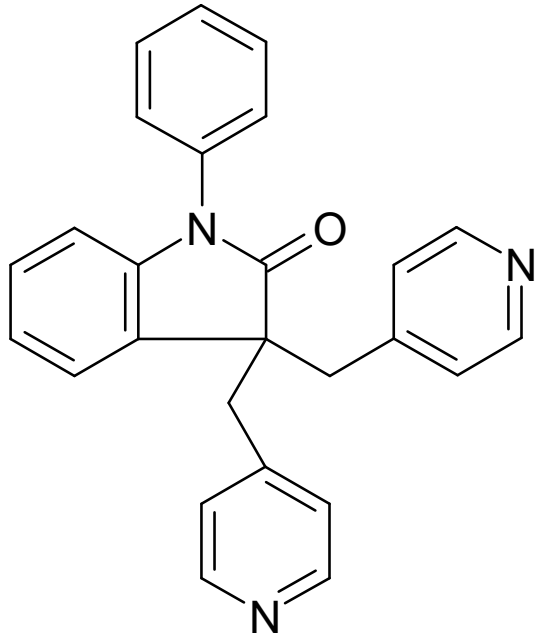
N-(2,6-dimethylphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide
nefiracetam

- Betzing et al. 1982
- close structural analogue of lidocaine
- some antiepileptic and antidysrhythmic activity



1-(4-methoxybenzoyl)pyrrolidin-2-one
aniracetam
•also antiradical activity

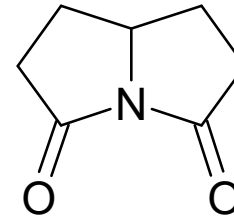
Cognitive functions enhancers Racetams



1-phenyl-3,3-bis(pyridine-4-ylmethyl)-
1,3-dihydroindole-2-one

linopirdine

- treatment of Alzheimer disease (AD)



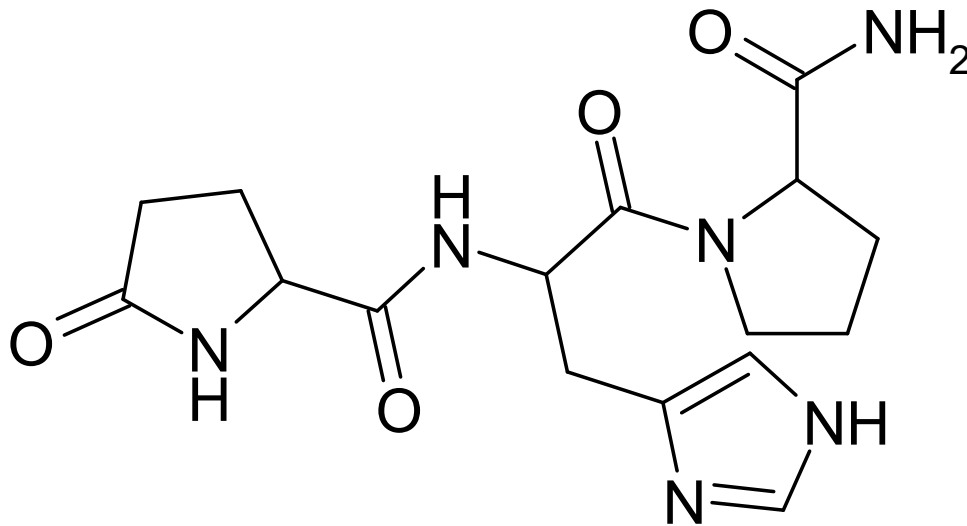
tetrahydro-3*H*-pyrrolizine-3,5-dione
rolziracetam

Cognitive functions enhancers

Racetams

Protirelin – synthetic thyrotropin-releasing hormone (TRH)

- a hormone of hypothalamus stimulating thyrotropine and prolactin synthesis in hypophyse
- also neurotransmitter in CNS taking part in food intake and energy metabolism control etc.



protirelin

5-oxopropyl-L-histidyl-L-proline amide

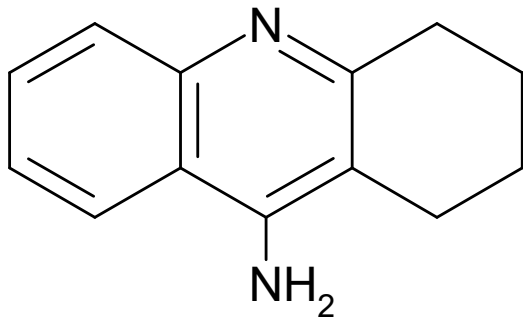
Protirelinum PhEur

- structure elucidated 1969, used between 1976 - 1994
- administered *p.o.*
- used as cognitive functions enhancer for treatment of consequences of brain and spinal cord damage and neurodegenerative diseases (Alzheimer, Parkinson)

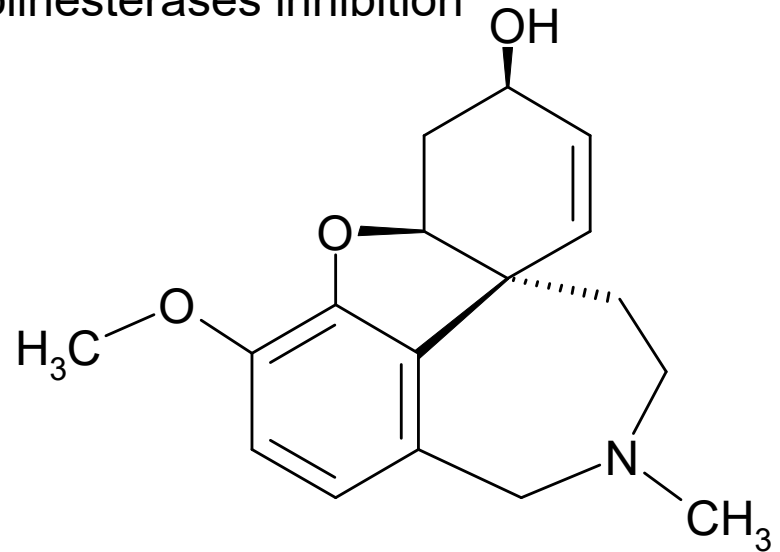
Cognitive functions enhancers

2. Cholinergics acting in CNS

- compounds ↑ availability of t acetylcholine in CNS
- mode of action: cholinesterases inhibition



9-amino-1,2,3,4-tetrahydroaridine
tacrine

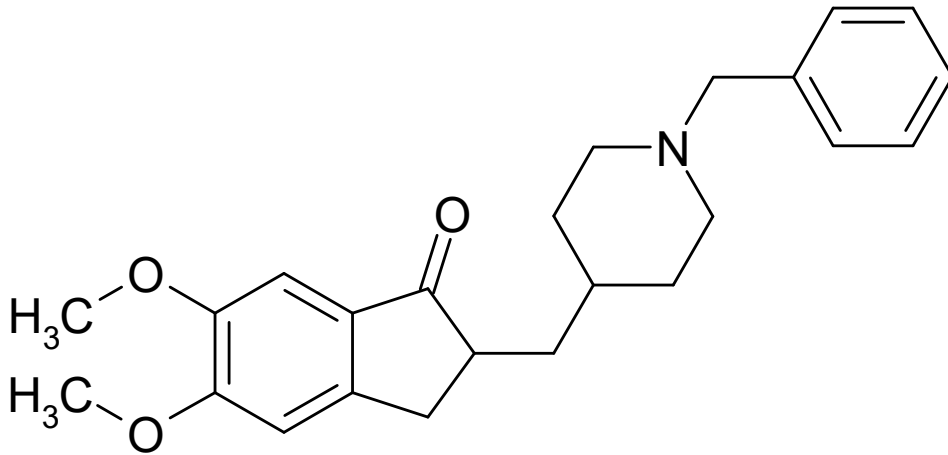


galantamine

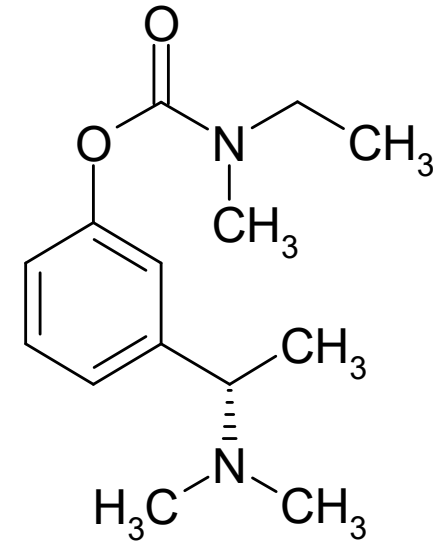
- alkaloid isolated from bulbs of *Galanthus woronovii*, *G. elwesii* and others (*Amaryllidaceae*)
- Reminyl® tbl.

- AD treatment

Cognitive functions enhancers
2. Cholinergics acting in CNS



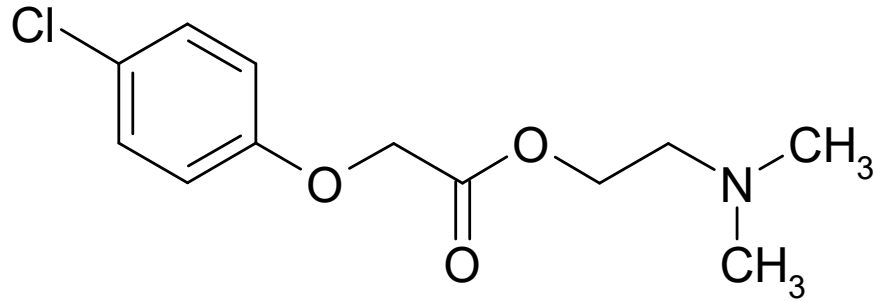
2-[(1-benzylpiperidin-4-yl)methyl]-
5,6-dimethoxyindane-1-one
donepezil
Aricept® tbl.



3-[(1S)-1-(dimethylamino)ethyl]phenyl-N-
ethyl-N-methylcarbamate
rivastigmine
Exelon® cps., Pronetal® cps.

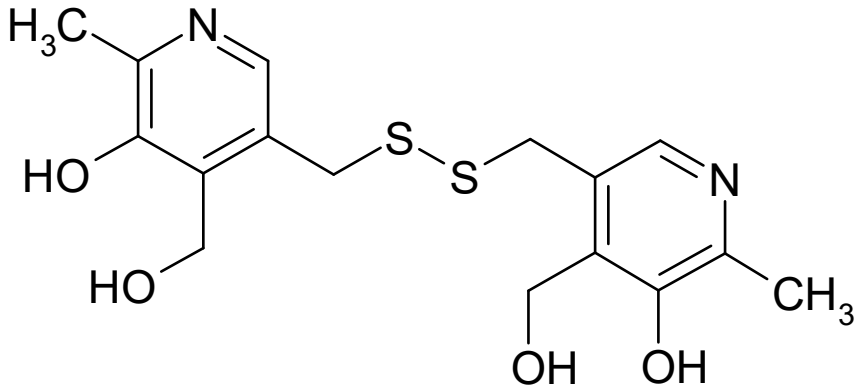
•AD treatment

Cognitive functions enhancers
3. Phenoxyalkanoic acids derivatives



2-dimethylaminoethyl-2-(4-chlorophenoxy)acetate
meclofenoxate

Cognitive functions enhancers
Compounds of other structures or modes of action

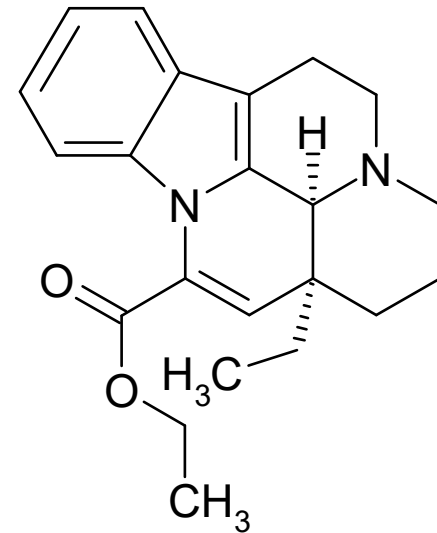


5-[(5-hydroxy-4-(hydroxymethyl)-6-methylpyridine-3-yl)methyl]dithio)methyl]-4-(hydroxymethyl)-2-methylpyridine-3-ol

pyritinol

- structural analogue of vitamin B6 – pyridoxol: 2 molecules linked with disulfide bridge

Encephabol® por. sus., Enerbol® tbl.



(+)-*cis*-11a-ethyl-2,3,4,5,11a,11b-hexahydro-1H-3a,9b-diazabenzocd]fluoranthene-10-carboxylic acid ethyl ester

vinpocetine

- derived from alkaloids of *Vinca* species
 - improves brain metabolism, ↑ consumption of O₂ and glucose by brain tissue
- Cavinton® tbl.

Halucinogens

= psychotomimetics, psychedelics, psychodysleptics

- cause „a condition similar to psychosis“
- cause changes of thinking, perception, mood, posture
- cause neither abuse nor addiction, do not stimulate CNS similarly to amphetamines (O'Brien 2001)
- stimulate serotonin 5HT_{2A} receptors in frontal cortex

„To sink in hell or soar angelic,
you'll need a pinch of psychedelic.“

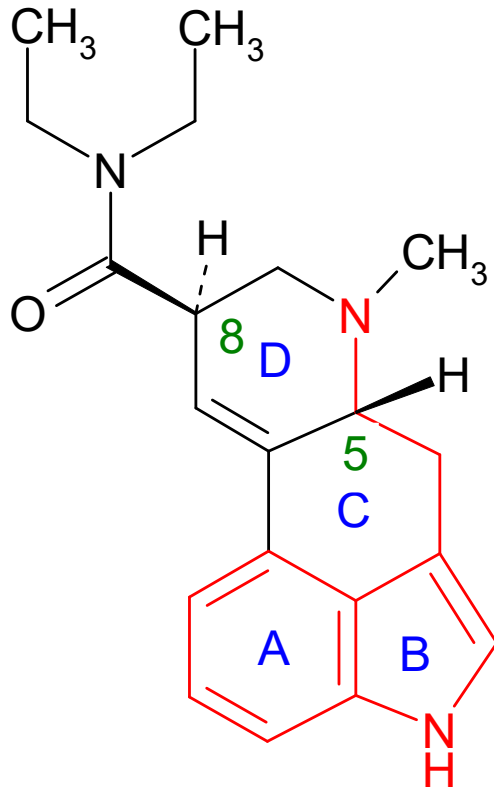
Humphry Osmond 1957

Halucinogens classification

1. Compounds with tryptamine fragment in the molecule
 - 1.1 Ergolines
 - 1.2 Simple tryptamine derivatives
2. Phenylalkylamine derivatives
3. Oxazole and isoxazole derivatives

Compounds with tryptamine fragment in the molecule

1.1 Ergolines

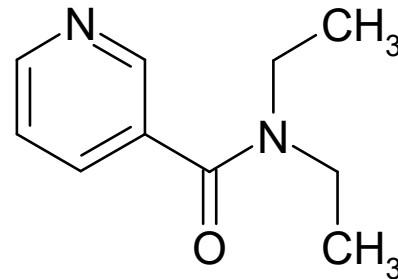


D-LSD

Lysergic acid diethylamide (LSD)
syn. **lysergide**, Heavenly Blue, Wedding Bells...

Lysergsäure Diethylamid \Rightarrow LSD-25

- prepared by Stoll and Hofmann in 1938 in the frame of niketamide analogues research, the effect found accidentally 16th April 1943
- effective dose $\geq 25\mu\text{g}$
- acts on serotonin receptors



nicotinic acid diethylamide

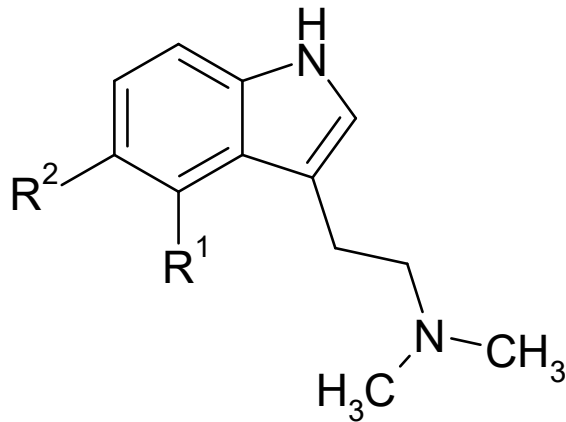
nikethamide

- respiratory and circulation analeptic (obsolete)

Compounds with tryptamine fragment in the molecule

1.2 Simple tryptamine derivatives

- halucinogenic alkaloids of animals, plants and mushrooms



R¹

R²

-H

-H

N,N-dimethyltryptamine (DMT)
Anadenanthera (Fabaceae)

-H

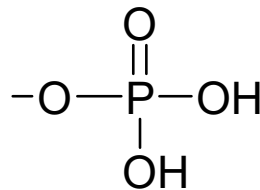
-OH

bufotenin *Bufo alvarius*,
Anadenanthera

-H

-OCH₃

5-methoxydimethyltryptamine (5-MeO-DMT)
Bufo alvarius



-H

psilocybine
Psilocybe mexicana

-OH

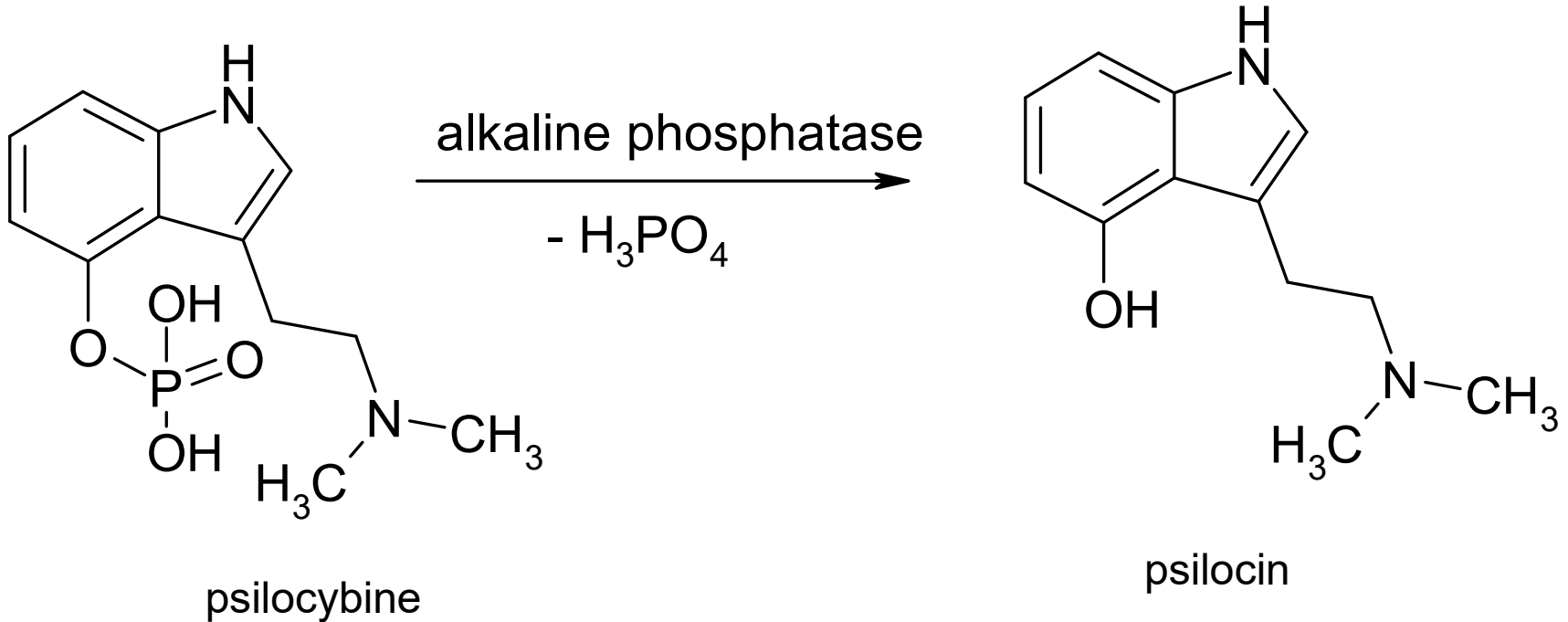
-H

psilocin
Psilocybe mexicana

Compounds with tryptamine fragment in the molecule

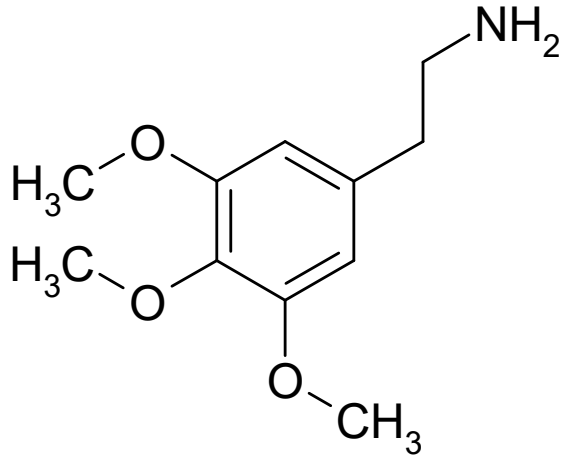
1.2 Simple tryptamine derivatives

- psilocybin is a prodrug of psilocin



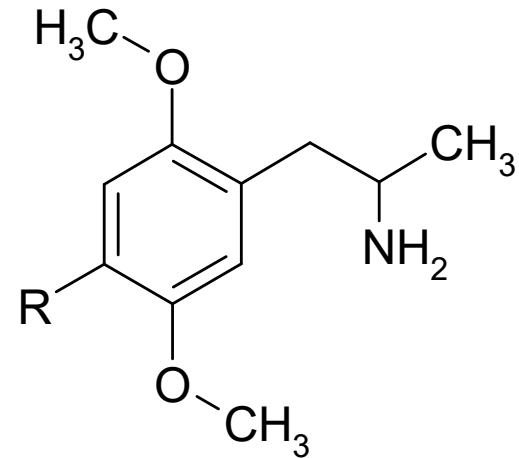
- alkaline phosphatase is active in GIT, kidneys and blood
- psilocin as itself is not absorbed from GIT

2. Phenylalkylamin derivatives



2-amino-2-(3,4,5-trimethoxyphenyl)ethane
mescaline

Lophophora williamsii,
Trichocereus peruvianus



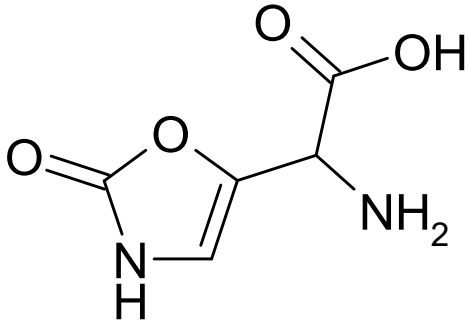
R=-CH₃ 2-amino-1-(2,5-dimethoxy-4-methylphenyl)propane
DOM

R=-Br 2-amino-1-(4-bromo-2,5-dimethoxyphenyl)propane
DOB

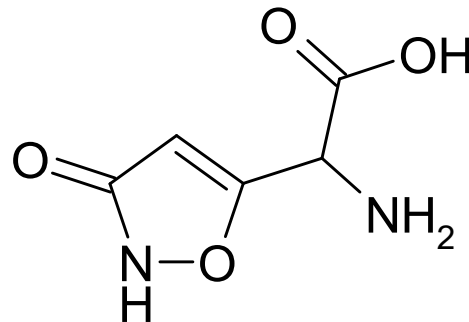
R=-I 2-amino-1-(4-jodo-2,5-dimethoxyphenyl)propan
DOI

- highly active synthetic halucinogenes used for 5-HT receptors research etc.

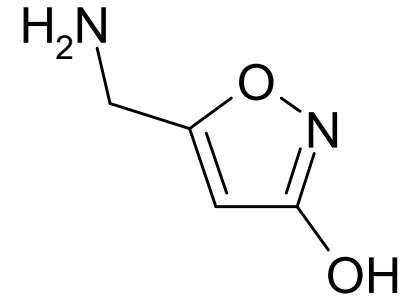
3. Oxazole and isoxazole derivatives



2-amino-2-(2-oxo-2,3-dihydrooxazole-5-yl)acetic acid
muscazone
•hallucinogen



2-amino-2-(3-oxo-2,3-dihydroisoxazole-5-yl)acetic acid
ibotenic acid
•glutamate receptor agonist
•agitated toxic delirium



3-hydroxy-5-aminomethylisoxazole
muscimol
•GABA receptor agonist
•weak sedative

fly mushroom *Amanita muscaria*, panther mushroom *A. pantherina*