Anti-anxiety agents

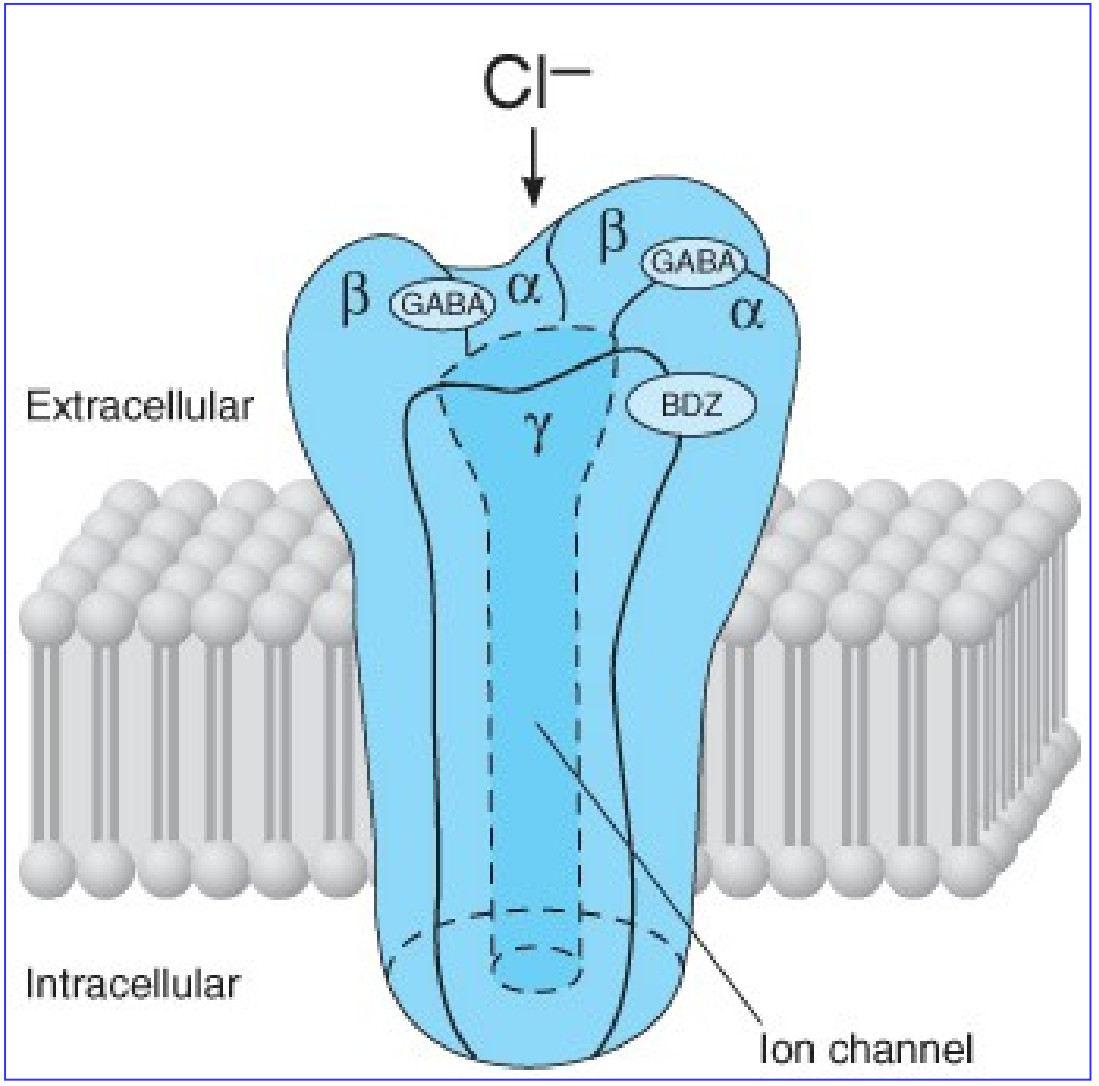
= anxilolytics = ataractics = „minor tranquilizers“

•drugs for treatment of conditions characterized with fear and anxiety

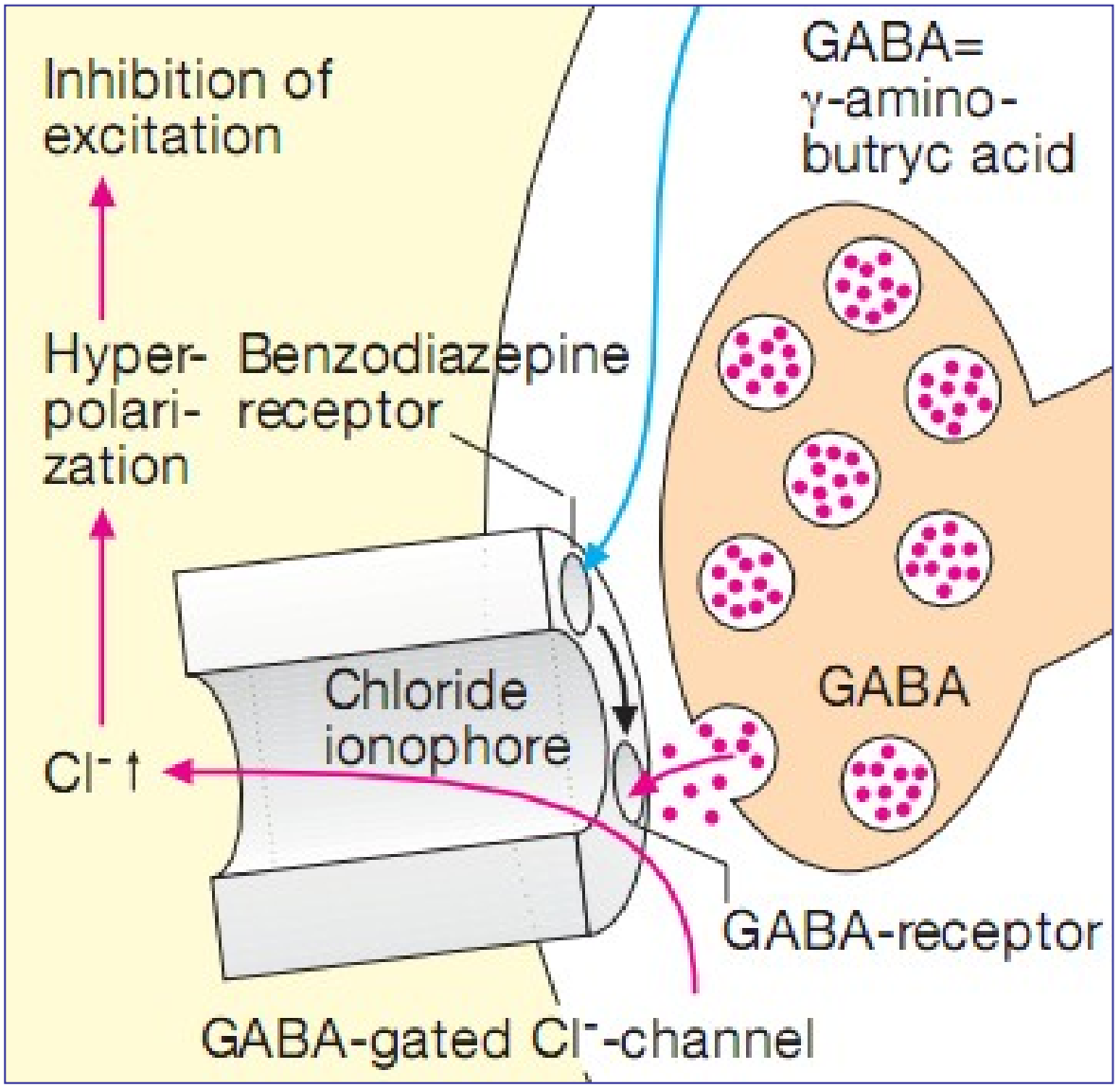
Benzodiazepins

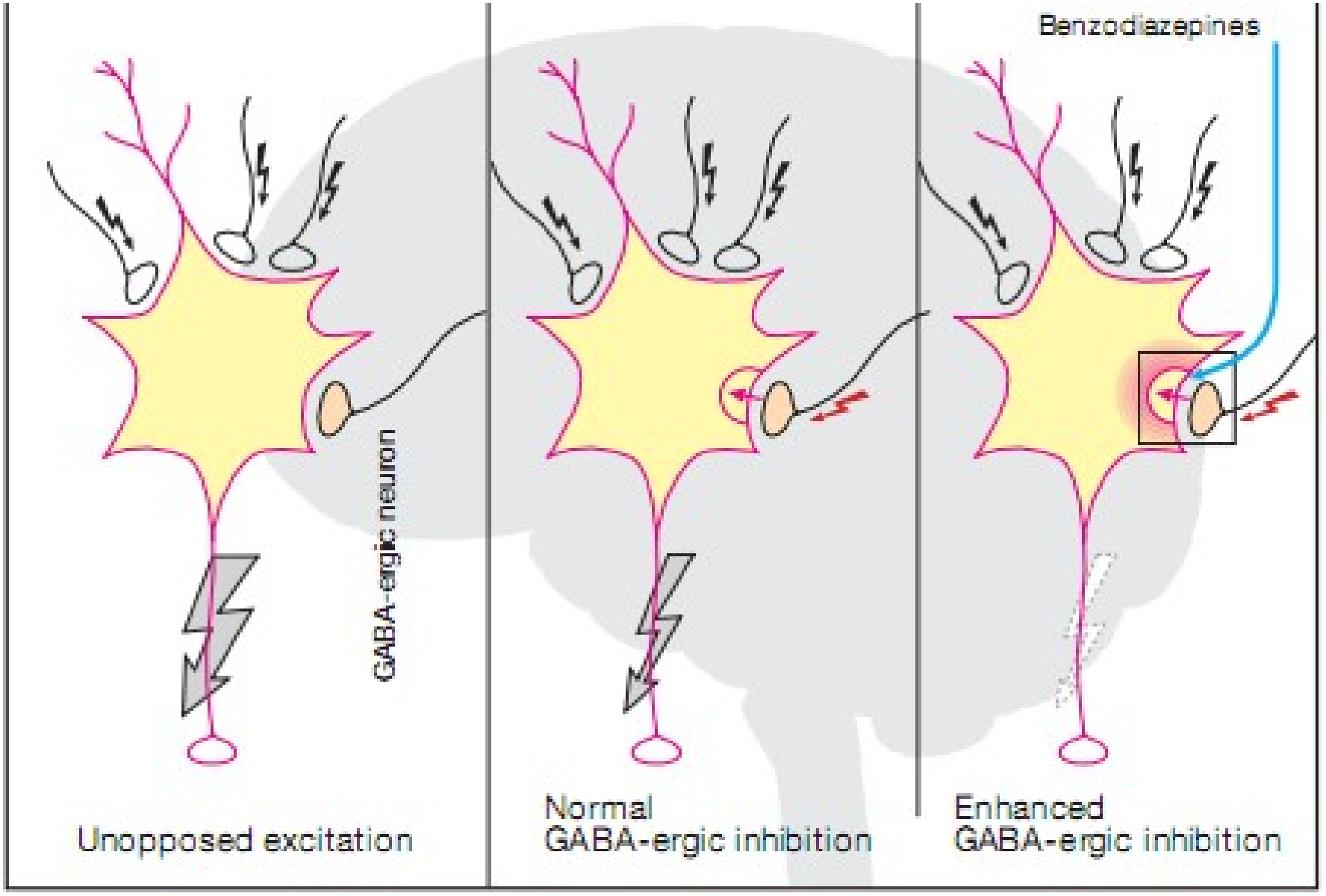
•binding of GABA to $GABA_A$ receptor ⇒ increase of Cl^- channel permeablity ⇒ ↑ conc. Cl^- inside the neuronu ⇒ decrease of excitability

•benzodiazepins enhance GABA effectivity by lowering its concentration needed for channel opening

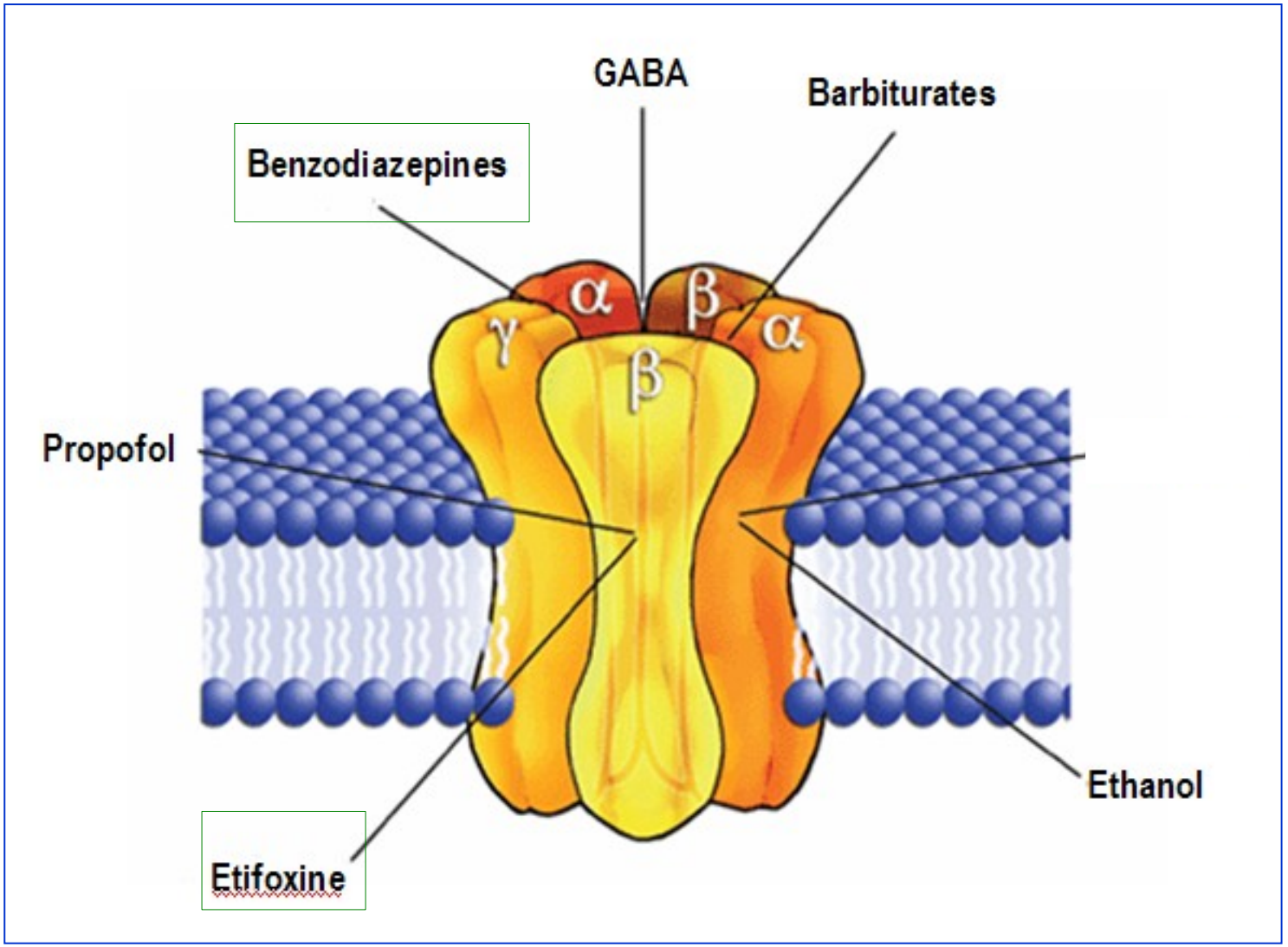


Benzodiazepine receptor is a part of chloride channel (ionophore)



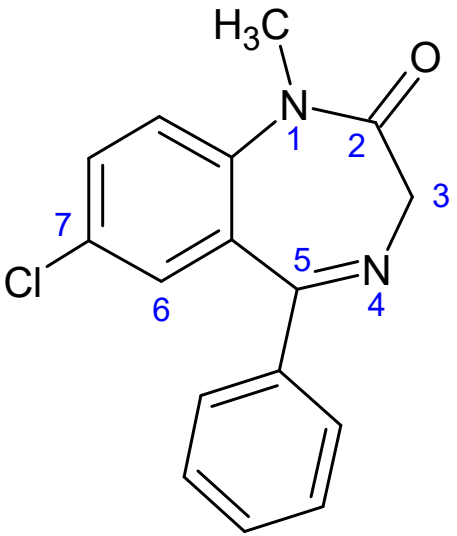


Benzodiazepins amplify GABA-ergic inhibition of impulse conducting in CNS



$GABA_A$-receptor-chloride channel with marked binding sites for various types of inhibiting drugs

Benzodiazepins
1,4-benzodiazepins

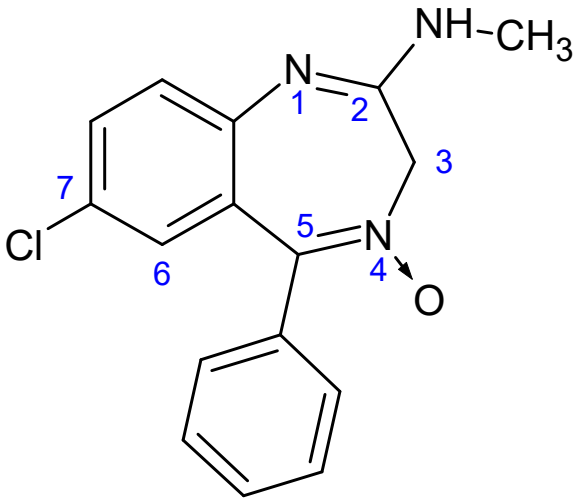


diazepam

Diazepamum PhEur

•also prevention of convulsions in neonates and babies

Apaurin®, Diazepam Slovakofarma®



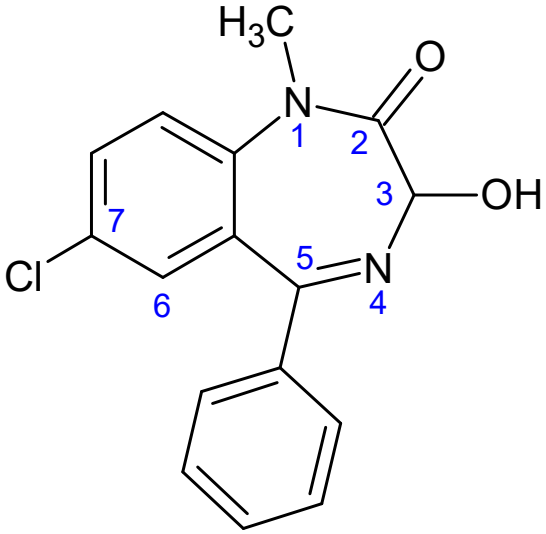
chlordiazepoxid

•since 1960

•N-oxide

•amidine structure enables forming of salts with acids

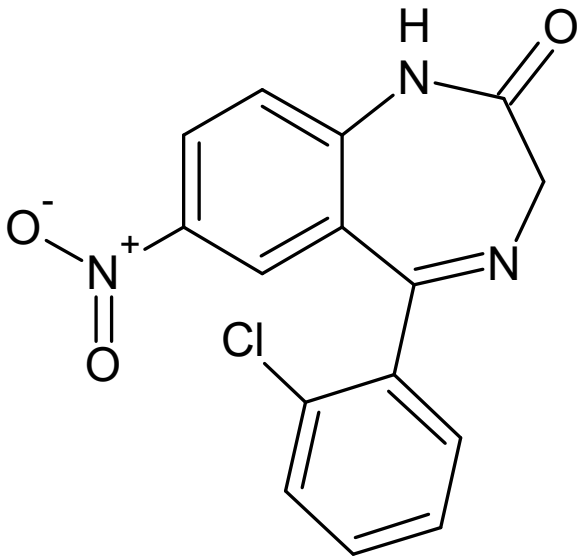
Elenium®



oxazepam

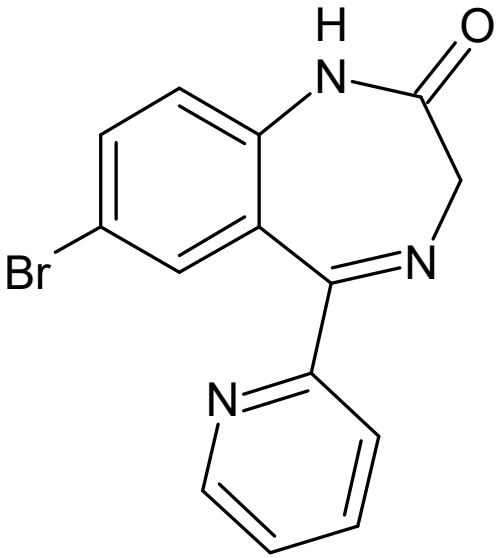
Oxazepam Léčiva®

Benzodiazepins
1,4-benzodiazepins



clonazepam

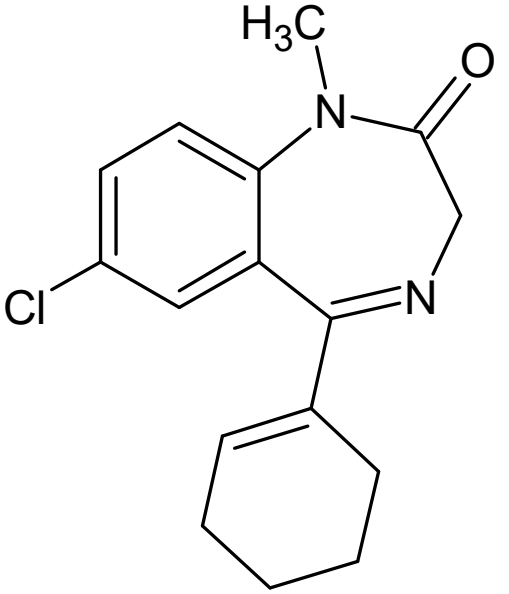
Clonazepamum PhEur



bromazepam

Bromazepamum PhEur

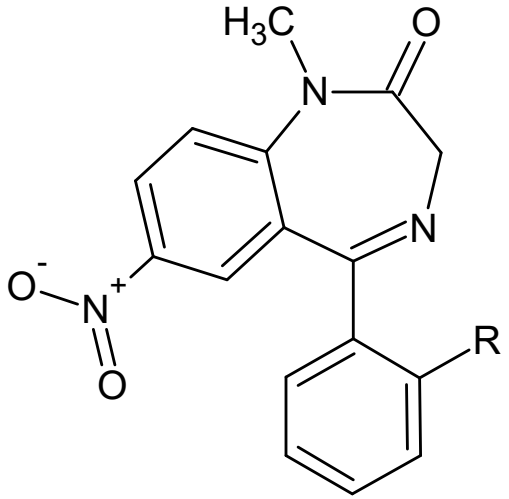
Lexaurin®



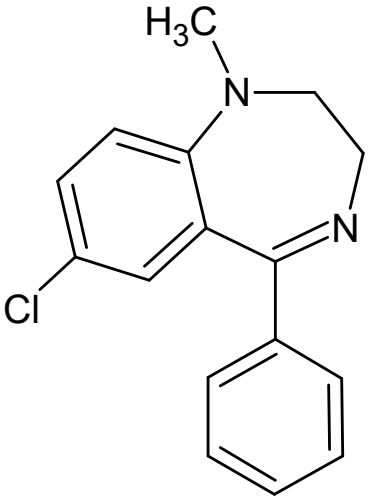
tetrazepam

Tetrazepamum PhEur

Benzodiazepins
1,4-benzodiazepins

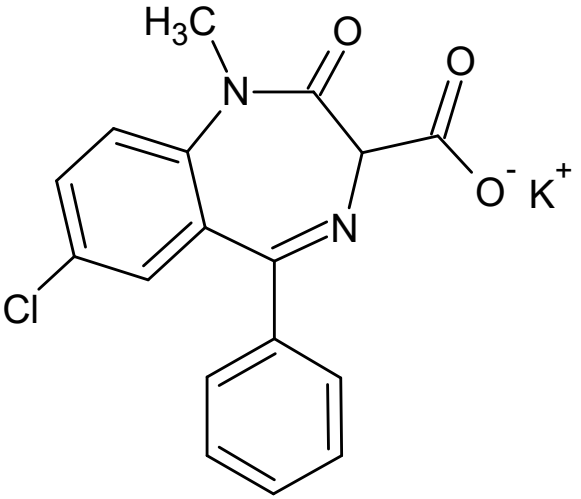


R = H **nitrazepam**
R = F **flunitrazepam**
(Rohypnol®)



medazepam

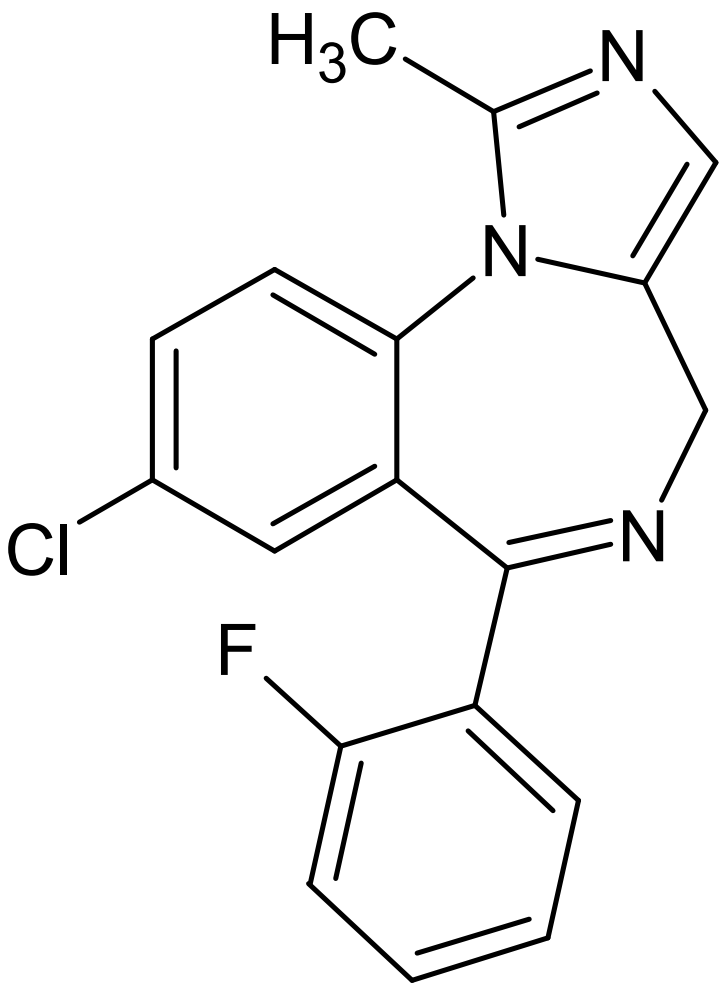
Ansilan®



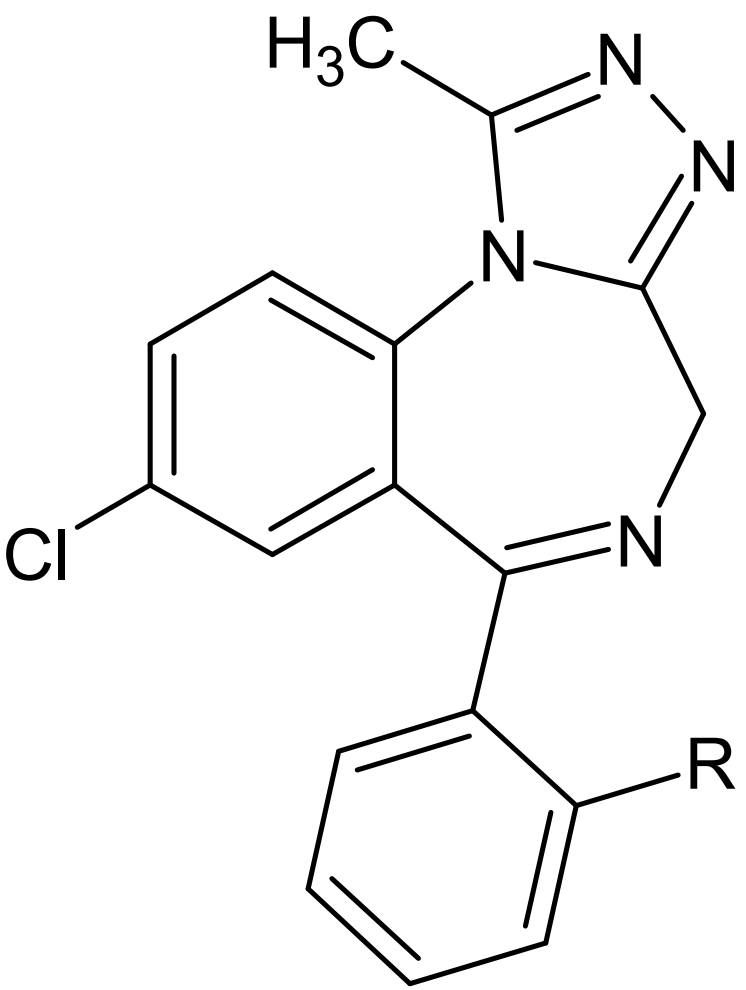
potassium clonazepate

Benzodiazepins

Fused 1,4-benzodiazepins: 4*H*-imidazo[1,5-a] and 4*H*-[1,2,4]-triazolo[4,3-*a*][1,4]benzodiazepins

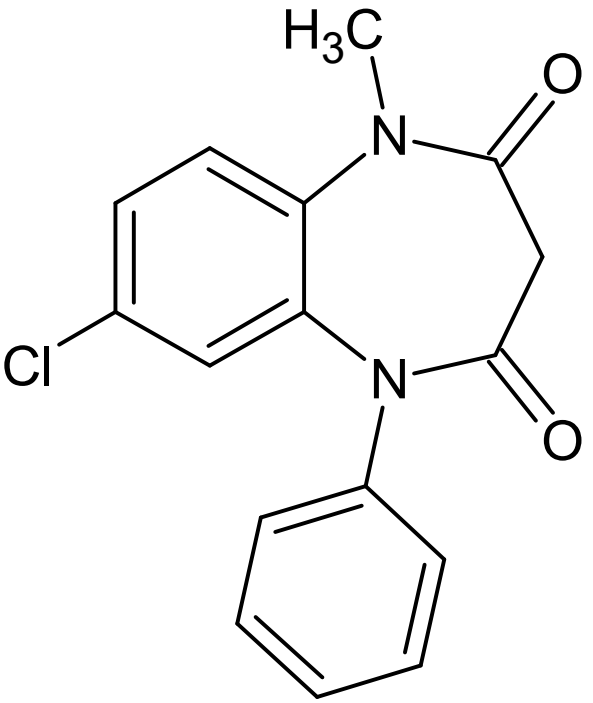


midazolam
Dormicum ®



R = H **alprazolam**
Frontin ® , Neurol ® , Xanax ®
R = Cl **triazolam**

Benzodiazepins
1,5-benzodiazepins



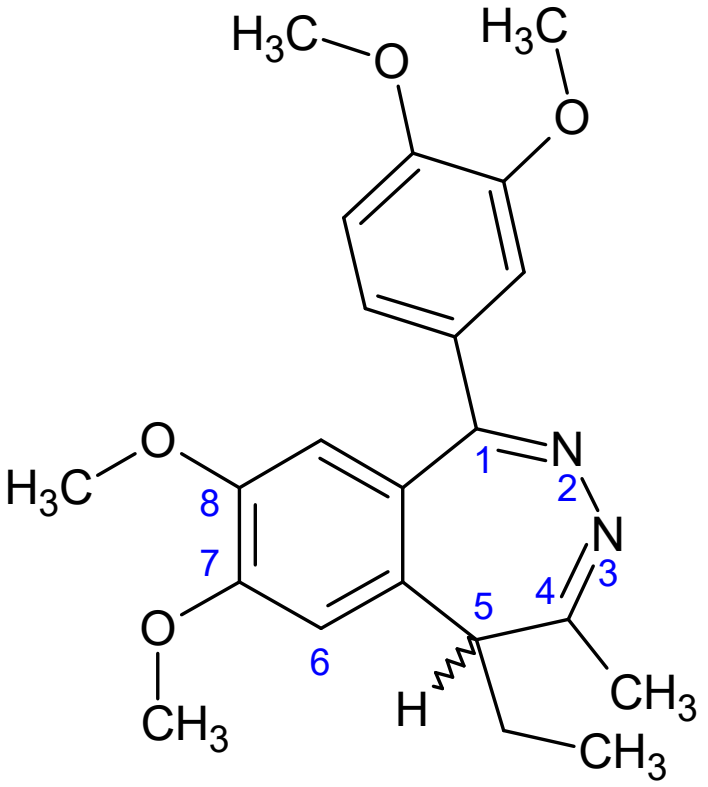
clobazam

Clobazamum PhEur

•also anticonvulsant

Frisium®

Benzodiazepins
2,3-benzodiazepins



R,S-(±): **tofisopam**

Grandaxin®

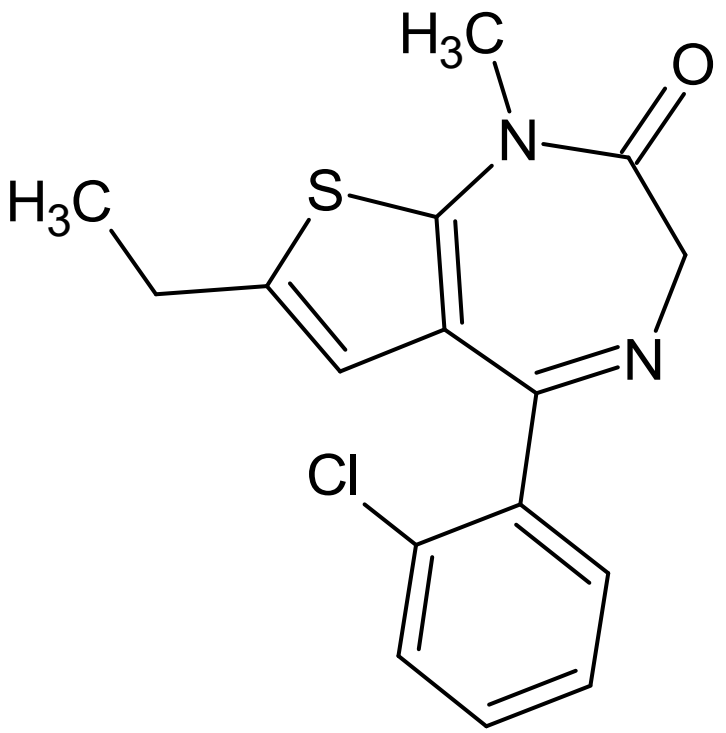
R-(+): **dextofisopam**

•anxiolytic, therapeutic of irritable colon and Crohn disease

S-(-): **levotofisopam**

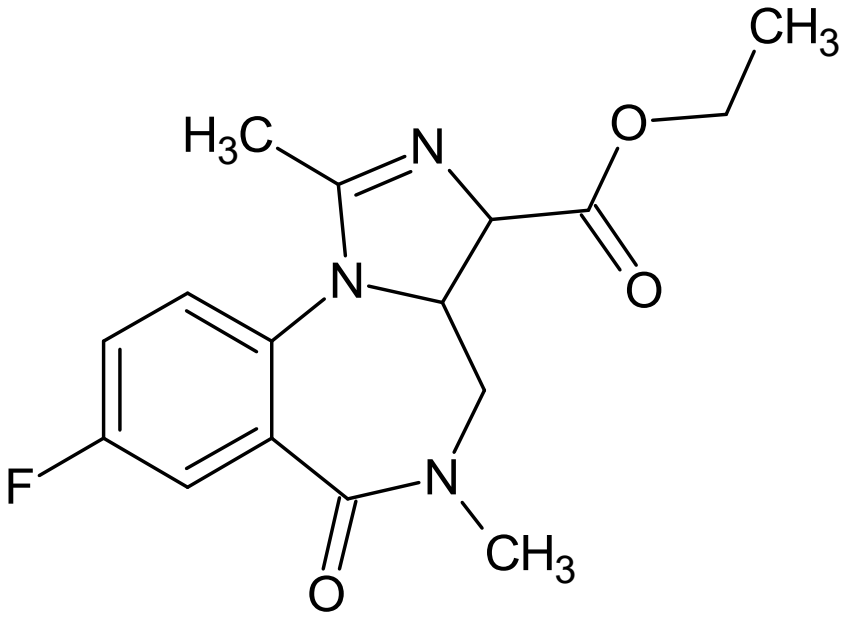
•anxiolytic

Isosteric analogues of benzodiazepins: 1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]-diazepins



clotiazepam

Benzodiazepine receptor antagonist



flumazenil
Flumazenilum PhEur
•treatment of intoxications

Effects of benzodiazepins

- anxiolytic
- anticonvulsive, antiepileptic
- muscle relaxant
- sedative – hypnotic – general anaesthetic

Mode of action

- alosteric effectors of $GABA_A$-receptor
- enhance inhibitory effect of GABA which is proceeded by Cl^- entrance into a cell
- increase of intracellular concentration of Cl^- leads to decrease of membrane irritability
- there is a close correlation between benzodiazepins activity and their afinity to their receptor
- endogenous ligands are not yet known

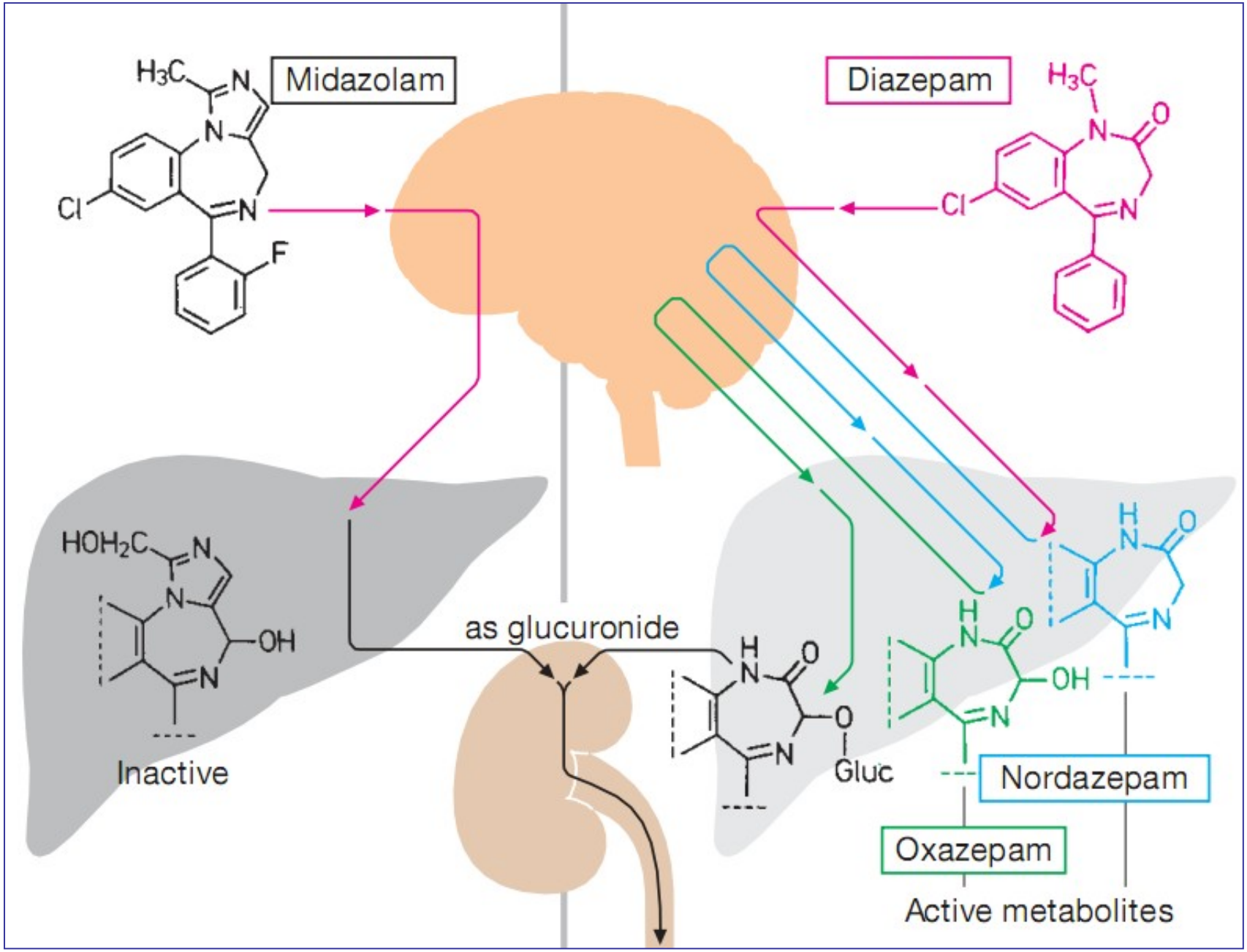
Structure-activity relationships (SAR)

- diazacykloheptane ring fused to an aromatic system is necessary for the effect
- fused benzene can be replaced with thiophene
- benzene rinng in pos. 5 can be replaced with pyridine without activity loss
- methyl in pos. 1 increases the activity
- electron-accepting substituents in pos. 7 increase the activity in the order F<Cl<Br<NO_2
- the activity is increased also by F or Cl in *o*-position of phenyl in pos. 5 of the ring system
- the activity is decreased by larger substituents in pos. 1 or by any substitution in pos. 3 or in *p*-position of phenyl in pos. 5 of the ring system
- OH in pos. 3 shorten the activity

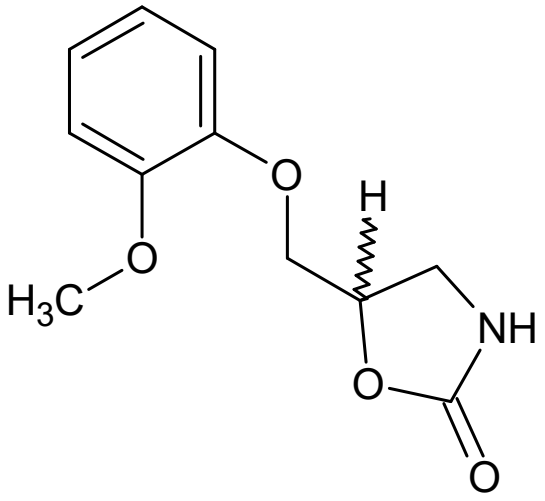
Biotransformation

- liver: oxidative dealkylation on N(2), conjugation with glucuronic acid, excretion by kidneys
- 7-nitrobenzodiazepins (flunitrazepam, nitrazepam): -NO_2 $\rightarrow$ –NH_2, N-acetylation or glucuronation
- fused benzodiazepines with futher azole ring (midazolam, triazolam): methyl on the azole ring is oxidized to hydroxymethyl, yielded inactive compound is conjugated with glucuronic acid and excreted by kidneys

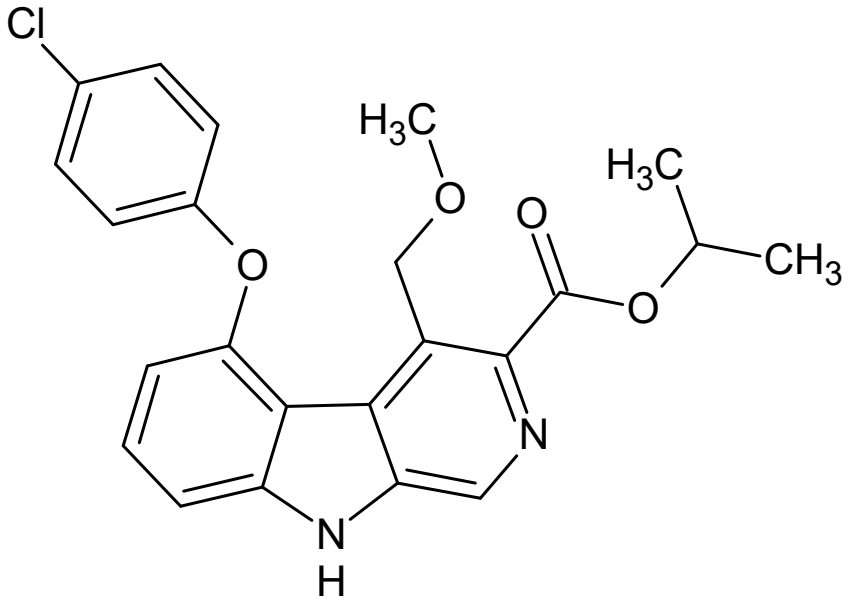
Benzodiazepins biotransformation



Other (non-benzodiazepin) anxiolytics

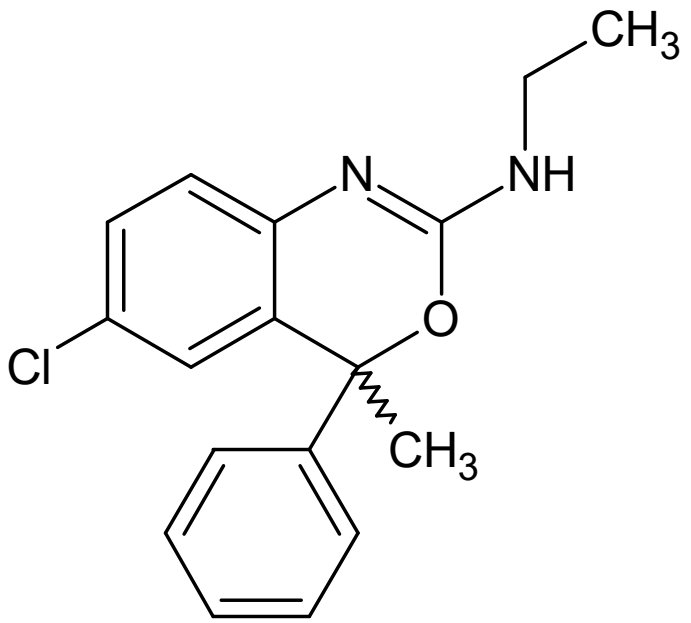


mephenoxalone
•weak anxiolytic
•central myorelaxant
Dimexol®, Dorsiflex®



gedocarnil
•β-carboline derivative
•prepared as glutamate receptor non-competitive antagonist

Other (non-benzodiazepin) anxiolytics

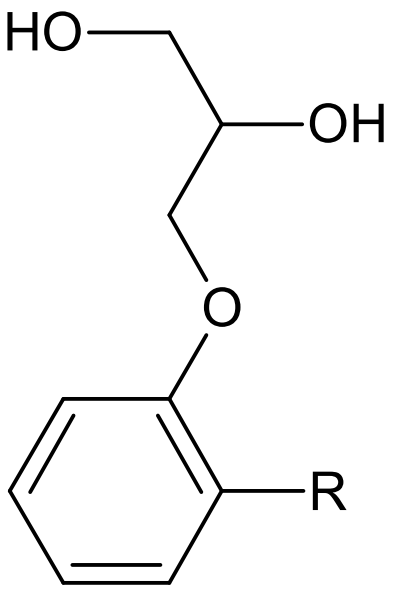


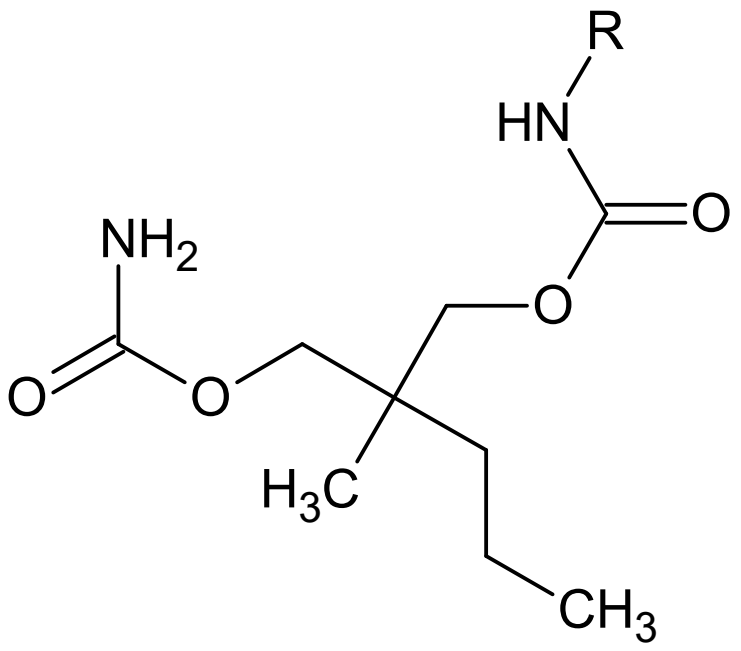
etifoxine

- $GABA_A$ agonist

- binds also to translocator protein (TPSO), $M_r \sim 18\,000$, formerly periferial benzodiazepine receptor situated on outer mitochondrial membrane $\Rightarrow$ regeneration of damaged periferial neurons

Other (non-benzodiazepin) anxiolytics
1,2- or 1,3-propanediole derivatives





R = CH_3 **mephenesin**
R = OCH_3 **guaifenesin**
Guaifenesinum PhEur
•very low toxicity
Guajacuran®
•anxiolytics
•centr. myorelaxants
•expectorants

R = H **meprobamate**
Meprobamatum PhEur
R = *iso*-C_3H_7 **carisoprodol**
Carisoprodolum PhEur
•anxiolytics
•centr. myorelaxants
(~~Scutamil C ®~~)