Central nervous system stimulants

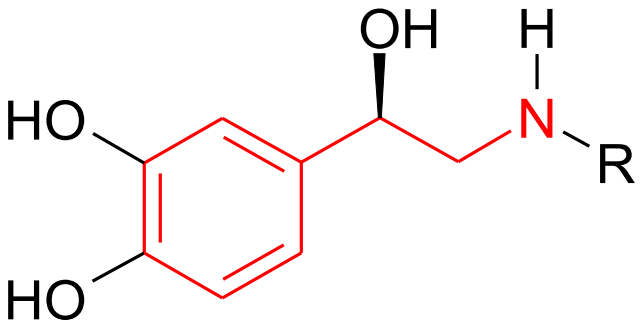
- compounds stimulating mental functions and physical performance

1. Phenylethylamine and phenylisopropylamine derivatives
2. Modafinil
3. Purine alkaloids
4. Compounds with tropane scaffold

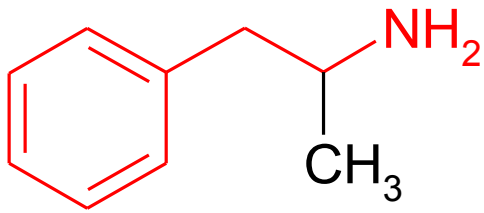
- different concept to those of Ashutosh Kar, Medicinal Chemistry, Anshan, Tunbridge Wells, UK, 2006, Chapter 8, pp. 194-209

1. Phenylethylamine and phenylisopropylamine derivatives

- natural catecholamines analogues



R = H
noradrenaline
R = CH_3
adrenaline



amphetamine

Phenylethylamine and phenylisopropylamine derivatives

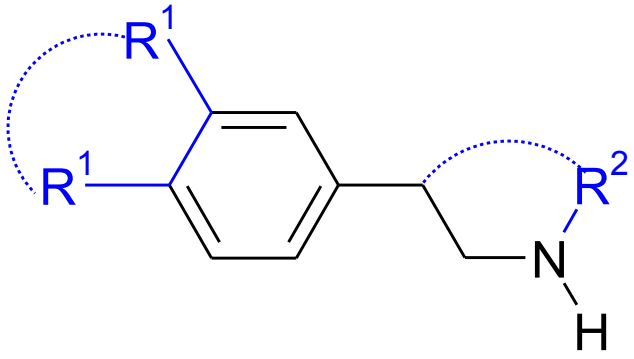
= indirect adrenergics – do not interact directly with adrenergic receptors in the brain but inhibit reuptake of catecholamines or increse their release from synapses; some of them act similarly also in serotoninergic system

•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)

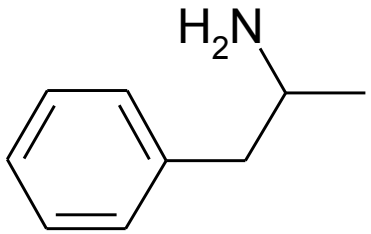
-OH group on the benzene ring are missing or etherified

phenylethylamine moiety can also be a part of a cycle



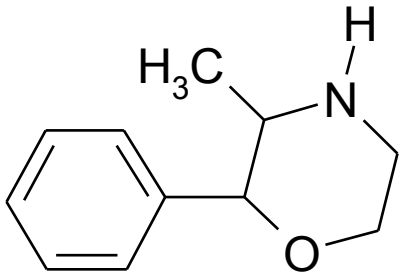
1. Phenylethylamine and phenylisopropylamine derivatives

Compounds used as therapeutics



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

amphetamine



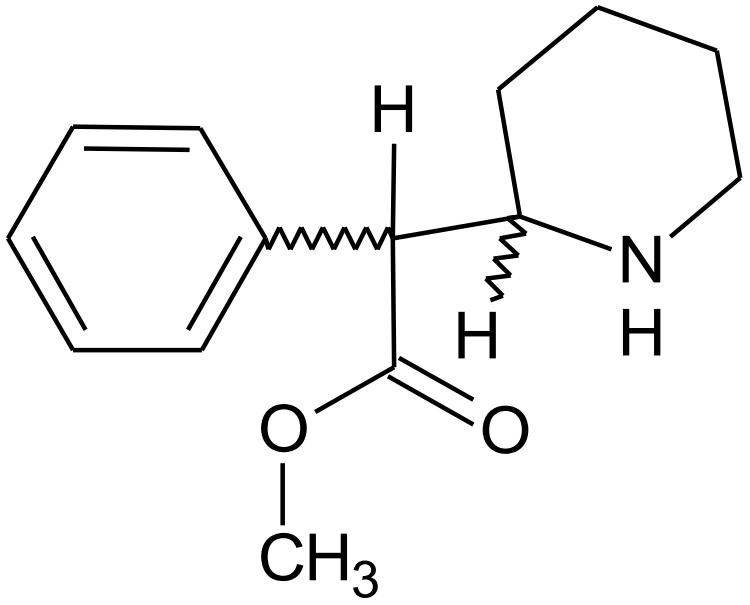
2-phenyl-3-methylmorpholine

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, dehydratation, circulation breakdown
- see further centrally acting anobesics (anorectics)

1. Phenylethylamine and phenylisopropylamine derivatives

Compounds used as therapeutics



methylphenidate

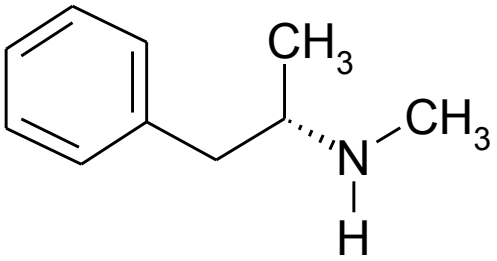
•for better concentration e.g. in childern with some form of autistic disorder
•kinetic disorder
Concerta ® , Ritalin ® , Medikinet ®

Phenylethylamine and phenylisopropylamine derivatives

Psychotropic compounds of amphetamine type

•belong among „hard drugs“

•physical addiction



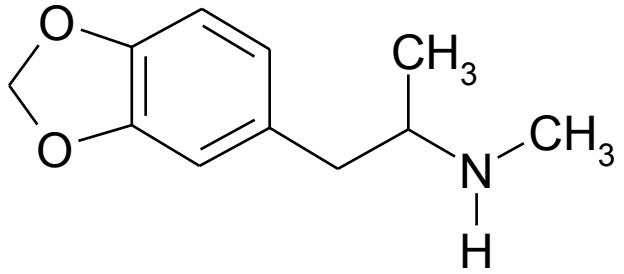
(*S*)-2-methylamino-1-phenylpropane

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. MDMA, Adam, XTC, „E“

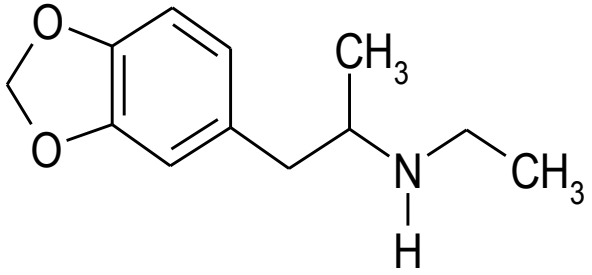
•so called dancing drug

•hallucinogenic effect ($5HT_{2A}$ rp.)

•Europe

Phenylethylamine and phenylisopropylamine derivatives

Psychotropic compounds of amphetamine type



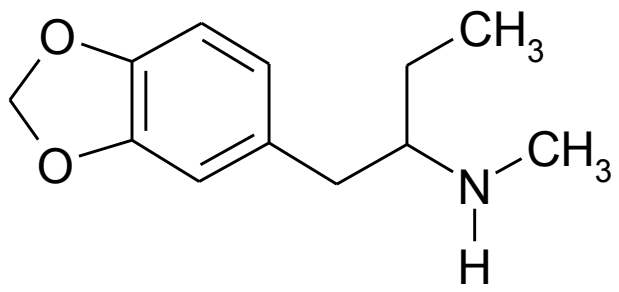
2-(ethylamino)-1-(3,4-methylenedioxyphenyl)propane

3,4-

methylendioxyetamphetamine

MDEA

syn. MDE, Eve



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

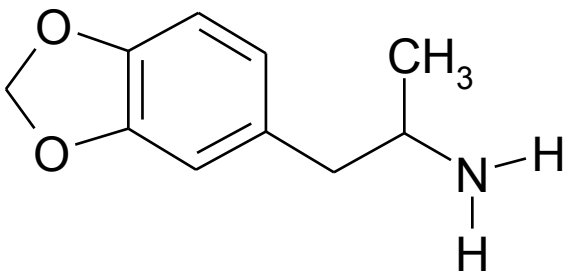
MBDB

syn. Eden, methyl J, MDP_2B

•Sweden

Phenylethylamine and phenylisopropylamine derivatives

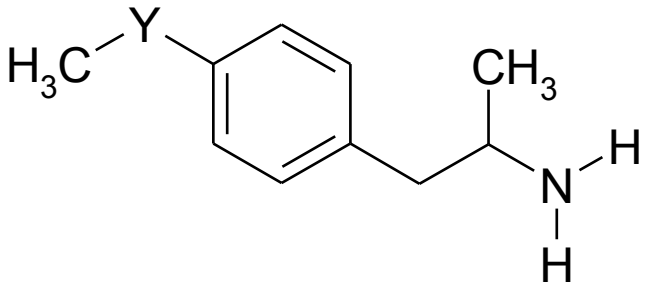
Psychotropic compounds of amphetamine type



2-amino-1-(3,4-methylendioxyphenyl)propaner

tenamphetamine

syn. MDA, love drug, love pill



Y = O

2-amino-1-(4-methoxyfenyl)propan

paramethoxyamphfetamine

syn. PMA, 4-MA

Y = S

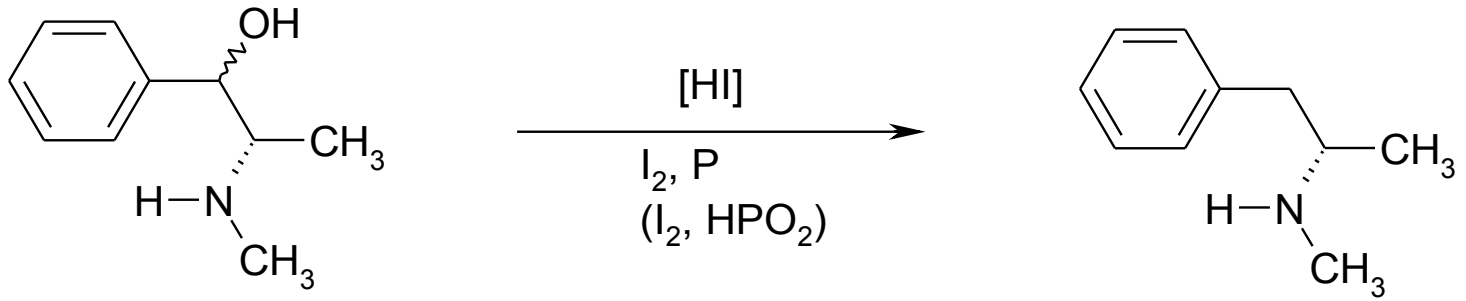
2-amino-1-(4-methylsulphanylphenyl)propane

4-methylthioamphetamine

syn. 4-MTA

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

Synthesis of methamphetamine

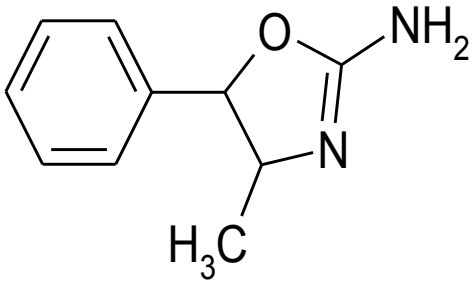


(*1R* or *1S,2S*)-1-fenyl-2-methylaminopropane-1-ol
(-)-ephedrine, (+)-pseudoephedrine

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

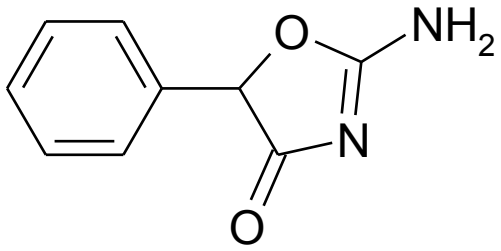
Phenylethylamine and phenylisopropylamine derivatives

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



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

4-methylaminorex

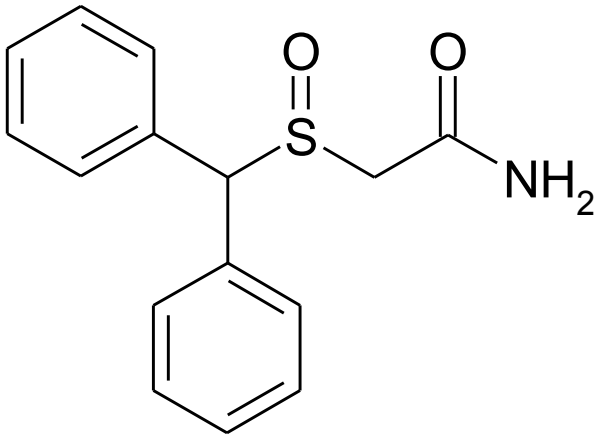


2-amino-5-phenyl-1,3-oxazole-4(5*H*)-one

pemolin

•formerly circulation and respiration stimulant

2. Modafinil



2-[(diphenylmethyl)sulphinyl]acetamide

modafinil

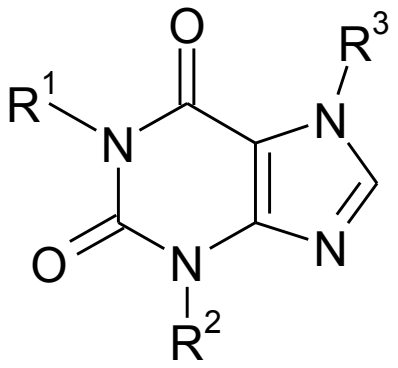
↑ vigility and mental acuity during the day

•treatment of narkolepsy and hypersomnia

•mode of action unclear

Vigil® tbl.

3. Purine alkaloids = „methylxanthins“



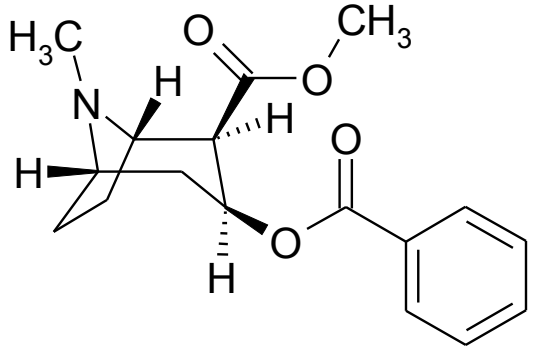
$R^1 = R^2 = R^3 = -CH_3$ **caffein**

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

$R^1 = -H$, $R^2 = R^3 = -CH_3$ **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, phsphodiesterase 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 anaest

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

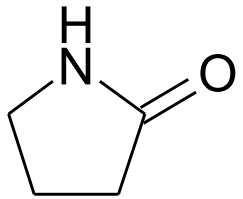
Cognitive functions enhancers classification

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

Cognitive functions enhancers

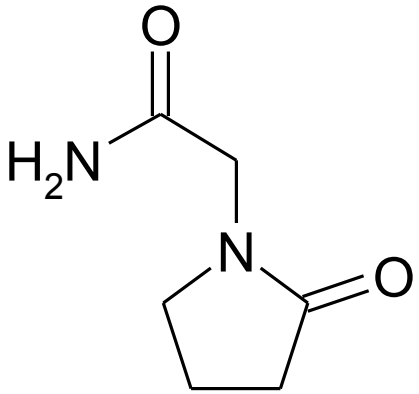
1. Racetams

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



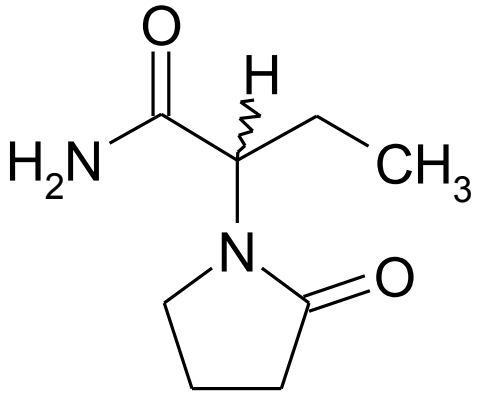
- influence glutamate neurotransmission
- increase glucose utlization by brain tissue

Cognitive functions enhancers
1. Racetams



2-(2-oxopyrrolidin-1-yl)acetamide
piracetam
Geratam® tbl., Nootropil® tbl.,
Oikamid ® cps., Kalicor® cps. …

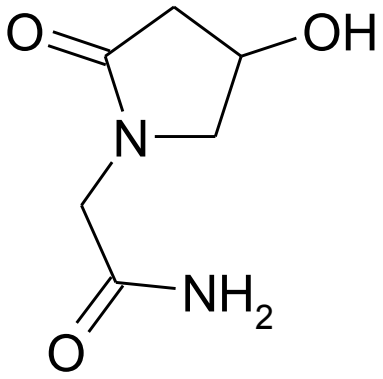
•low hydrophobicity ⇒ low penetration into brain ⇒ high doses necessary (1200 mg single dose)
•low toxicity



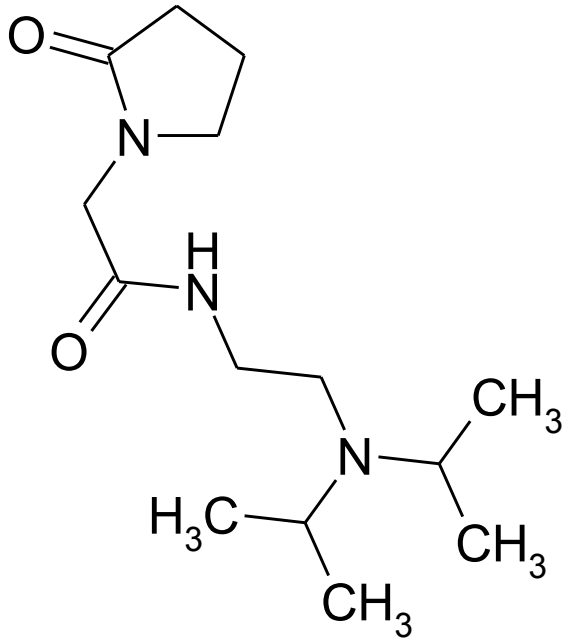
(*R,S*)-2-(2-oxopyrrolidin-1-yl)butanamide
etiracetam – cognitive function enhancer

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

Cognitive functions enhancers
Racetams

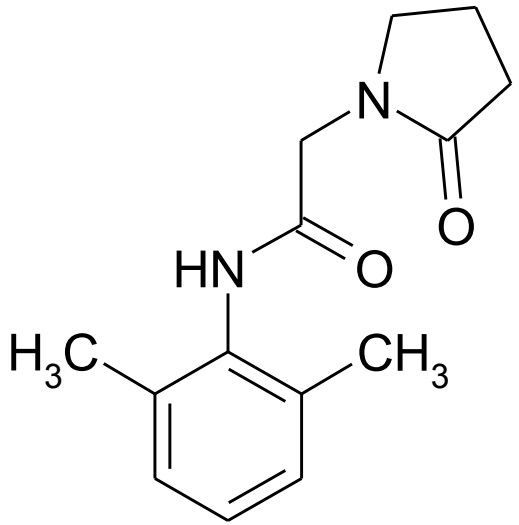


2-(4-hydroxy-2-oxopyrrolidin-1-yl)acetamide
oxiracetam

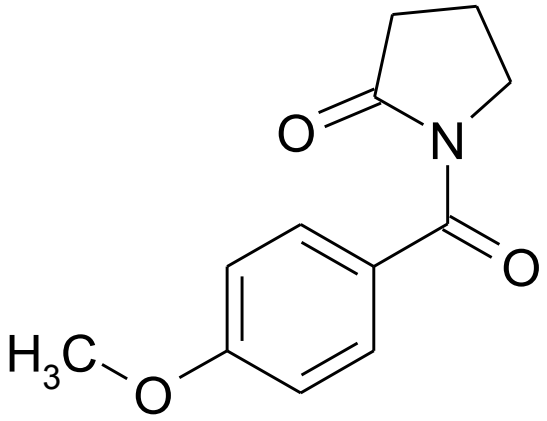


N-[2-(diisopropylamino)ethyl]-2-(2-oxopyrrolidin-1-yl)acetamide
pramiracetam

Cognitive functions enhancers
Racetams

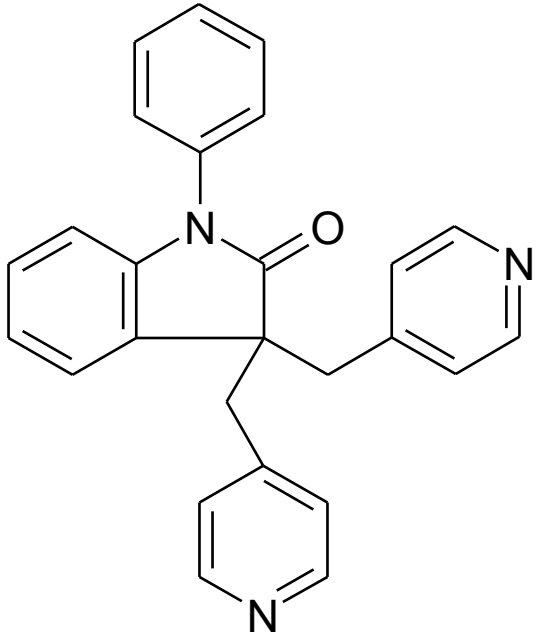


N-(2,6-dimethylphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide
nefiracetam
•Betzing et al. 1982
•close structural analogue of lidocaine
•some antiepileptic and antidysrythmic activity



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

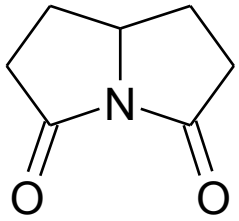
Cognitive functions enhancers
Racetams



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

linopirdine

- treatment of Alzheimer disease (AD)



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

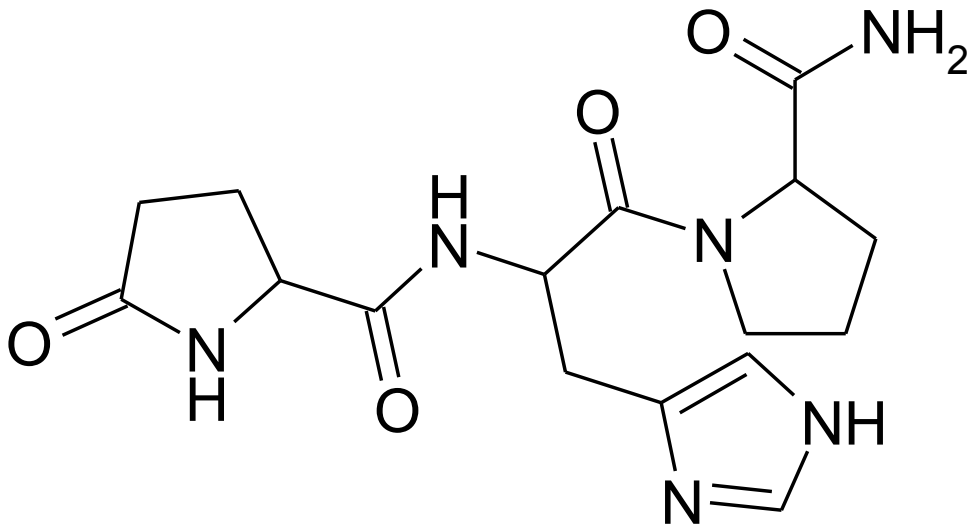
rolziracetam

Cognitive functions enhancers
Racetams

Protirelin – synthetic thyreotropin-releasing hormone (TRH)

•a hormone of hypothalamus stimulating thyreotropine and prolactine synthesis in hypophyse

•also neurotransmitter in CNS taking part in food intake and energy metabolism control etc.



protirelin

5-oxoprolyl-histidyl-prolinamide

Protirelinum PhEur

•structure elucidated 1969, used since 1976

•administered *p.o.*

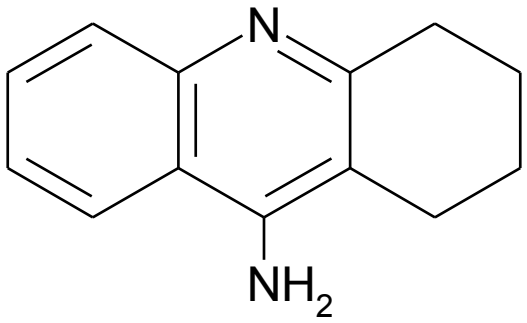
•used as cognitive functions enhancer for treatment of consequences of brain and spinal cord damage and neurodegenerative diseases (Alzheimer, Parkinson)

Cognitive functions enhancers

2. Cholinergics acting in CNS

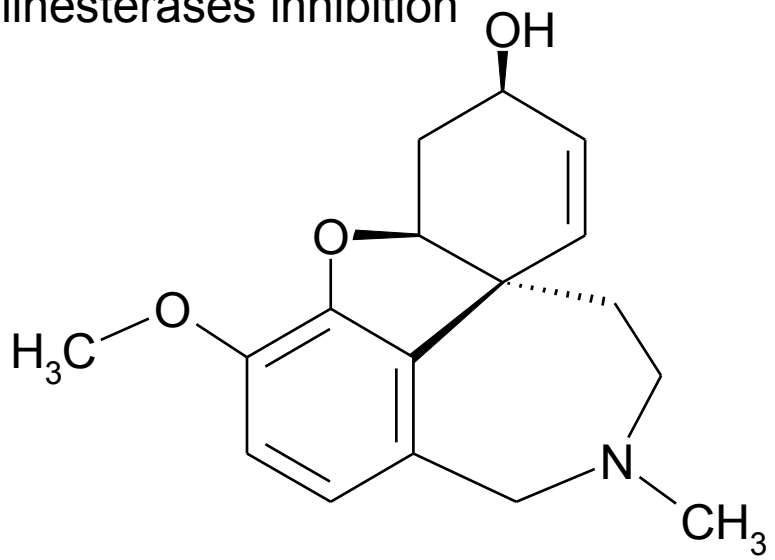
•compounds ↑ availability of t acetylcholine in CNS

•mode of action: cholinesterases inhibition



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

tacrine



galantamine

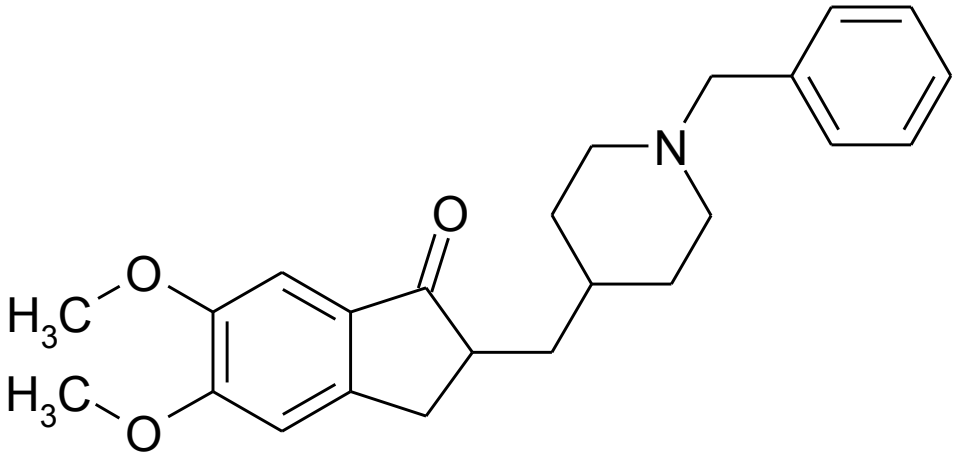
•alkaloid isolated from bulbs of *Galanthus woronovii, G. elwesii* and others (*Amarylidaceae*)

Reminyl® tbl.

•AD treatment

Cognitive functions enhancers

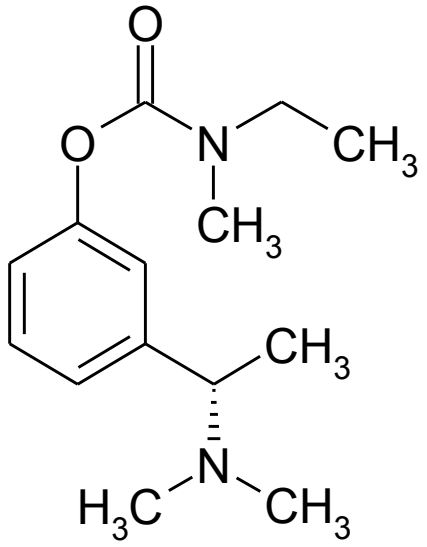
2. Cholinergics acting in CNS



2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dimethoxyindane-1-on

donepezil

Aricept® tbl.



3-[(1*S*)-1-(dimethylamino)ethyl]phenyl-N-ethyl-N-methylcarbamate

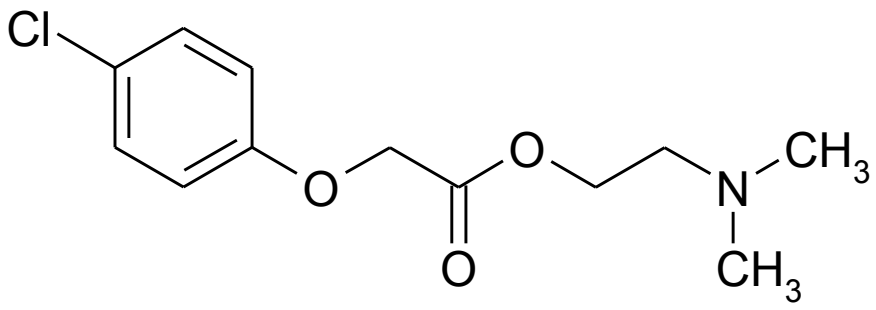
rivastigmine

Exelon® cps., Pronetal® cps.

•AD treatment

Cognitive functions enhancers

3. Phenoxyalkanoic acids derivatives

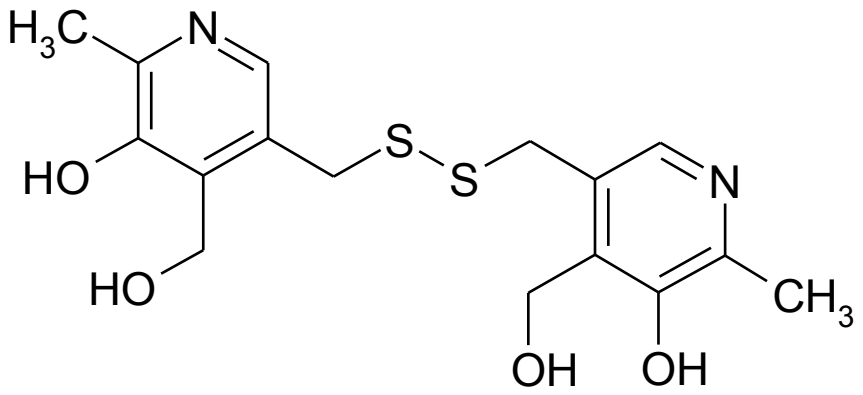


2-dimethylaminoethyl-2-(4-chlorphenoxy)acetate

meclofenoxate

Cognitive functions enhancers

Compounds of other structures or modes of action

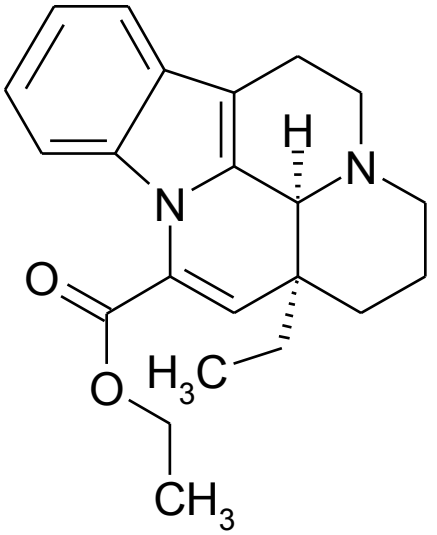


5-[({[5-hydroxy-4-(hydroxymethyl)-6-methylpyridine-3-yl]methyl}dithio)methyl]-4-(hydroxymethyl)-2-methylpyridine-3-ol

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-diazabenzo[cd]fluoranthen-10-carboxylic acid ethyl ester

vinpocetine

•derived from alkaloids of *Vinca* species

•improves brain metabolism, ↑ consumption of O_2 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 serotonine $5HT_{2A}$ receptors in frontal cortex

„To sink in hell or sour angelic,
you‘ll need a pinch of psychedelic.“
Humphry Osmond 1957

Halucinogens classification

1. Compounds with tryptamine fragment in the molecule

1.1 Ergolines

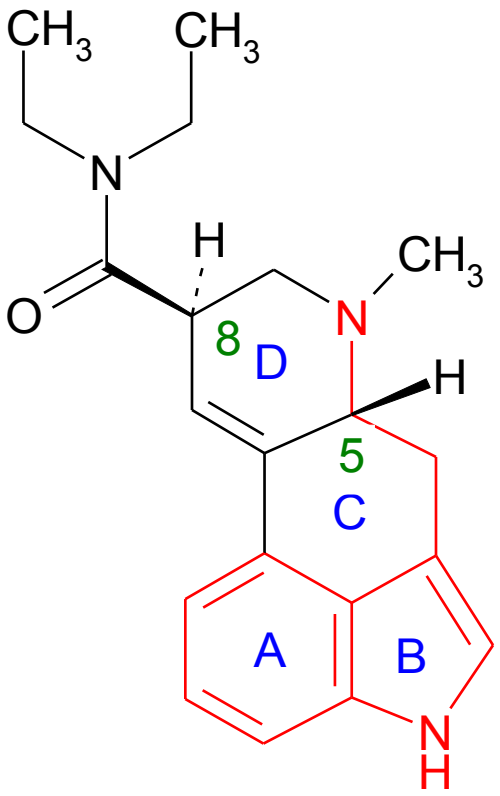
1.2 Simple tryptamine derivatives

2. Phenylakylamine derivatives

3. Oxazole and isoxazole derivatives

Compounds with tryptamine fragment in the molecule

1.1 Ergolines



D-LSD

Lysergic acid diethylamide (LSD)

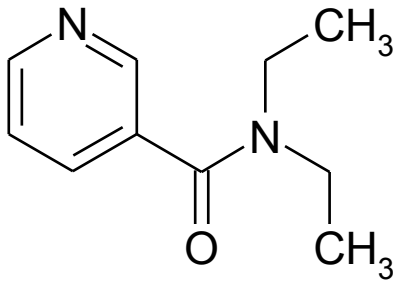
syn. **lysergide**, Heavenly Blue, Wedding Bells…

Lysergsäure Diethylamid ⇒ LSD-25

•prepared by Stoll and Hofmann in 1938 in the frame of niketamide analogues research, the effect found accidentally 16th April1943

•effective dose ≥ 25µg

•acts on serotinine receptors



ninotinic acid diethylamid

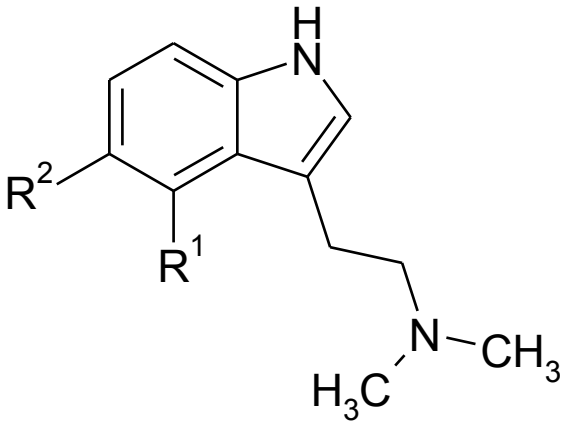
nikethamide

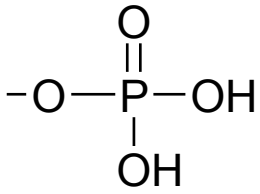
•respiratory and circulation analeptic (obsolete)

Compounds with tryptamine fragment in the molecule

1.2 Simple tryptamine derivatives

- halucinogenic alkaloids of animals, plants and mushrooms

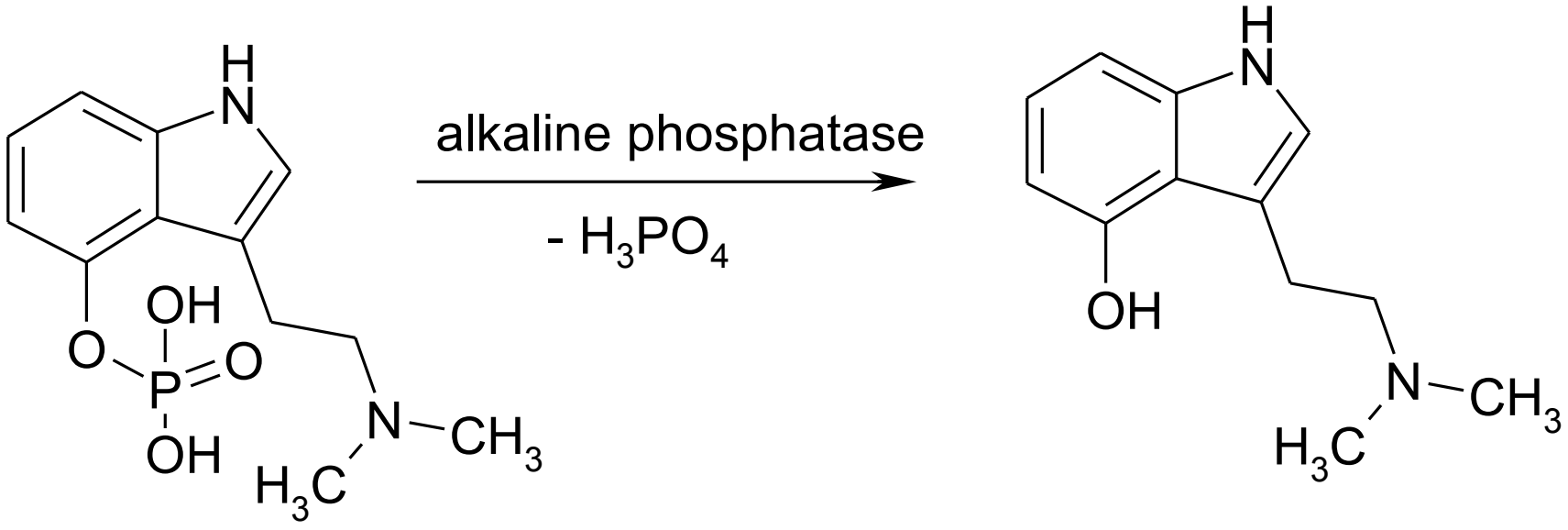


R^1	R^2	
-H	-H	**N,N-dimethyltryptamine (DMT)** *Anadenanthera (Fabaceae)*
-H	-OH	**bufotenin** *Bufo alvarius, Anadenanthera*
-H	$-OCH_3$	**5-methoxydimethyltryptamine (5-MeO-DMT)** *Bufo alvarius*
	-H	**psilocybine** *Psilocybe mexicana*
-OH	-H	**psilocin** *Psilocybe mexicana*

Compounds with tryptamine fragment in the molecule

1.2 Simple tryptamine derivatives

- psilcybin is a prodrug of psilocine

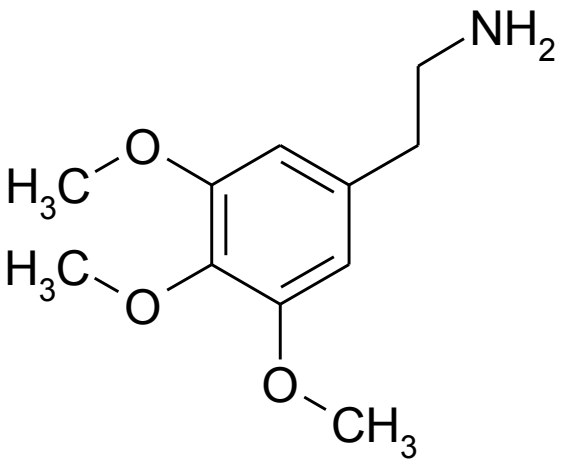


psilocybine

psilocin

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

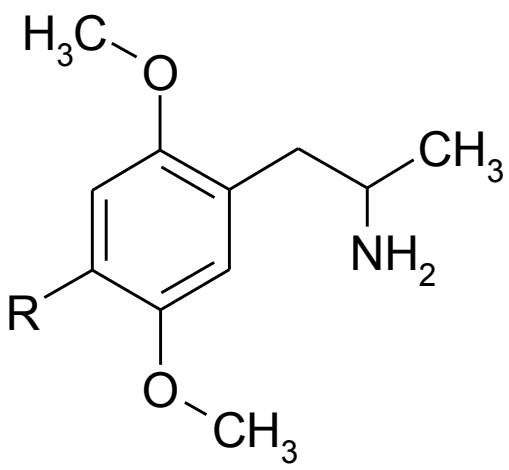
2. Phenylalkylamin derivatives



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

mescaline

Lophophora williamsii, Trichocereus peruvianus



R=-CH_3 2-amino-1-(2,5-dimethoxy-4-methylphenyl)propane

DOM

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

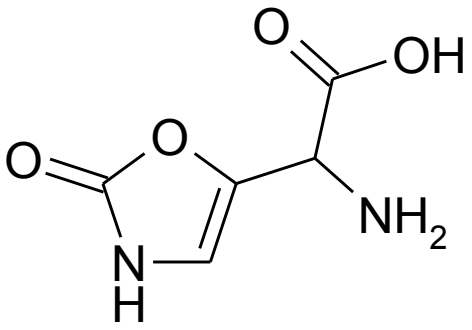
DOB

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

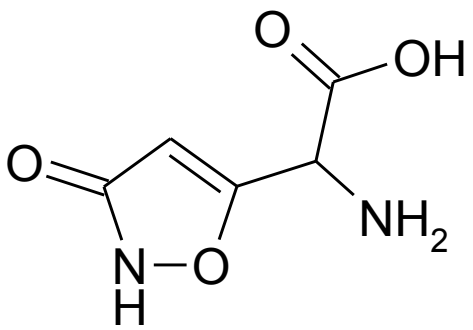
DOI

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

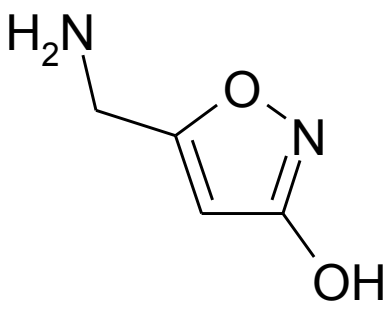
3. Oxazole and isoxazole derivatives



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*