DRUGS AFFECTING CENTRAL NERVOUS SYSTEM

PSYCHOTHERAPEUTIC DRUGS

ANXIOLYTIC DRUGS

Anxiolytic drugs are mostly used in the treatment of emotional disorders (neuroses).

An effective anxiolytic drug should act sedatively, remove excessive anxiety, restore psychic equilibrium and have a large range of dosage.

It should not act antipsychotically or affect the patient's reasoning ability.

No drug satisfies these requirements.

The majority of anxiolytic drugs induce sleep, act anticonvulsively and relax muscles.

These actions are also used in therapy:

- In the treatment of epilepsy (anticonvulsive and muscle-relaxing action)
- In the long-term treatment of muscle spasms or chronic excessive muscle tone
- As hypnotic agents and in general anesthesia.

Additionally, they can be used to treat depression with excitement and anxiety together with antidepressants but only in the initial period of therapy.

Depending on their chemical structure and mechanism of action anxiolytic drugs are classified as follows:

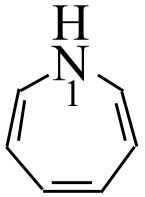
- **Benzodiazepine derivatives**, which bind with benzodiazepine site of the $GABA_A$ receptor
- **Azapirones (pirymidinylbutylpiperazines) - partial agonists of 5-HT_{1A} receptors** (buspirone, gepirone, ipsapirone) **and serotonine reuptake inhibitors (SSRIs –** escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline)
- **Other anxiolytic drugs** (hydroxyzine, benzoctamine, mephenoxalone; are used in Europe).

Benzodiazepine derivatives are the largest group of anxiolytic drugs. They also have anticonvulsive and sedative-hypnotic action.

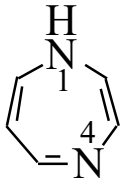
Their disadvantage is that they cause drug dependence.

It is hoped that drugs acting agonistically on 5-HT_{1A} receptors that do not demonstrate any or only slight drug dependence action will prove better than benzodiazepine derivatives.

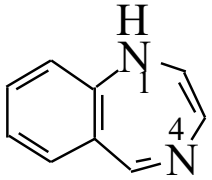
Benzodiazepines (BDA)



1*H*-Azepine



1,4- Diazepine



1,4-Benzdiazepine

Benzodiazepines act on the following areas of the brain:

- **The spinal cord – muscle relaxation**
- **The brain stem – anticonvulsive action**
- **The cerebrellum – ataxia**
- **The limbic system and cerebral cortex – emotional control.**

The mechanism of action

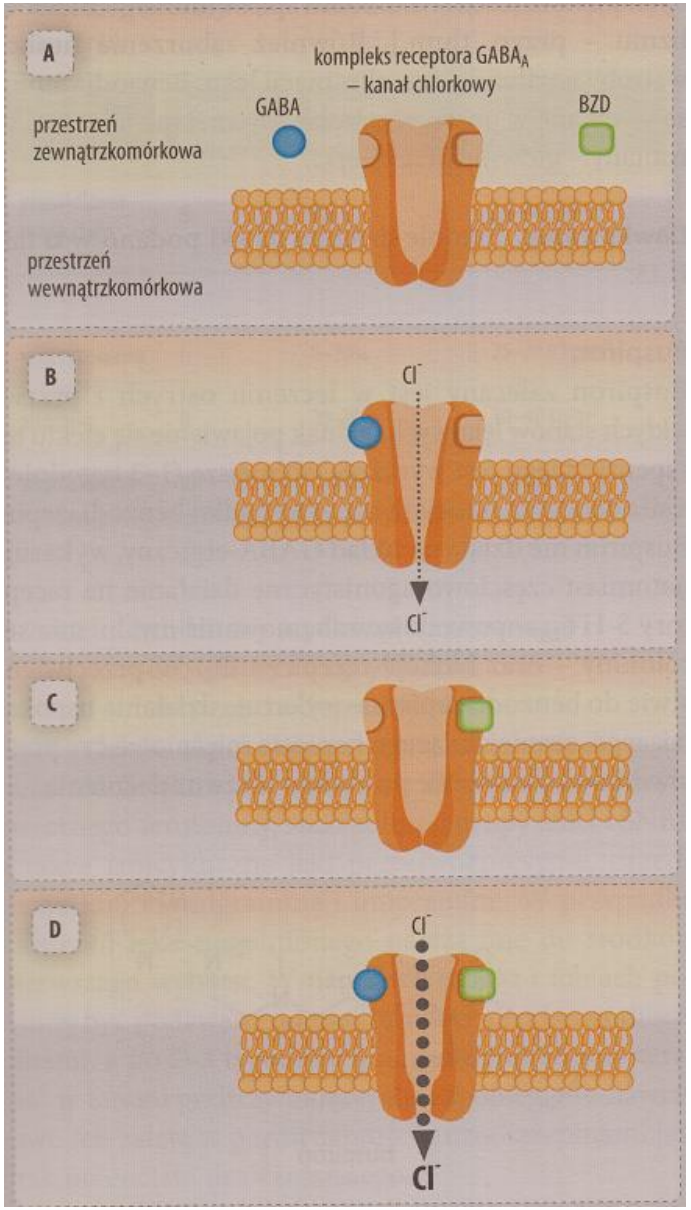
Benzodiazepines act on the GABA system by increasing the inhibition function of GABA neurons. Benzodiazepine bind at benzodiazepine site of the $GABA_A$ receptor (ionotropic receptor connected with the chloride channel).

The binding of benzodiazepines with receptor enhances the affinity of GABA receptors for these neurotransmitters resulting in a more frequent opening of adjacent chloride channels. This in turn results in enhanced hyperpolarization and further inhibition of neuronal firing.

Similarly, GABA agonists increase the binding of benzodiazepine derivatives with specific benzodiazepine site.
The chloride channel modulated by $GABA_A$ receptors is $2\alpha,2\beta,\gamma$-heteropentamer.

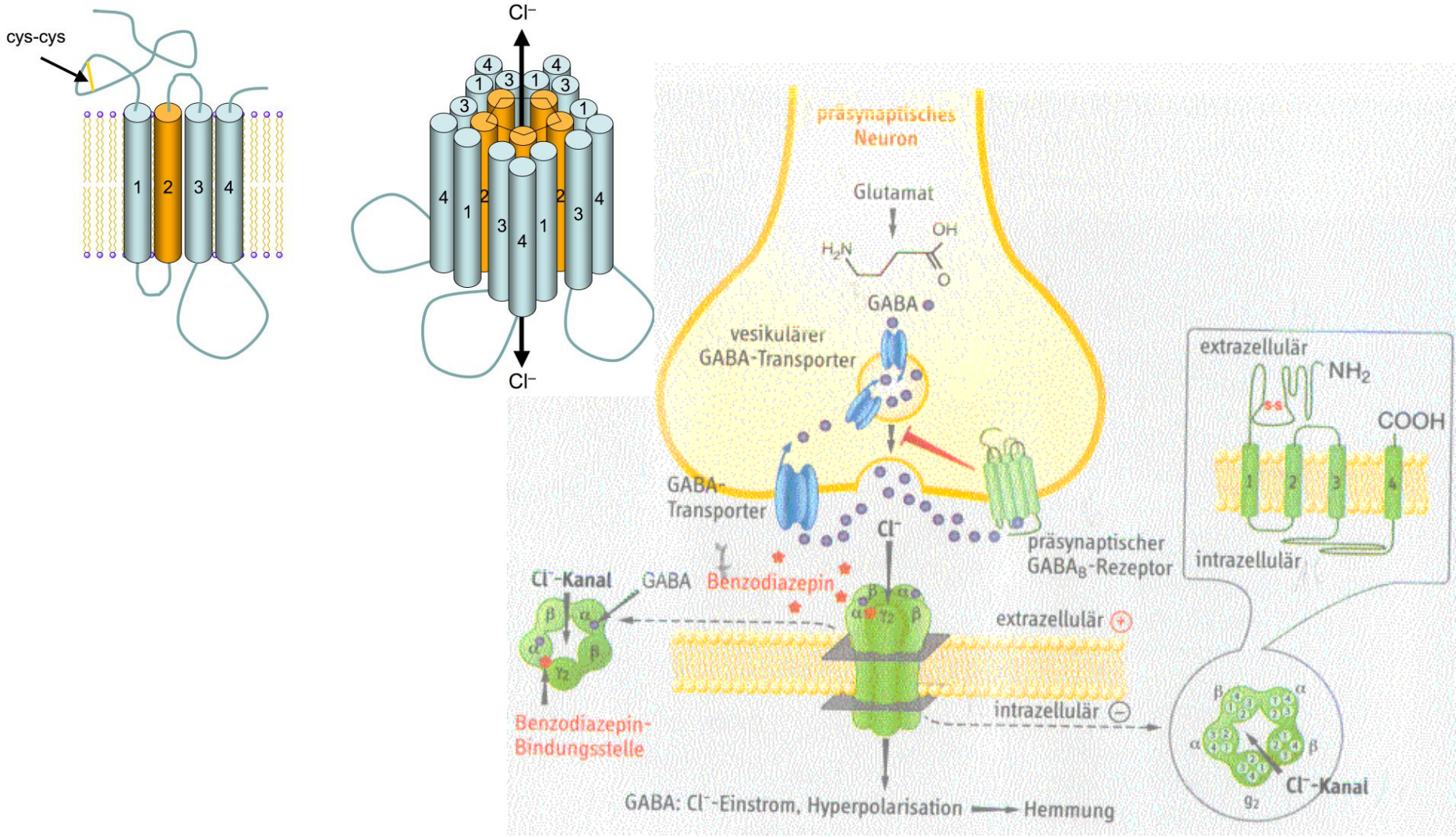
The benzodiazepins do not bind to the GABA site and can only produce effects if presynaptic GABA has been released and is present at the receptors.

Benzodiazepins allosterically modulate the $GABA_A$ receptor, increasing the frequency of the chloride channel opening when GABA is bound, thus potentiating the response of exogenously released GABA.

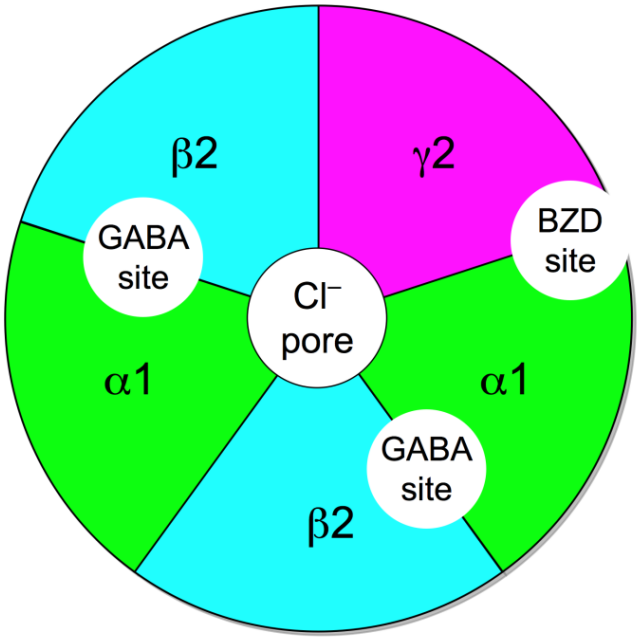


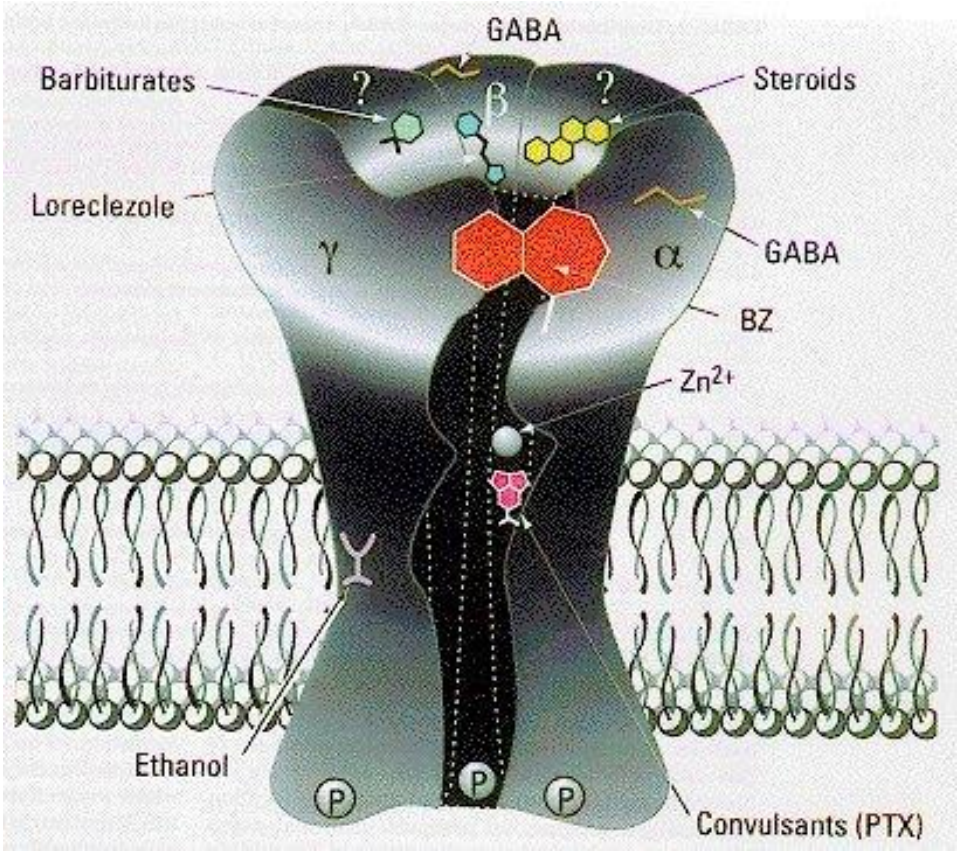
Clinically BDAs are very safe when used alone in the absence of CNS depressants, because they are not active on GABA receptors alone.

This is in contrast to the barbiturates that can directly activate the $GABA_A$ receptor when present at higher concentration and, thus, have a much lower therapeutic index.



Five subunits can combine in different ways to form $GABA_A$ channels, but the most common type in the brain is a pentamer comprising two α's, two β's, and a γ ($\alpha_2\beta_2\gamma$).





The receptor binds two GABA molecules, at the interface between an α and a β subunit.

Subunits

$GABA_A$ receptors are members of the large "*Cys*-loop" super-family of evolutionarily related and structurally similar ligand-gated ion channels that also includes

- **nicotinic acetylcholine receptors,**
- **glycine receptors, and**
- **the 5-HT_3 receptor.**

There are numerous subunit isoforms for the $GABA_A$ receptor, which determine the receptor's agonist affinity, chance of opening, conductance, and other properties.

In humans, the units are as follows:

- six types of α subunits
- three β's
- three γ's
- as well as a δ, an ε ,a π and θ

Different benzodiazepines have different affinities for $GABA_A$ receptors made up of different collection of subunits, and this means that their pharmacological profile varies with subtype selectivity.

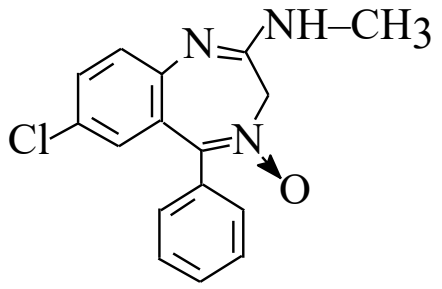
For instance, benzodiazepine site ligands with high activity at the α_1 and/or α_5 tend to be more associated with sedation, ataxia and amnesia, whereas those with higher activity at $GABA_A$ receptors containing α_2 and/or α_3 subunits generally have greater anxiolytic activity.

Anticonvulsant effects can be produced by agonists acting at any of the $GABA_A$ subtypes, but current research in this area is focused mainly on producing α_2-selective agonists as anticonvulsants which lack the side effects of older drugs such as sedation and amnesia.

The chemical structure

Chlordiazepoxide was the first benzodiazepine to be marketed for clinical use in 1960. Its effectiveness and wide margin of safety were major advances over compounds, such as barbiturates, used previously.

Subsequently, thousand of BDA derivatives were synthesized, and more than two dozen BDA are in clinical use in the U.S.



The chemical structure

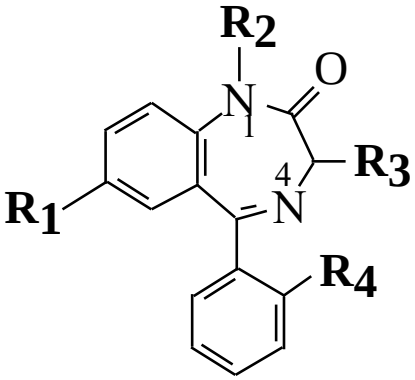
Benzodiazepines used in therapy are mainly 1,4-diazepine derivatives, with the exception of

clobazam (1,5-benzodiazepine derivative) and

tofizopam (2,3- benzodiazepine derivative).

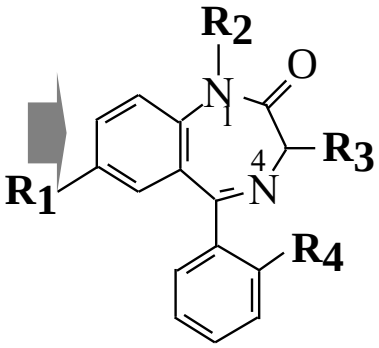
Among 1,4-benzodiazepine derivatives, 1,4 benzodiazepin-2-on derivatives are a large group (Class A BDA).

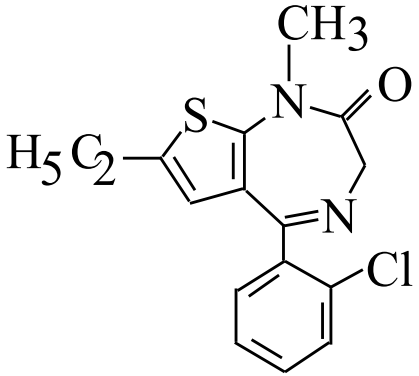
The chemical structure-activity relationship for this group has been defined.



Ring A

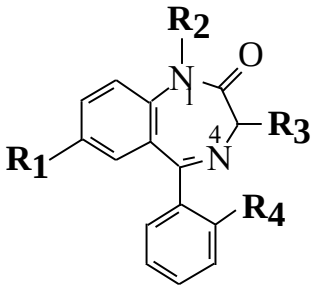
- **The substituent at position C7 is very important.**
  The electronegative group (halogen or nitro) at this position markedly increases functional anxiolytic activity.
  Generally, compounds with the nitro group (nitrazepam, flunitrazepam) have strong hypnotic action.
- Substituents at positions 6, 8 or 9 decrease anxiolytic activity.
- Other 1,4-diazepine derivatives in which the benzene ring is replaced by a heterocycle ring show weak binding affinity *in vitro* and even less pharmacological activity *in vivo* compared to phenyl-substituted analogs.





Clotiazepam, TRECALMO

Ring B

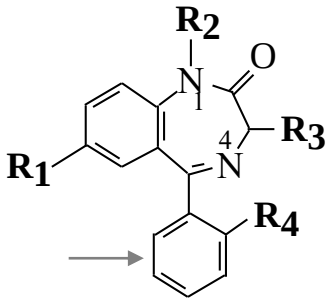


- The proton-accepting group (e.g. the carbonyl moiety) in the position 2 of ring B appears to be necessary, perhaps to interact with a receptor histidine rest that serves as a proton source and is believed to be involved in ligand binding. It is thought that the electrons of the protonaccepting group need to be in the same plane as the aromatic ring A, favoring a coplanar spatial orientation of the two moieties.

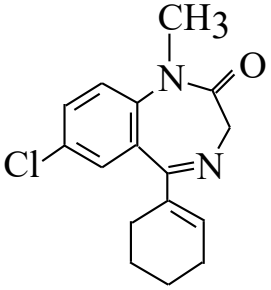
- Derivatives substituted with a 3-hydroxy moiety have comparable potency to nonhydroxylated analogs but as they are excreted faster the duration of their action is shorter and their resorption is diminished. The esterification of a 3-hydroxy moiety also is possible without any loss of potency.

- Many analogs used clinically are not N_1-alkilated. The presence of the methyl group at this position increases action and facilitates resorption. However, larger substituents decrease action slightly.
- The 4,5-double bond is required for *in vivo* anxiolytic activity.

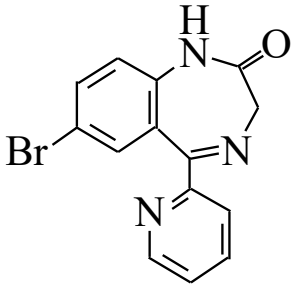
Ring C



- The 5-phenyl ring C is not required for the binding of BDA with their receptors *in vitro*; however, this aromatic ring may contribute favorable hydrophobic or steric interaction to receptor binding and its relationship to ring A planarity may be important.
- The introduction of a chlorine atom to the 5-phenyl ring in *orto* position increases activity, but in *meta* or *para* position diminishes activity.
- 1,4-Benzodiazepine derivatives also include compounds with a substituent at position C5 other than phenyl, e.g. bromazepam has a 2-pyridil and tetrazepam a Δ1-cyclohexyl substituent.



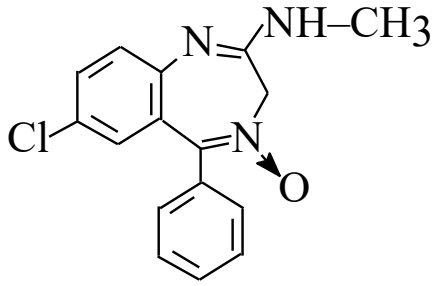
Tetrazepam
MYOLASTAN



Bromazepam
LEXOTAN

It is difficult to determine more precisely the relationship between the chemical structure and activity of these derivatives because of their hepatic metabolism to active metabolites.

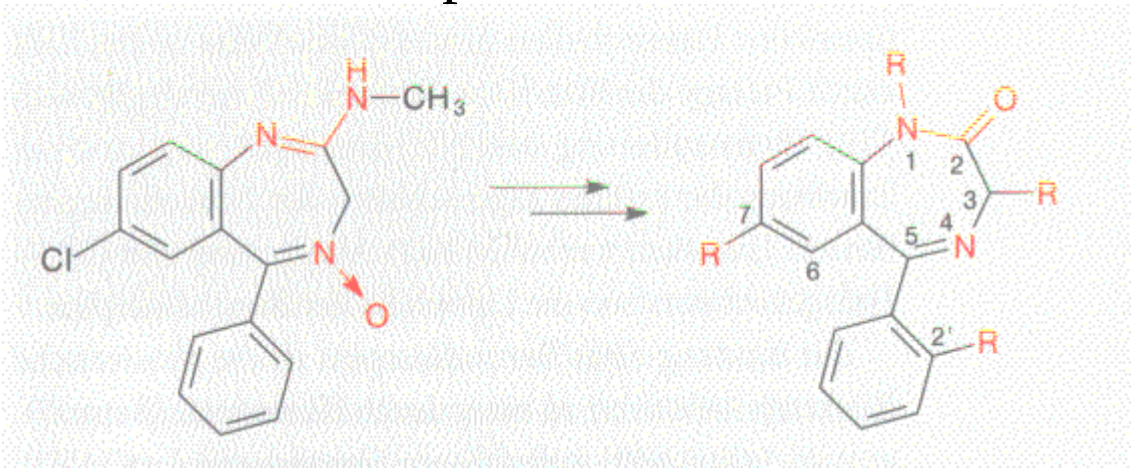
The chemical structure



Chlordiazepoxide,
ELENIUM, LIBRIUM

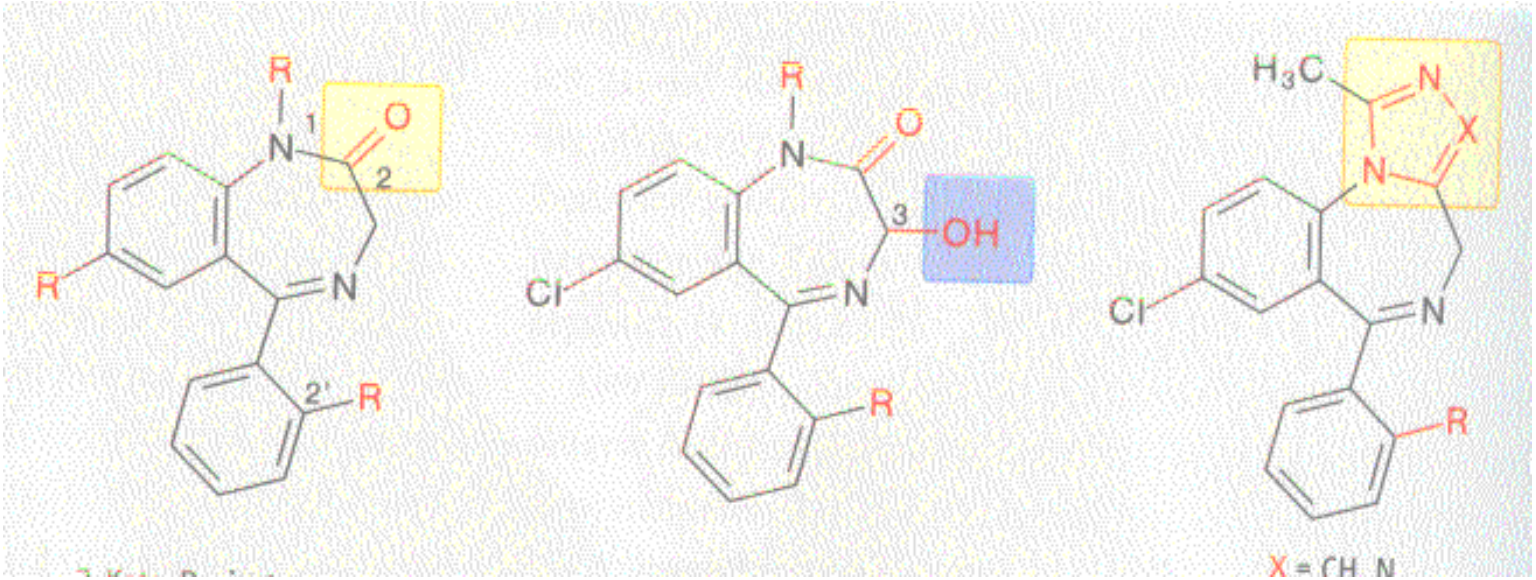
Chlordiazepoxide is the only benzodiazepine with N-oxide and amidine groups, used in therapy.

It is metabolized to 1,4-benzodiazepin-2-one derivative.

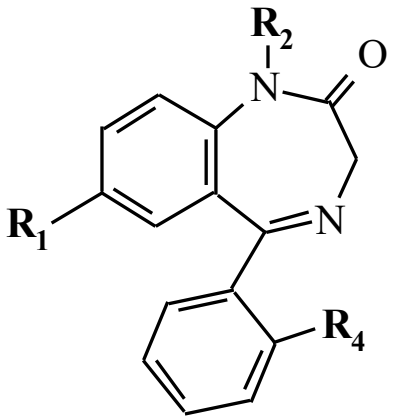


Depending on chemical structure of benzodiazepines they are classified as follows:

⇒ 1,4-benzodiazepin-2-ones (2-ketoderivatives)
⇒ 3-hydroxy-1,4-benzodiazepin-2-ones (3-hydroxyderivatives)
⇒ tricyclic benzodiazepine derivatives
⇒ other: i.g. 1,5-benzodiazepin derivatives (clobazam),



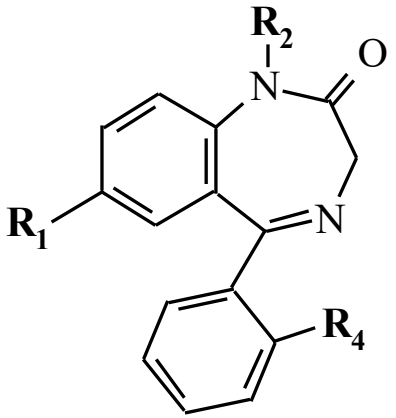
1,4-Benzodiazepin-2-one derivatives



R_1 = Cl

Diazepam, RELANIUM	$R_2 = CH_3$,	R_4 = H,
Prazepam, REAPAM	$R_2 = -CH_2$-cyclopropyl,	R_4 = H
Halazepam, ALAPRYL	$R_2 = -CH_2-CF_3$,	R_4 = H
Pinazepam, DUNA	$R_2 = -CH_2-C{\equiv}CH$,	R_4 = H
Flurazepam, FLUZEPAM	$R_2 = -CH_2-CH_2-N(C_2H_5)_2$,	R_4 = F
Nordazepam, LOMAX	R_2 = H,	R_4 = H
Chlordesmetyldiazepam	R_2 = H,	R_4 = Cl

1,4-Benzodiazepin-2-one derivatives



$R_1 = -NO_2$

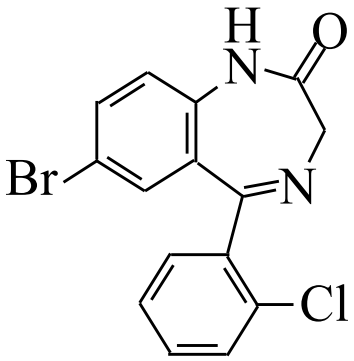
Nitrazepam, NITRAZEPAM (R_2 = H, R_4 = H)

Clonazepam, CLONAZEPAMUM (R_2 = H, R_4 = Cl)

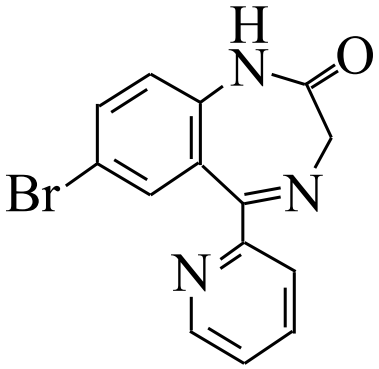
Flunitrazepam, ROHYPNOL (R_2 = CH_3, R_4 = F)

1,4-benzodiazepin-2-one derivatives

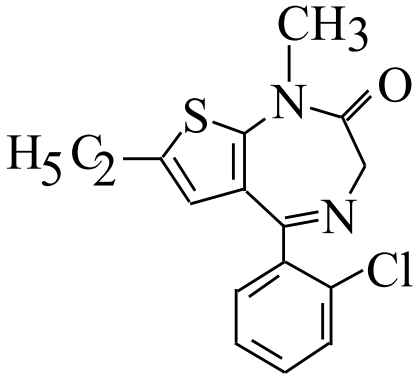
R_1 = Br



Fenazepam,

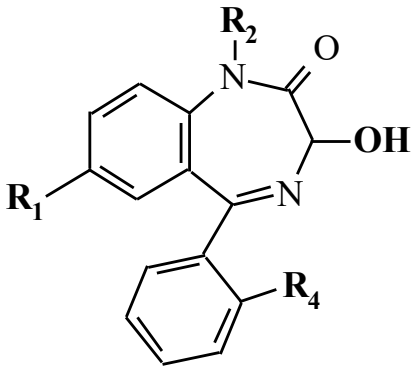


Bromazepam, LEXOTAN



Clotiazepam, TRECALMO

3-Hydroksy-1,4-benzodiazepin-2-one derivatives



R_1 = Cl

Temazepam, SIGNOPAM ($R_2 = CH_3$, $R_4 = H$)

Oxazepam, OXAZEPAM ($R_2 = H$, $R_4 = H$)

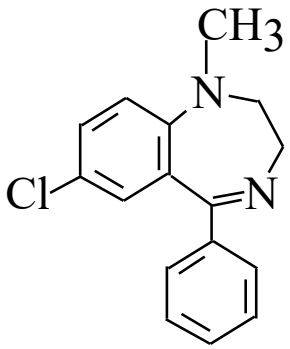
Lorazepam, LORAFEN ($R_2 = H$, $R_4 = Cl$)

Lormetazepam, NOCTOFER ($R_2 = CH_3$, $R_4 = Cl$)

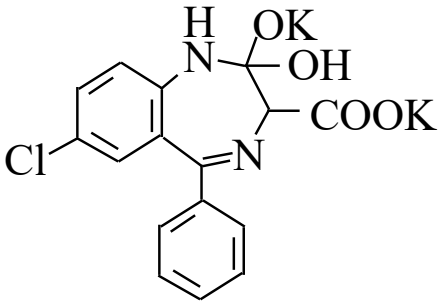
Oxazepam, lorazepam, lormetazepam and **temazepam**, because of their hydrophillic properties, are resorbed more slowly than keto-derivatives.

Other 1,4-benzodiazepine derivatives

Medazepam, RUDOTEL



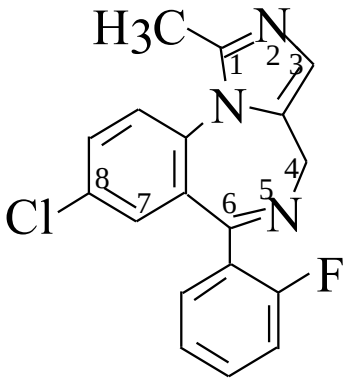
Clorazepate dipotassium, TRANXENE
CLORANXEN



Tricyclic benzodiazepine derivatives (Class B DBA)

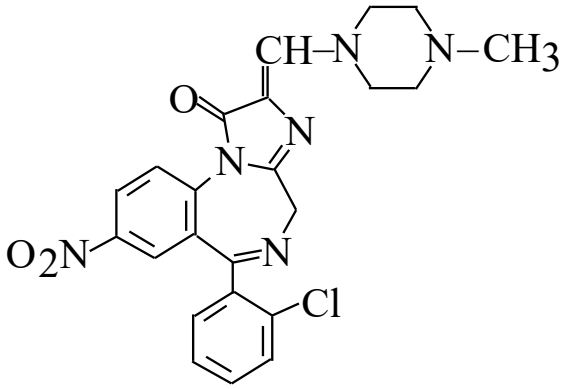
- **Imidazo-1,4-benzodiazepine derivatives**

Midazolam, DORMICUM



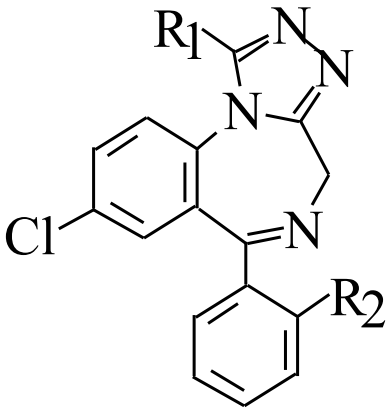
8-Chlor-6 (2-fluorophenyl)-1-methyl-4*H*-imidazol[1.5-a] [1,4]benzodiazepine

Loprazolam, DORMONACT, SOMNOVIT



Tricyclic benzodiazepine derivatives

- **Triazol-1,4-benzodiazepine derivatives**



Estazolam, ESTAZOLAM (R_1 = H R_2 = H)

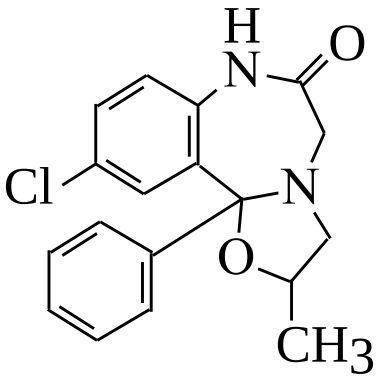
Alprazolam, ALPROX (R_1 = CH_3 R_2 = H)

Triazolam, TRIZAM (R_1 = CH_3 R_2 = Cl)

Tricyclic benzodiazepine derivatives

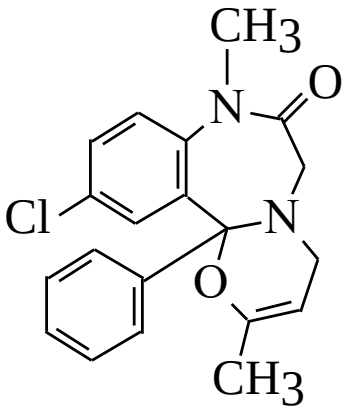
- **Oxazol-1,4-benzodiazepine derivative**

Oxazolam, TRANQUIT



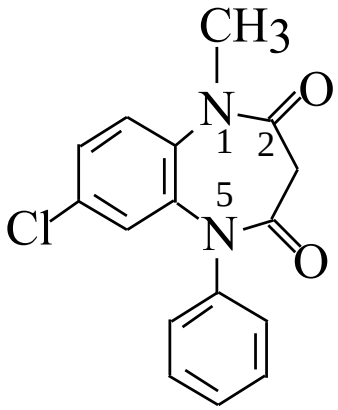
- **Oxazin-1,4-benzodiazepine derivative**

Ketazolam, CONTAMNEX



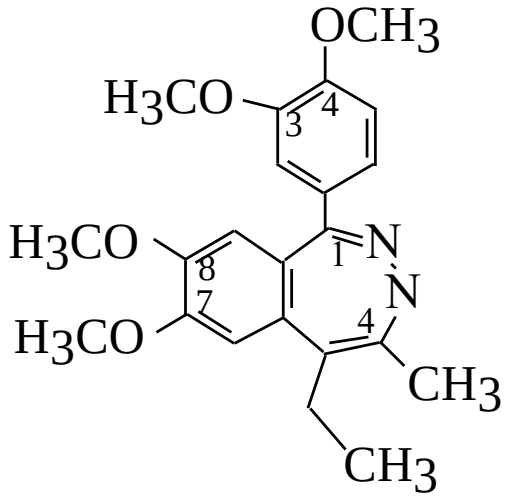
- **1,5-Benzodiazepine derivative**

Clobazam, FRISIUM



- **2,3-Benzodiazepine derivative**

Tofisopam, GRANDAXIN



Therapeutic uses of benzodiazepin

Benzodiazepines are used as:

⇒ **anxiolytics**

⇒ **hypnotics**

⇒ **antiepileptics**

⇒ **musculrelaxant**

The action of benzodiazepine derivatives

The BDA that are specifically promoted as anxiolytics:

bromazepam, clobazam, chlordiazepoxide,
clotiazepam, clorazepat, diazepam, lorazepam, medazepam
oxazepam, prazepam, alprazolam

A compound with slower absorption, active metabolites, and low lipophilicity would be a more effective antianxiety agent but less helpfull as a hypnotic.

The action of benzodiazepine derivatives

The BDA that are specifically promoted as sleep inducers:

flurazepam, quazepam, temazepam, estazolam, triazolam

A compound that is rapidly absorbed, highly lipid soluble, and without active metabolites would be useful as a hypnotic but less useful for treatment of a chronic anxiety state.

The action of benzodiazepine derivatives

In therapy of seizures the following benzodiazepines are effective: diazepam, lorazepam, clonazepam, clorazepate dipotassium and midazolam.

The duration of action is short for diazepam (2 hours) and midazolam (3-4 hours), longer for clonazepam (24 hours) and much longer for lorazepam (up to 72 hours) but it is not correlated with the plasma concentration-time profiles for these drugs.

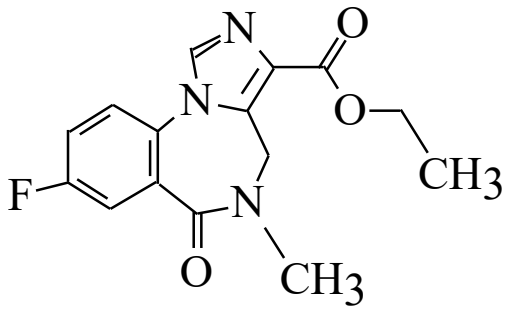
The action of benzodiazepine derivatives

The differences between derivatives of benzodiazepines are as follows:

- various affinity for receptors and resulting potency
- various duration of action
  - long half-life: 2-4 days,
  - intermediate half-life: 8-20 hours
  - short half-life: 2-3 hours.

The action of benzodiazepine derivatives

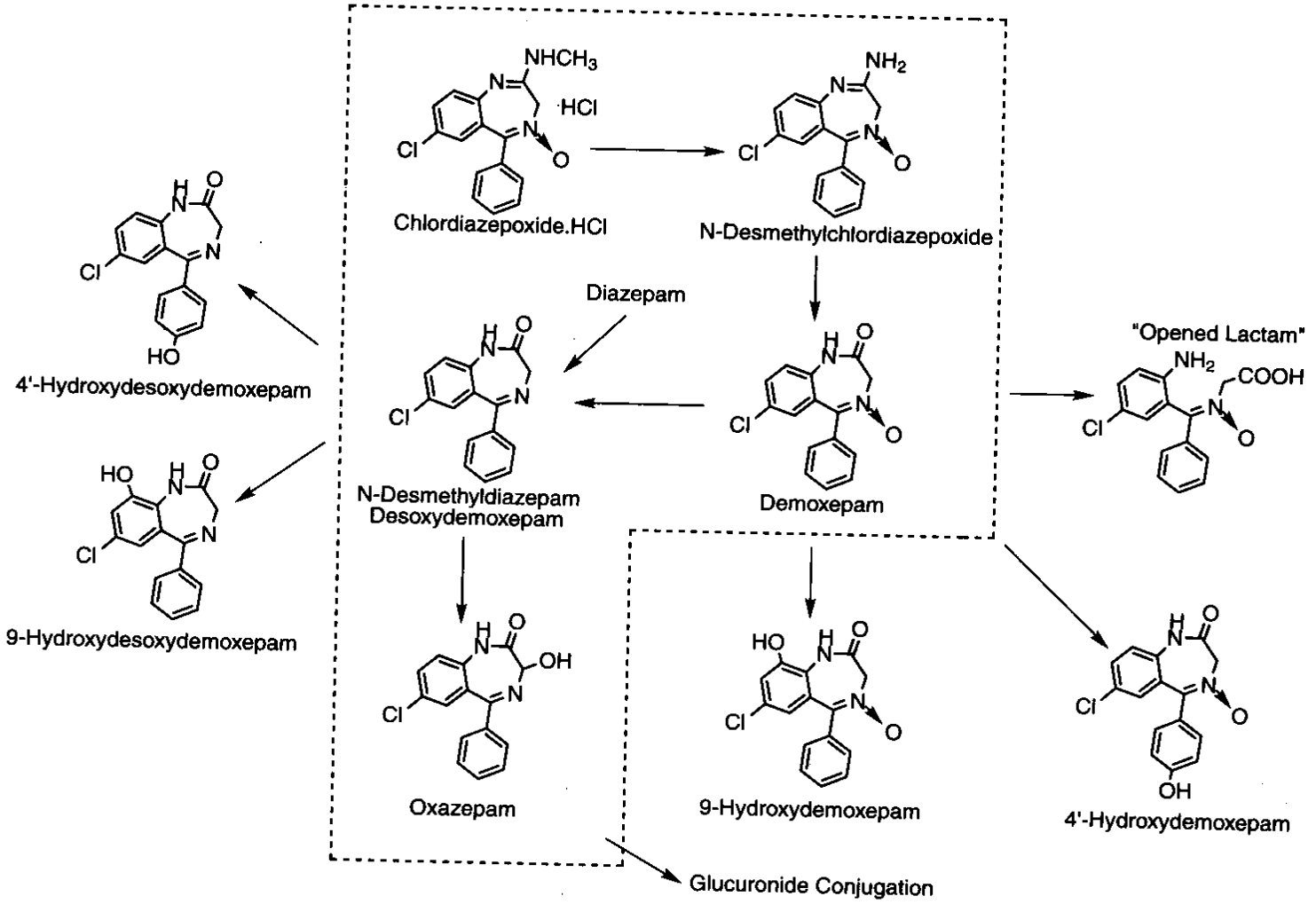
***Flumazenil*,**
ANEXATE



Flumazenil antagonizes the action of BDA derivatives.

Flumazenil is used in acute BDA intoxication and to remove the effects of BDA used in general anesthesia.

Metabolism of the benzodiazepines



Metabolism of chlordiazepoxide.

The metabolism of BDA

BDA metabolites can have biological half-life similar to their compounds (e.g. alfahydroxyalprazolam) or significantly longer (demethyldiazepam approx. 100 hours). It causes the danger of accumulation of those BDAs that metabolize to demethyldiazepam.

BDAs are mainly eliminated by the kidneys as hydroxyl derivatives and/or their products of coupling with UDPGA.

In older people and those with liver dysfunction the biotransformation and elimination of BDAs is slower, so their action is longer.

In some cases the primary compounds of BDAs (e.g. prazepam) are inactive, while their metabolites are active.

Adverse effects

The adverse effects of BDA may include:

- toxic action – the effect of overdose
- adverse effects caused by therapeutic dosage
- drug tolerance and dependence.

Adverse effects

Overdosing BDAs causes long-term sleep without any serious effect on the patient's respiration and circulation, but in the presence of other drugs acting depressively on the CNS (including alcohol) BDAs can cause life-threatening depression of breath.

The main adverse effects are sleepiness, confusion, amnesia and coordination disorders, which make certain activities impossible, for example driving. BDAs should not be used in the first trimester of pregnancy because of mutagenic action (fetus deformation).

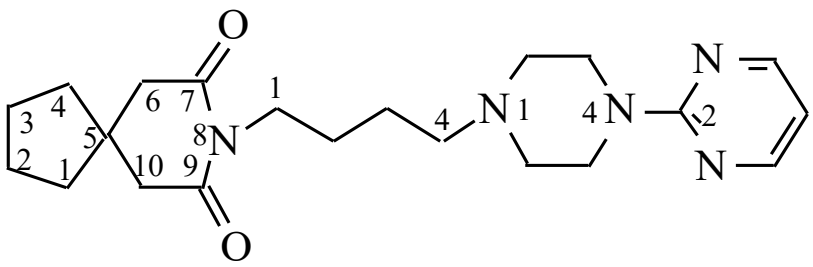
Even small amount of alcohol increases adverse effects.

Anxiolytic drugs should not to be used for a long time because they can cause psychic (low-dose) and physical (high-dose) dependence.

2. Partial agonists of 5-HT_{1A} receptors

5-HT_{1A} receptors are located presynaptically and postsynaptically. The stimulation of presynaptic 5-HT_{1A} receptors diminishes the release of 5-HT from neurons. Agonists of these receptors act anxiolytically.

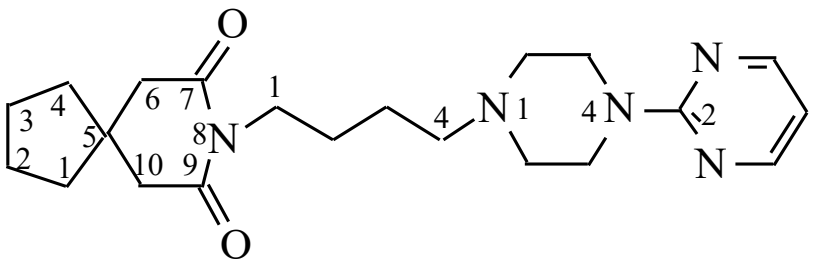
Buspiron, gepiron and ipsapiron are partial agonists of 5-HT_{1A} receptors. They do not act anticonvulsively and do not relax muscles.



Buspiron, BUSPAR

8-[4-[4-(pyrimidin-2-yl)piperazyn-1-yl)butyl]-
8-azaspiro[4,5]dekan-7,9-dion

Buspiron



Buspiron, in comparison with BDAs, has weaker hypnotic action and less often causes drug dependence.

Buspiron is used in acute and chronic anxiety states.

Its anxiolytic action appears after a longer period of use (from one to several weeks) and because of that it is not effective in the treatment of bouts of panic fear.

Adverse effects

Adverse effects are observed very seldom and may include headache, dizziness, anxiety, sleeplessness, fatigue, increased sweating and gynecomastia.

Contraindications for the use of buspiron are hypersensitivity, epilepsy, pregnancy, previous therapy including drugs acting depressively on the CNS, serious damage of the liver and kidneys, acute narrow angle glaucoma, bouts of cramps and serious myasthenia.

Buspiron should not be used simultaneously with MAO inhibitors because of the possibility of a hypertensive crisis.

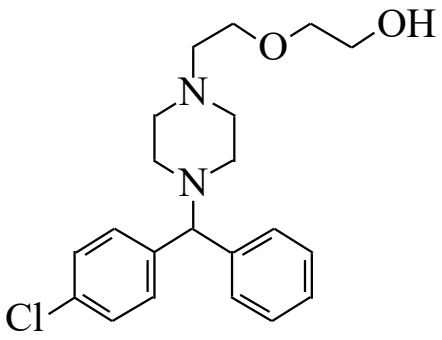
Serotonine reuptake inhibitors

Several selective serotonin reuptake inhibitors (SSRIs), including escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline are effective as first-line treatment of some anxiety disorders, with the purported advantage that they lack the addictive properties of BDAs.

Specifically, the SSRIs has been shown to be effective in obsessive-compulsive disorder, panic disorder and social phobia.

The mechanism of action of these drugs in anxiety may differ with their role in the treatment of depression.

3. Other anxiolytic drugs



Hydroxizine, ATARAX, HYDROXYZINUM

Hydroxyzine (diphenylmetane derivative) inhibits aggressive behavior and acts sedatively and anxiolytically.

Additionally, it has antihistaminic, antispasmatic, antivomiting, local anesthetic and cholinolytic properties.

It does not act anticonvulsively and does not relax skeletal muscles.

Hydroxyzine is used in the treatment of emotional neurosis with anxiety and in excitement states in alcoholics.

Hydroxizine

Cholinergic action causes adverse effects such as xerostomia and tachycardia.

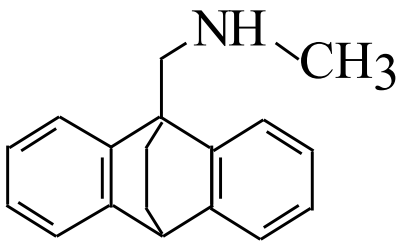
The damage of the hemopoietic system (leukocytopenia) may occur and then the administration of hydroxyzine must be stopped.

Allergic symptoms like nettle rash, prurities, other dermatic changes and hypotension may also appear.

Hydroxyzine can cause drug dependence but less often than BDAs.

It should not be used in patients with epilepsy.

3. Other anxiolytic drugs



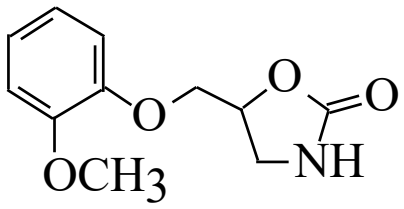
Benzoctamine, TACITIN

Benzoctamine (dibenzocyclooctadiene derivative) acts centrally and peripherally. It has centrally suppressive action on the limbic system, the reticular structure and the system of gamma motoneurons.

Benzooctamine is used in anxiety states and psychic tension caused by organic diseases.

High dosage may result in xerostomia, fatigue, sleepiness, headache, dizziness and nausea.

3. Other anxiolytic drugs



Mephenoxalone, DORSIFLEX

Mephenoxalone acts sedatively and in high doses hypnotically, similarly to meprobamat. It relaxes striated muscles.

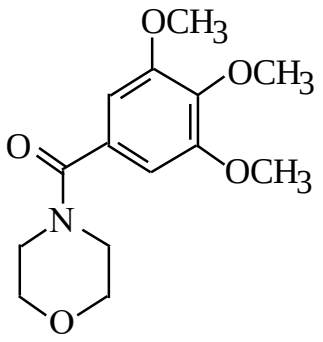
Mephenoxalone is used in states of anxiety, psychic tension and muscle contracture.

Contraindications are glaucoma and prostatic adenoma.

Sometimes mephenoxalone may cause dizziness, headache and nausea.

If allergic reaction is observed, the administration of the drug must be stopped.

Trimetazine



Trimetazine (morpholine derivative) has sedative and slightly hypnotic action.

It does not act anticonvulsively and does not relax muscles.

Action starts rapidly and lasts approx. 4 hours.

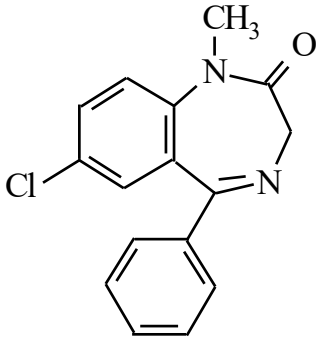
Which of the following formulas is correct for

a) Chlordiazepoxide

b) Diazepam

c) Flumazenil

d) Midazolam



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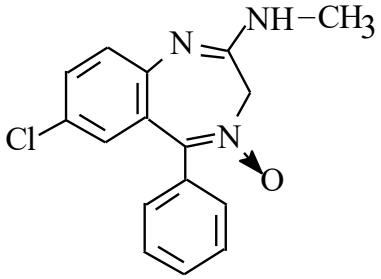

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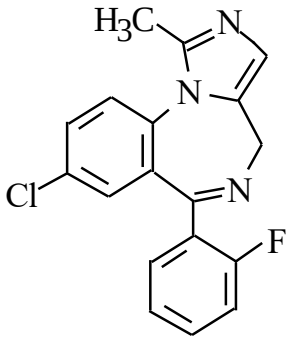

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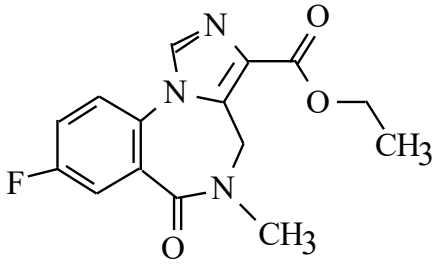

4

1. Benzodiazepines act on the GABA system by **increasing/ decreasing** the inhibition function of GABA neurons.
2. The binding of benzodiazepines with receptor **enhances/decreases** the affinity of GABA receptors for these neurotransmitters resulting in a more frequent opening of adjacent chloride channels.
3. GABA agonists **increase/decrease** the binding of benzodiazepine derivatives with specific benzodiazepine site.

Benzodiazepine site ligands with high activity at the $\boldsymbol{\alpha_1}$ / $\boldsymbol{\alpha_2}$ tend to be more associated with sedation, ataxia and amnesia,

whereas those with higher activity at $GABA_A$ receptors containing $\boldsymbol{\alpha_2}$ / $\boldsymbol{\alpha_1}$ subunits generally have greater anxiolytic activity.

Benzodiazepine site ligands with high activity at the α_1 and/or α_5 tend to be more associated with sedation, ataxia and amnesia,

whereas those with higher activity at $GABA_A$ receptors containing α_2 and/or α_3 subunits generally have greater anxiolytic activity.

3-Hydroxy-1,4-benzodiazepin-2-one derivatives - oxazepam, lorazepam, lormetazepam and temazepam, because of their **hydrophillic/lypophyllic** properties, are resorbed more slowly than keto-derivatives.

$GABA_A$ receptor is an ionotropic receptor connected with the chloride channel.

The binding of benzodiazepines with **GABA** receptor **increases the inhibition function of GABA neurons.**

The electronegative group (halogen or nitro) at 7 position markedly increases functional anxiolytic activity.

The presence of the methyl group at 1 position increases action and facilitates resorption.

The 4,5-double bond is required for anxiolytic activity.