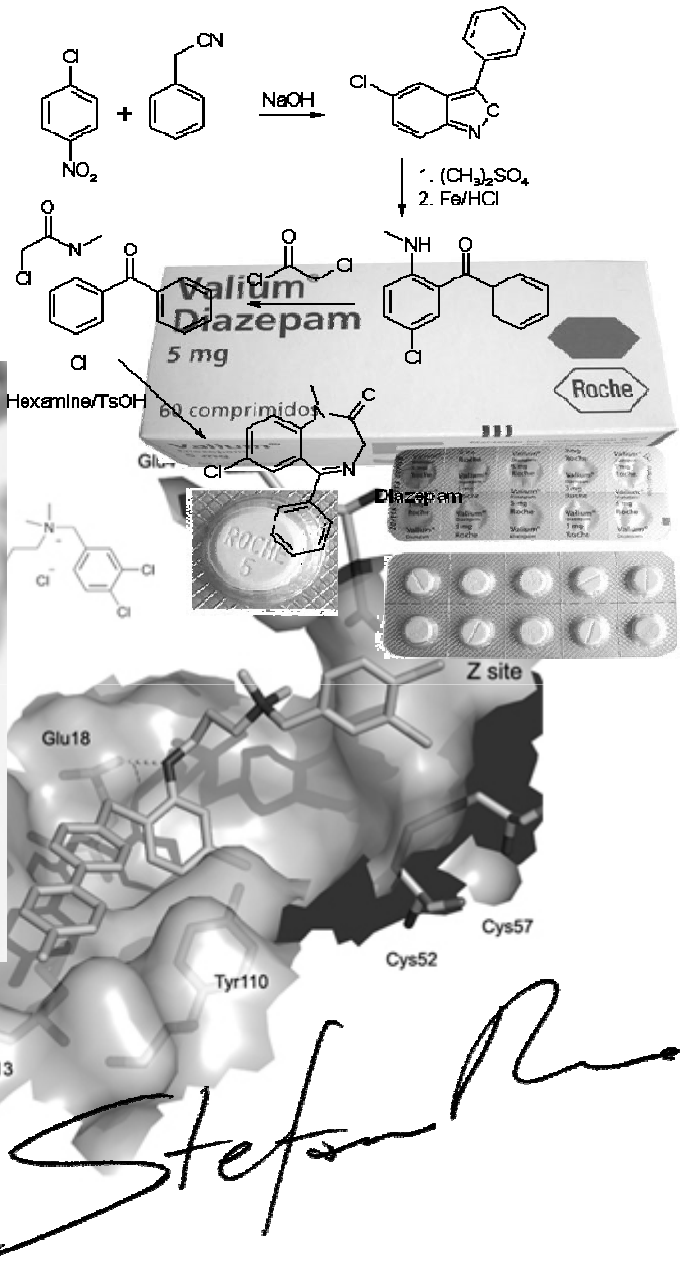
Chimica Farmaceutica e Tossicologica – Parte II



Psychotic Disorders

Neurobiology of Depression and Antidepressants

Parte I

Mi ripeto ancora… la più importante per noi!

NON CONFONDEREMO MAI LA *CALCOLATRICE* CON LE *CIFRE* CHE ESSA PRODUCE!!!

e questo sarà per noi un prezioso strumento!

Pathways across the blood–brain barrier

Lipophilicity: $0 \leq logP \leq 3$

Molecular weight: < 450

Polar surface area (PSA): $60 \div 90$ Å^2

Hydrogen bonding (O + N): ≤ 5

Charge: $4 \leq pKa \leq 10$

1. Psychotic disorders introduction

The psychotic disorders are classified into 3 major groups:

1. **Anxiety disorders** (*phobia and sleeping disorders*)
2. **Effective/mood disorders** (*depression*)
3. **Personality disorders** (*schizophrenia*)

1. Psychotic disorders introduction

Neurotransmitters and related psychotic disorders:

• Dopamine ↑	• Schizophrenia
• Norepinephrine ↓	• Depression
• Serotonin ↓	• Depression
• Acetylcholine ↓	• Alzheimer's disease
• γ-aminobutyric acid (GABA) ↓	• Anxiety

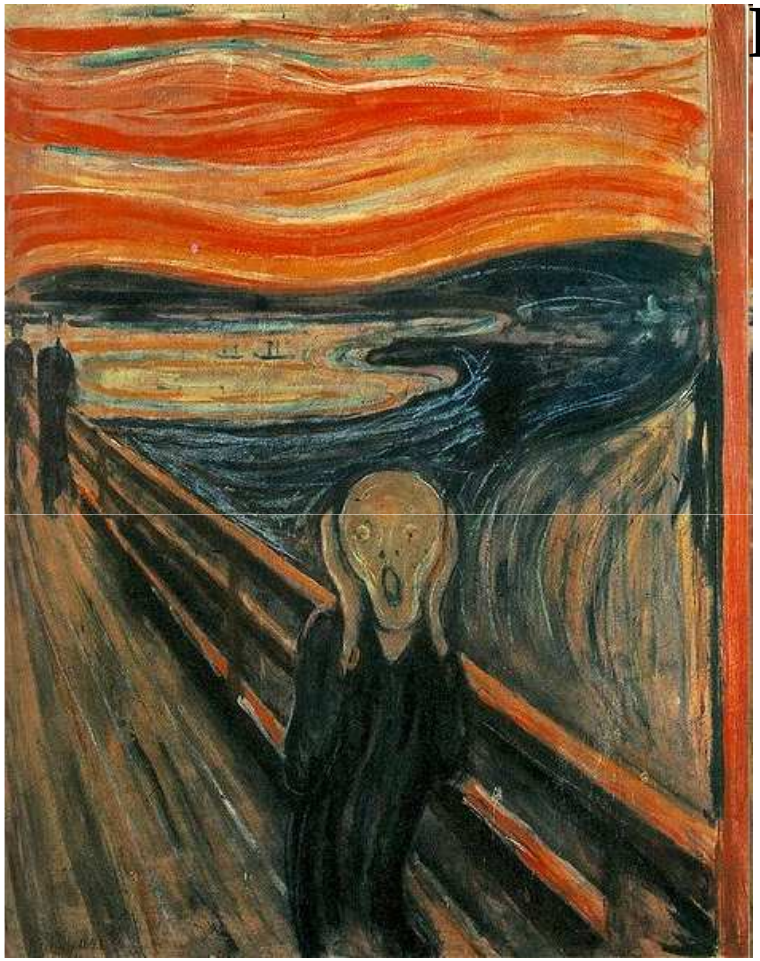
1. Psychotic disorders introduction

- **Anxiolytic Drugs:**
  - **Benzodiazepines (BDZ)**
  - **Barbiturate**
  - **Azapirones (Buspirone)**

- **Antidepressant Drugs:**
- **Tricyclic/Plycyclic**
  - **Monoamine oxidase inhibitors**
  - **Selective serotonin-reuptake inhibitors (SSRI)**

- **Neurolytic Drugs:**
  - **Phenothiazin**
  - **Buteopheanol**

2. Anxiety and anxiolytic drugs



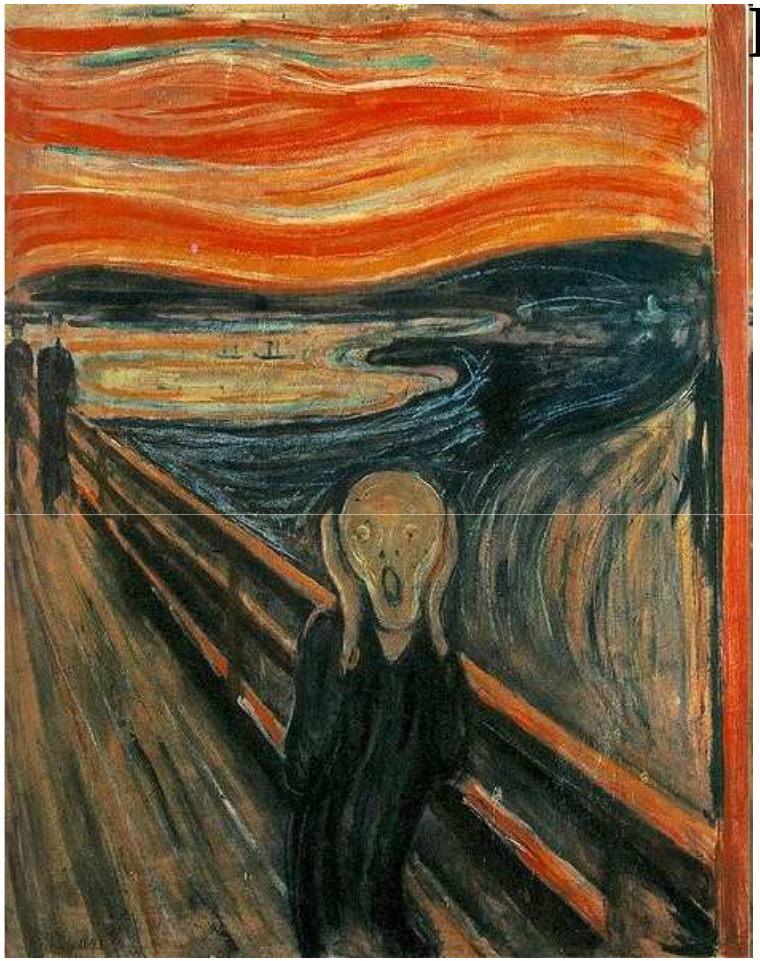
The Scream **an expressionist painting by Norwegian artist Edvard Munch depicts an episode of extreme anxiety that Munch felt.**

Definition:

Anxiety disorders are blanket terms covering several different forms of abnormal and pathological *fear* and *anxiety* which only came under the aegis of psychiatry at the very end of the 19th century.

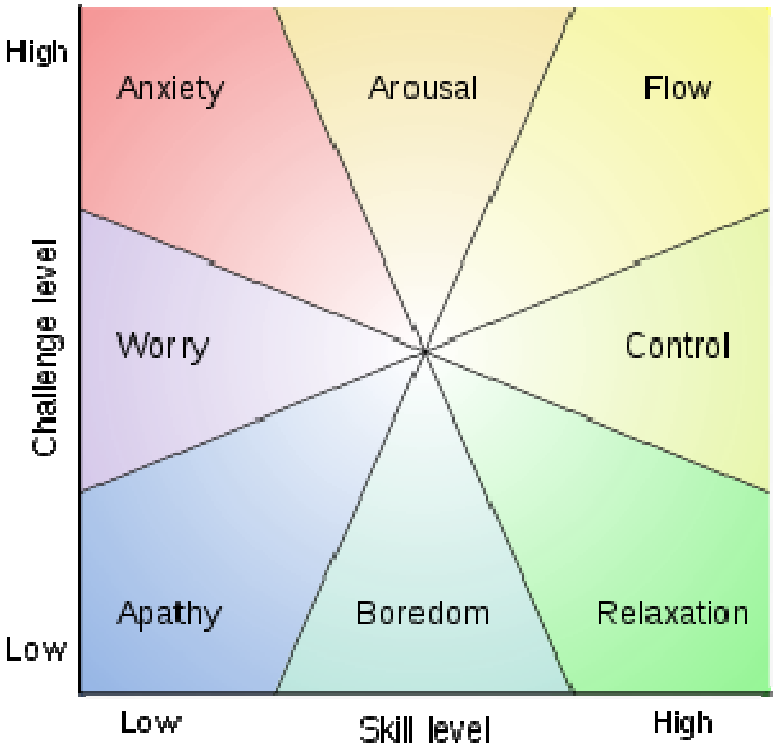
Although in casual discourse the words anxiety and fear are often used interchangeably, in clinical usage, they have distinct meanings; *anxiety* is defined as an unpleasant emotional state for which the cause is either not readily identified or perceived to be uncontrollable or unavoidable, whereas *fear* is an emotional and physiological response to a recognized external threat. The term anxiety disorder, however, includes fears (phobias) as well as anxieties.

2. Anxiety and anxiolytic drugs



The Scream **an expressionist painting by Norwegian artist Edvard Munch depicts an episode of extreme anxiety that Munch felt.**

Definition:



2. Anxiety and anxiolytic drugs

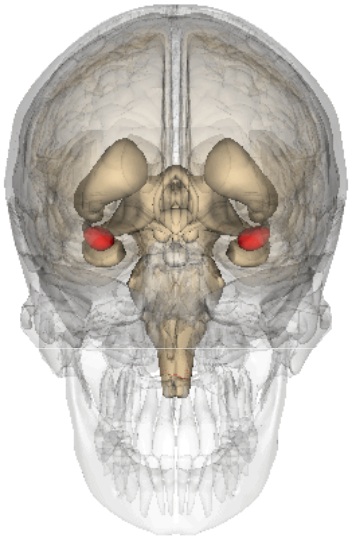
Types of anxiety disorders:

1. ***Generalized anxiety disorder***
2. ***Panic disorder***
3. ***Phobias***
4. ***Obsessive–compulsive disorder***
5. ***Post-traumatic stress disorder***
6. ***Separation anxiety***

Symptoms:

- *Tachycardia*
- *Sweating*
- *Palpitations*
- *Sympathetic activation*

2. Anxiety and anxiolytic drugs

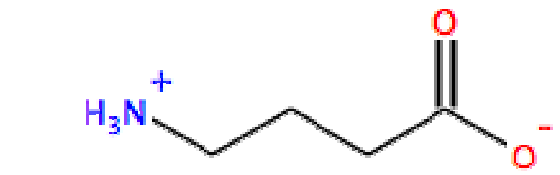


Consensus of data shows the *amygdala* has a substantial role in mental states, and is related to many psychological disorders. The amygdala perform a primary role in the processing and memory of emotional reactions and it is considered part of the limbic system. It is central to the processing of fear and anxiety, and its function may be disrupted in anxiety disorders.

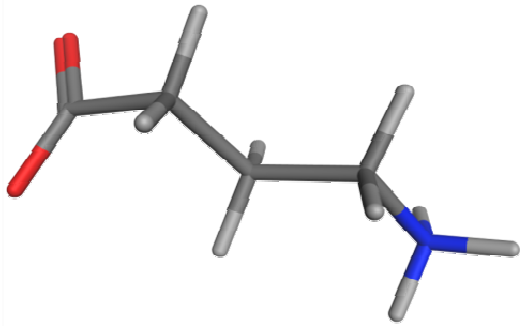
Low levels of **GABA**, a neurotransmitter that reduces activity in the central nervous system, contribute to anxiety. A number of anxiolytics achieve their effect by modulating the GABA receptors.

2. Anxiety and anxiolytic drugs

2.1 γ-aminobutyric acid (GABA)



Gamma-aminobutyric acid (GABA)

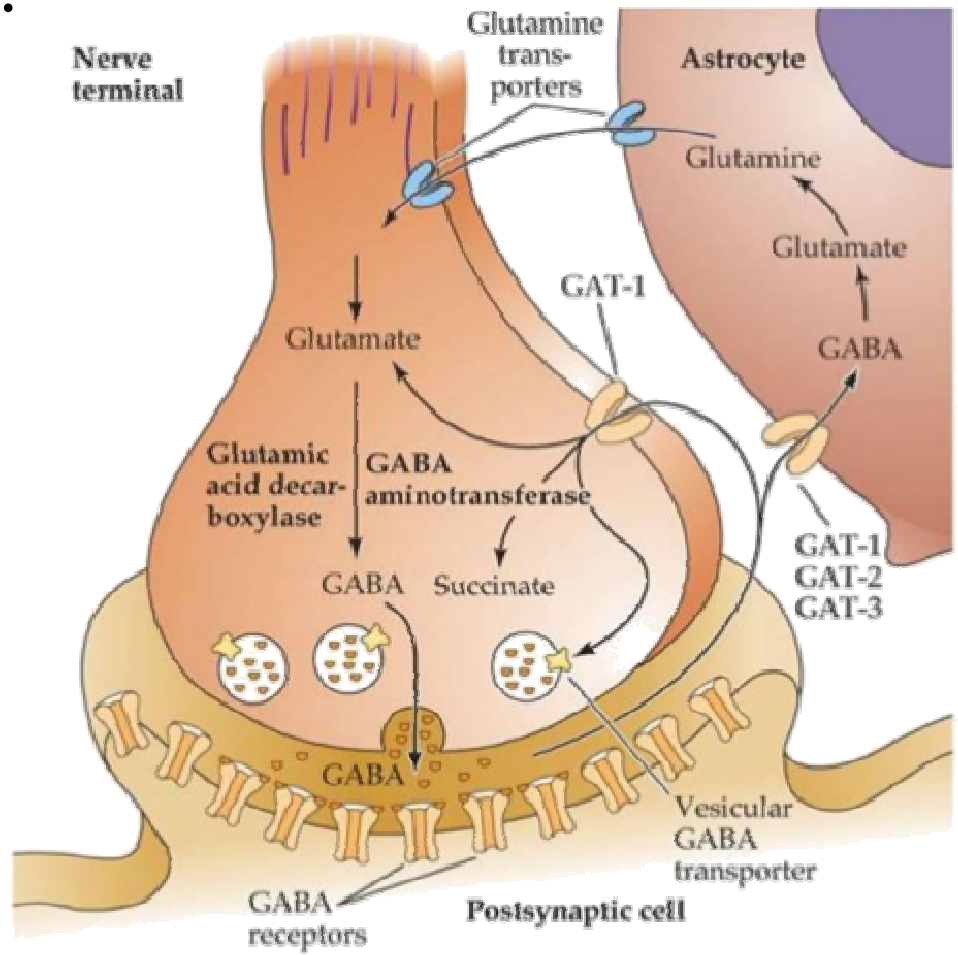


γ-aminobutyric acid (GABA) is the brain's major inhibitory neurotransmitter. When GABA binds to a GABA receptor in the brain, it causes a reduction in the ability of that neuron to conduct a neural impulse. Thus, GABA has the ability to "shut down" nerve cells throughout the central nervous system (CNS).

2. Anxiety and anxiolytic drugs

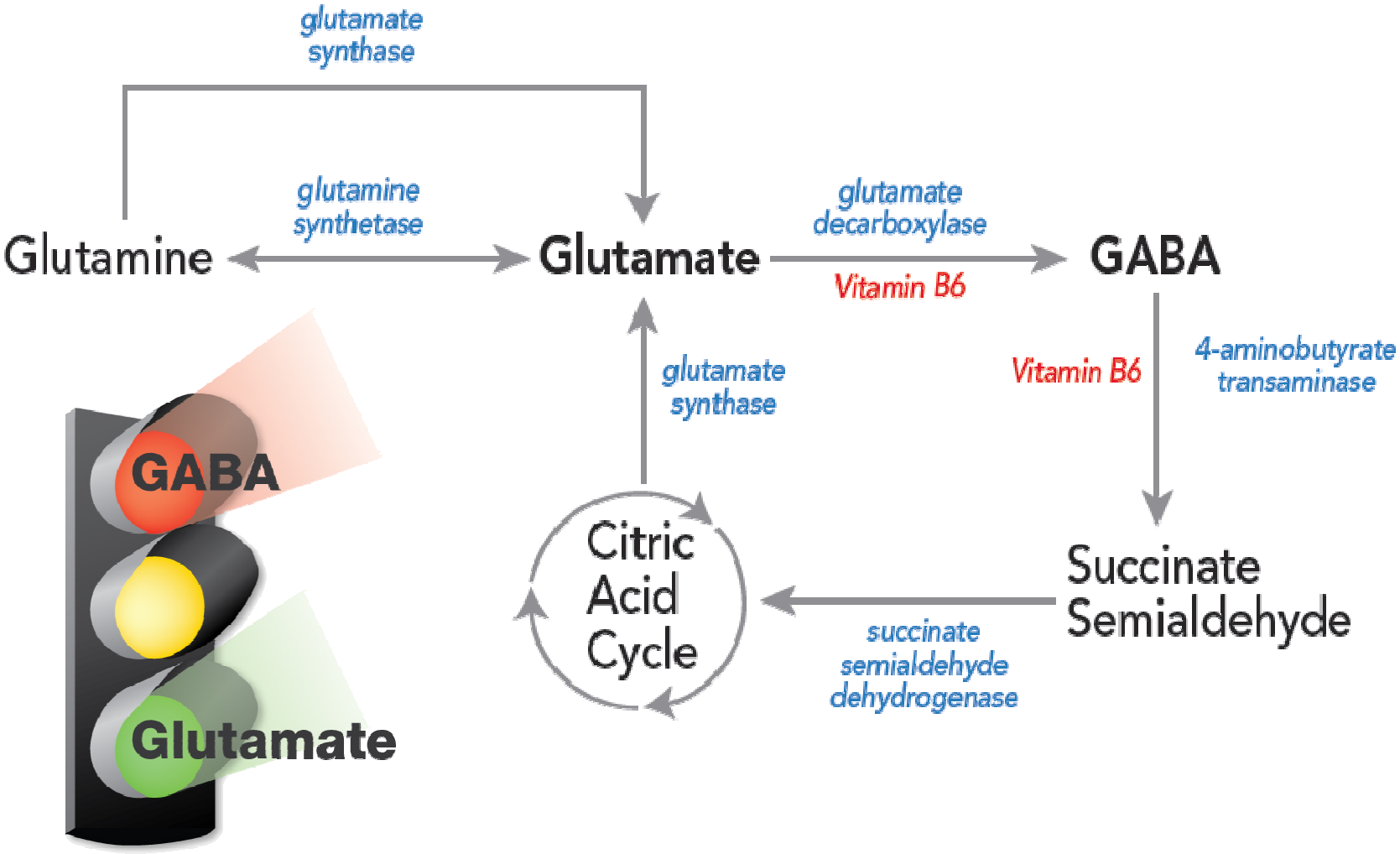
2.1 γ-aminobutyric acid (GABA)

GABA is synthesized by decarboxylation of glutamate by the enzyme ***glutamic acid decarboxylase (GAD)***.



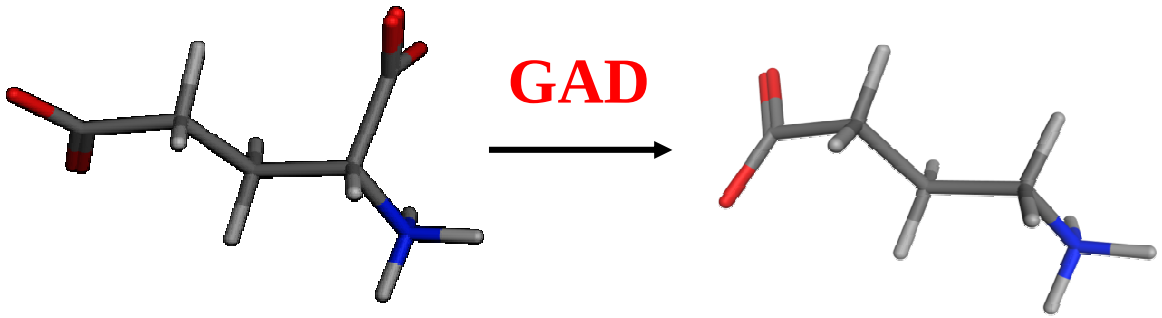
2. Anxiety and anxiolytic drugs

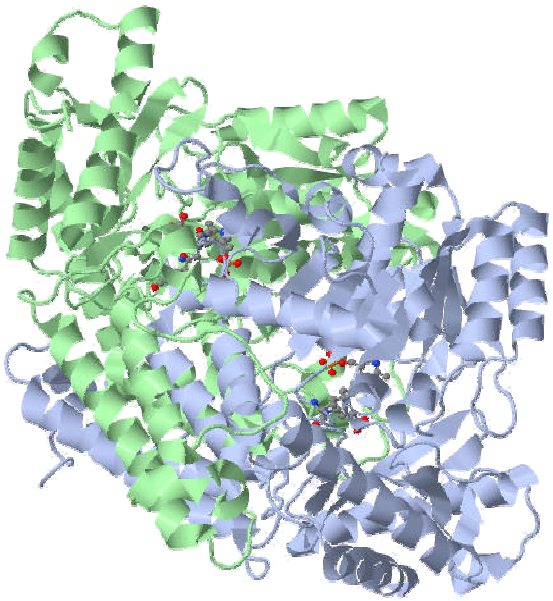
Brain glutamate-glutamine cycle



2. Anxiety and anxiolytic drugs

2.1 γ-aminobutyric acid (GABA)



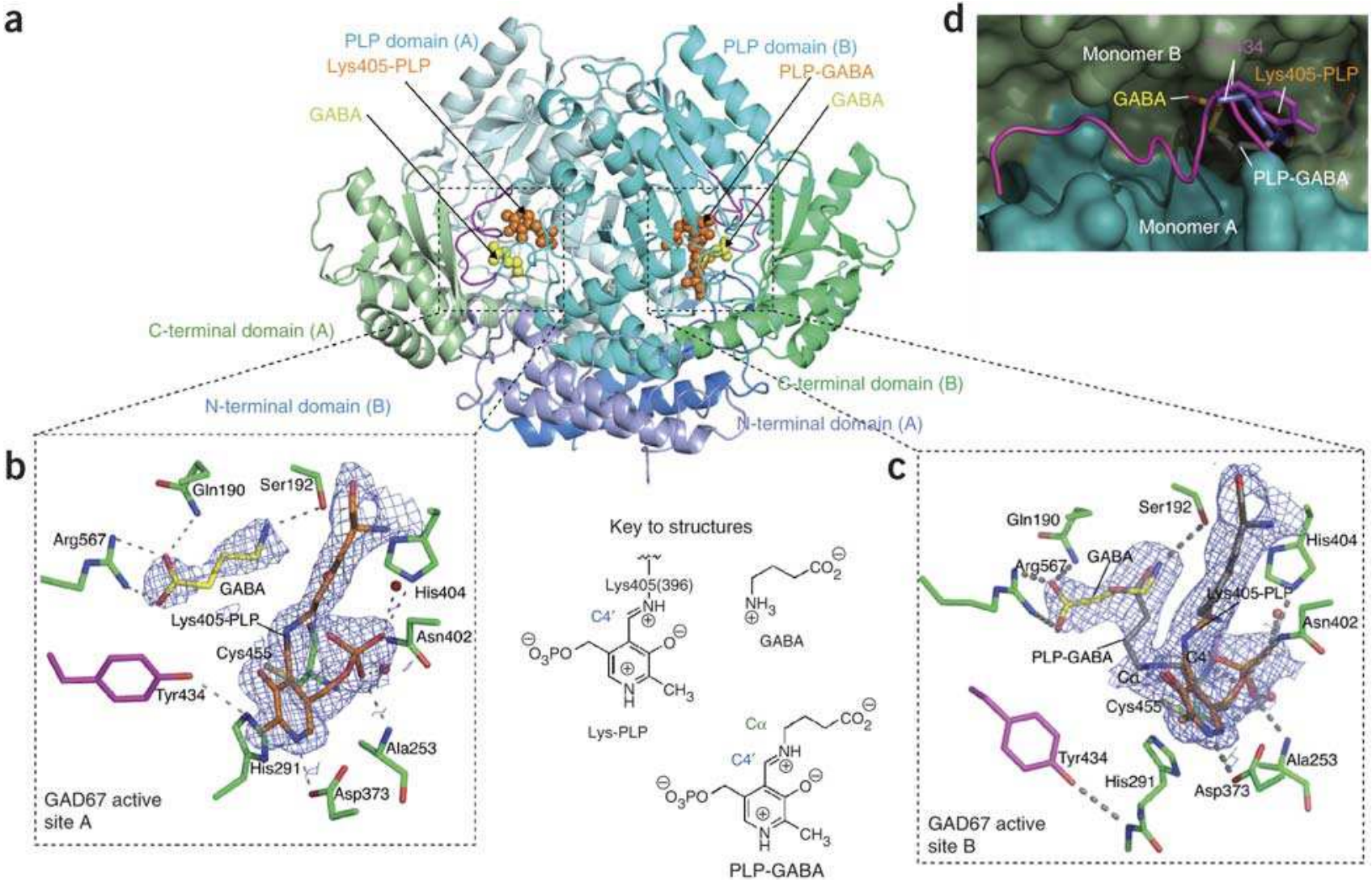


GAD67 derivated from PDB 2okj

The magic role of GAD: **GABA is synthesized from glutamate by the enzyme glutamic acid decarboxylase (GAD). In mammals, GAD exists in two isoforms encoded by two different genes - GAD1 and GAD2. These isoforms are GAD67 and GAD65 with molecular weights of 67 and 65 kDa, respectively. GAD1 and GAD2 are expressed in the brain where GABA is used as a neurotransmitter, GAD2 is also expressed in the pancreas. GAD requires a cofactor, pyridoxal phosphate, derived from *vitamin B6*. Consequently, a dietary deficiency of vitamin B6 can lead to diminished GABA synthesis, resulting in seizures and mental retardation.**

2. Anxiety and anxiolytic drugs

2.1 γ-aminobutyric acid (GABA)

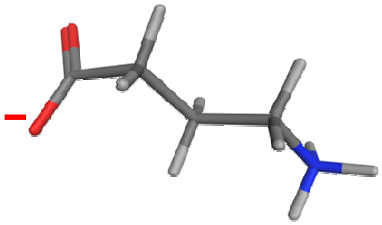


2. Anxiety and anxiolytic drugs

2.1 GABA transporters

2. Anxiety and anxiolytic drugs

2.1 GABAergic receptors

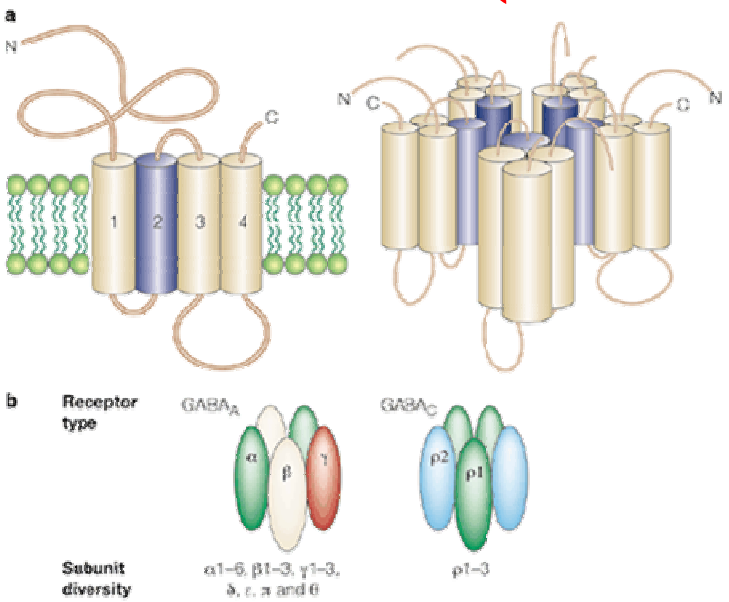


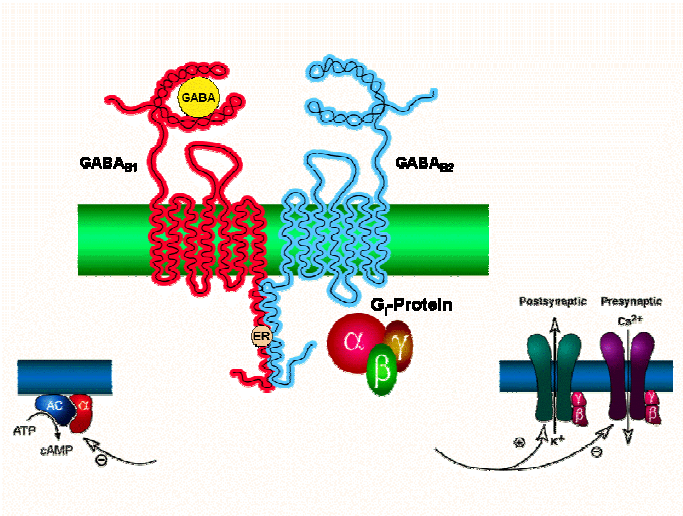
Ion channels

GPCRs (Family C)

GABA-A and GABA-C (GABA-Arho)

GABA-B





2. Anxiety and anxiolytic drugs

2.1 The role of GABA receptors

GABA-A receptors:

- **mediate fast inhibitory synaptic transmission**
- **regulate neuronal excitability**
- **responsible for rapid mood changes (e.g. anxiety, panic and stress response)**

GABA-B receptors:

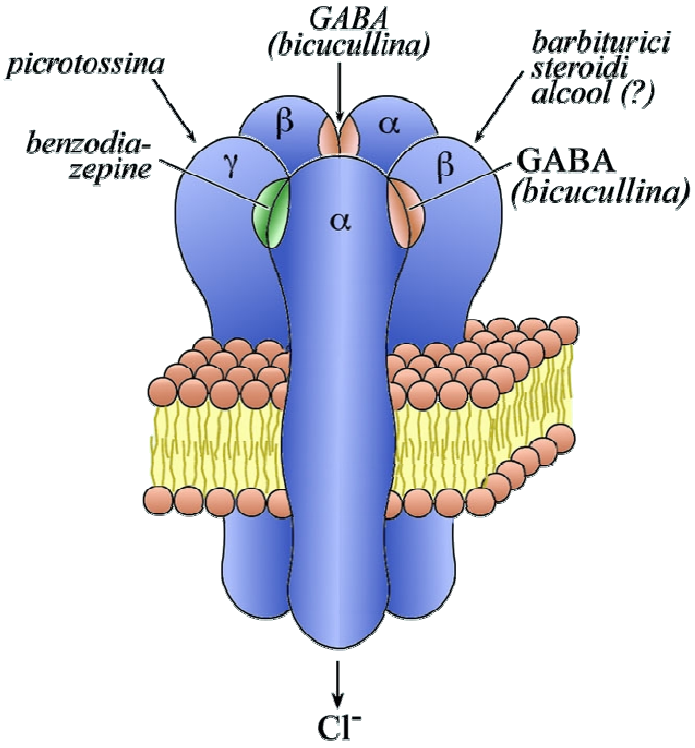
- **mediate slow inhibitory potentials**
- **effects on memory and mood (depression)**
- **effects on pain response**

GABA-C (GABA-Arho) receptors

- **especially high expression in the retina**
- **insensitive to typical allosteric modulators of GABA-A receptor channels such as benzodiazepines and barbiturates.**
- **physiological roles still unclear**

2. Anxiety and anxiolytic drugs

2.1 GABA-A Receptors

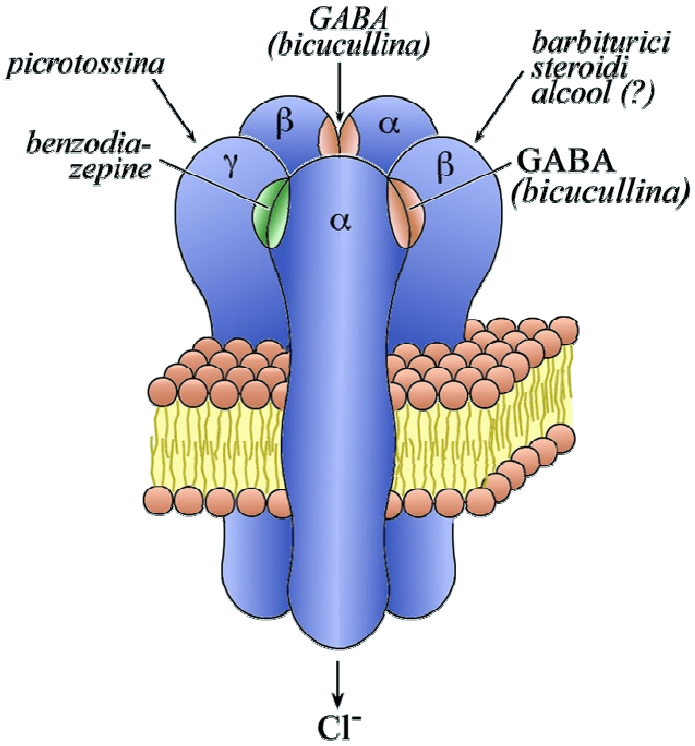


GABA controls the excitability of neurons by binding to the GABA-A receptor. The GABA-A receptor is a protein complex located in the synapses of neurons. All GABA-A receptors contain an ion channel that conducts chloride ions across neuronal cell membranes and two binding sites for the neurotransmitter γ-aminobutyric acid (GABA), while a subset of GABA-A receptor complexes also contain a single binding site for benzodiazepines. Binding of benzodiazepines to this receptor complex promotes binding of GABA, which in turn increases the conduction of chloride ions across the neuronal cell membrane. This increased conductance raises the membrane potential of the neuron resulting in inhibition of neuronal firing.

Interest in the behavioral and psychological roles of GABA has focused on the bonding of GABA to the GABA-A receptor, which is widely distributed throughout the brain; 60-75% of all synapses in the CNS are GABAergic!

2. Anxiety and anxiolytic drugs

2.1 GABA-A Receptors

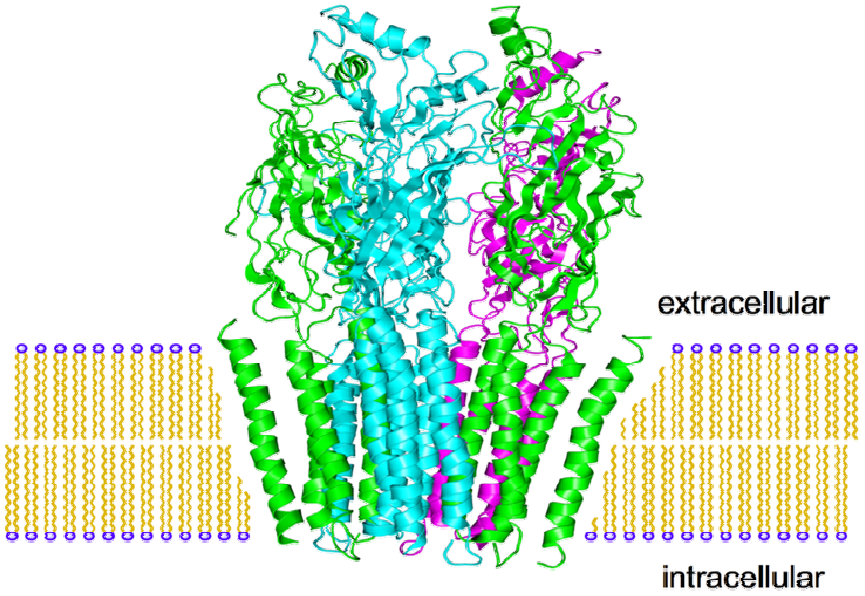


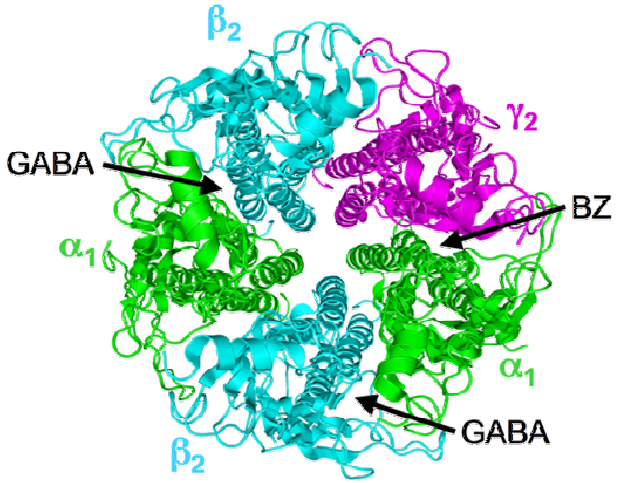
GABA-A receptors are very heterogeneous, with at least **19** different subunits producing potentially over 150,000 different receptor types. It has recently been discovered that some of these subunits mediate specific behavioral and pharmacological effects. For example, the high-affinity binding of GABA-A receptors to benzodiazepines requires the presence of a γ2 subunit and an adjacent α1, α2, α3, or α5 subunit.

Different GABA-A receptor subtypes have varying distributions within different regions of the brain and therefore control distinct neuronal circuits. Hence, activation of different GABA-A receptor subtypes by benzodiazepines may result in distinct pharmacological actions. In terms of the mechanism of action of benzodiazepines, their similarities are too great to separate them into individual categories such as anxiolytic or hypnotic. For example, a hypnotic administered in low doses will produce anxiety relieving effects, whereas a benzodiazepine marketed as an anti-anxiety drug will at higher doses induce sleep.

2. Anxiety and anxiolytic drugs

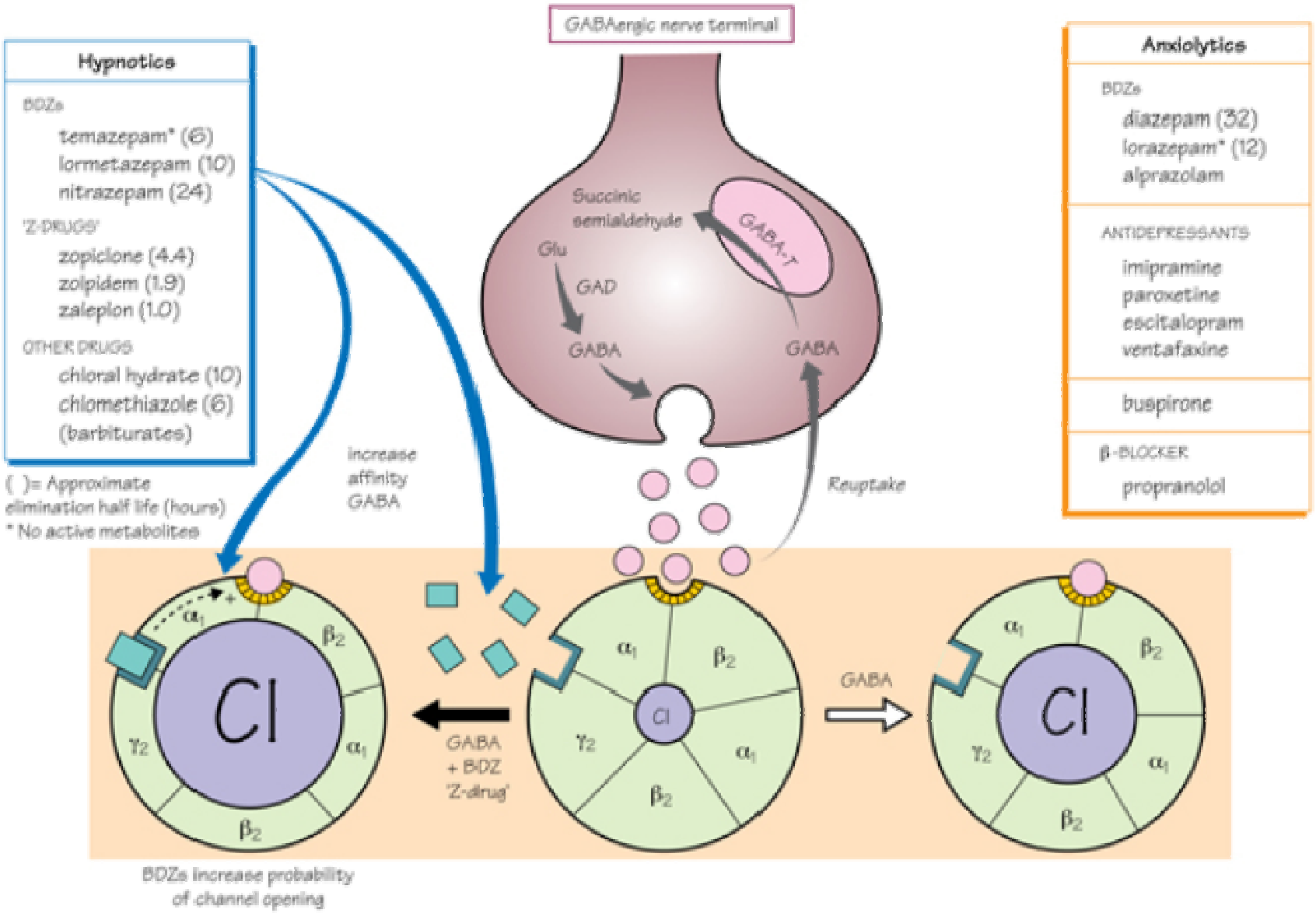
2.1 GABA-A Receptors





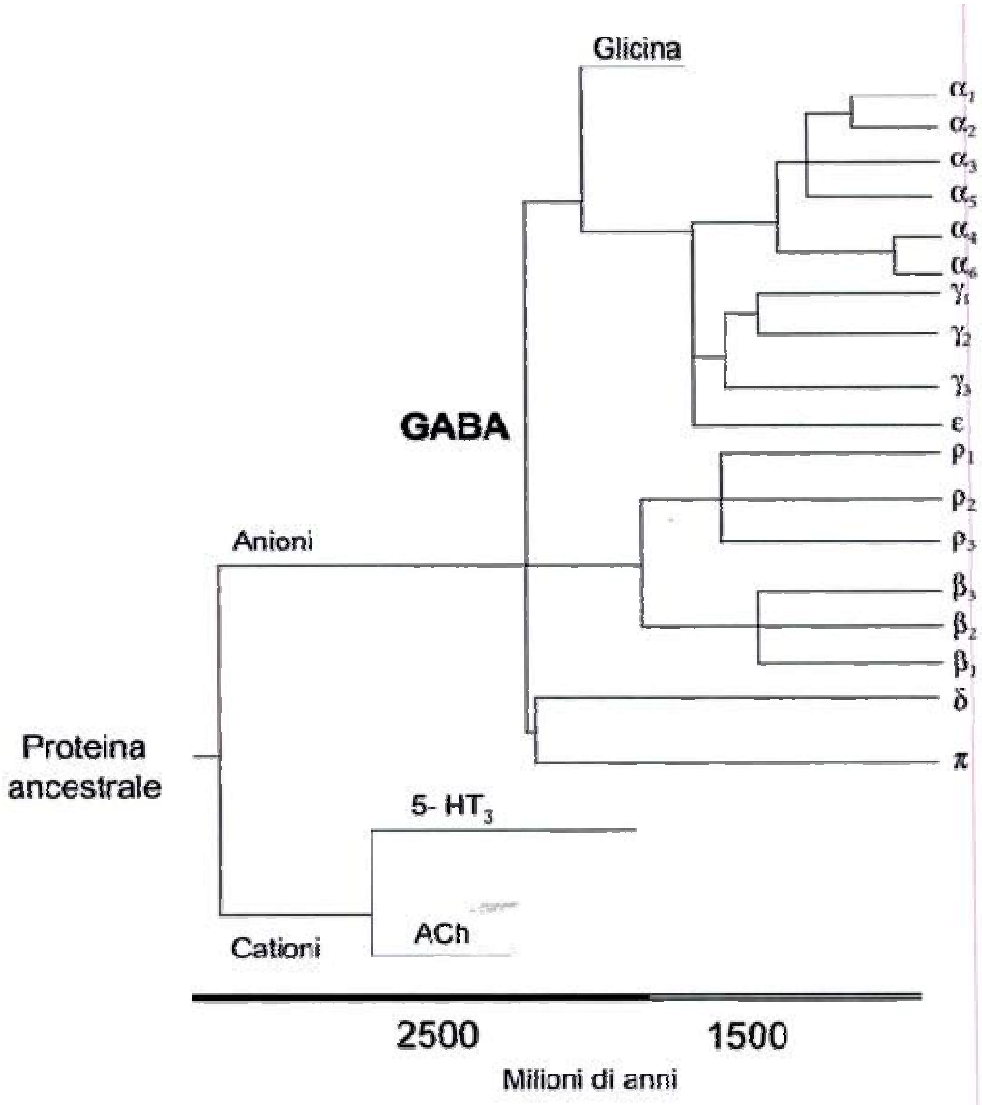
The superfamily of the ligand-gated ion channels contains cys-loop receptors such as ***GABAA receptors*** (GABAAR), ***glycine*** (GlyR), ***serotonin*** (5HT3) and ***nicotinic acetylcholine*** (nAChR) receptors, ***ionotropic glutamate receptors*** (AMPA, Kainate and NMDA) and ***ATP-gated channels*** (P2X).

The structure of the nicotinic acetylcholine receptor (nAchR: PDB code **2BG9**) can be used to simulate the GABAA receptor. Bottom: view of the receptor from the extracellular face of the membrane. The subunits are labelled according to the GABAA nomenclature and the most prominent GABAA receptor subtype is displayed. The approximate locations of the GABA and benzodiazepine (BZ) binding sites are noted (between the α subunits and β subunits and between the α subunits and γ subunits respectively).


GABAergic nerve terminal
Hypnotics
BDZs
temazepam* (6)
lormetazepam (10)
nitrazepam (24)
'Z-DRUGS'
zopiclone (4.4)
zolpidem (1.9)
zaleplon (1.0)
OTHER DRUGS
chloral hydrate (10)
chlomethiazole (6)
(barbiturates)
( )= Approximate elimination half life (hours)
* No active metabolites
Anxiolytics
BDZs
diazepam (32)
lorazepam* (12)
alprazolam
ANTIDEPRESSANTS
imipramine
paroxetine
escitalopram
ventafaxine
buspirone
β-BLOCKER
propranolol
Succinic semialdehyde
GABA-T
Glu
GAD
GABA
GABA
increase affinity GABA
Reuptake
Cl
GABA + BDZ 'Z-drug'
GABA
BDZs increase probability of channel opening

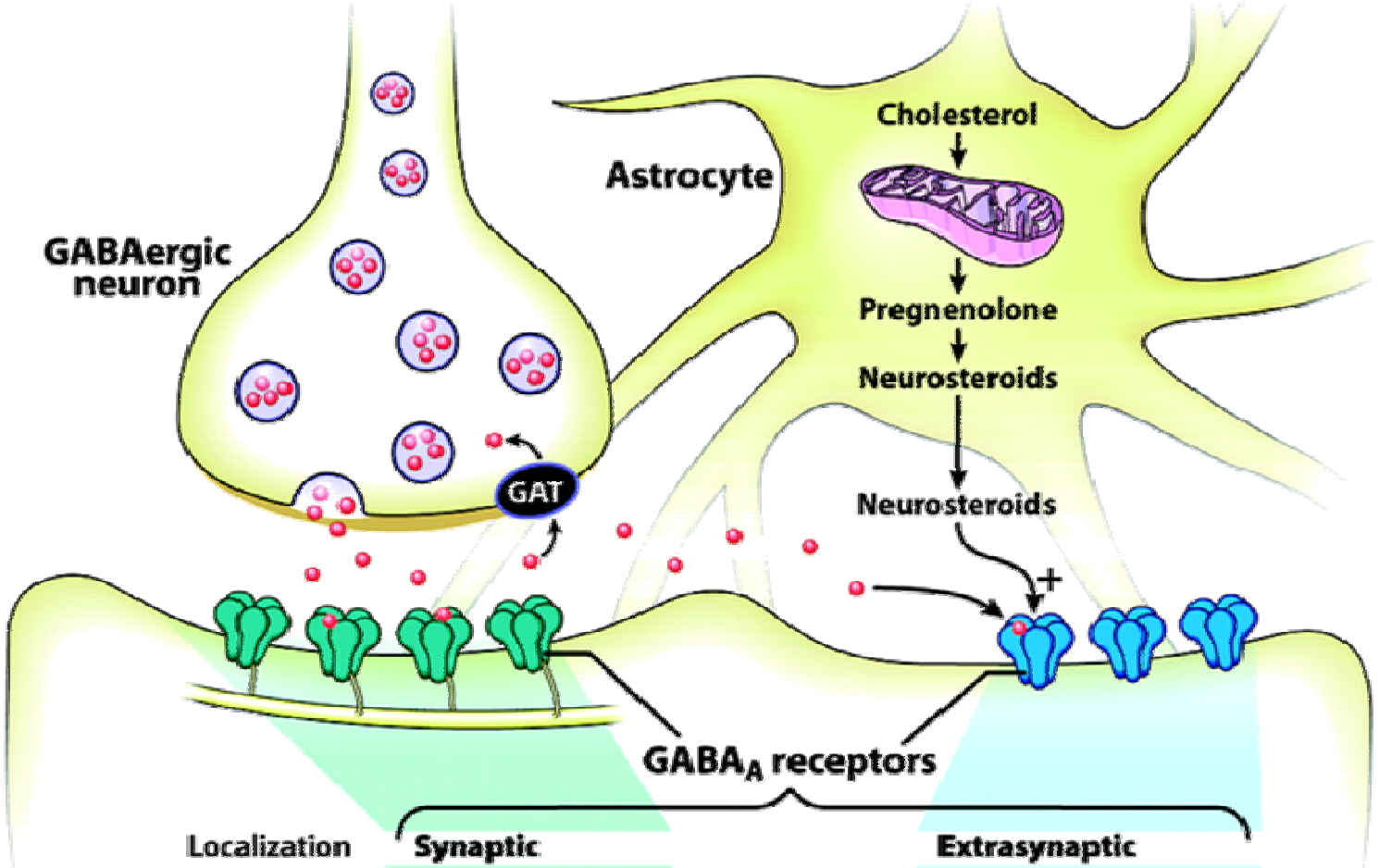
2. Anxiety and anxiolytic drugs

2.1 GABA-A Receptors



2. Anxiety and anxiolytic drugs

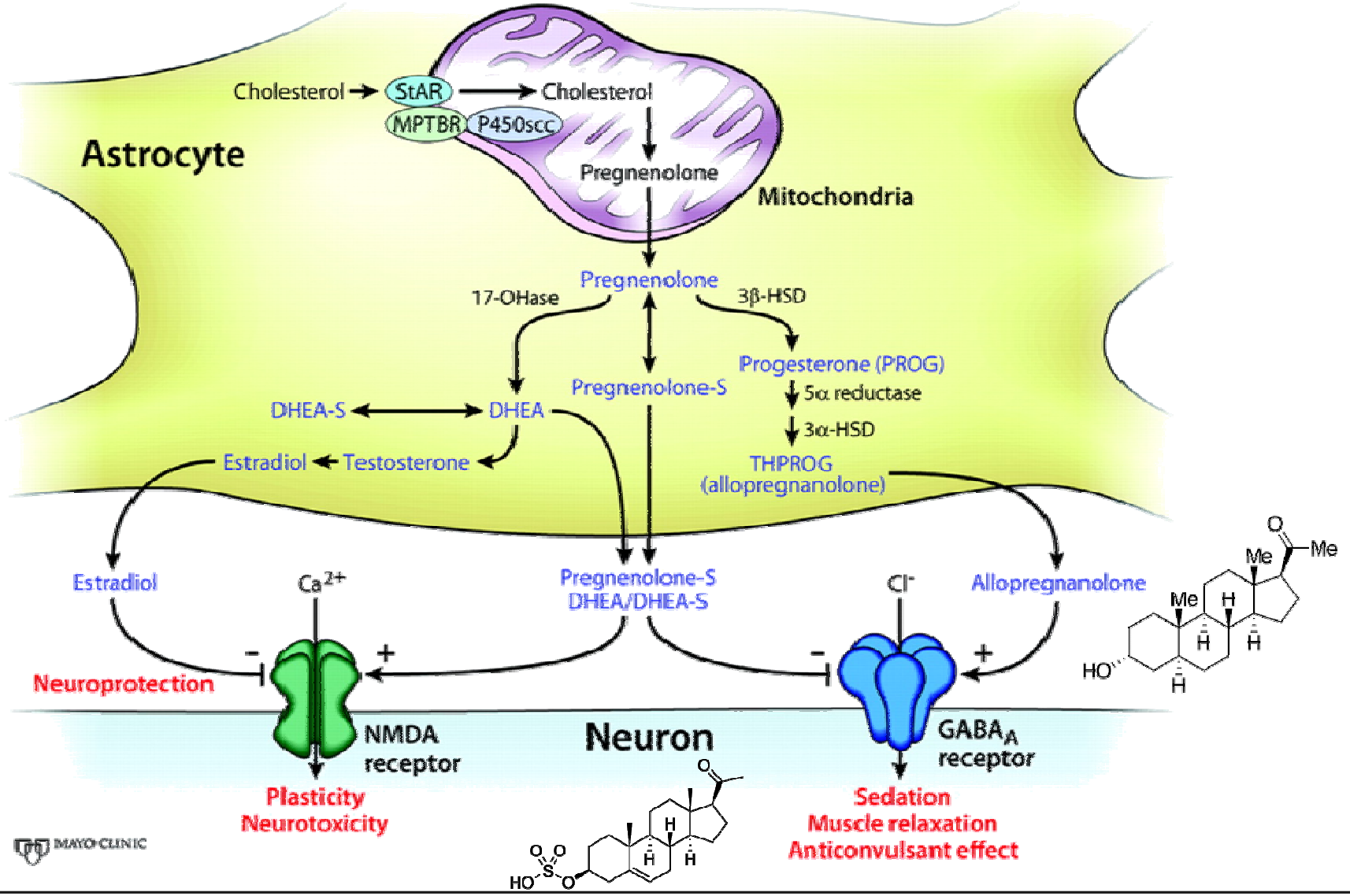
2.1 GABA-A Receptors: two distinct localizations



Localization	Synaptic	Extrasynaptic
Subunit	γ2(α1-α3)	δ(α4 or α6)
Function	Phasic inhibition	Tonic inhibition
Positive modulators	Benzodiazepines	Neurosteroids, alcohol general anesthetics

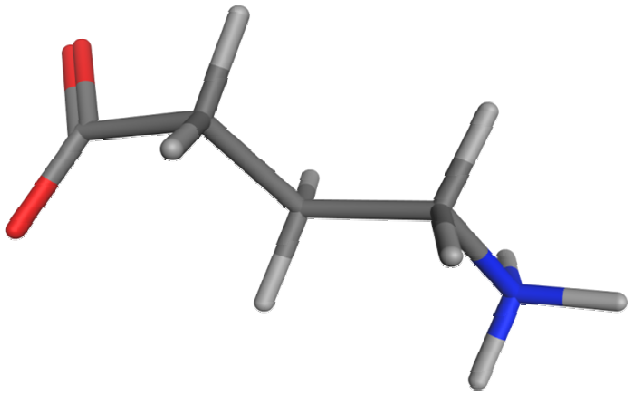
2. Anxiety and anxiolytic drugs

2.1 GABA-A Receptors… and neurosteroids



2. Anxiety and anxiolytic drugs

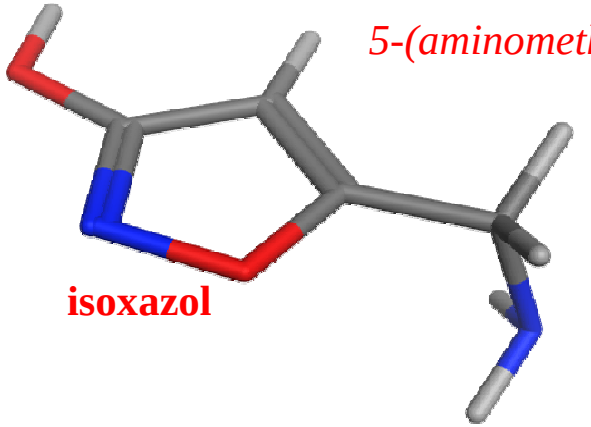
2.2 GABA receptors agonists



GABA

Muscimol

5-(aminomethyl)-isoxazol-3-ol

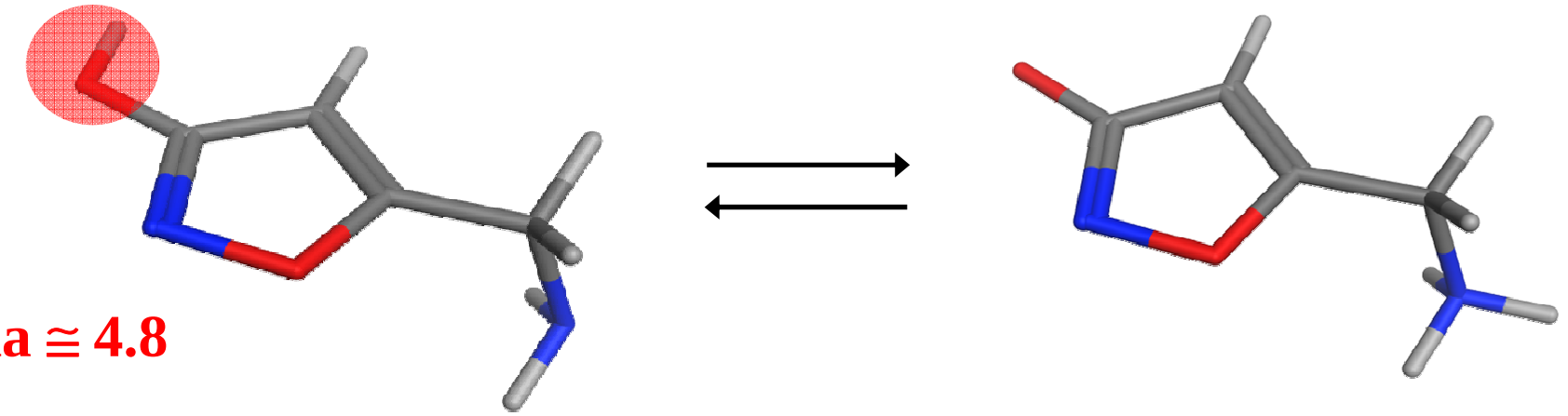


isoxazol

Muscimol is the major psychoactive alkaloid present in many mushrooms of the *Amanita* genus. While muscimol is conventionally thought of as a selective GABA-A agonist, it is also a potent partial agonist at the GABA-C receptor, and so its range of effects results from a combined action at both targets. It is one of the agents responsible for the distinctive *hallucinations experienced* when these mushrooms are consumed in small amounts. If consumed in high doses, it can be fatal, explaining why some *Amanita* species are considered poisonous and unfit for human consumption.

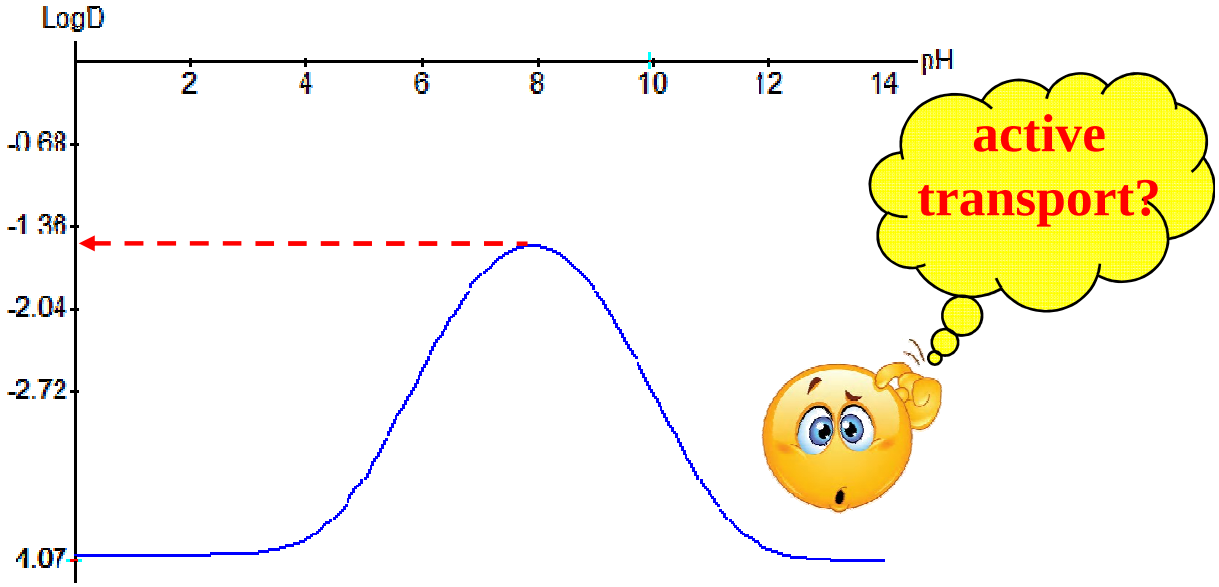
2. Anxiety and anxiolytic drugs

2.2 GABA receptors agonists



pKa ≅ 4.8

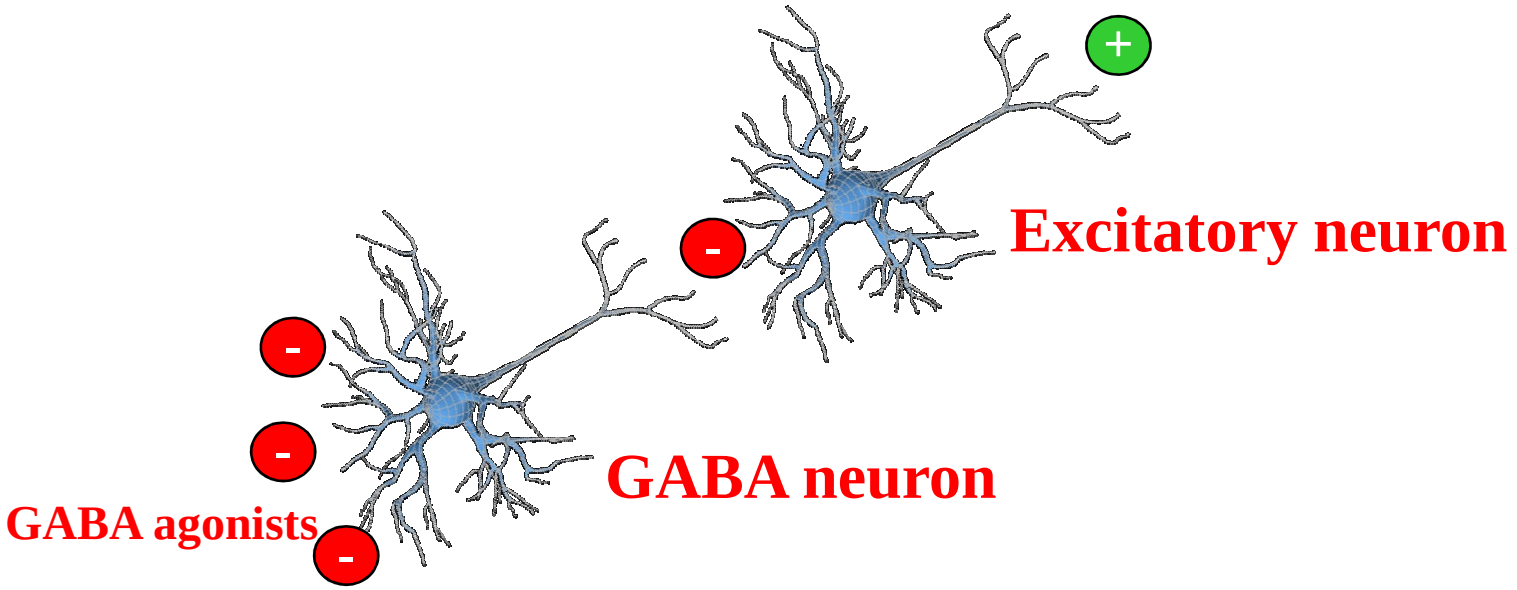
logD: logP *f* (pH)



2. Anxiety and anxiolytic drugs

2.2 GABA receptors agonists

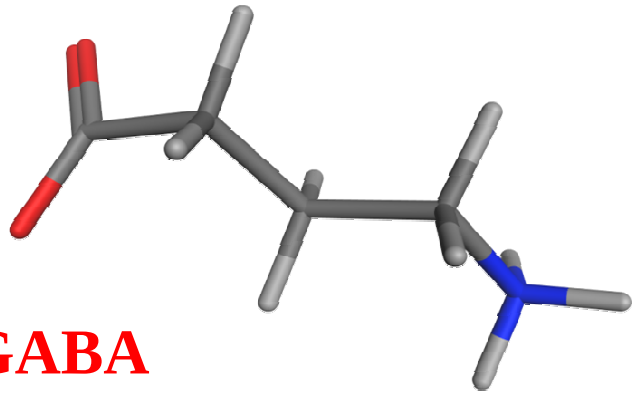
Why often GABA-A receptor agonists present initially SNC excitatory effects, like hallucinations, modification of the vision and presence of sounds…



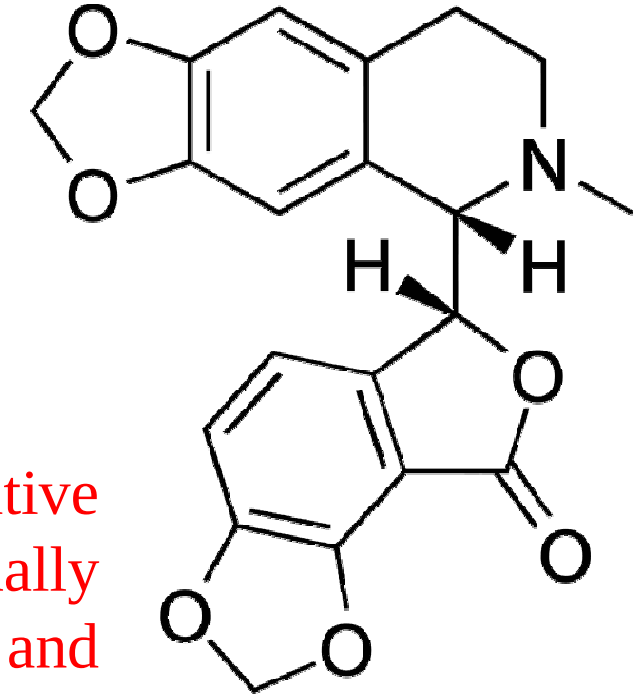
GABA-A neurons, apparently, are silenced first…

2. Anxiety and anxiolytic drugs

2.2 GABA receptors antagonists



GABA



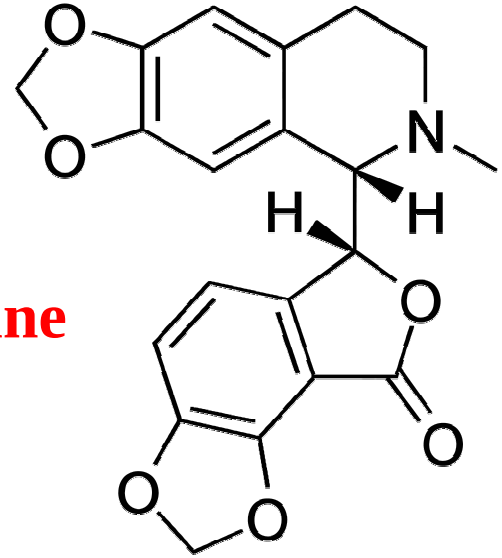
Bicuculline

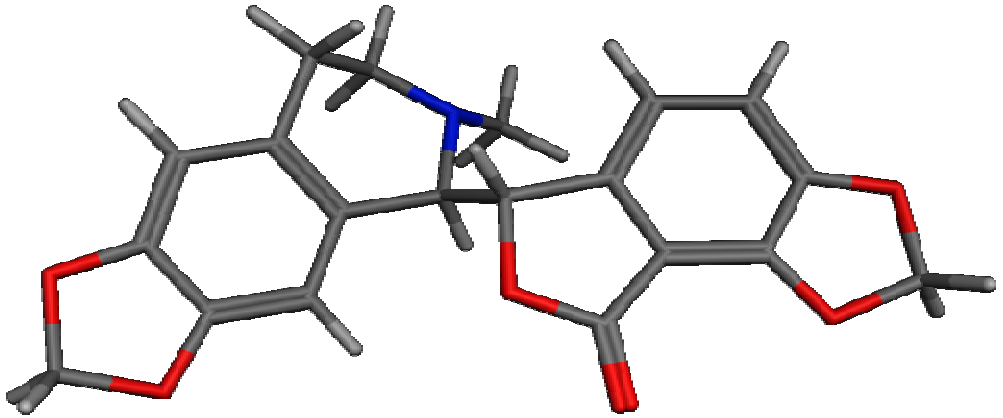
Bicuculline is a light-sensitive competitive antagonist of GABA-A receptors. It was originally identified in 1932 in plant alkaloid extracts and has been isolated from *Dicentra cucullaria*, *Adlumia fungosa*, *Fumariaceae*, and several *Corydalis* species. Since it blocks the inhibitory action of GABA receptors, ***the action of bicuculline mimics epilepsy***.

2. Anxiety and anxiolytic drugs

2.2 GABA receptors antagonists

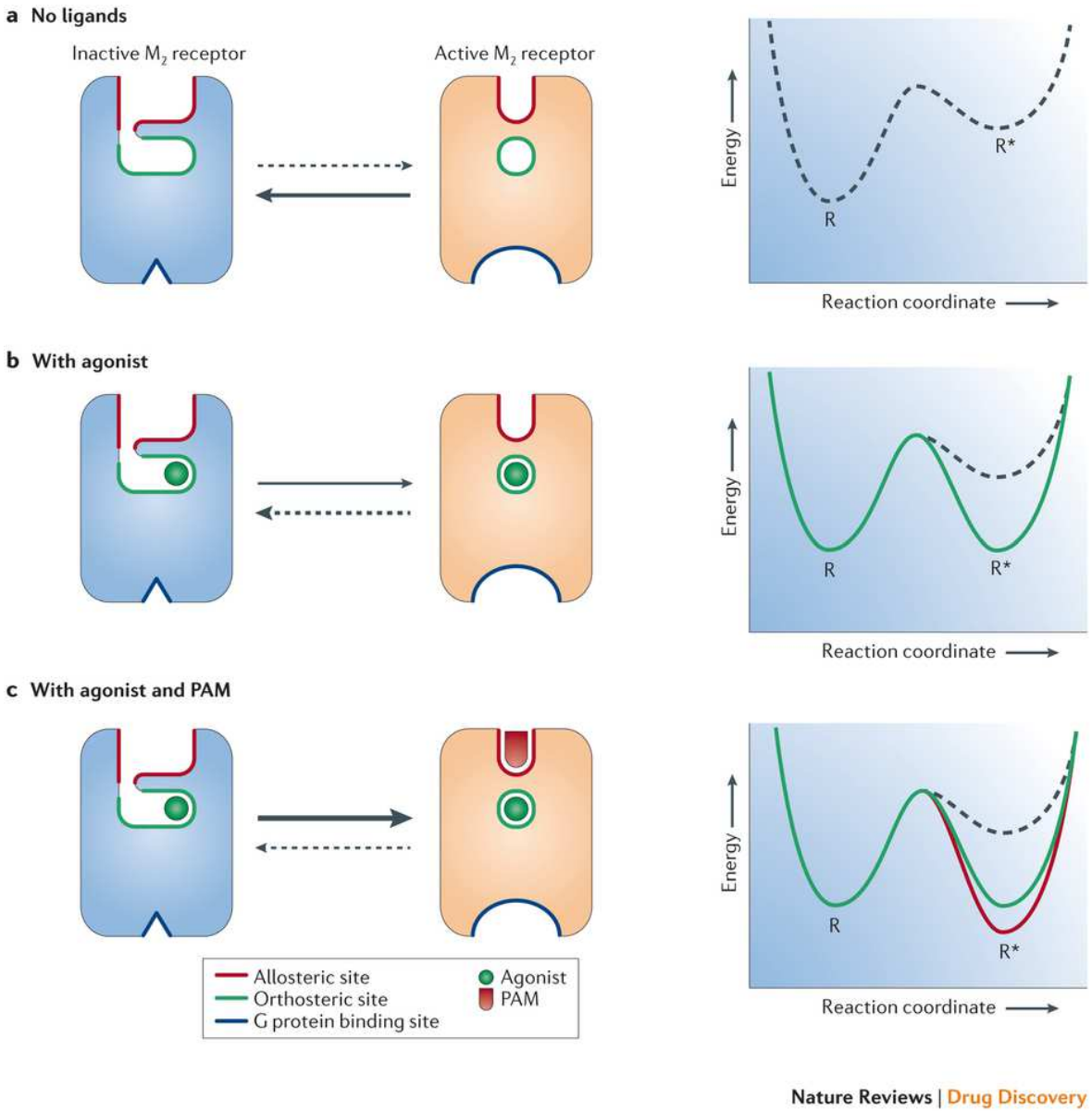
Bicuculline





logP = 2.7
pKa = 7.5
PSA ≅ 66 Å²

Welcome to the magic kingdom of PAM!



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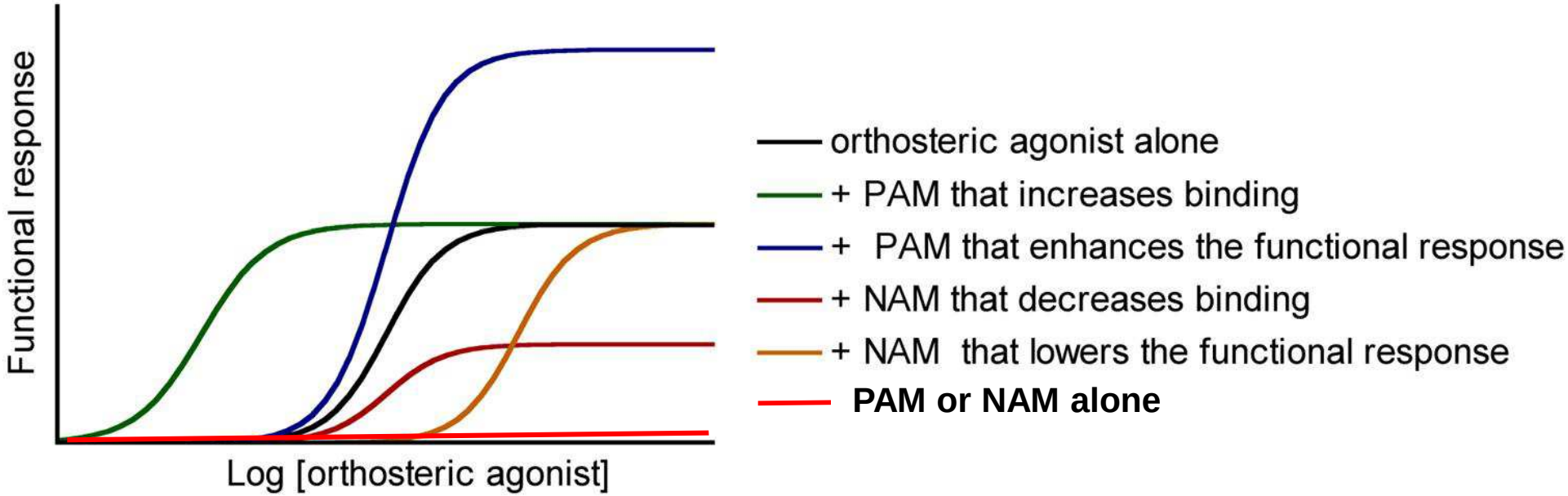
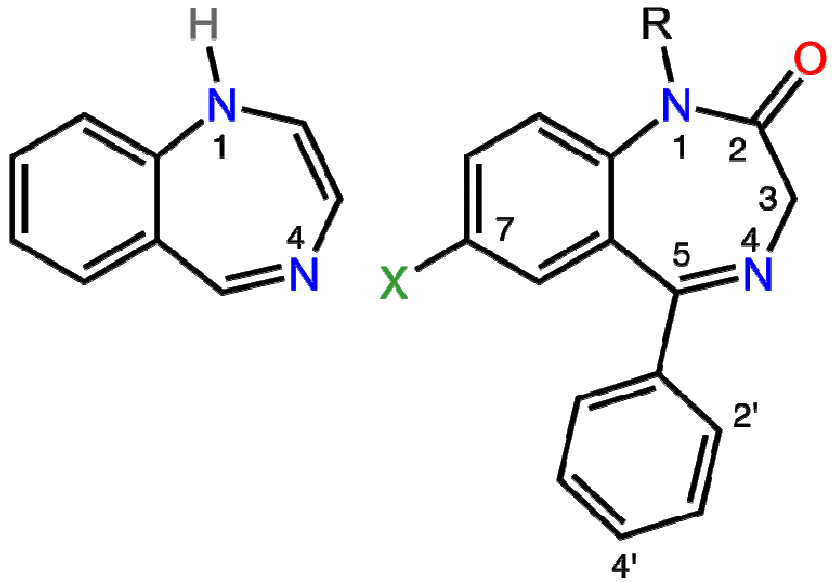


2. Anxiety and anxiolytic drugs

2.3 Benzodiazepine

A **benzodiazepine is a** psychoactive drug whose core chemical structure is the fusion of a benzene ring and a ***1,4-diazepine ring***.

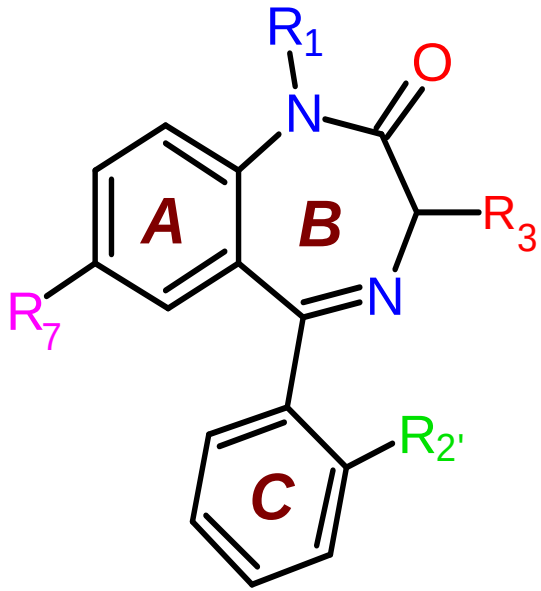


5-phenyl-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one

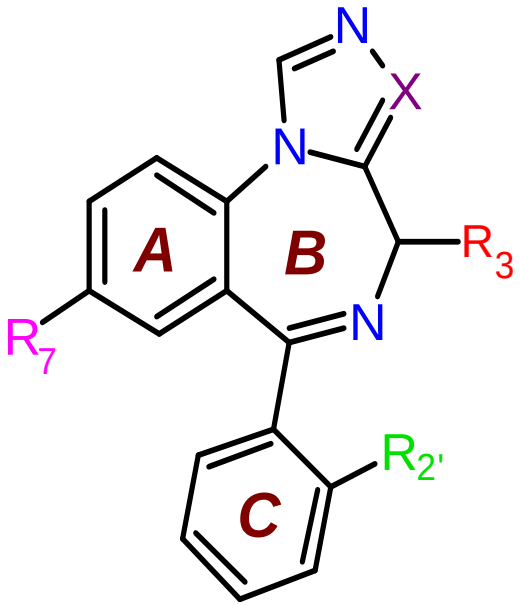
2. Anxiety and anxiolytic drugs

2.3 Benzodiazepine

Traditional benzodiazepines (first generation)



Heterocycle benzodiazepines (second generation)

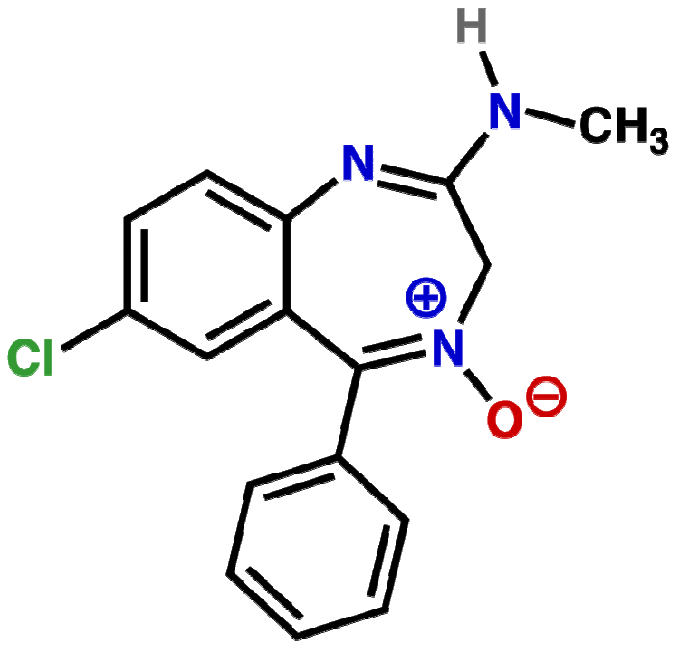


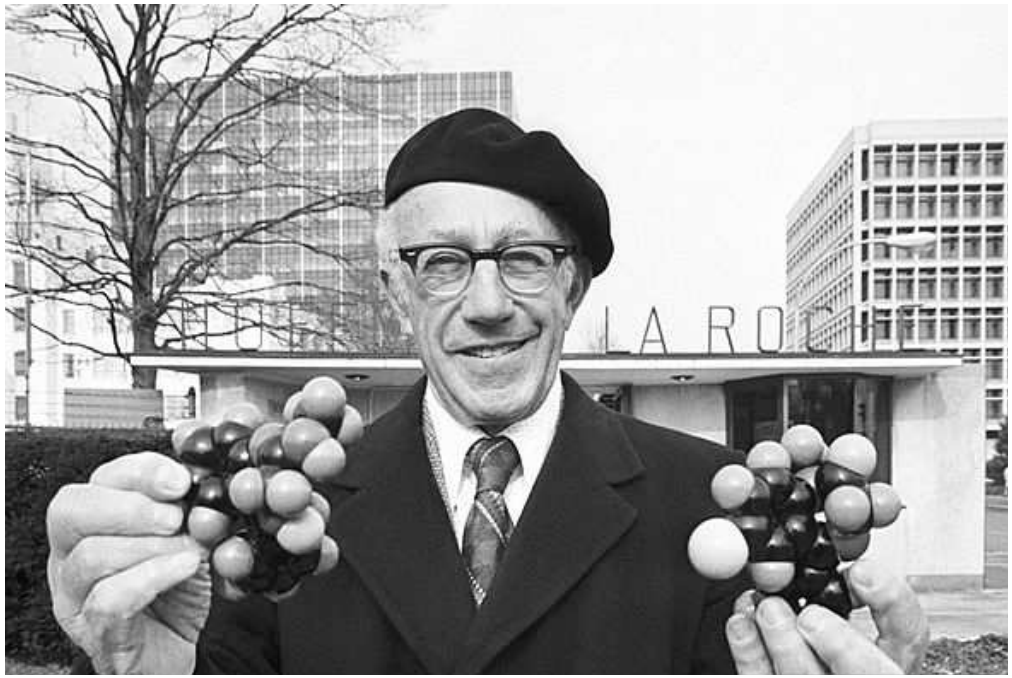
Imidazolo-benzodiazepines, X = CH
Triazolo-benzodiazepines, X = N

2. Anxiety and anxiolytic drugs

2.3 Benzodiazepine

The first benzodiazepine ***chlordiazepoxide*** (Librium), initially called ***methaminodiazepoxide,*** was discovered accidentally by Leo Sternbach in 1955, and made available in 1960 by Hoffmann–La Roche, which has also marketed diazepam (Valium) since 1963.

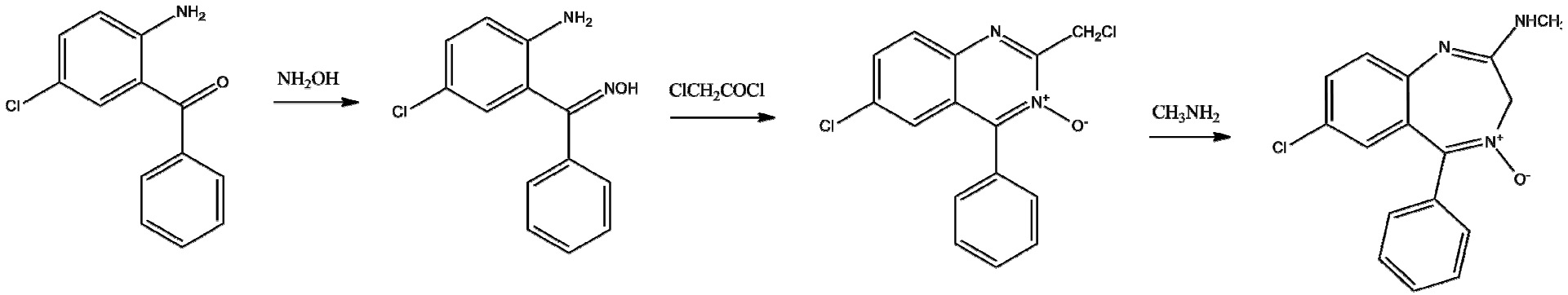




2. Anxiety and anxiolytic drugs

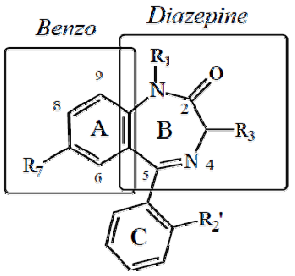
2.3 Benzodiazepine

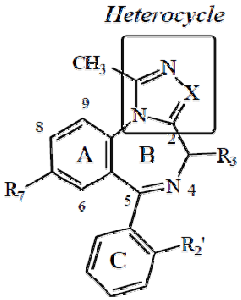
Synthesis of ***chlordiazepoxide*** (Librium):



2. Anxiety and anxiolytic drugs

2.3 Benzodiazepine: a flavor of SAR



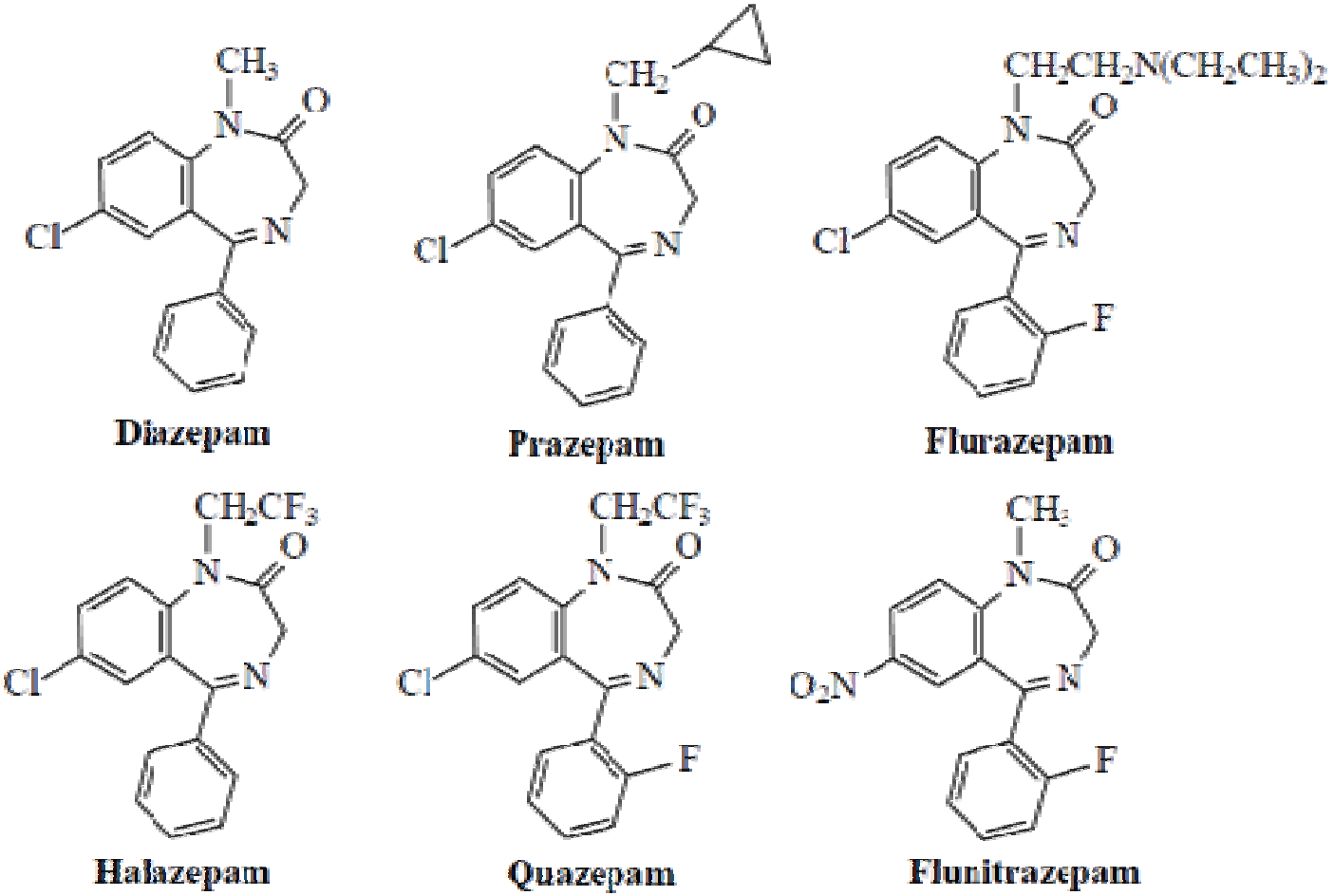


- Rings A, B and C are required for BDZ-receptor binding activity:
- Ring A participates in "pi-pi stacking " interactions with a complimentary functionality on the receptor
  - An electron withdrawing group at R_7 (usually Cl or NO_2) is required for optimal receptor affinity
  - Substitution on other positions of this ring may decrease activity
- Ring C contributes to BDZ-receptor binding through hydrophobic and steric interactions:
  - Position R_2' may be unsubtituted or contain a halogen atoms. Halogenation (F, Cl) generally increases BDZ activity
  - Substitution on other positions of this ring may decrease activity (4')
- Ring B is required for optimal BDZ-receptor binding, BUT
  - Neither the amide C=O or N-alkyl groups (R_1) directly contribute to binding. **R_1 can be H, CH_3, or relatively small alkyl groups.**
  - **Amide can be replaced with an amidine group as in chlordiazepoxide**
  - **Amide can be replaced with heterocycle such as imidazole or triazole**
  - The 3-position may be unsubstituted (R_3 – H) or hydroxylated (R_3 – OH)
  - The 4-5-imino group is not required for activity
- **Substituents at positions 1, 3 and to a lesser extent 7 influence pharmacokinetics as described in the sections that follow!**

2. Anxiety and anxiolytic drugs

2.3 Benzodiazepine: classification

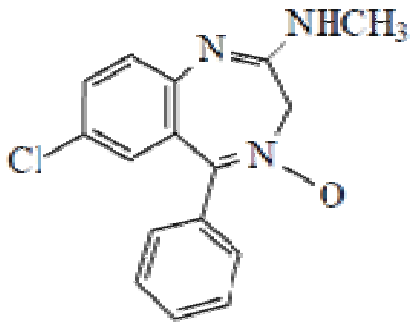
N-1-Substituted-3-Unsubstituted Benzodiazepines ("Diazepams")



2. Anxiety and anxiolytic drugs

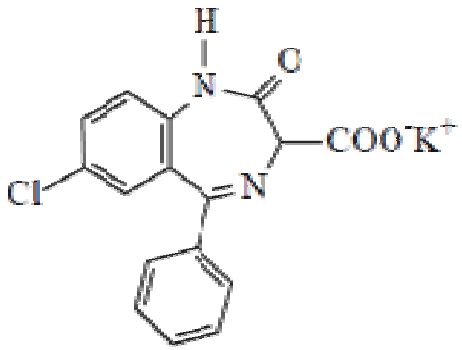
2.3 Benzodiazepine: classification

Aminidino-N-oxide Benzodiazepines (Chlordiazepoxide)



Chlordiazepoxide

3-Carboxyl-N-1-Unsubstituted Benzodiazepines (Chlorazepate)

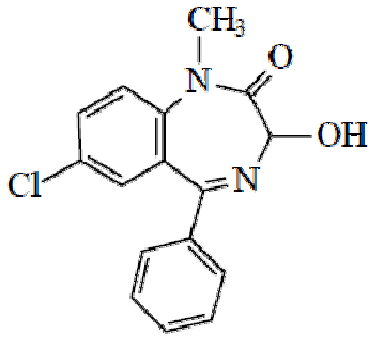


Chlorazepate

2. Anxiety and anxiolytic drugs

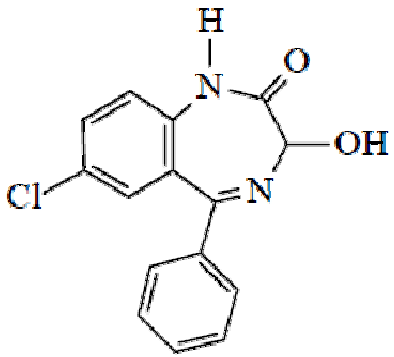
2.3 Benzodiazepine: classification

N-1-Substituted-3-Hydroxy Benzodiazepines ("N-Alkyl-Oxazepams")

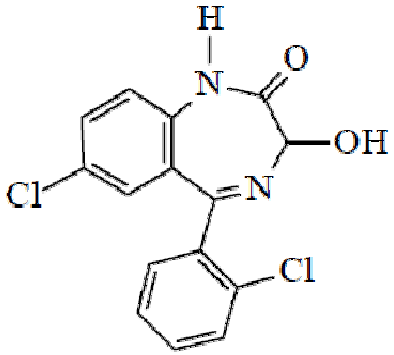


Temazepam

N-1-Unsubstituted-3-Hydroxy Benzodiazepines ("Oxazepams")



Oxazepam

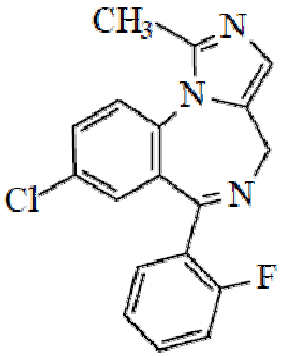


Lorazepam

2. Anxiety and anxiolytic drugs

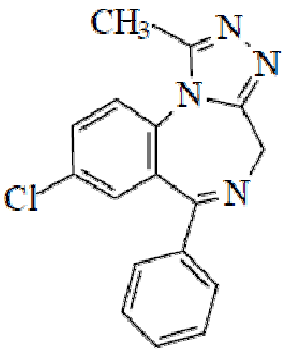
2.3 Benzodiazepine: classification

Imidazo-Benzodiazepines

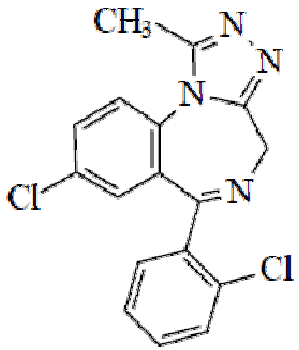


Midazolam

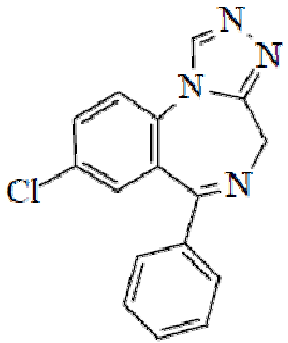
Triazolo-Benzodiazepines



Alprazolam



Triazolam

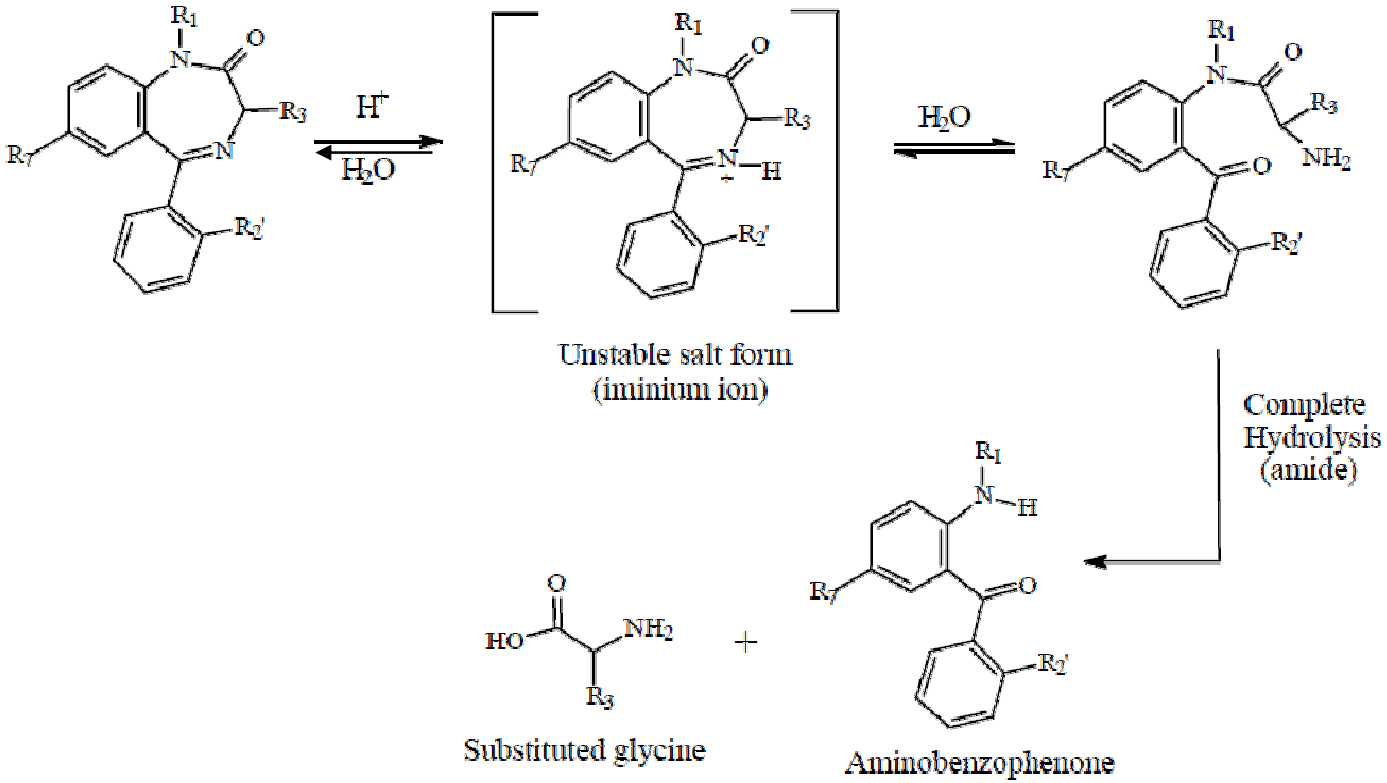


Estazolam

2. Anxiety and anxiolytic drugs

2.3 Basicity and Reactivity of the "Traditional Benzodiazepines"

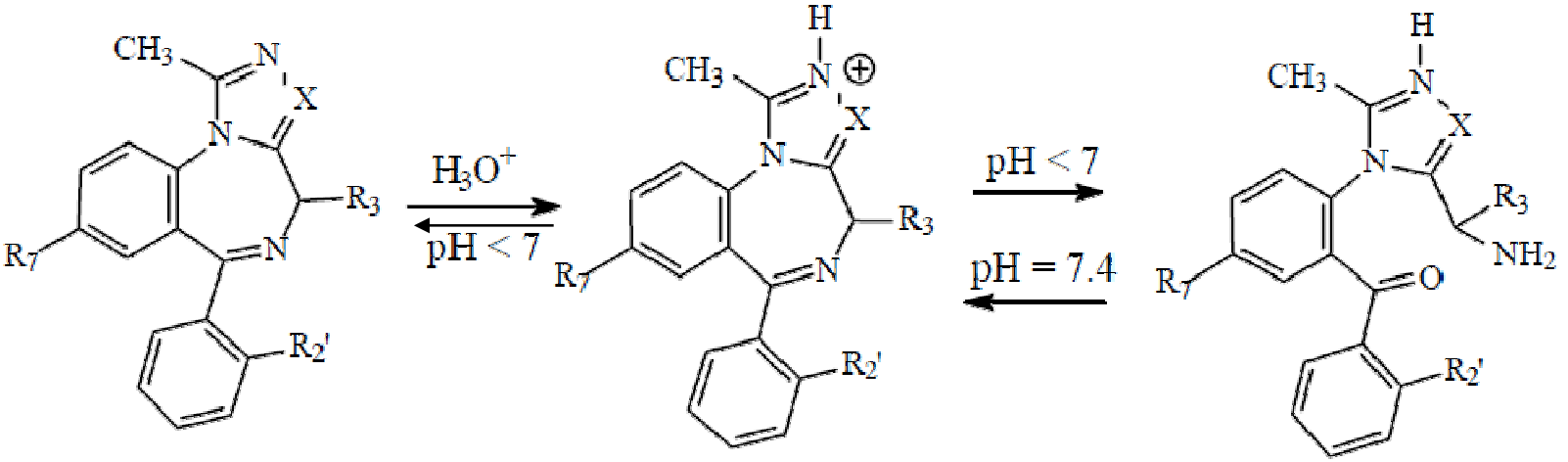
The BDZs are weak organic bases with the most basic nitrogen being the imine N4 (amide at positions 1,2 is non-basic). Thus BDZ salts can only be formed with strong acids. Unfortunately, such strong acid salts are unstable and readily undergo sequential hydrolyses, first at the imine bond and then at the amide to yield inactive products. **The first hydrolysis reaction (imine hydrolysis) is reversible, however the second (amide hydrolysis) eliminates GABA receptor activity**.



2. Anxiety and anxiolytic drugs

2.3 Basicity and Reactivity of the "Imidazo- and Triazolo-Benzodiazepines"

The salts formed from the heterocyclic benzodiazepines are more stable than salts formed from the traditional drugs! When placed in aqueous media the heterocyclic salts may undergo imine hydrolysis similar to the traditional agents (see above), however no further hydrolysis (to inactive products) can occur since the heterocyclic compounds no longer have an acid labile amide group; in these compounds the amide was replaced with the heterocyclic group. Thus at acidic pHs imine hydrolysis may occur as shown below but the reaction does not proceed, and at physiologic pH (post-injection) reformation of he benzodiazepine ring is favored 9as shown below):



Imidazo/Triazolo-BDZs

Not hydrolyzed further!

2. Anxiety and anxiolytic drugs

2.3 Basicity and Reactivity of the "Imidazo- and Triazolo-Benzodiazepines"

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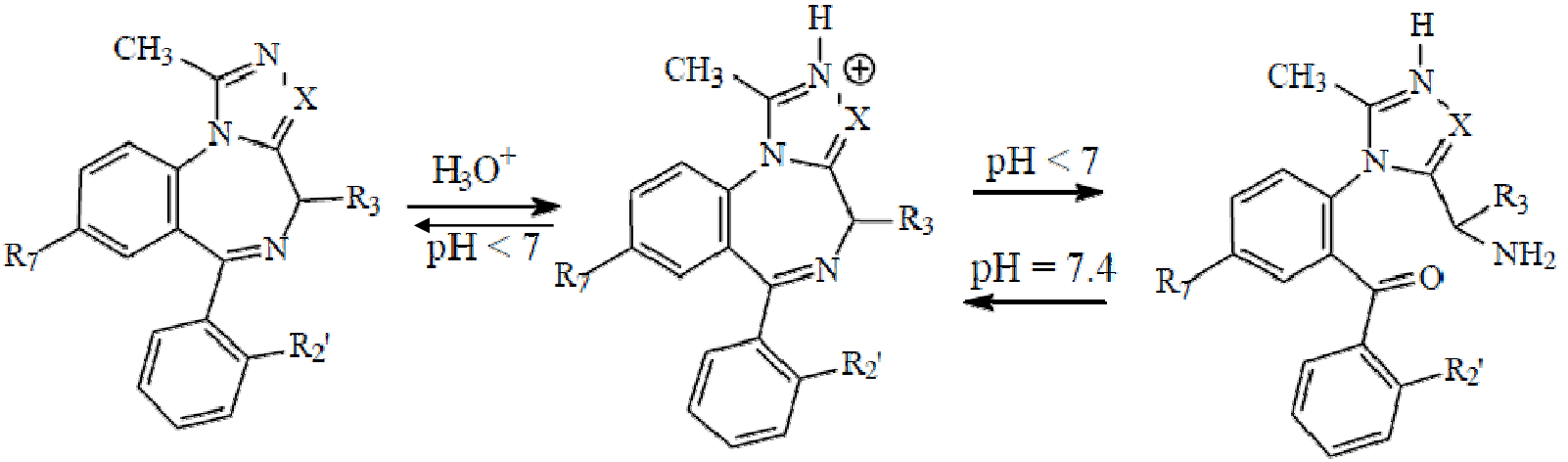


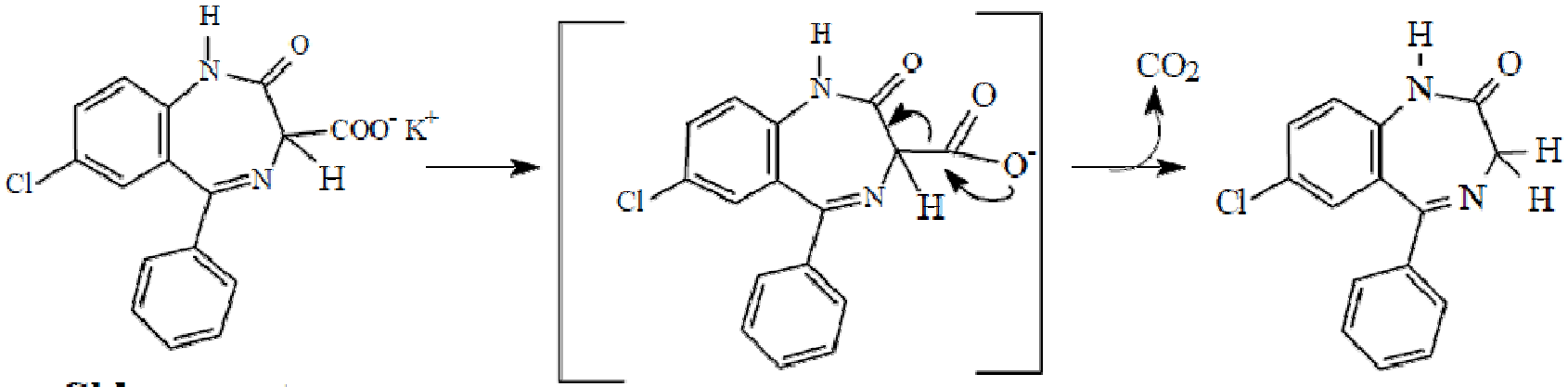
Imidazo/Triazolo-BDZs

Not hydrolyzed further!

2. Anxiety and anxiolytic drugs

2.3 Clorazepate and the 3-Carboxylate Benzodiazepines: Prodrugs

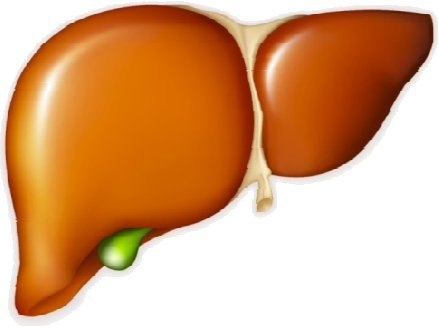
The 3-carboxylate benzodiazepines are unique in that they contain a 3-COO^-M^+ functionality which allows for water solubility. These drugs, of which **chlorazepate** is the prototype, function as water soluble prodrugs for the more traditional benzodiazepines. When administered (orally) they are readily protonated in the upper GI tract and spontaneously decarboxylate (loss of CO_2) as shown below to yield an active benzodiazepine which is absorbed from the gut. **This is a chemical reaction and not an enzyme-catalyzed reaction!**

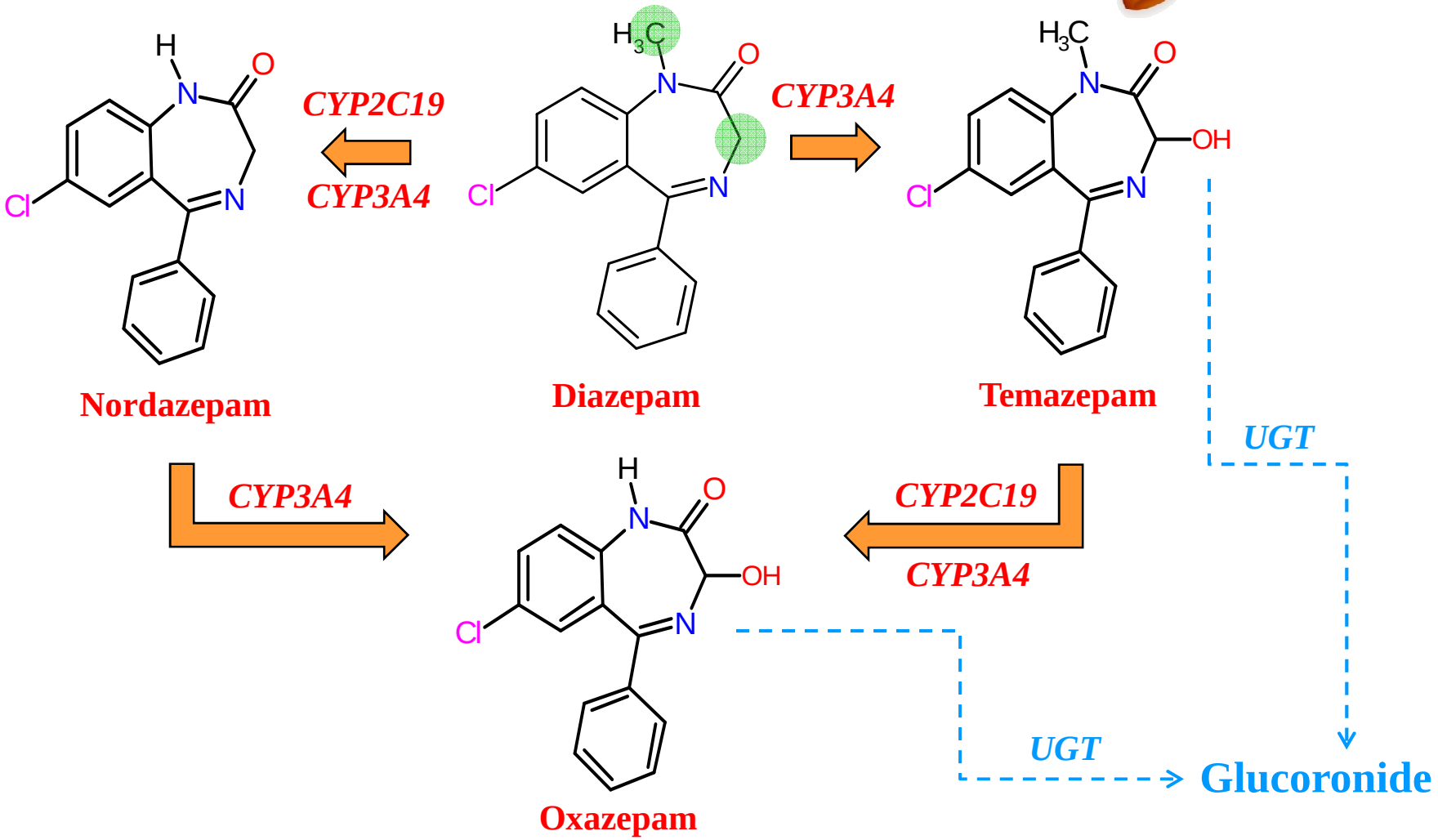


Chlorazepate **Nordiazepam**

2. Anxiety and anxiolytic drugs

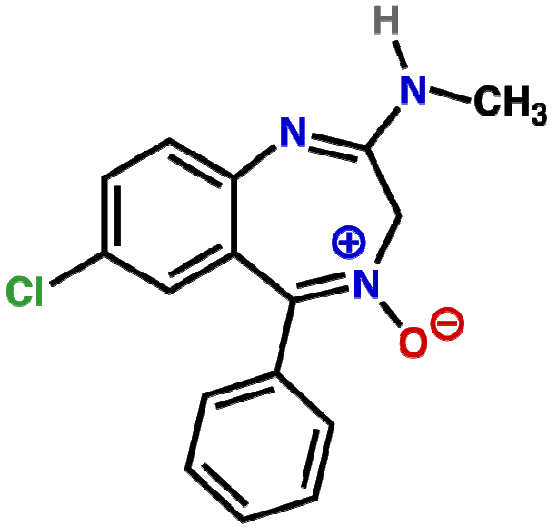
2.3 Benzodiazepine: metabolism

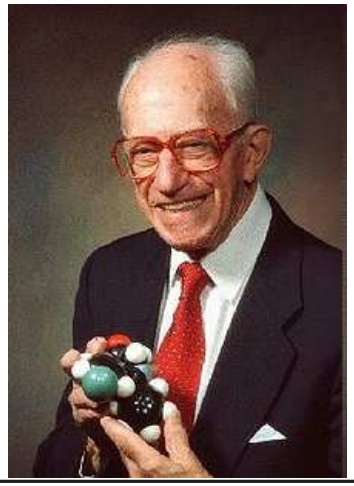




2. Anxiety and anxiolytic drugs

2.3 Benzodiazepine



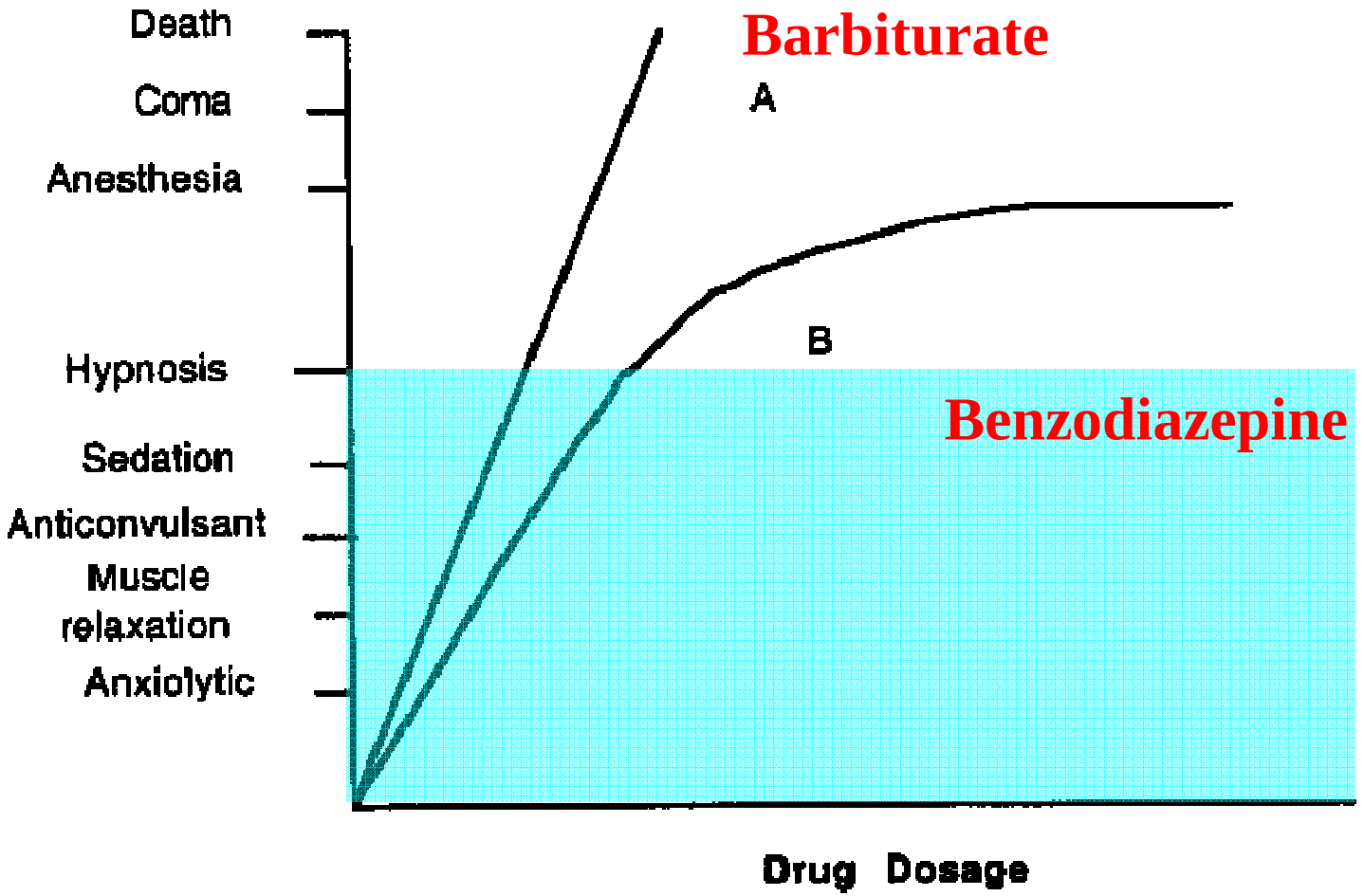


The first benzodiazepine, **chlordiazepoxide** (*Librium*), was synthesized in 1955 by Leo Sternbach while working at Hoffmann–La Roche on the development of tranquilizers. The pharmacological properties of the compounds prepared initially were disappointing, and Sternbach abandoned the project. Two years later, in April 1957, co-worker Earl Reeder noticed a "nicely crystalline" compound left over from the discontinued project while spring cleaning in the lab. This compound, later named *chlordiazepoxide*, had not been tested in 1955 because of Sternbach's focus on other issues. Expecting the pharmacology results to be negative and hoping to publish the chemistry-related findings, researchers submitted it for a standard battery of animal tests. Unexpectedly, the compound showed very strong sedative, anticonvulsant and muscle relaxant effects. These impressive clinical findings led to its speedy introduction throughout the world in 1960 under the brand name *Librium*.

Sternbach L (1979) The Benzodiazepine Story. *J Med Chem* 22: 1-7.

2. Anxiety and anxiolytic drugs

2.3 Benzodiazepine



2. Anxiety and anxiolytic drugs

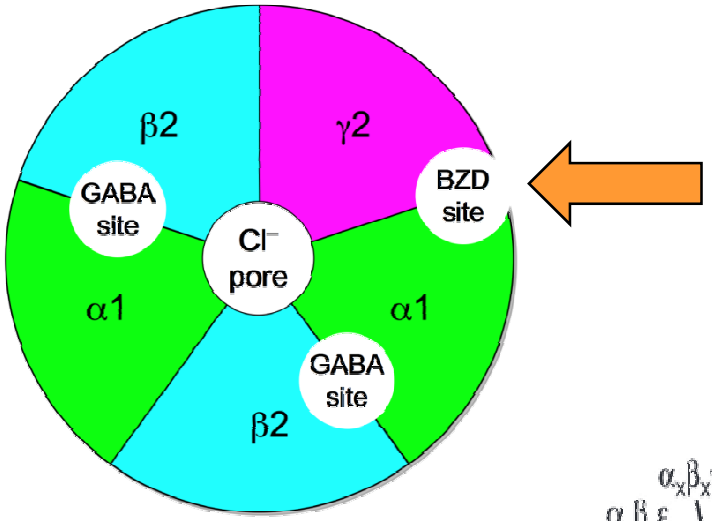
2.3 Benzodiazepine

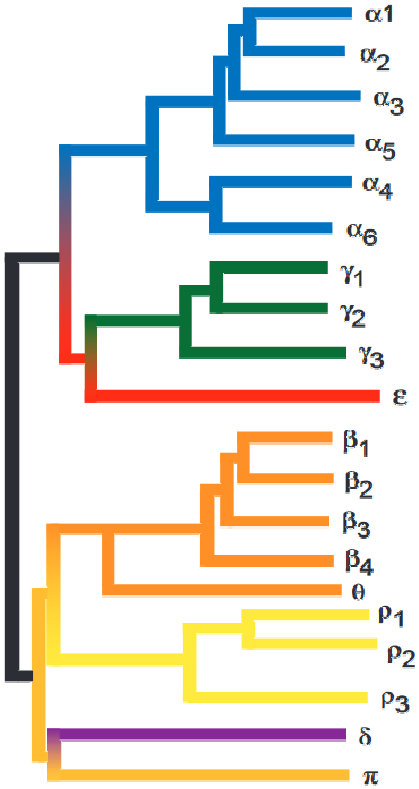
Therapeutic:

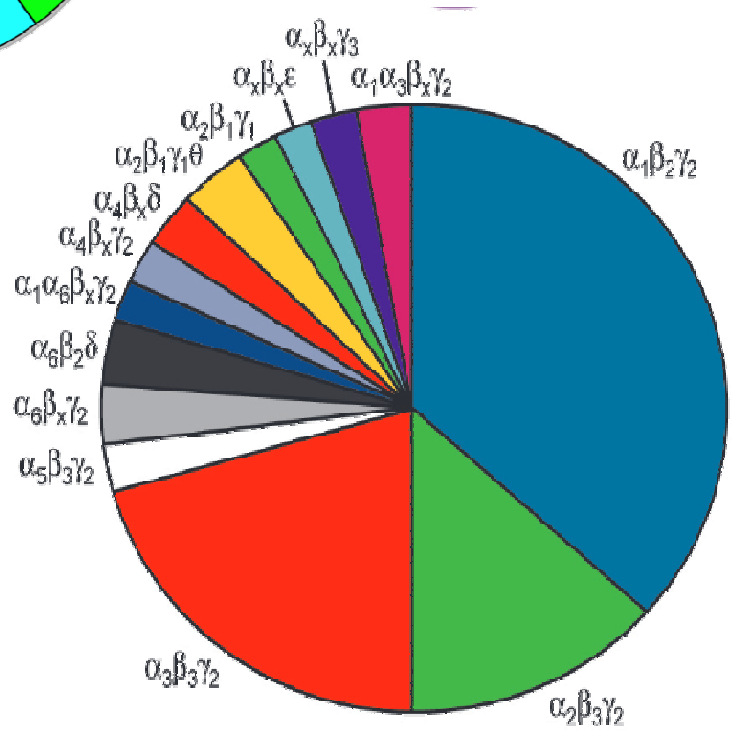
- **Anxiolytic** (diazepam, alprazolam)
- **Hypnotic** (triazolam)
- **Muscle relaxant** (diazepam, lorazepam)
- **Anticonvulsant** (diazepam, lorazepam, clonazepam)
- **Sedation** (midazolam)

About 50 different kinds of benzodiazepines were being used throughout the world.

What about benzodiazepines selectivity profile?







What about benzodiazepines selectivity profile?

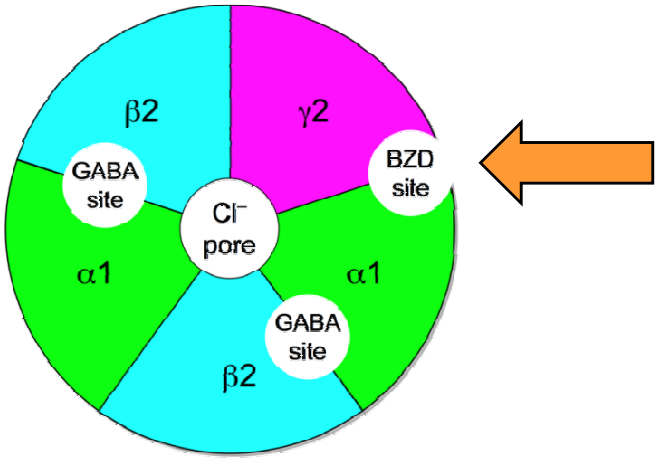
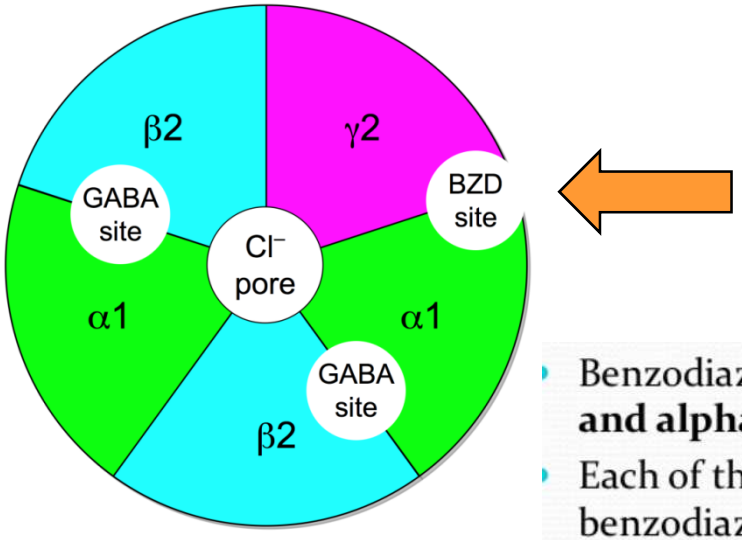


Table 1—The Roles of Select $GABA_A$ Receptor Subunits[21]

	α_1	α_2	α_3	α_5	γ_2	β_2	β_3	δ
Effects of benzodiazepines:								
Sedation	+	-	-	-		+		
Anxiolysis	-	+	-/+	-				
Amnesia	+			+				
Myorelaxation	-		+					
Motor impairment	-	-	-					
Anticonvulsant	+	-	-	-				
Ethanol reinforcement	-			+				
Effects of anesthetics	+					+	+	+
Anxiety					+			
Learning/memory				+				+

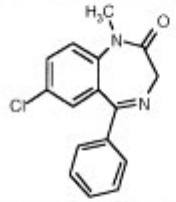
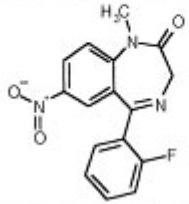
Adapted from Rudolph U, 1999.[21]

What about benzodiazepines selectivity profile?



- Benzodiazepines bind to GABA-A alpha subunits: **alpha 1, alpha 2, alpha 3 and alpha 5.**
- Each of these subunits is associated with different effects, and thus benzodiazepines not only cause sedation but are also anxiolytic, cause muscle relaxation, and have alcohol potentiating actions.

Non-selective compounds

Compound	Structure	Ki, nM: $\beta_3\gamma_2$ subunits plus			
		α_1	α_2	α_3	α_5
Diazepam		14	20	15	11
Flunitrazepam		2.2	2.5	4.5	2.1

Problems associated with the long-term use of benzodiazepines :

Adverse effects

- Drowsiness and falls
- Impairment in judgement and dexterity
- Increased risk of experiencing a road traffic accident
- Forgetfulness, confusion, irritability, aggression and paradoxical disinhibition

Complications related to long-term use

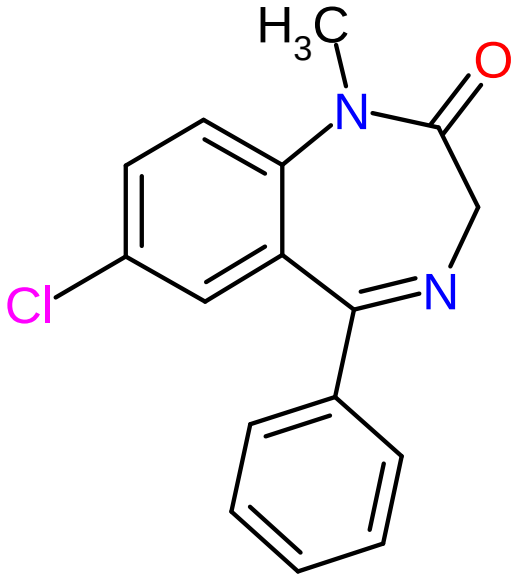
- Depression
- Reduction in coping skills
- Tolerance and dependence

Problems associated with the long-term use of benzodiazepines :

Dependence:

- Patients gradually **'need'** benzodiazepines to carry out normal day-to-day activities
- Patients continue to take benzodiazepines although the original indication for the prescription is **no longer relevant**
- Patients have **difficulty stopping** treatment or reducing dosage due to withdrawal symptoms
- Short acting benzodiazepines may cause patients to **develop anxiety** symptoms between doses
- Patients contact their doctor **regularly** to obtain repeat prescriptions
- Patients become **anxious** if the next prescription is not readily available
- Patients may **increase the dosage** stated in the original prescription
- Despite benzodiazepine therapy, patients may **present with recurring** anxiety **symptoms**, panic, agoraphobia, insomnia, depression and an increase in physical symptoms of anxiety

2. Anxiety and anxiolytic drugs

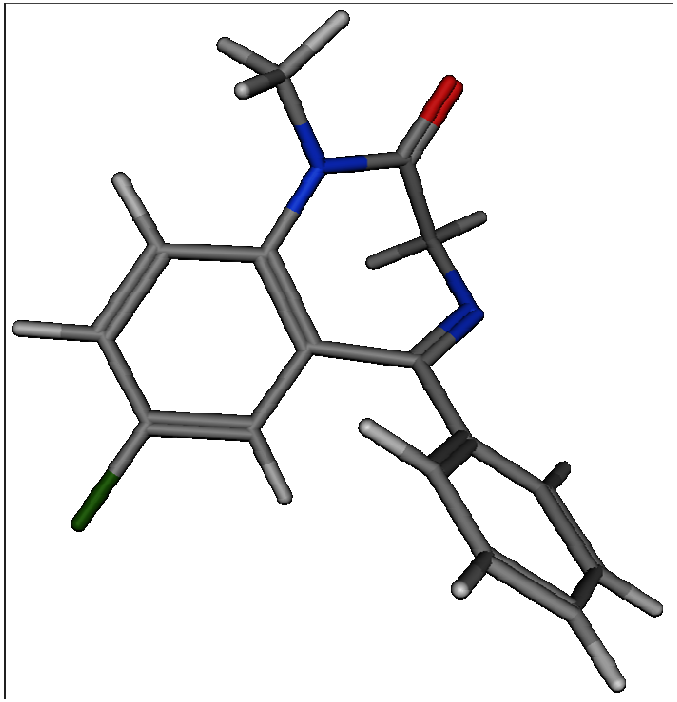


Diazepam

7-chloro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-one

logP = 2.9
pKa = 3.4
PSA ≅ 33 Å²

on set = 1÷1.5 hours
half life = 20÷100 hours



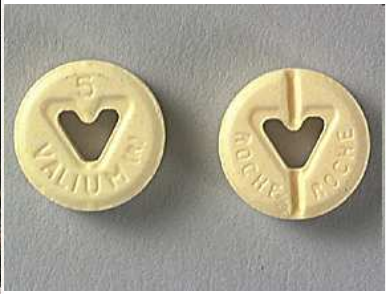
Diazepam, first marketed as **Valium** by Hoffmann-La Roche, is a benzodiazepine derivative drug. It is commonly used for treating anxiety, insomnia, seizures including status epilepticus, muscle spasms, restless legs syndrome, alcohol withdrawal, and Ménière's disease. It may also be used before certain medical procedures (such as endoscopies) to reduce tension and anxiety, and in some surgical procedures to induce amnesia. It possesses anxiolytic, anticonvulsant, hypnotic, sedative, skeletal muscle relaxant, and amnesic properties.

2. Anxiety and anxiolytic drugs

Diazepam has a broad spectrum of indications, including:

Treatment of ***anxiety***, ***panic attacks***, and ***states of agitation***
Treatment of neurovegetative symptoms associated with ***vertigo***
Treatment of the symptoms of ***alcohol***, ***opiate*** and ***benzodiazepine withdrawal***
Short-term treatment of ***insomnia***
Treatment of ***tetanus***, together with other measures of intensive-treatment
Adjunctive treatment of ***spastic muscular paresis*** (para-/tetraplegia) caused by cerebral or spinal cord conditions such as stroke, multiple sclerosis, spinal cord injury (long-term treatment is coupled with other rehabilitative measures)
Palliative treatment of stiff person syndrome
Pre-/postoperative sedation, anxiolysis and/or amnesia (e.g., before endoscopic or surgical procedures)
Treatment of ***complications with hallucinogens***, such as LSD or overdose of CNS stimulants, such as cocaine, or methamphetamine

2. Anxiety and anxiolytic drugs



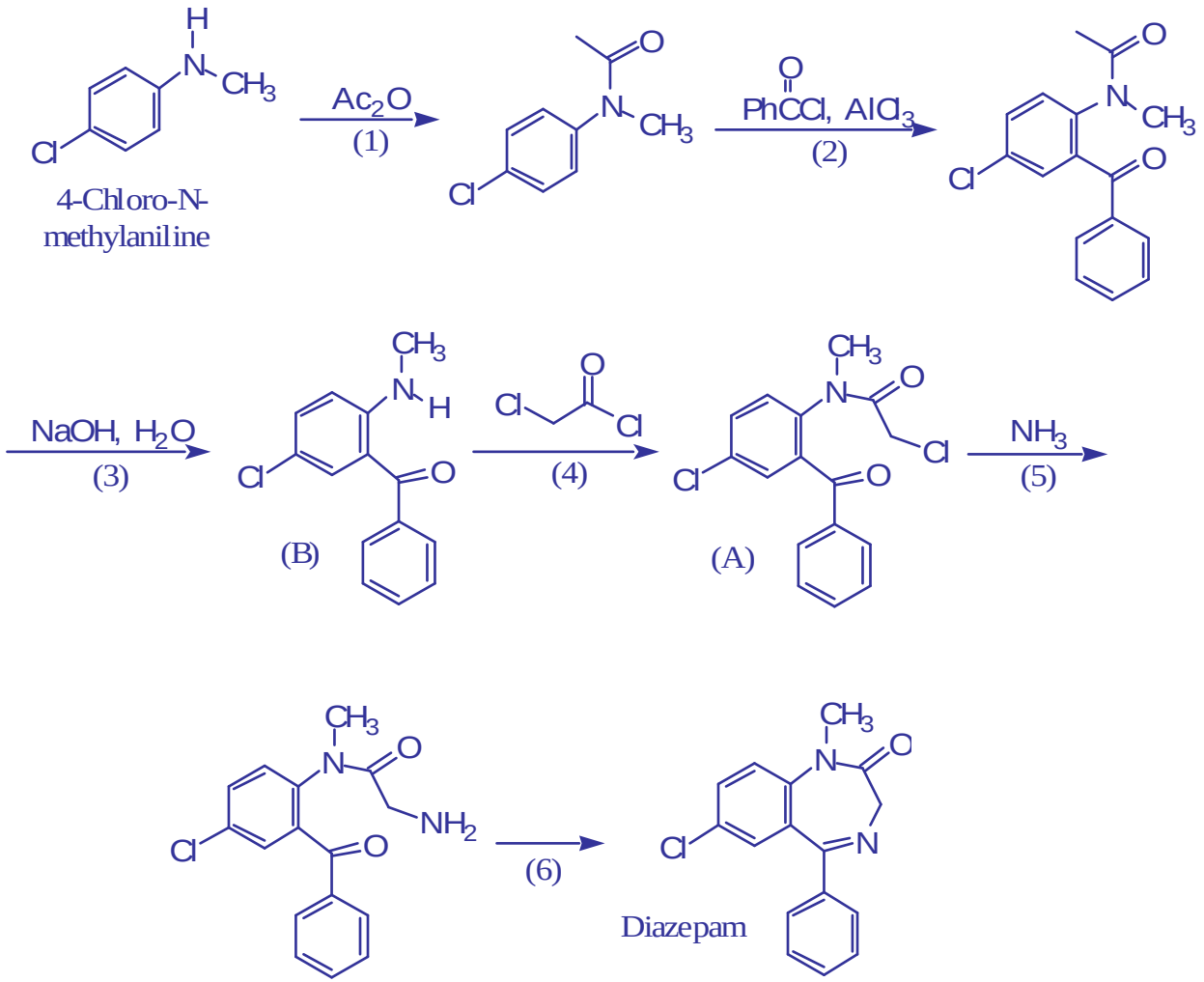
"Mother's Little Helper"

Historically, tranquilizers were not the drug of choice among the biggest drug users of the 1960s. College students, hippies, and concert going youths of that decade were more likely to experiment with hallucinogenic drugs. Benzodiazepines and minor tranquilizers were associated more with stay-at-home moms. Their practice of taking Valium—the "little yellow pill"—was widespread in the United States and the United Kingdom during this time. The Rolling Stones recorded a song in 1966 called "Mother's Little Helper" about this trend. As noted on *CNN.com*, the Stones sang: "Mother needs something today to calm her down / And though she's not really ill, There's a little yellow pill / She goes running for the shelter of a mother's little helper.…"

It is estimated that in the 1970s, as many as 30 million women were taking minor tranquilizers. "In promoting these drugs, the manufacturers portrayed stresses of everyday life as disease states treatable by prescribing their products," explained Andrew Weil and Winifred Rosen in *From Chocolate to Morphine.* Some advertisements "suggested giving tranquilizers to harried mothers and bored housewives." One particular ad aimed at physicians suggested they carry syringes of injectable diazepam "ready to use, when something must be done to calm the patient in emotional crisis." As Weil pointed out, ads like these always seemed to feature pictures of women as emotionally distressed patients in need of help. Psychiatrists were freely prescribing these minor tranquilizers to women with little regard of their potential for addiction.

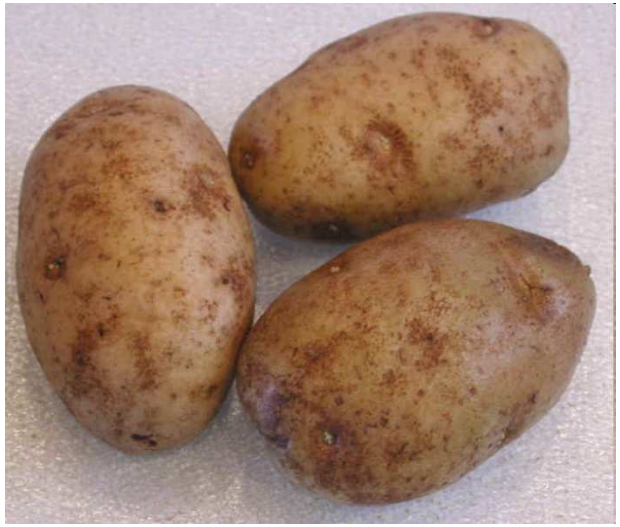
2. Anxiety and anxiolytic drugs

Synthesis Path

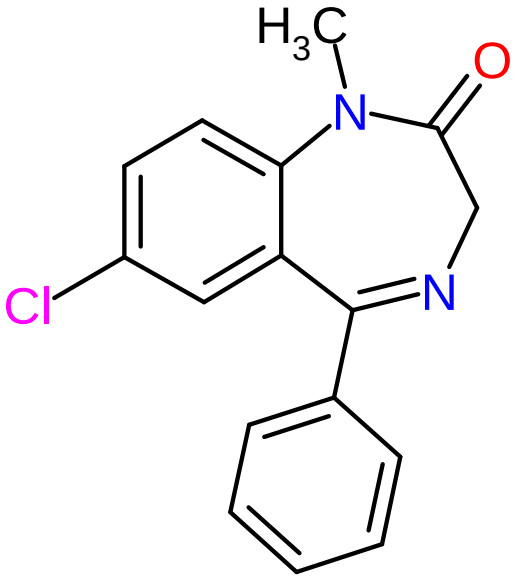


2. Anxiety and anxiolytic drugs

Natural benzodiazepine (?)



The Potato Eaters is a painting by the Dutch painter Vincent van Gogh



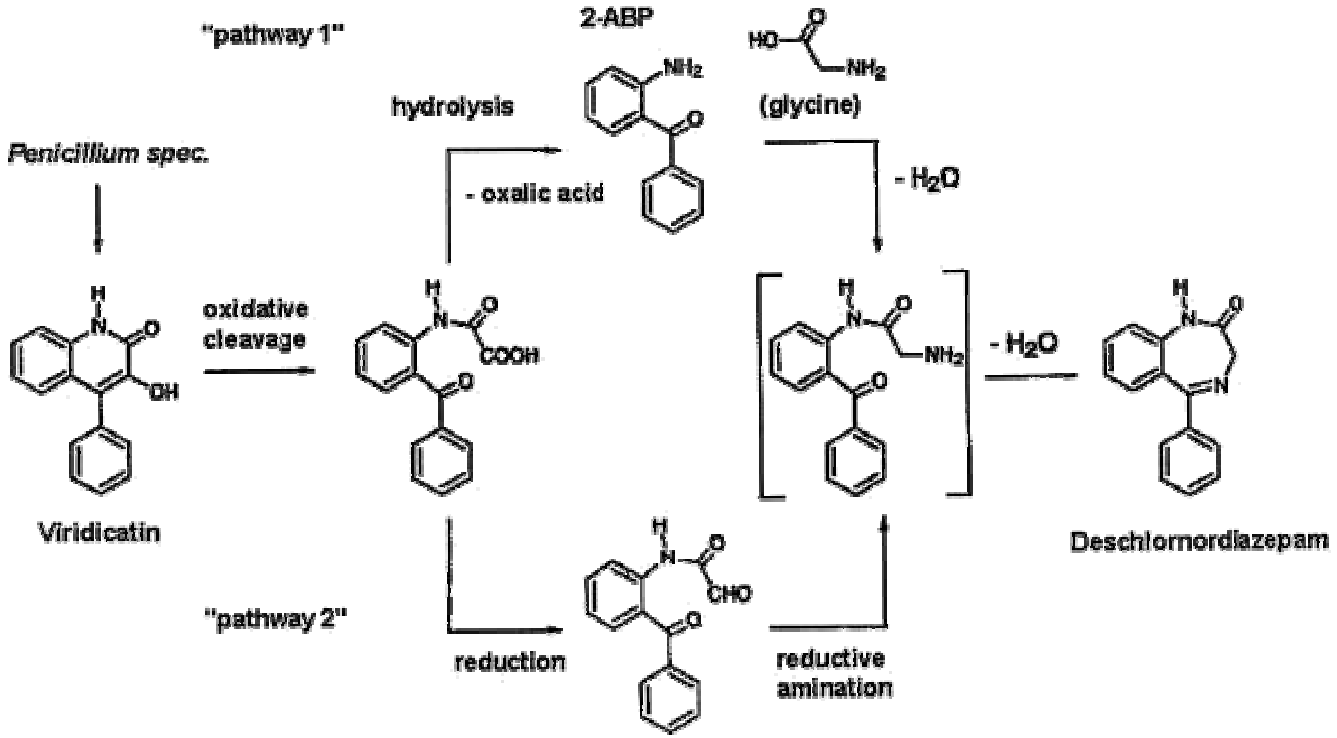
Natural benzodiazepines are present in different vegetables and fruits (potatoes, cherries, corn…)

Even if we need 1 ton of potatoes to reach a pharmacological dose of diazepam, we have consider the accumulation process of benzodiazepines in our body (medium permanence time >40 hours)

2. Anxiety and anxiolytic drugs

Natural benzodiazepine (?)

There are a number of plants/organisms that can synthesize the 1,4-benzodiazepine core, but apparently bacteria are the best.
This is the biosynthetic pathway proposed for formation of diazepam-like BZDs.



They claim that halogens can be further introduced by bacterial haloperoxidase enzymes.

2. Anxiety and anxiolytic drugs

Natural benzodiazepine

Many physiological benefits are attributed to milk. In folk wisdom, milk intake would improve sleep or provide a calming effect. Milk proteins are the only proteins synthesized by mammals in order to feed their young. The effects of caseins in addition to being nitrogen providers for the newborn are considered, because many works have shown in the past 15 years that their enzymatic hydrolysis produces peptides with various biological activities. The peptides found are opioid and opioid-antagonist peptides, angiotensine-converting-enzyme inhibitors, immunostimulating peptides, platelet aggregation inhibitors, phosphopeptides carriers of minerals (Ca^{2+}, Fe^{2+}), mitogenic peptides, antibacterial peptides, and protease inhibitors.

In this study, we have shown evidence of a novel anxiolytic activity in a tryptic hydrolysate of bovine αs1-casein. **Only one peptide, named α-casozepine, corresponding to the 91–100 fragment from bovine αs1-casein, expressed affinity for GABA-A receptor.**

The α-casozepine amino acid sequence could be related to the carboxy-terminal sequence of the polypeptide diazepam binding inhibitor, an endogenous ligand of the central GABA-A and peripheral-type benzodiazepine receptors.

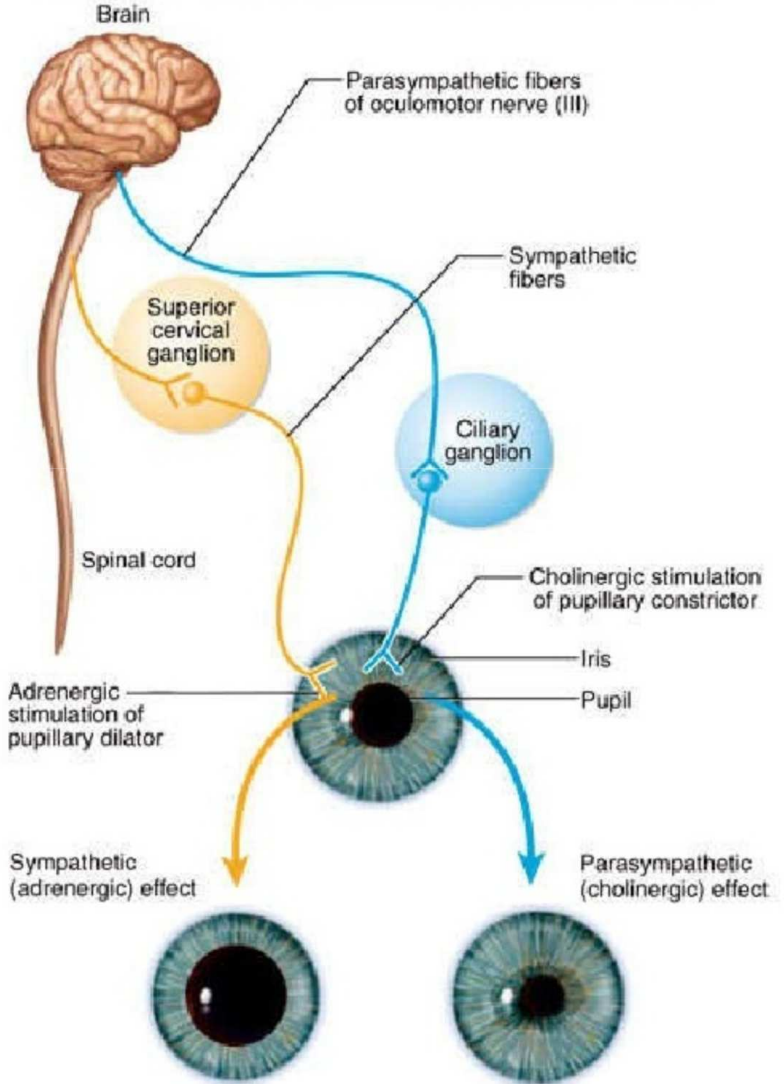
FASEB J. 2001 Aug;15(10):1780-2.

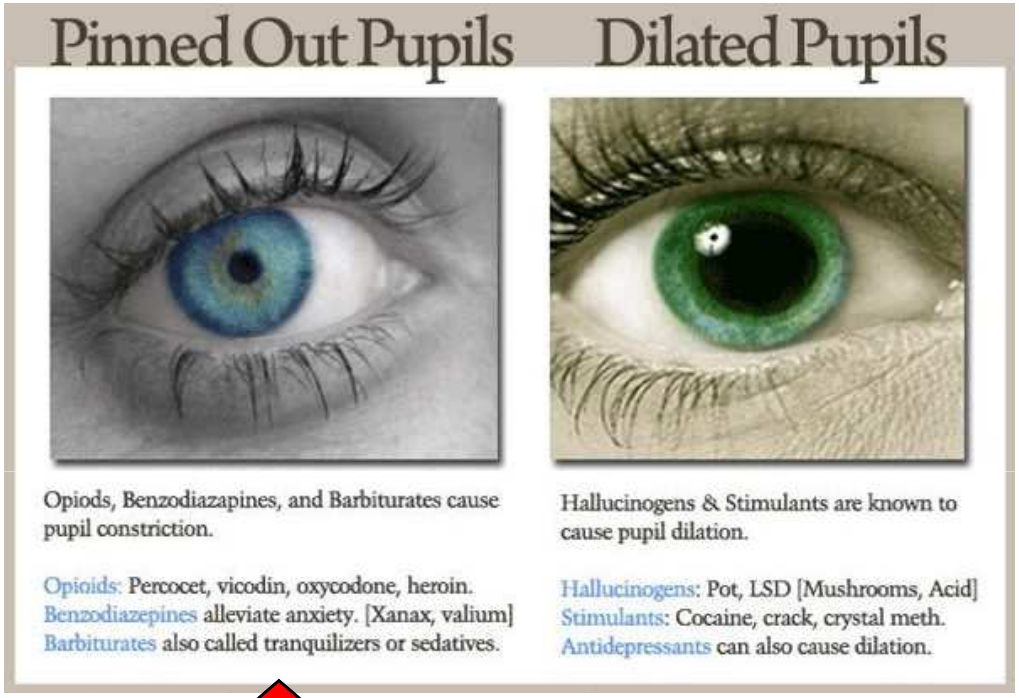
Characterization of alpha-casozepine, a tryptic peptide from bovine alpha(s1)-casein with benzodiazepine-like activity.

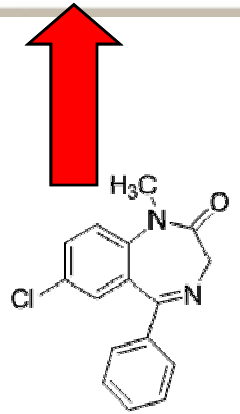
Miclo L, Perrin E, Driou A, Papadopoulos V, Boujrad N, Vanderesse R, Boudier JF, Desor D, Linden G, Gaillard JL.

Laboratoire des Biosciences de l'Aliment UA 885 INRA, Faculté des Sciences, Université Henri Poincaré-Nancy 1, Vandoeuvre-lès-Nancy, France. Laurent.Miclo@scbiol.uhp-nancy.fr

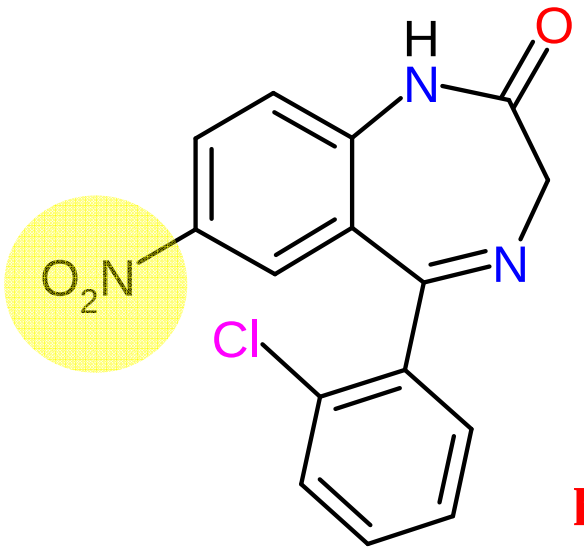
The eyes don't lie!!!



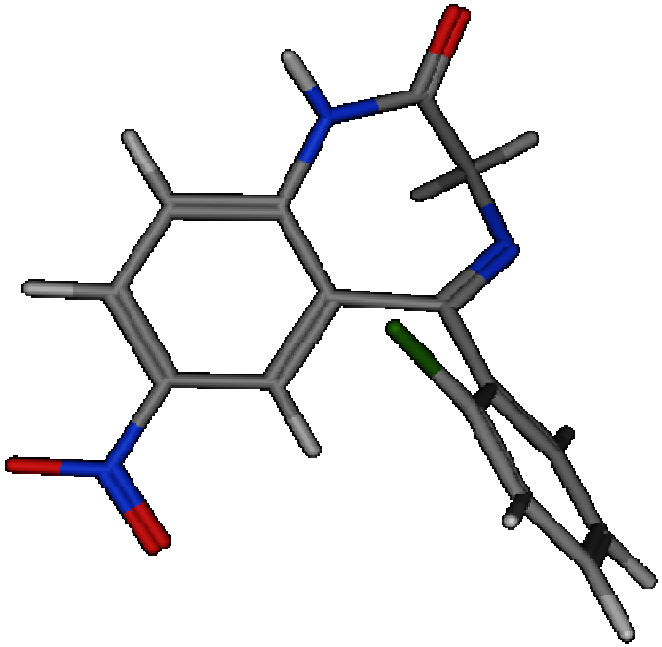




2. Anxiety and anxiolytic drugs



logP = 2.4
pKa = 1.5
PSA ≅ 87 Å²

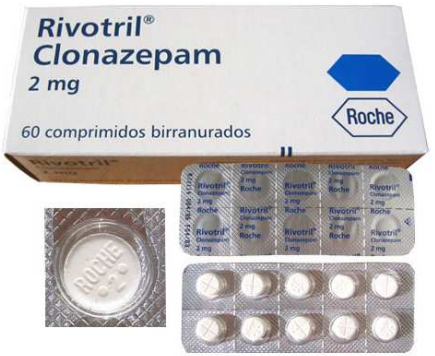


on set = 1÷4 hours
half life = 18÷50 hours

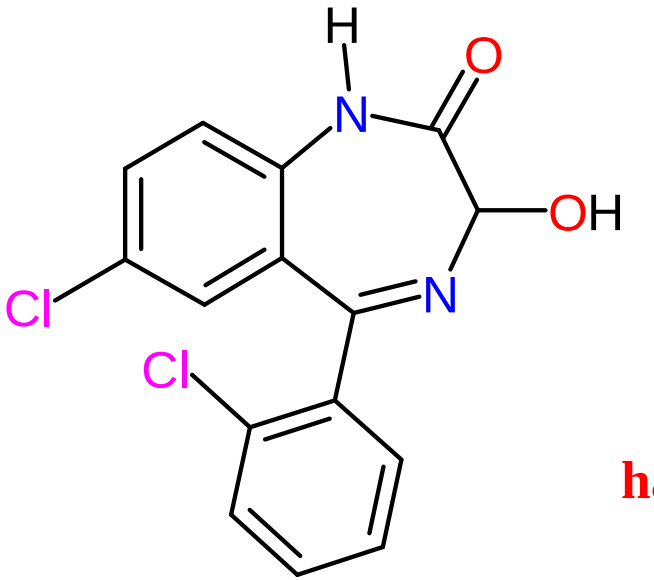
Clonazepam

5-(2-chlorphenyl)-7-nitro-2,3-dihydro-1,4-benzodiazepin-2-one

Clonazepam is a benzodiazepine derivative with anticonvulsant, muscle relaxant, and anxiolytic properties. Clonazepam is generally considered to be among the *long-acting* benzodiazepines. Clonazepam is classified as a high potency benzodiazepine and is sometimes used as a second line treatment of epilepsy. Clonazepam like other benzodiazepines while being first line treatments for acute seizures are not first line for the long-term treatment of seizures due to the development of tolerance to the anticonvulsant effects.

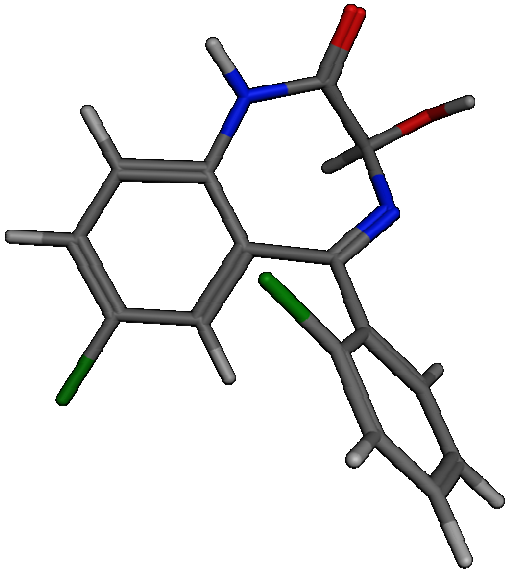


2. Anxiety and anxiolytic drugs



logP = 2.4
pKa = 13 (OH)
pKa = 1.3 (N4)
PSA ≅ 62 Å²

on set = 2÷4 hours
half life = 5÷10 hours

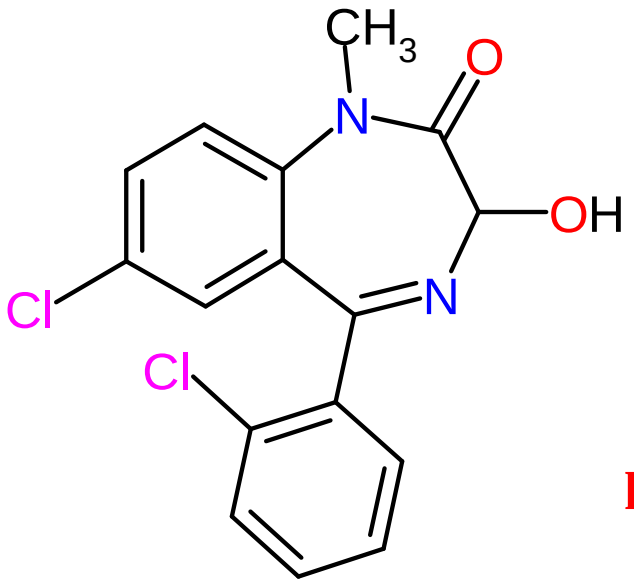


Lorazepam

(*R*,*S*)-7-chloro-5-(2-chlorophenyl)-3-hydroxy--1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one

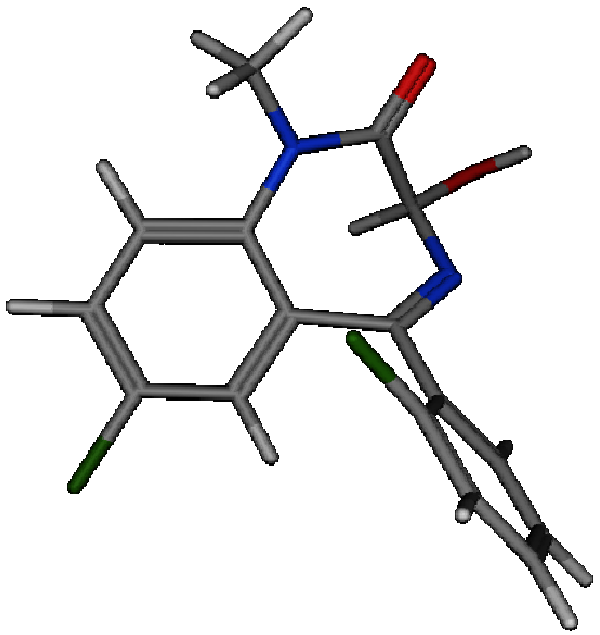
Lorazepam, initially marketed under the brand names **Ativan**, is a high potency benzodiazepine drug which has all five intrinsic benzodiazepine effects: anxiolytic, amnesic, sedative/hypnotic, anticonvulsant and muscle relaxant. Lorazepam is used for the short-term treatment of anxiety, insomnia, acute seizures including status epilepticus, sedation of hospitalized patients as well as sedation of aggressive patients. **Lorazepam is sometimes used as an alternative to *haloperidol* when there is the need for rapid sedation of violent or agitated individuals.**

2. Anxiety and anxiolytic drugs



logP = 3.1
pKa = 12.5 (OH)
pKa = 1.3 (N4)
PSA ≅ 53 Å²

on set = 0.5÷1 hours
half life = 5÷10 hours

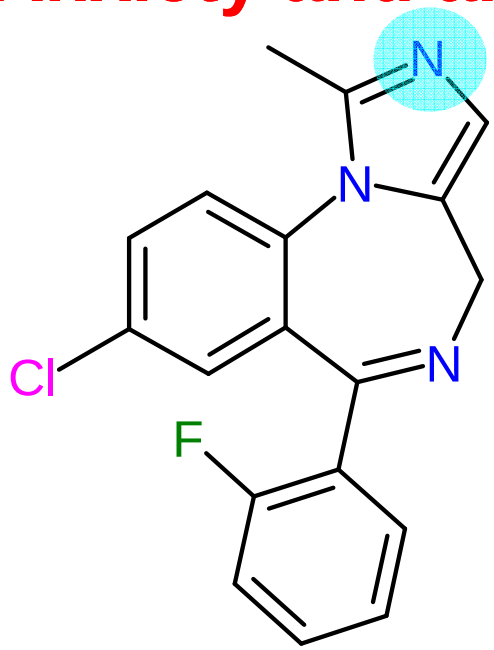


Lormetazepam

(*R*,*S*)-7-chloro-5-(2-chlorophenyl)-3-hydroxy-1-methyl--1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one

Lormetazepam (methyl-lorazepam) is a drug which is a **short** to **intermediate** acting 3-hydroxy benzodiazepine derivative. It possesses hypnotic, anxiolytic, anticonvulsant, sedative and skeletal muscle relaxant properties. Lormetazepam is officially indicated for **moderate to severe insomnia.** Lormetazepam is a short-acting benzodiazepine (max. 6 hours) and is used in patients who have difficulty in maintaining sleep or falling asleep. *It does not cause episodes of sleepiness-residual sedation upon awakening (the so-called hangover effect)*

2. Anxiety and anxiolytic drugs

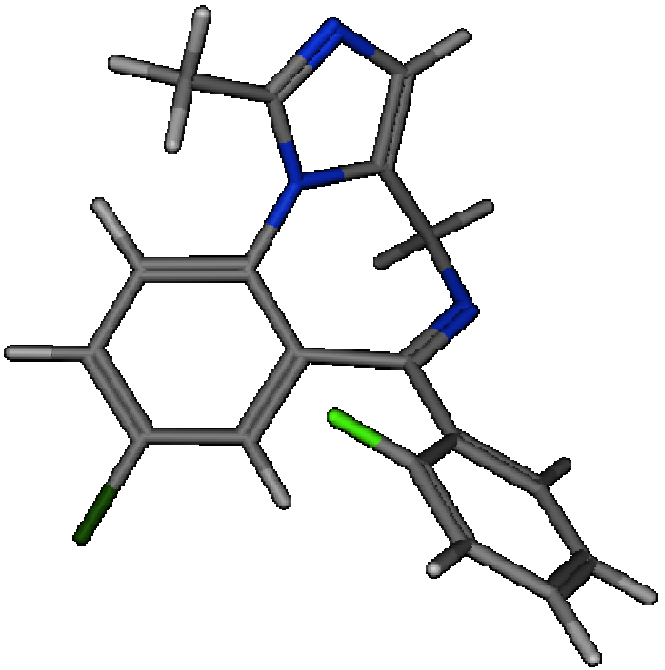


Midazolam

8-chloro- 6-(2-fluorophenyl)- 1-methyl- 4H-imidazo[1,5-a] [1,4]benzodiazepine

logP = 3.8
pKa = 6.1 (Ni)
PSA ≅ 30 Å^2

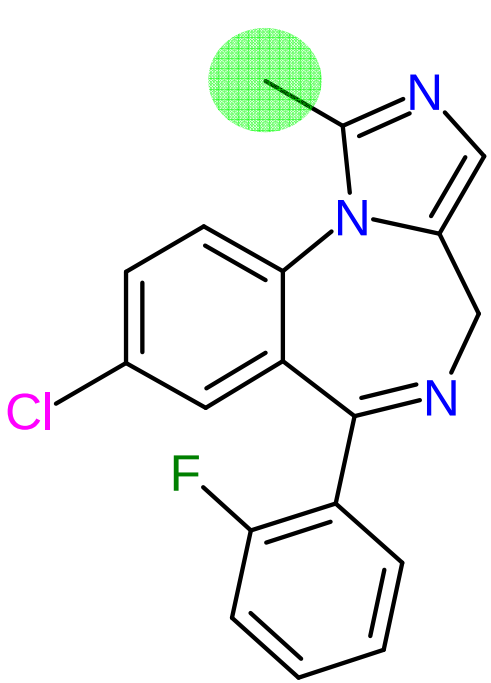
on set = 0.5÷1 hour
half life = 2÷6 hours



Midazolam is a short-acting drug in the benzodiazepine class that is used for treatment of acute seizures and for inducing sedation and amnesia before medical procedures. It has potent anxiolytic, amnestic, hypnotic, anticonvulsant, skeletal muscle relaxant, and sedative properties. Midazolam has a fast recovery time and ***is the most commonly used benzodiazepine as a premedication for sedation***; less commonly it is used for induction and maintenance of anesthesia**.**

2. Anxiety and anxiolytic drugs

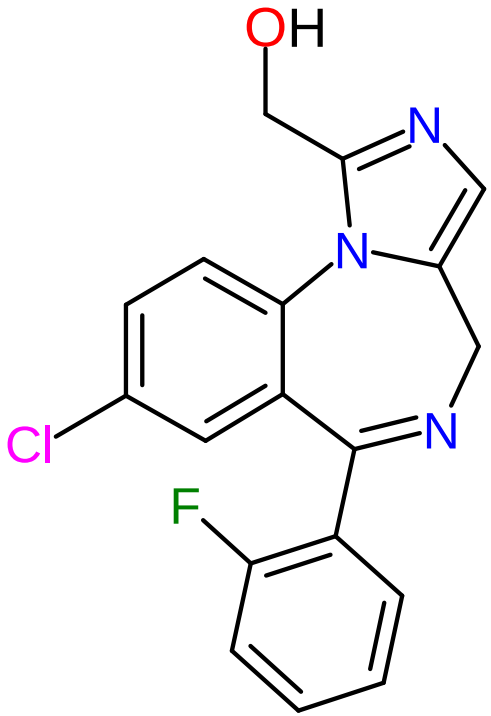
Alternative metabolism pathway:



Midazolam

P450 3A4

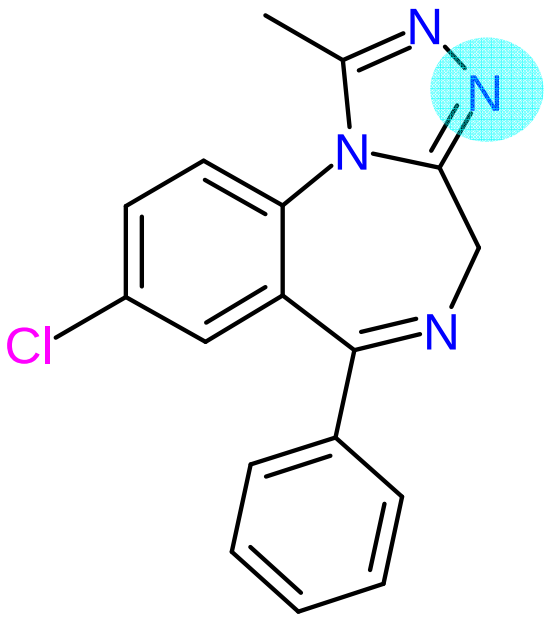
30 – 60 %



1’- or α-hydroxy-Midazolam

Glucuro-conjugated

2. Anxiety and anxiolytic drugs

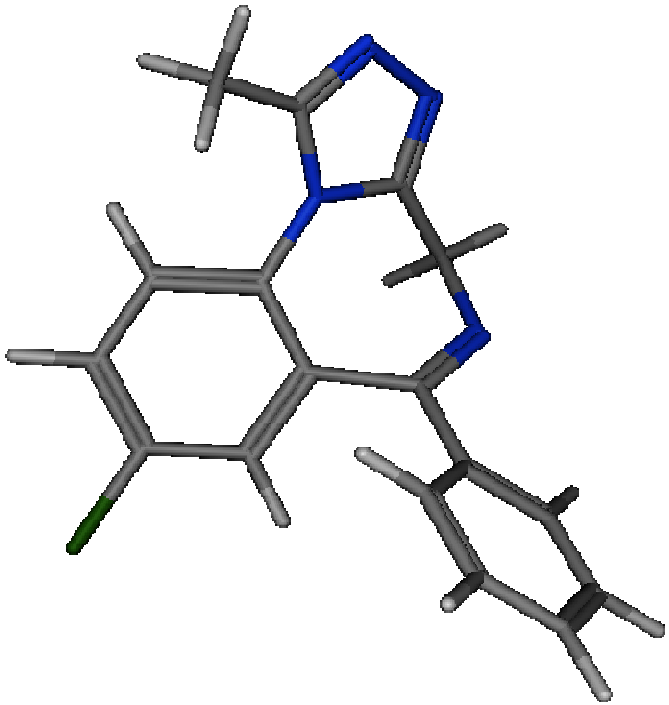


Alprazolam

8-chloro-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

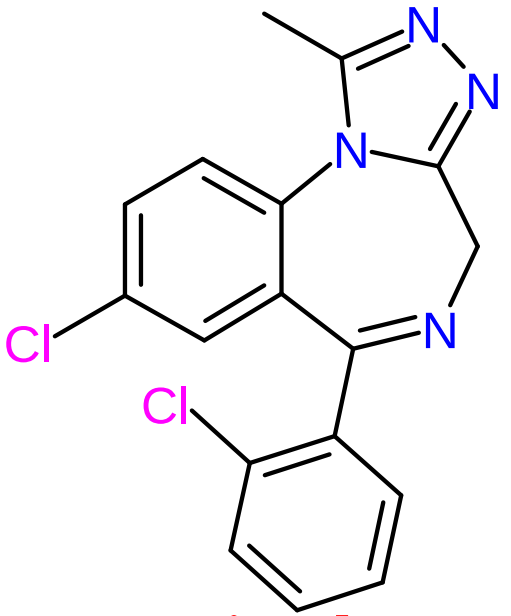
logP = 2.1
pKa = 2.4 (Ni)
PSA ≅ 43 Å²

on set = 1÷2 hour
half life = 6÷12 hours



Alprazolam, also known under the trade names Xanax, Xanor, Alprax, and Niravam, is a highly potent short-acting drug of the benzodiazepine class. ***It is primarily used to treat moderate to severe anxiety disorders*** (e.g., social anxiety disorder) ***and panic attacks***, and is used as an adjunctive treatment for anxiety associated with moderate depression. Alprazolam possesses anxiolytic, sedative, hypnotic, anticonvulsant, and muscle relaxant properties.

2. Anxiety and anxiolytic drugs

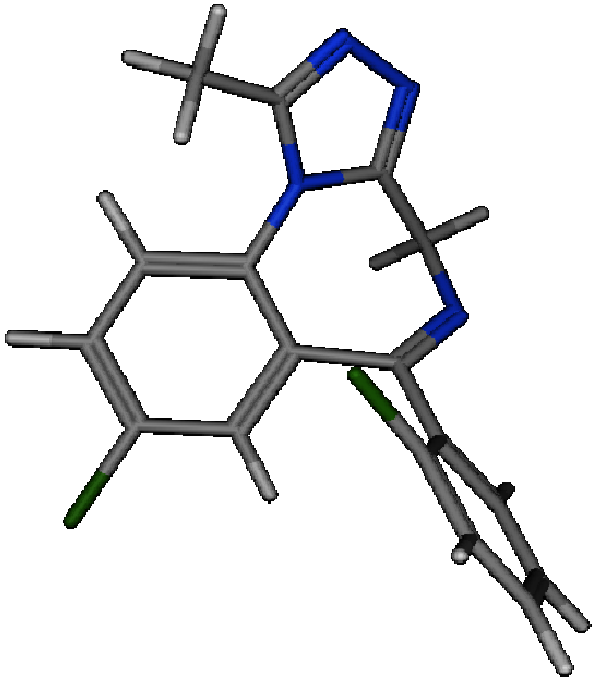


Triazolam

8-chloro-6-(2-chlorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

logP = 2.5
pKa = 2.3 (Ni)
PSA ≅ 43 Å^2

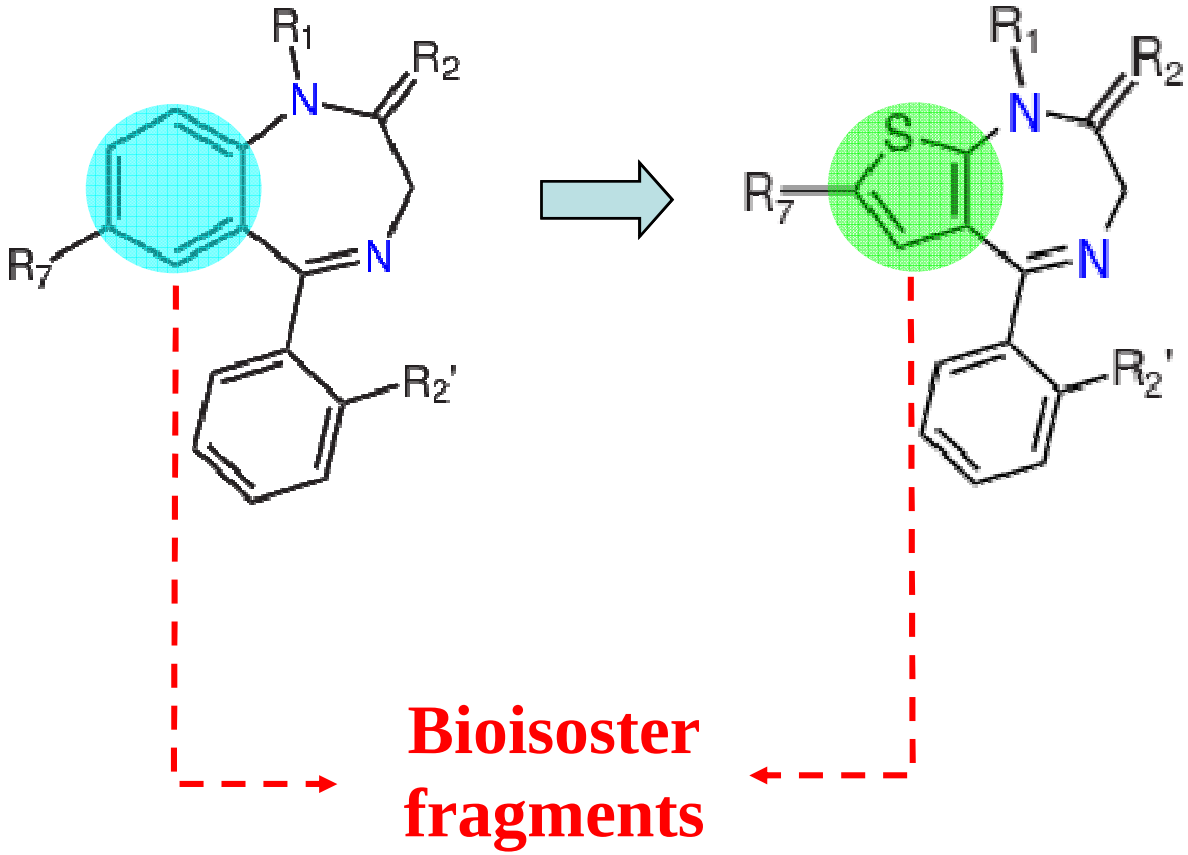
on set = 0.5÷2 hour
half life = 2÷4 hours



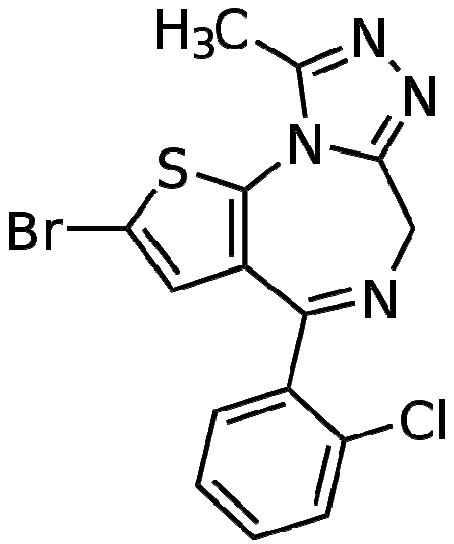
Triazolam is a benzodiazepine derivative drug. It possesses pharmacological properties similar to that of other benzodiazepines, but it is ***generally only used as a sedative to treat insomnia***. In addition to the hypnotic properties triazolam possesses, amnesic, anxiolytic, sedative, anticonvulsant and muscle relaxant properties are also present. Due to its short half-life, triazolam is not effective for patients that suffer from frequent awakenings or early wakening.

2. Anxiety and anxiolytic drugs

From benzodiazepine to thienodiazepine



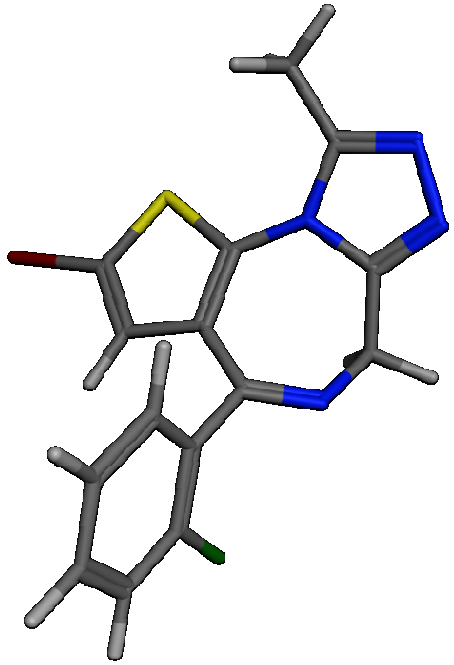
2. Anxiety and anxiolytic drugs



Brotizolam

logP = 2.8
pKa = 2.3 (Ni)
PSA ≅ 43 Å²

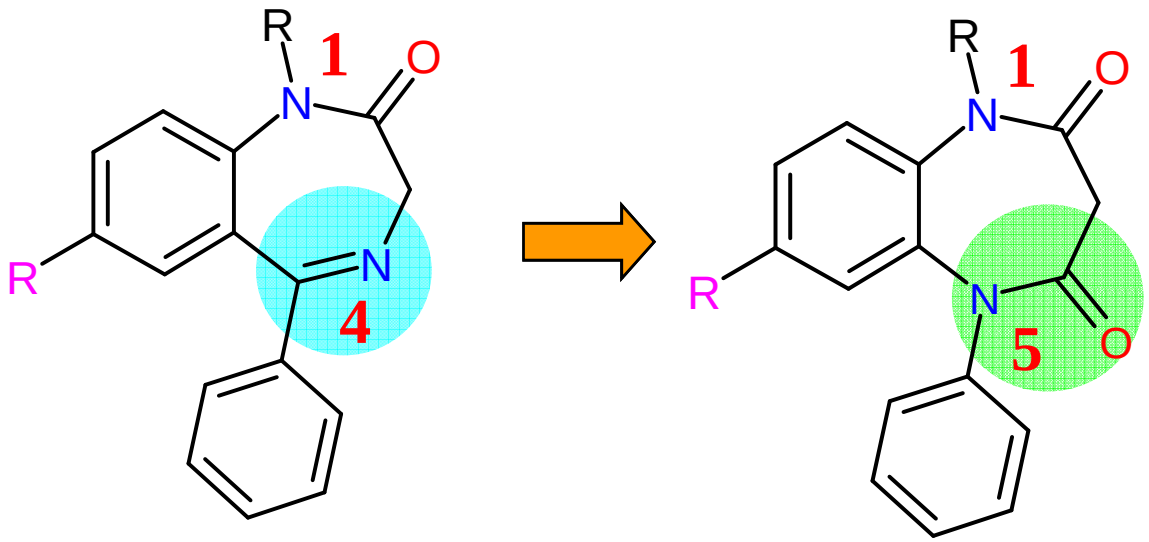
on set = 0.5÷2 hour
half life = 4÷5 hours



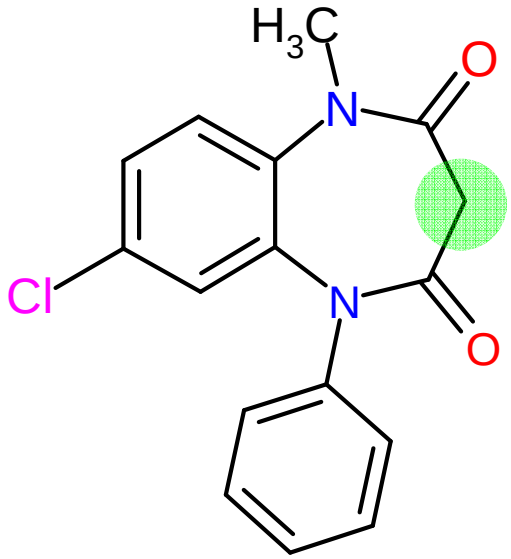
Brotizolam has been shown in animal studies to be a very high potency benzodiazepine, and it may be the most potent benzodiazepine used on humans. Although further studies need to be done to confirm this. The elimination half-life of Brotizolam is 4–5 hours. Brotizolam is a sedative-hypnotic thienodiazepine drug. It possesses anxiolytic, anticonvulsant, hypnotic, sedative and skeletal muscle relaxant properties, and is considered to be similar in effect to short-acting benzodiazepines such as Triazolam.

2. Anxiety and anxiolytic drugs

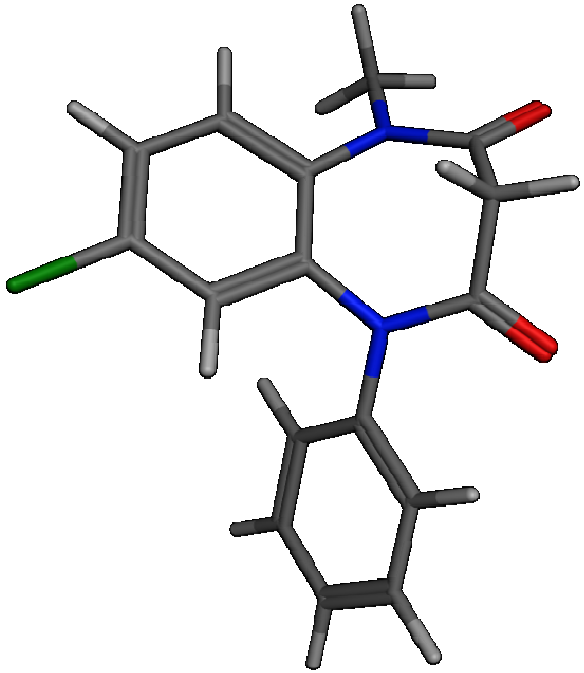
Only 1,4-benzodiazepines? No, also 1,5…



2. Anxiety and anxiolytic drugs



logP = 2.1
pKa = 4.1
PSA ≅ 41 Å²



on set = 2÷3 hour
half life = 32 hours

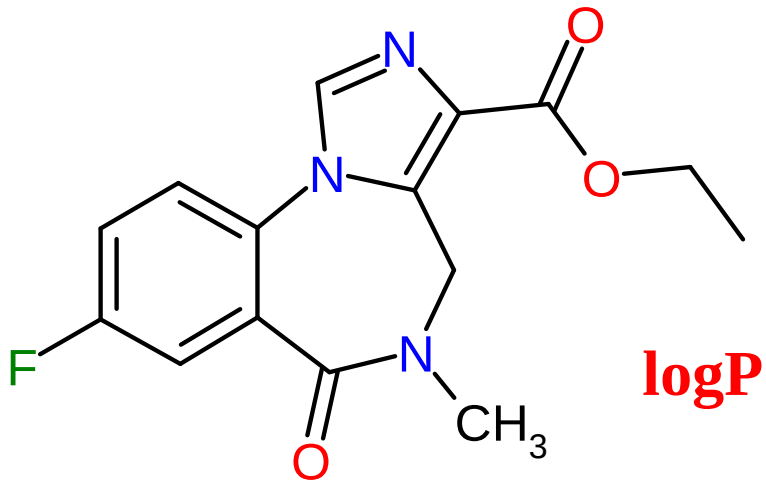
Clobazam

1-phenyl-5-methyl-8-chloro-1,2,4,5-tetrahydro-2,4-dioxo-3H-1,5-benzodiazepine

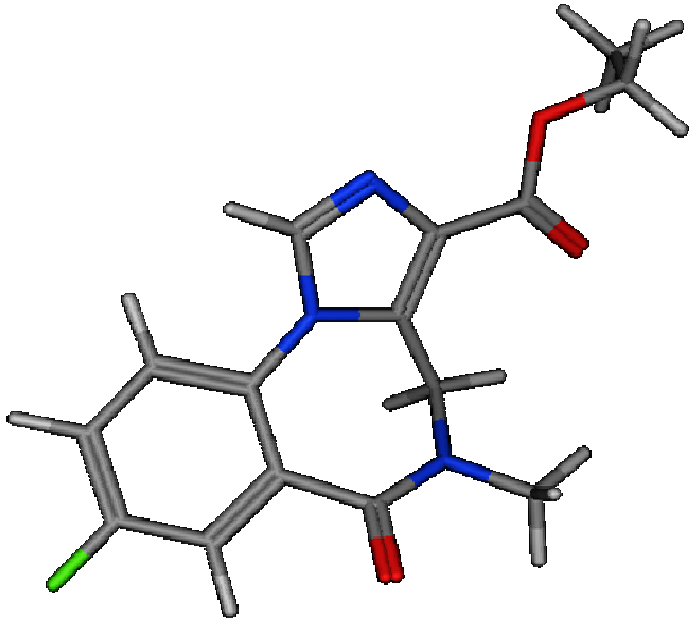
Clobazam belongs to the 1,5-benzodiazepine class of drugs and is expected to have a better side-effect profile compared to older 1,4-benzodiazepines. It has been marketed as an *anxiolytic* since 1975 and an *anticonvulsant* since 1984. Clobazam is extensively metabolized in the liver via N-demethylation and hydroxylation: N-desmethylclobazam (norclobazam) and 4'-hydroxyclobazam, the former of which is active. Norclobazam is one-fourth the potency of clobazam.

2. Anxiety and anxiolytic drugs

Benzodiazepine antagonist (antidote)



logP = 1.9



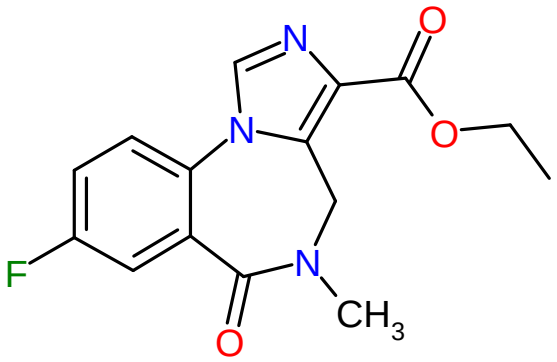
Flumazenil

ethyl 8-fluoro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate

Flumazenil is a benzodiazepine antagonist. It was introduced in 1987 by Hoffmann-La Roche under the trade name *Anexate*. Flumazenil antagonizes the CNS effects produced by benzodiazepines and Z-drugs, but does not antagonize the central nervous system effects of drugs affecting GABA-ergic neurons by means other than the benzodiazepine receptor (including ethanol, barbiturates,
or general anesthetics) and does not reverse the effects
of opioids.

2. Anxiety and anxiolytic drugs

Benzodiazepine antagonist (antidote)



Its use, however, is controversial as it has numerous contraindications!!

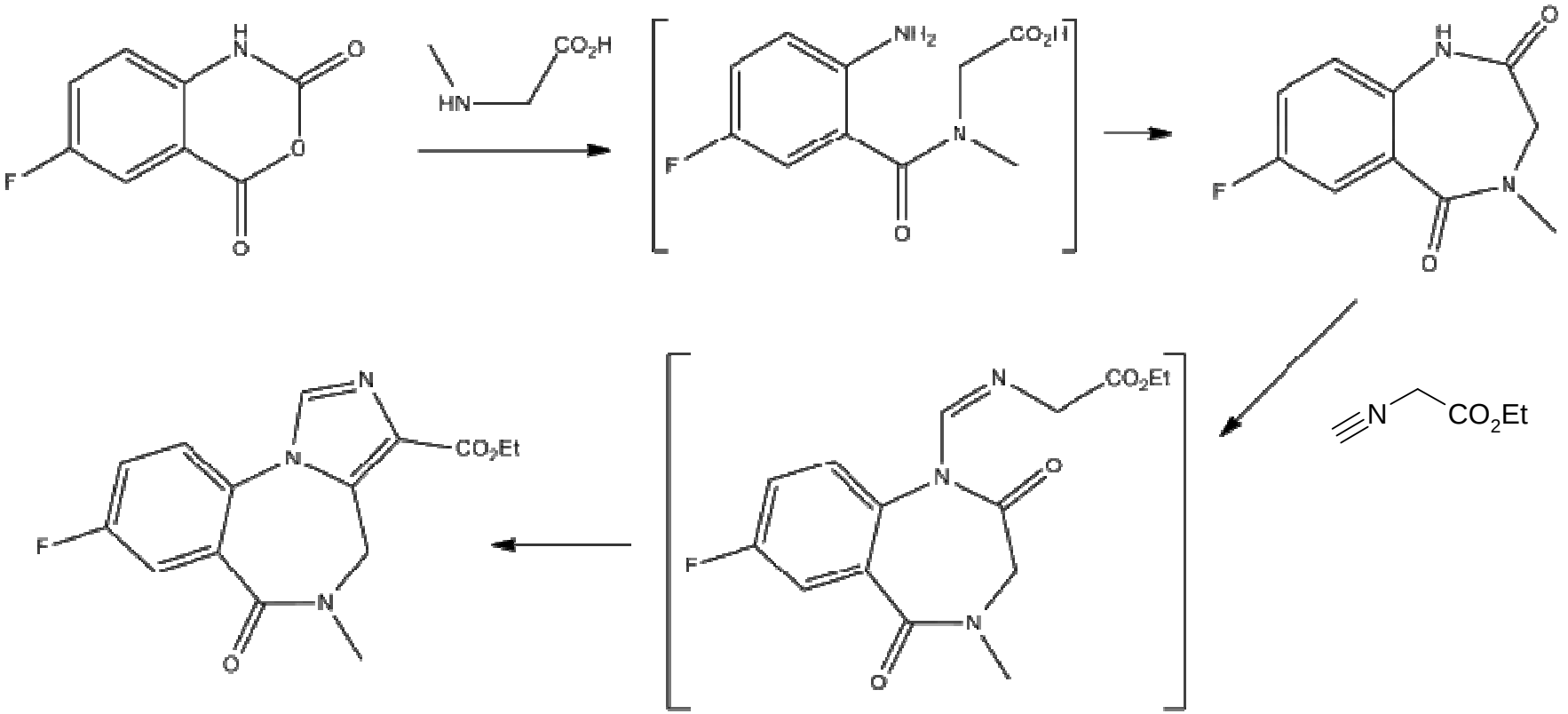
Flumazenil is very effective at reversing the CNS depression associated with benzodiazepines but is less effective at reversing respiratory depression. One study found that only 10% of the patient population presenting with a benzodiazepine overdose are suitable candidates for flumazenil.

Due to its short half life, the duration of action of flumazenil is usually less than 1 hour, and multiple doses may be needed. When flumazenil is indicated the risks can be reduced or avoided by slow dose titration of flumazenil. Due to risks and its many contraindications, flumazenil should be administered only after discussion with a medical toxicologist.

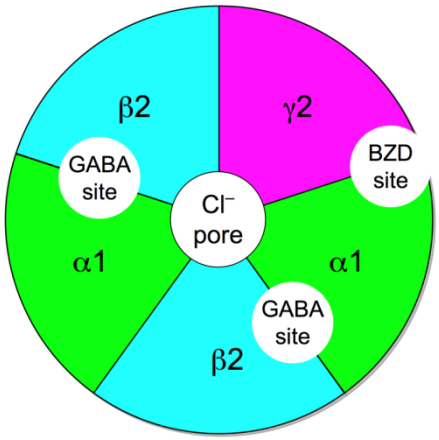
Seger DL "Flumazenil--treatment or toxin". *J. Toxicol. Clin. Toxicol.* 2004, 42, 209–16.

2. Anxiety and anxiolytic drugs

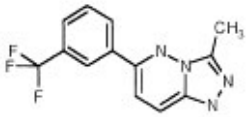
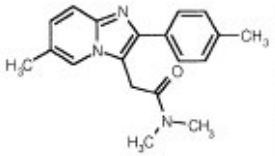
Synthesis Path



Besides benzodiazepines: Z-drugs

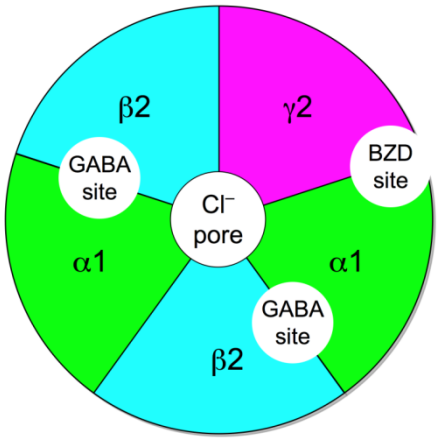


α_1 selective compounds

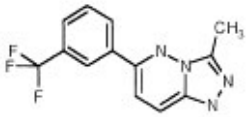
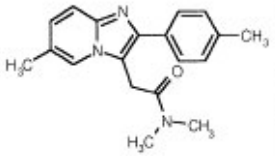
Compound	Structure	Ki, nM: $\beta_3\gamma_2$ subunits plus			
		α_1	α_2	α_3	α_5
CL-218,872		57	1960	1160	560
Zolpidem		27	160	380	>10,000

Z-drugs are a group of *nonbenzodiazepine* drugs with effects similar to benzodiazepines, which are used in the treatment of insomnia and most of whose names start with the letter "Z". Some Z-drugs may have advantages over benzodiazepines. Benzodiazepines actually worsen *sleep architecture*, whereas the Z-drug zaleplon (Sonata) may have less or no disruption of sleep architecture.

Besides benzodiazepines: Z-drugs



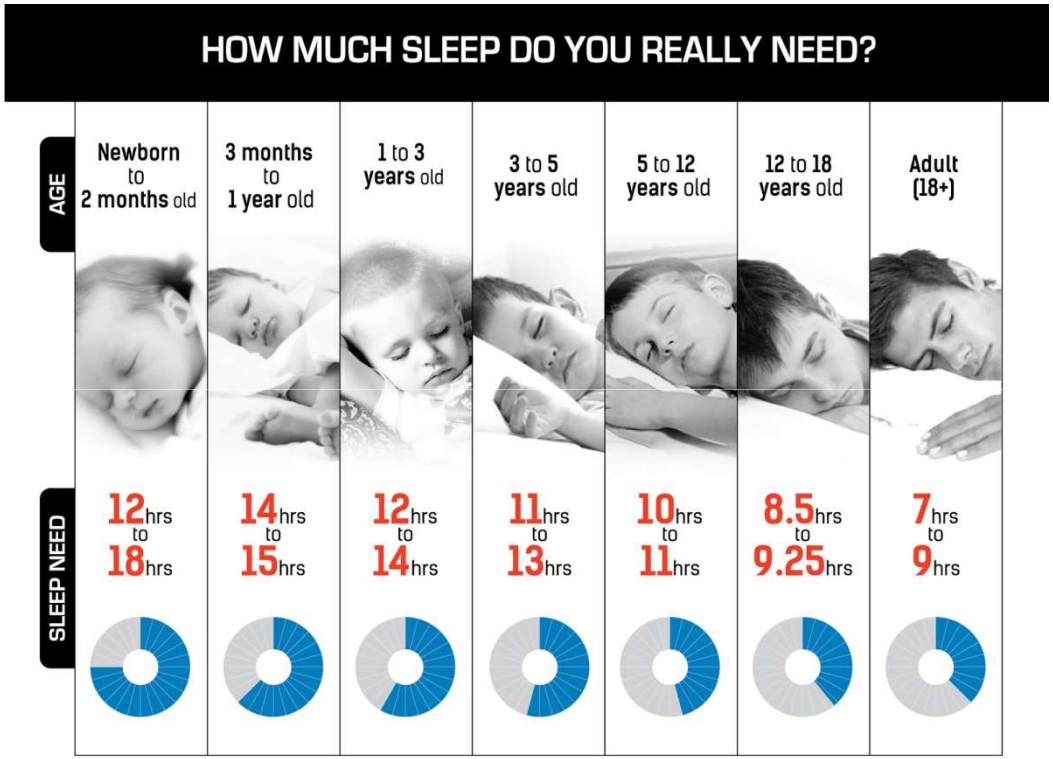
α_1 selective compounds

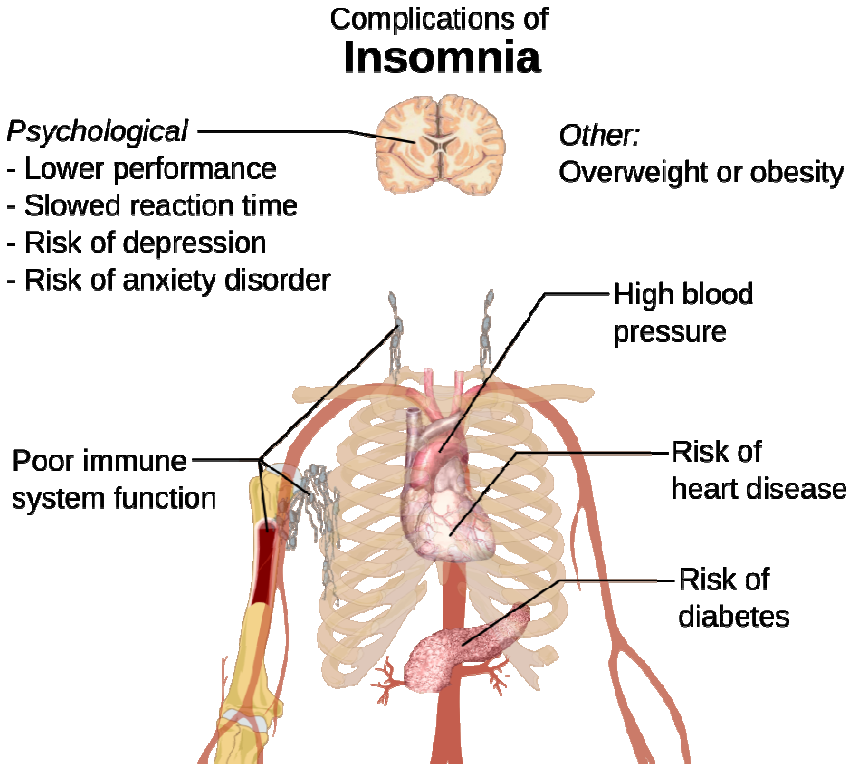
Compound	Structure	Ki, nM: $\beta_3\gamma_2$ subunits plus			
		α_1	α_2	α_3	α_5
CL-218,872		57	1960	1160	560
Zolpidem		27	160	380	>10,000

Z-drugs emerged in the last years of the 1980s and early 1990s, with *zopiclone* (Imovane) approved by the British National Health Service as early as 1989, quickly followed by Sanofi with *zolpidem* (Ambien). By 1999, King Pharmaceuticals had finalized approval with the American Food and Drug Administration (FDA) to market *zaleplon* (Sonata, Starnoc) across the US. In 2005, the FDA approved *eszopiclone* (Lunesta) the (*S*)-enantiomer of zopiclone. That same year, 2005, the FDA finalized approval for Ambien CR, or extended-release zolpidem. Most recently, in 2012 the FDA approved Intermezzo, which still utilizes zolpidem as its active ingredient, but is marketed for middle-of-the-night insomnia, available in doses only half of the strength of immediate-release Ambien to avoid residual next-day sedation.

2. Anxiety and anxiolytic drugs

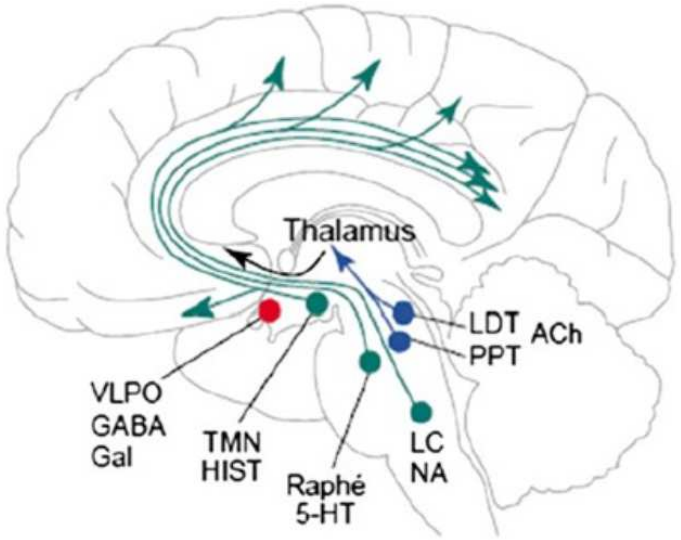
Insomnia…





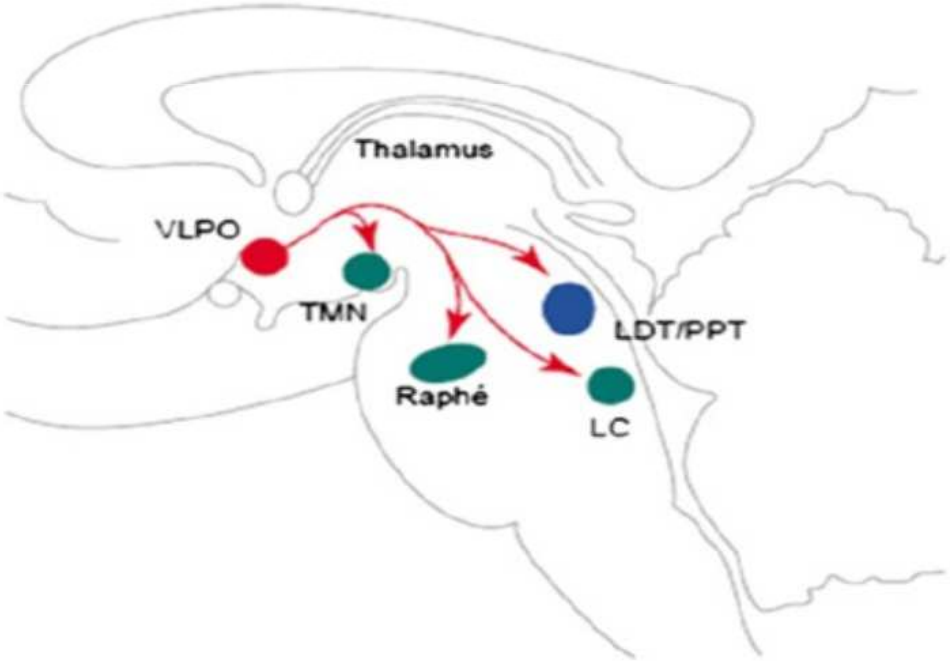
Neurotransmitters in wake:

Neurotransmitter (Activating/Arousal Promoting)	Location
Acetylcholine	- Basal forebrain - Pedunculopontine tegmentum (PPT)/laterodorsal tegmentum (LDT)
Dopamine	- Ventral periaqueductal gray matter - Substantia nigra
Glutamate	- Ascending reticular activating system - Thalamocortical system
Histamine	- Tuberomammillary nucleus (TMN)/posterior hypothalamus
Hypocretin/Orexin	- Lateral hypothalamus
Norepinephrine	- Locus coeruleus (LC)
Serotonin	- Raphe nuclei, thalamus



Neurotransmitters in sleep:

Neurotransmitter (Sleep Promoting)	Location
Adenosine	- Basal forebrain
Melatonin	- Pineal gland
GABA (located in 30% of all brain synapses)	- Ventrolateral preoptic nucleus (VLPO)
Galanin	- Ventrolateral preoptic nucleus (VLPO)



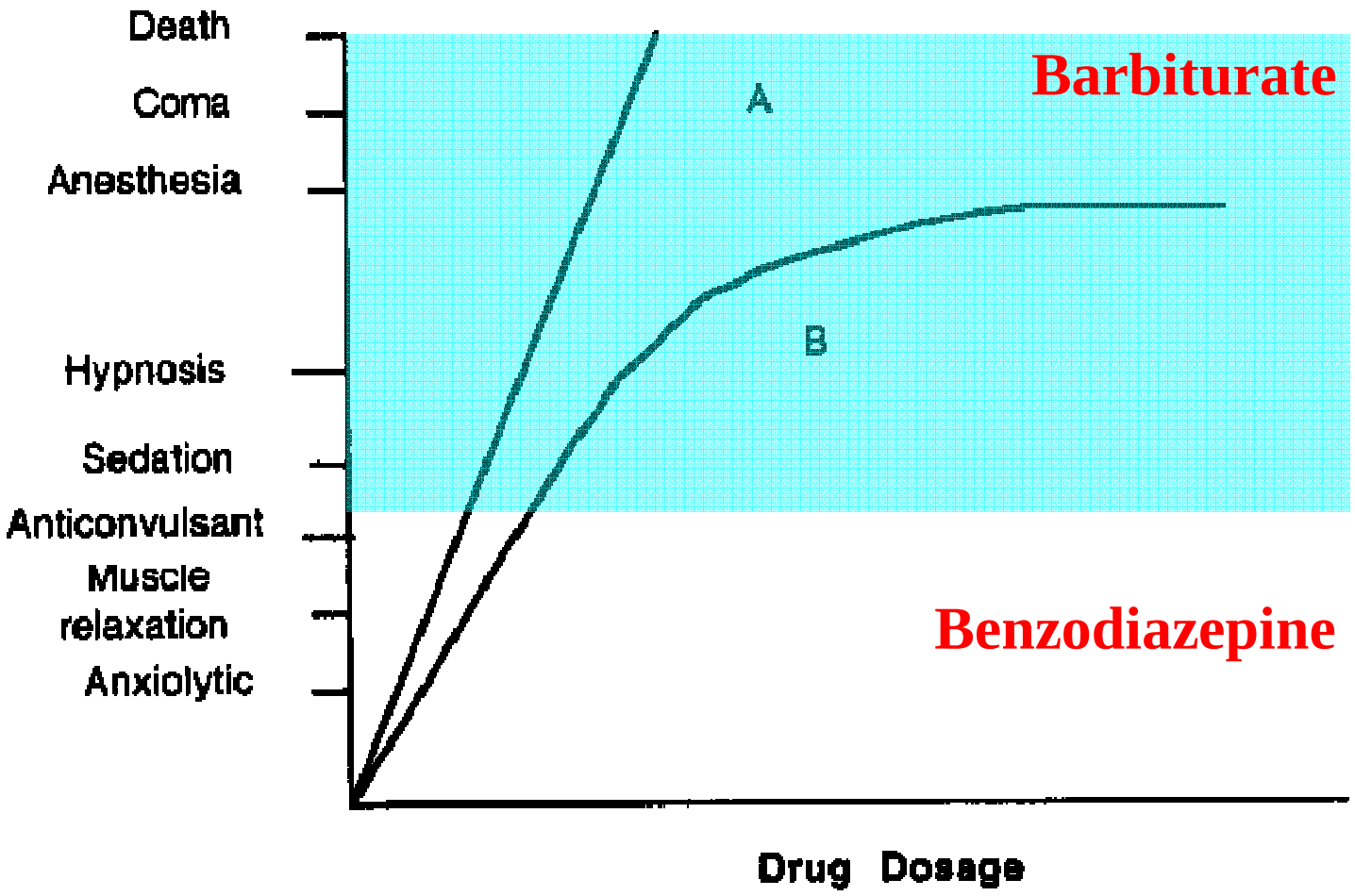
Neurotransmitters in sleep:

Medication	Dose (mg)	Onset (min)	Half-life (hr)	Active metabolite	Indication
Benzodiazepines:					
Estazolam	0.5 – 2.0	15 – 30	8- 24	No	SMI
Flurazepam	15 – 30	30 – 60	2- 5[a] 47 – 120[b]	Yes	SMI
Quazepam	7.5 – 30	20 – 45	15 - 40[a] 39 – 120[b]	Yes	SMI
Temazepam	7.5 – 30	45 – 60	8 – 20	No	SMI
Triazolam	0.125 – 0.25	15 – 30	1.5 – 5	No	SOI
Benzodiazepine Receptor Agonists (BzRAs):					
Eszopiclone	1 – 3	60	6.0	No	SMI
Zaleplon	5 – 10	15	1.0	No	SOI, SMI
Zolpidem	5 – 10	30	1.5 – 4.5	No	SOI
Zolpidem ER	6.25 – 12.5	90	1.6 – 4.0	No	SOI, SMI
Zolpidem SL	1.75 – 3.5	35	1.4 – 3.6	No	SMI
Melatonin Receptor Agonist					
Ramelteon	8	30 – 90	1 – 2.6[a] 2 – 5[b]	Yes	SOI
Tricyclic Antidepressant					
Doxepin	3-6	210	15.3[a] 31.0[b]	Yes	SMI

[a] = parent compound; [b] = active metabolite; SMI = sleep maintenance insomnia; SOI = sleep onset insomnia

2. Anxiety and anxiolytic drugs

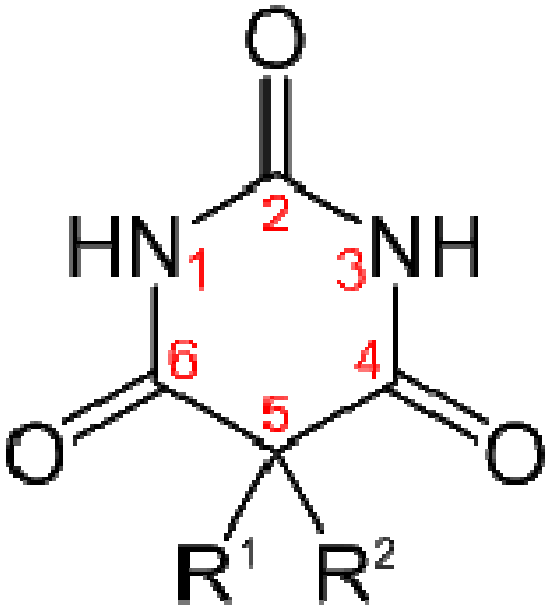
2.5 Barbiturate



2. Anxiety and anxiolytic drugs

2.5 Barbiturate

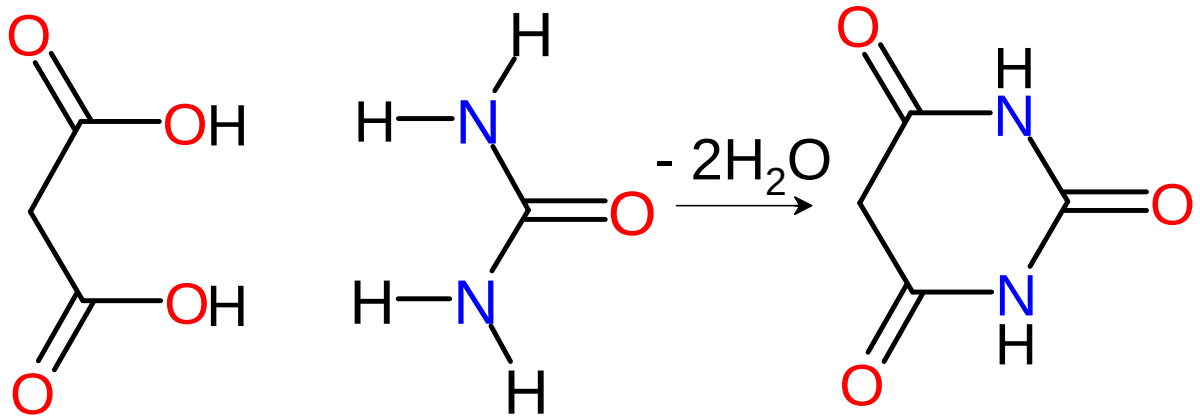
Barbiturates are drugs that act as central nervous system depressants, and, by virtue of this, they produce a wide spectrum of effects, ***from mild sedation to total anesthesia***. They are also effective as anxiolytics, as hypnotics, and as anticonvulsants. They have addiction potential, both physical and psychological. Barbiturates have now largely been replaced by benzodiazepines in routine medical practice - for example, in the treatment of anxiety and insomnia – mainly because benzodiazepines are significantly less dangerous in overdose. However, barbiturates are still used in general anesthesia, as well as for epilepsy. Barbiturates are derivatives of barbituric acid.



2. Anxiety and anxiolytic drugs

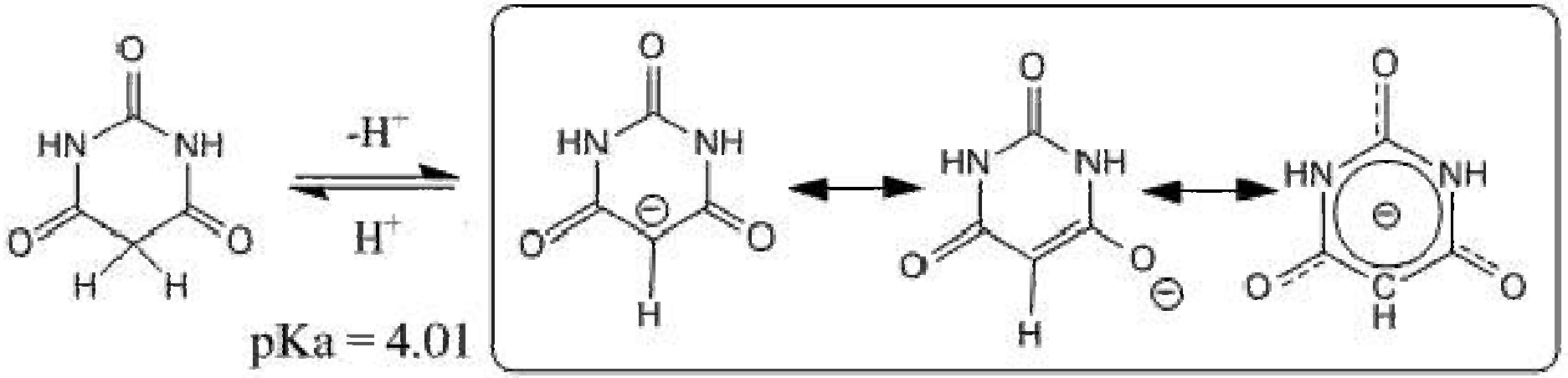
2.5 Barbiturate

Barbituric acid or malonylurea or 6-hydroxyuracil is an organic compound based on a pyrimidine heterocyclic skeleton. It is an odorless powder soluble in hot water. Barbituric acid is the parent compound of barbiturate drugs, although barbituric acid itself is not pharmacologically active. The compound was discovered by the German chemist **Adolf von Baeyer** on December 4, 1864, the feast of *Saint Barbara* (who gave the compound its namesake), by combining urea and malonic acid in a condensation reaction.
Malonic acid has since been replaced by diethyl malonate, as using the ester avoids the problem of having to deal with the acidity of the carboxylic acid and its unreactive carboxylate.



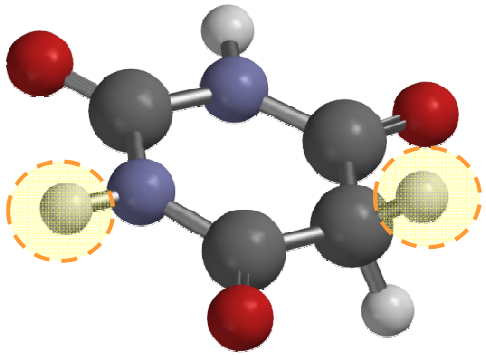
2. Anxiety and anxiolytic drugs

2.5 Barbiturate: why acid?

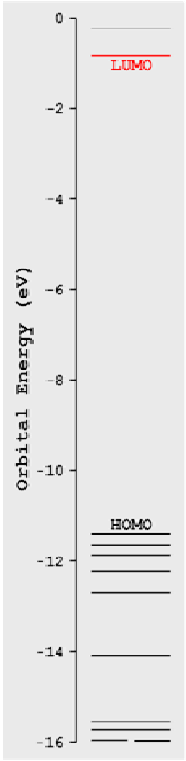


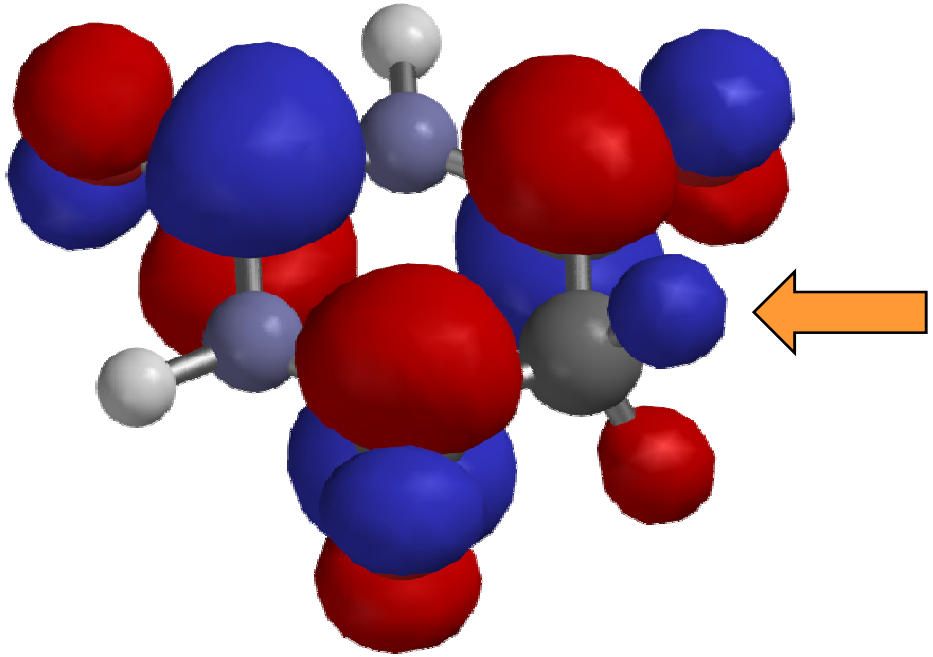
The α-carbon has a reactive hydrogen atom and is quite acidic (pKa = 4.01) even for a diketone species (cf. dimedone with pKa 5.23 and acetylacetone with pKa 8.95) because of the additional aromatic stabilization of the carbanion. Using the Knoevenagel condensation reaction, barbituric acid can form a large variety of barbiturate drugs.

The magic property of Barbituric to be… acid!!!

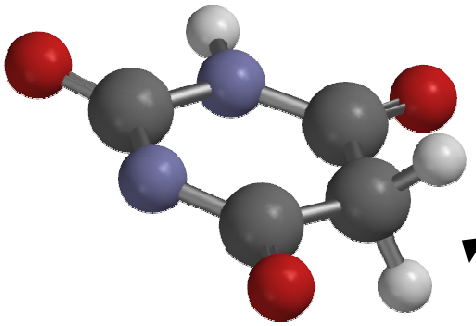


$+ B^-$ ⇌ …



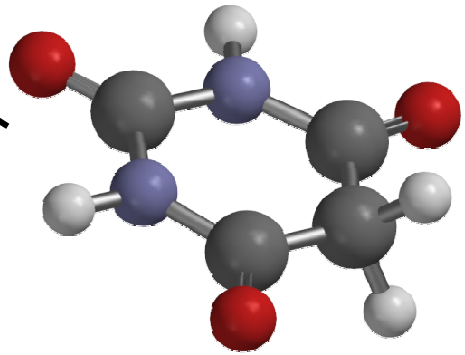


The magic property of Barbituric to be… acid!!!



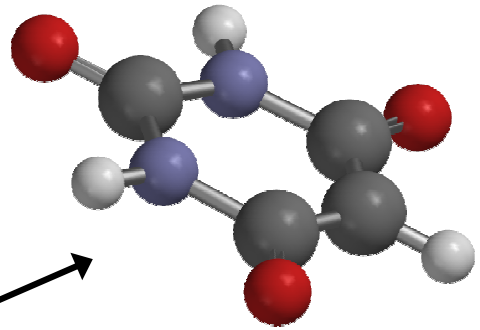
N_anion
Energy = -743.4 kJ/mol

- H^+

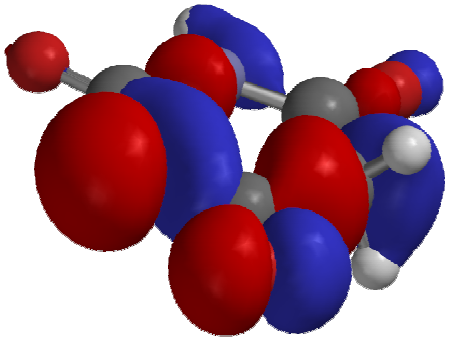


Barbituric acid
Energy = -553.2 kJ/mol
logP = - 1.4

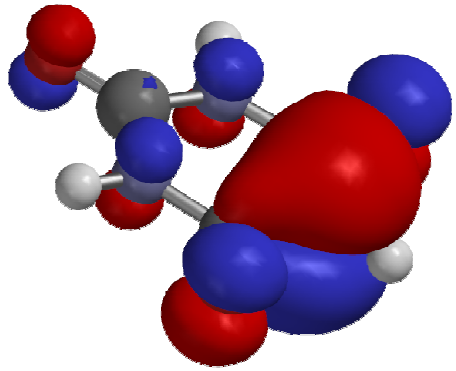
- H^+



C_anion
Energy = -807.3 kJ/mol



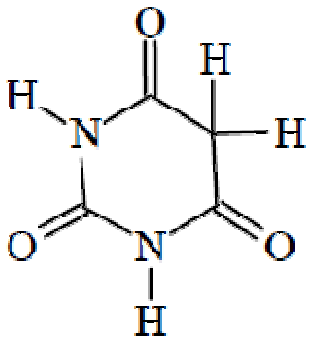
N_anion
HOMO = -6.10 eV



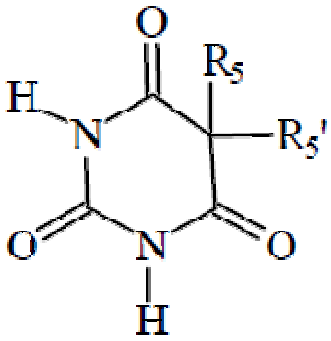
C_anion
HOMO = -5.34 eV

2. Anxiety and anxiolytic drugs

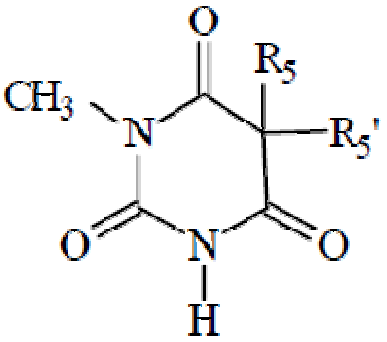
2.5 Barbiturate: why acid?



Barbituric acid: pKa 4.12



5,5'-Disubstituted barbituric acid: pKa 6.5-8

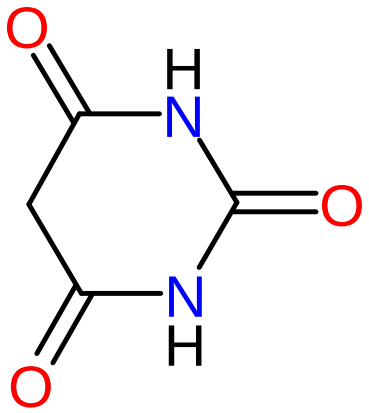


3,5,5'-Trisubstituted barbituric acid: pKa > 8

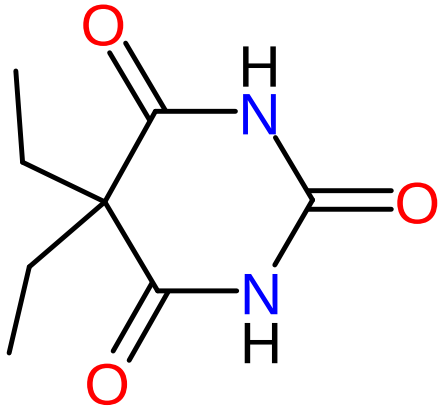
2. Anxiety and anxiolytic drugs

2.5 Barbiturate

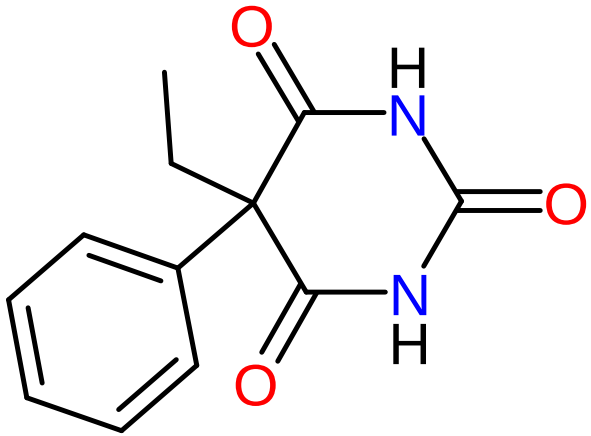
As of 2007, more than 2550 barbiturates and related compounds have been synthesised, with 50 to 55 in clinical use around the world at present. The first to be used in medicine was ***barbital*** (Veronal) starting in 1903, and the second, phenobarbitone a.k.a. ***phenobarbital*** (Luminal) was first marketed in 1912.



Barbituric acid (not active)



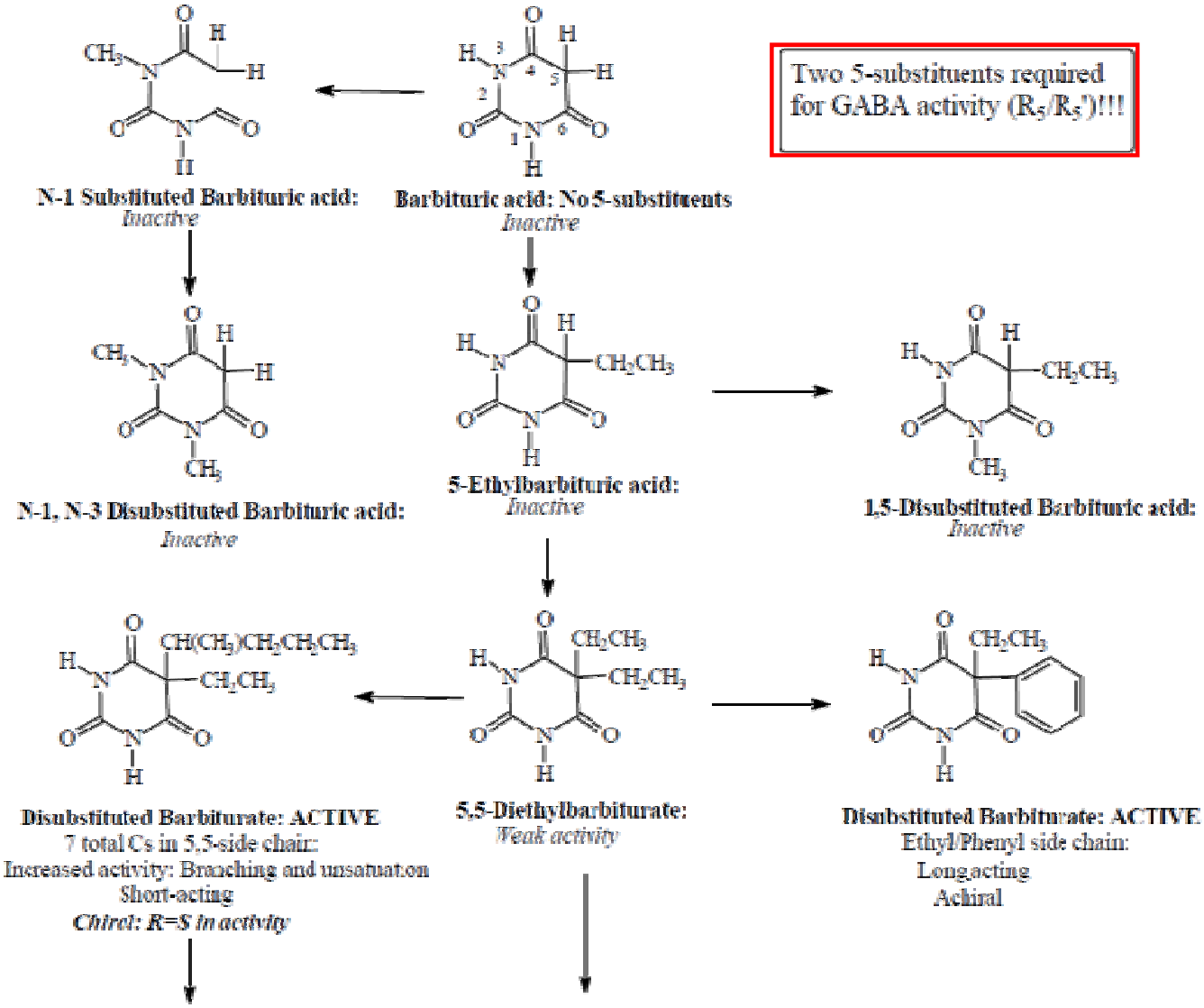
Barbital (Veronal)



Phenoarbital (Luminal)

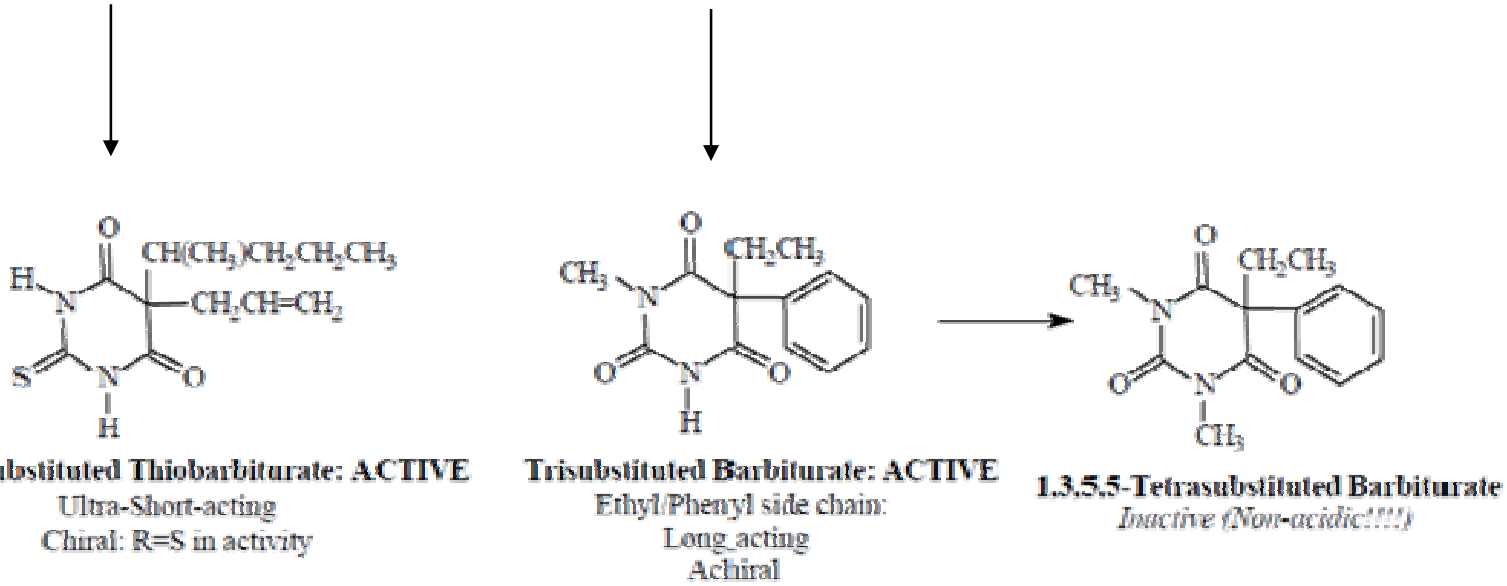
2. Anxiety and anxiolytic drugs

2.5 Barbiturate: SAR

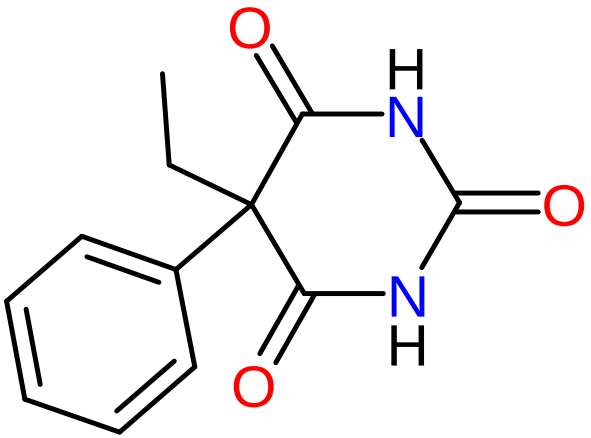


2. Anxiety and anxiolytic drugs

2.5 Barbiturate: SAR

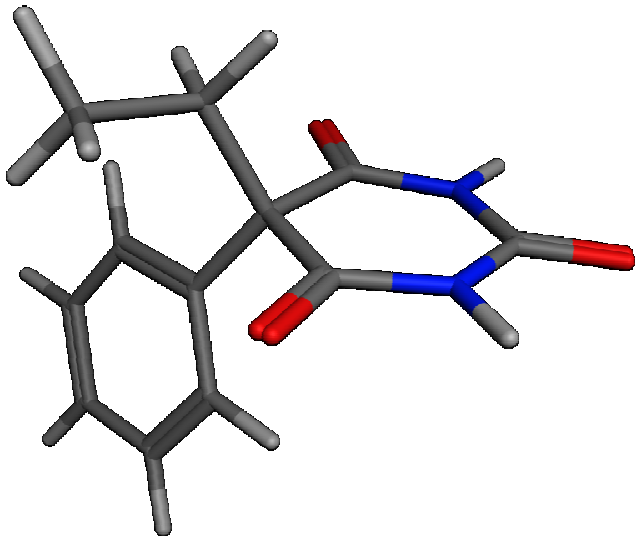


2. Anxiety and anxiolytic drugs



logP = 1.5
pKa = 7.3
PSA ≅ 75 Å²

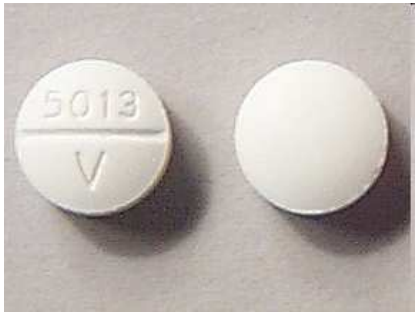
on set = 0.5÷1 hour
half life = 53÷110 hours



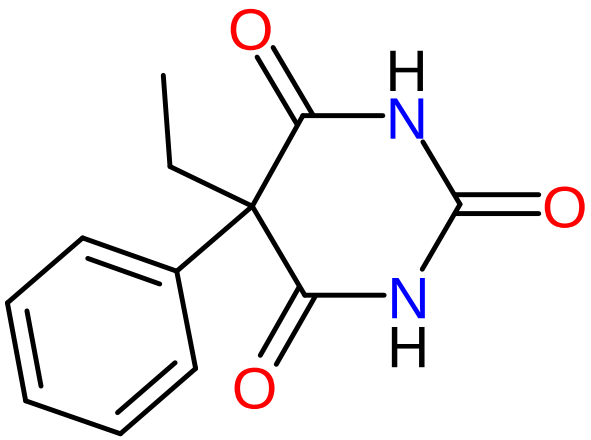
Phenobarbital

5-ethyl-5-phenylpyrimidine-2,4,6(1H,3H,5H)-trione

Phenobarbital or **phenobarbitone** is a barbiturate, first marketed as **Luminal** by Friedr. Bayer et comp. It is the most widely used ***anticonvulsant worldwide*** and the oldest still commonly used. It also has sedative and hypnotic properties but, as with other barbiturates, has been superseded by the benzodiazepines for these indications.



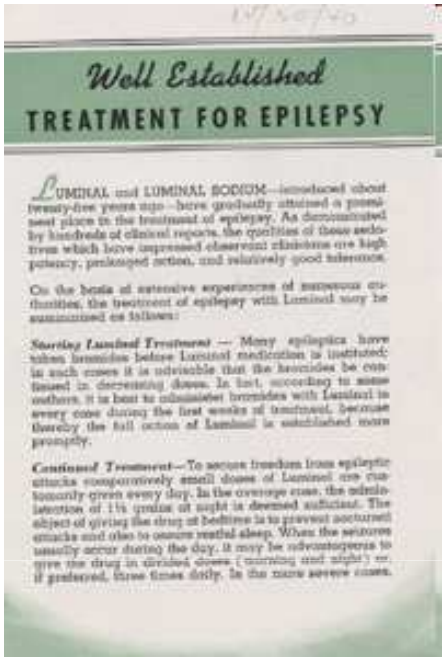
2. Anxiety and anxiolytic drugs



Phenobarbital

Treatment of phenobarbital overdose is supportive, and consists mainly in the maintenance of airway potency (through *endotracheal intubation* and *mechanical ventilation*), correction of bradycardia and hypotension (with intravenous fluids and vasopressors, if necessary) and removal of as much drug as possible from the body. Depending on how much time has elapsed since ingestion of the drug, this may be accomplished through *gastric lavage* (stomach pumping) or use of *activated charcoal*. *Hemodialysis* is effective in removing phenobarbital from the body, and may reduce its half-life by up to 90%. **There is no specific antidote for barbiturate poisoning.**

2. Anxiety and anxiolytic drugs



Well Established

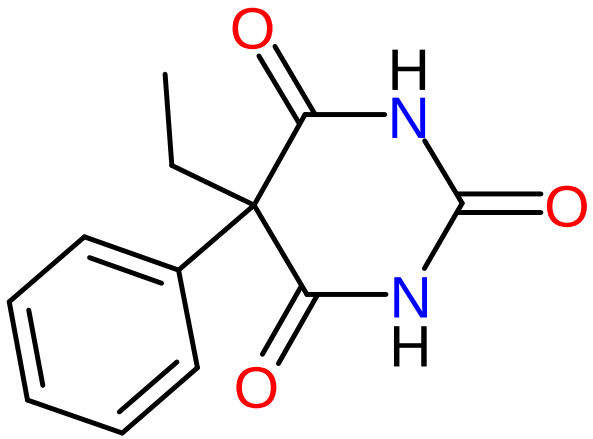
TREATMENT FOR EPILEPSY

LUMINAL and LUMINAL SODIUM—introduced about twenty-five years ago—have gradually attained a prominent place in the treatment of epilepsy. As demonstrated by hundreds of clinical reports, the qualities of these medicines which have impressed observant clinicians are high potency, prolonged action, and relatively good tolerance.

On the basis of extensive experiences of numerous authorities, the treatment of epilepsy with Luminal may be summarized as follows:

Starting Luminal Treatment — Many epileptics have taken bromides before Luminal medication is instituted; in such cases it is advisable that the bromides be continued in decreasing doses. In fact, according to some authors, it is best to administer bromides with Luminal in every case during the first weeks of treatment, because thereby the full action of Luminal is established more promptly.

Continued Treatment—To secure freedom from epileptic attacks comparatively small doses of Luminal are customarily given every day. In the average case, the administration of 1½ grains at night is deemed sufficient. The object of giving the drug at bedtime is to prevent nocturnal attacks and also to ensure restful sleep. When the seizures usually occur during the day, it may be advantageous to give the drug in divided doses (morning and night) or, if preferred, three times daily. In the more severe cases,

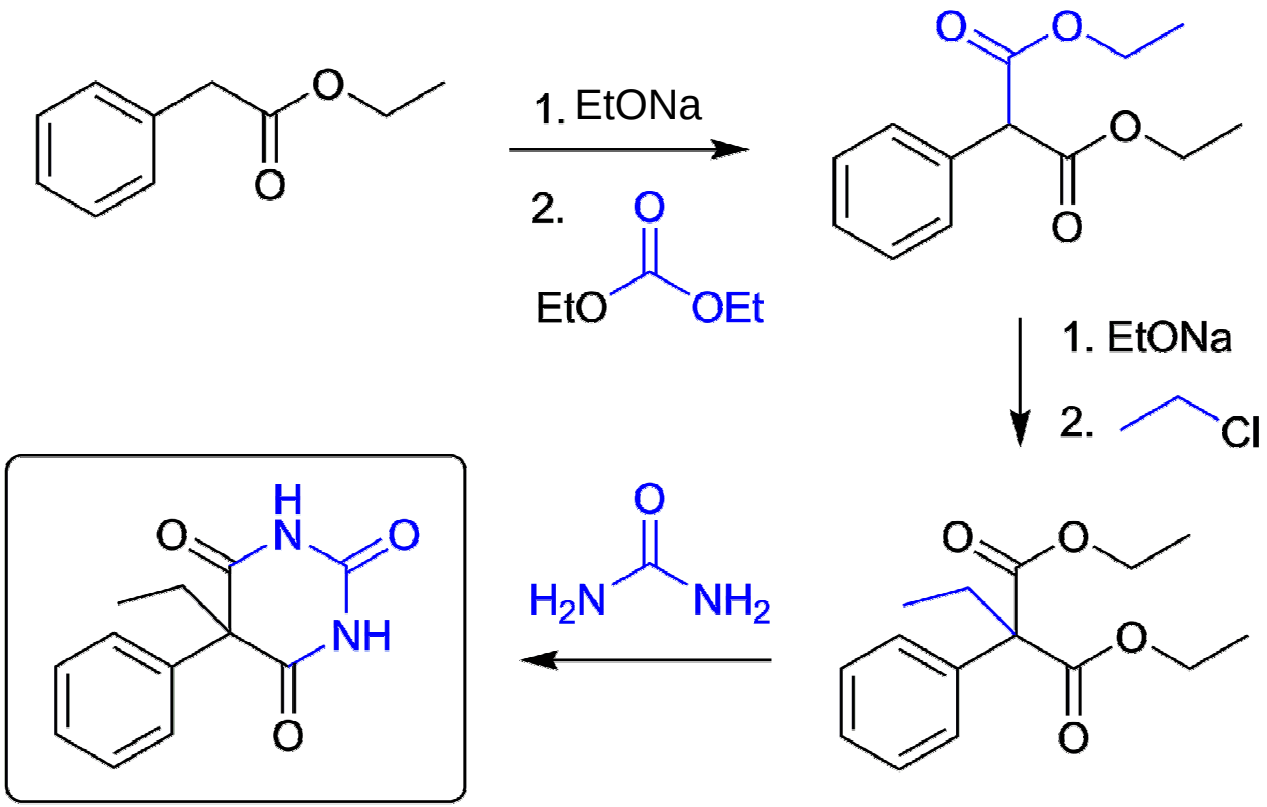


Phenobarbital

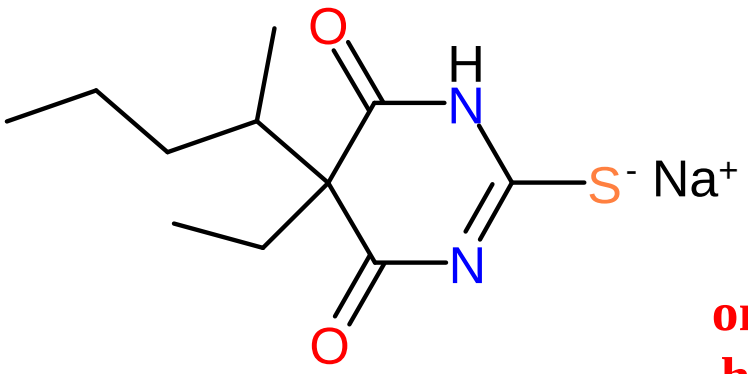
Potassium bromide (KBr) is a salt, widely used as an anticonvulsant and a sedative in the late 19th and early 20th centuries. Its action is due to the bromide ion (sodium bromide is equally effective). There would not be a better drug for epilepsy until phenobarbital in 1912. The therapeutic index (ratio of effectiveness to toxicity) is very small for bromide. As with other antiepileptics, sometimes even therapeutic doses (3 to 5 grams per day, taking 6 to 8 weeks to reach stable levels) may give rise to intoxication (***bromism***: is caused by a neurotoxic effect on the brain which results in somnolence, psychosis, seizures and delirium.)

2. Anxiety and anxiolytic drugs

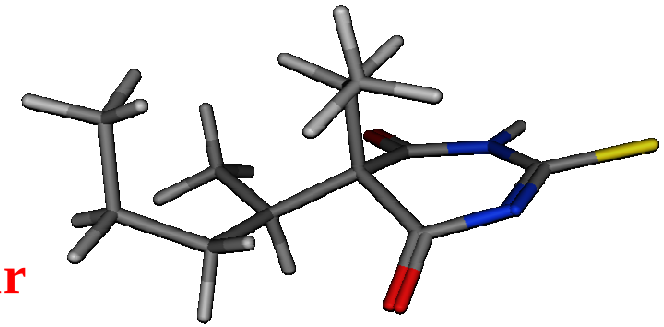
Synthesis Path



2. Anxiety and anxiolytic drugs



logP = 2.3
pKa = 7.4
PSA ≅ 59 Å²



on set = 0.2÷0.5 hour
half life = 3÷8 hours

Thiopental

(*RS*)-[5-ethyl-4,6-dioxo-5-(pentan-2-yl)-1,4,5,6-tetrahydropyrimidin-2-yl]sulfanide sodium

Sodium thiopental, better known as Sodium Pentothal (a trademark of Abbott Laboratories), is an ultra-short-acting barbiturate and has been used commonly in the induction phase of general anesthesia. In addition to anesthesia induction, thiopental was historically used to induce medical comas. Thiopental is used intravenously for the purposes of euthanasia. *Along with pancuronium bromide and potassium chloride, thiopental is used in 34 states of the U.S. to execute prisoners by lethal injection.* Thiopental is still used in some places as a truth serum.

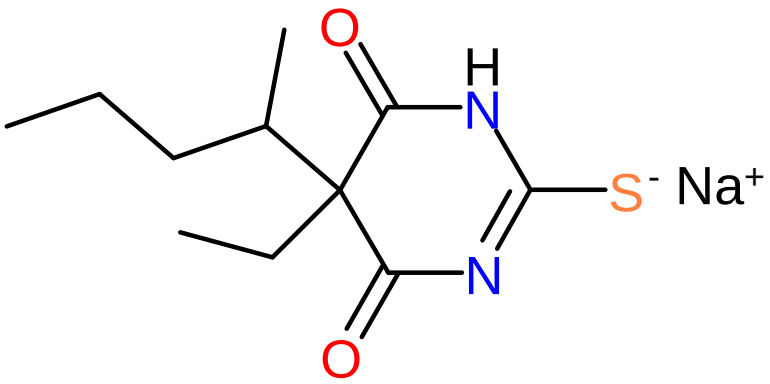
2. Anxiety and anxiolytic drugs

Induced coma

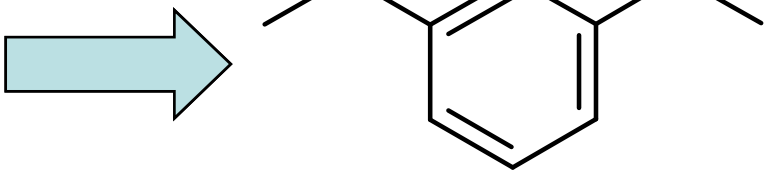
A coma (from the Greek koma, meaning *deep sleep*) is a profound state of unconsciousness from which a person cannot be awakened.

Induced Coma: a temporary coma is sometimes deliberately induced (by a controlled dose of a barbiturate drug, usually pentobarbital or thiopental) to reduce swelling of the brain after injury.

2. Anxiety and anxiolytic drugs



Thiopental



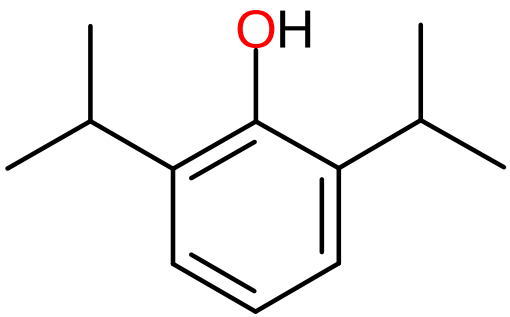
Propofol

2,6-diisopropylphenol

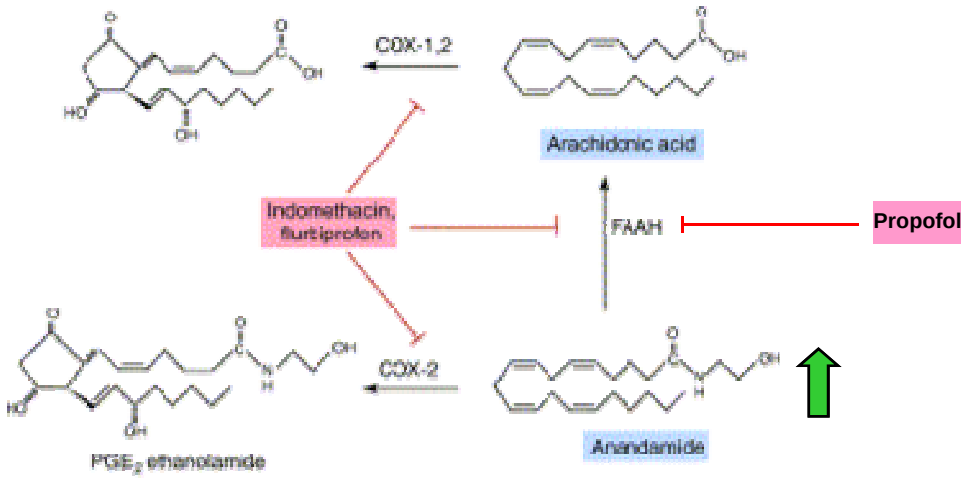
logP = 3.8
pKa = 11.1
PSA ≅ 20 Å²

Propofol (marketed as **Diprivan** by AstraZeneca) is a short-acting, intravenously administered hypnotic agent. Its uses include the induction and maintenance of general anesthesia, sedation for mechanically ventilated adults, and procedural sedation. Propofol is also commonly used in veterinary medicine. Chemically, propofol is unrelated to barbiturates, and has largely replaced sodium thiopental (Pentothal) for induction of anesthesia because recovery from propofol is more rapid and "clear" when compared with thiopental. Propofol is not considered an analgesic, so opioids such as fentanyl may be combined with propofol to alleviate pain.

2. Anxiety and anxiolytic drugs



Propofol

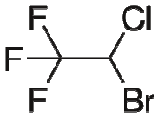


Recent evidence from studies in experimental animals has suggested that three clinically used drugs, the anaesthetic agent **propofol** and the non-steroidal anti-inflammatory drugs **indomethacin** and **flurbiprofen** (when given spinally), activate ***cannabinoid receptors*** as an important part of their actions. **Δ9-Tetrahydrocannabinol (THC)**, the principal active ingredient in cannabis, exerts most of its actions in the body via effects on two G protein-coupled receptors, termed cannabinoid CB1 and CB2 receptors. CB1 receptors are located primarily in the CNS, and among other actions mediate the 'high' sought by recreational cannabis users. CB2 receptors are localized in immune tissues.

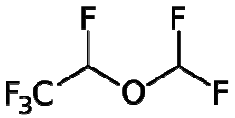
3. Anaesthetics

A. inhalational anesthetics

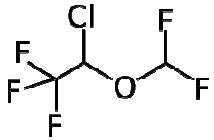
Halothane



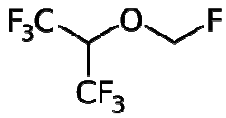
Desflurane



Isoflurane



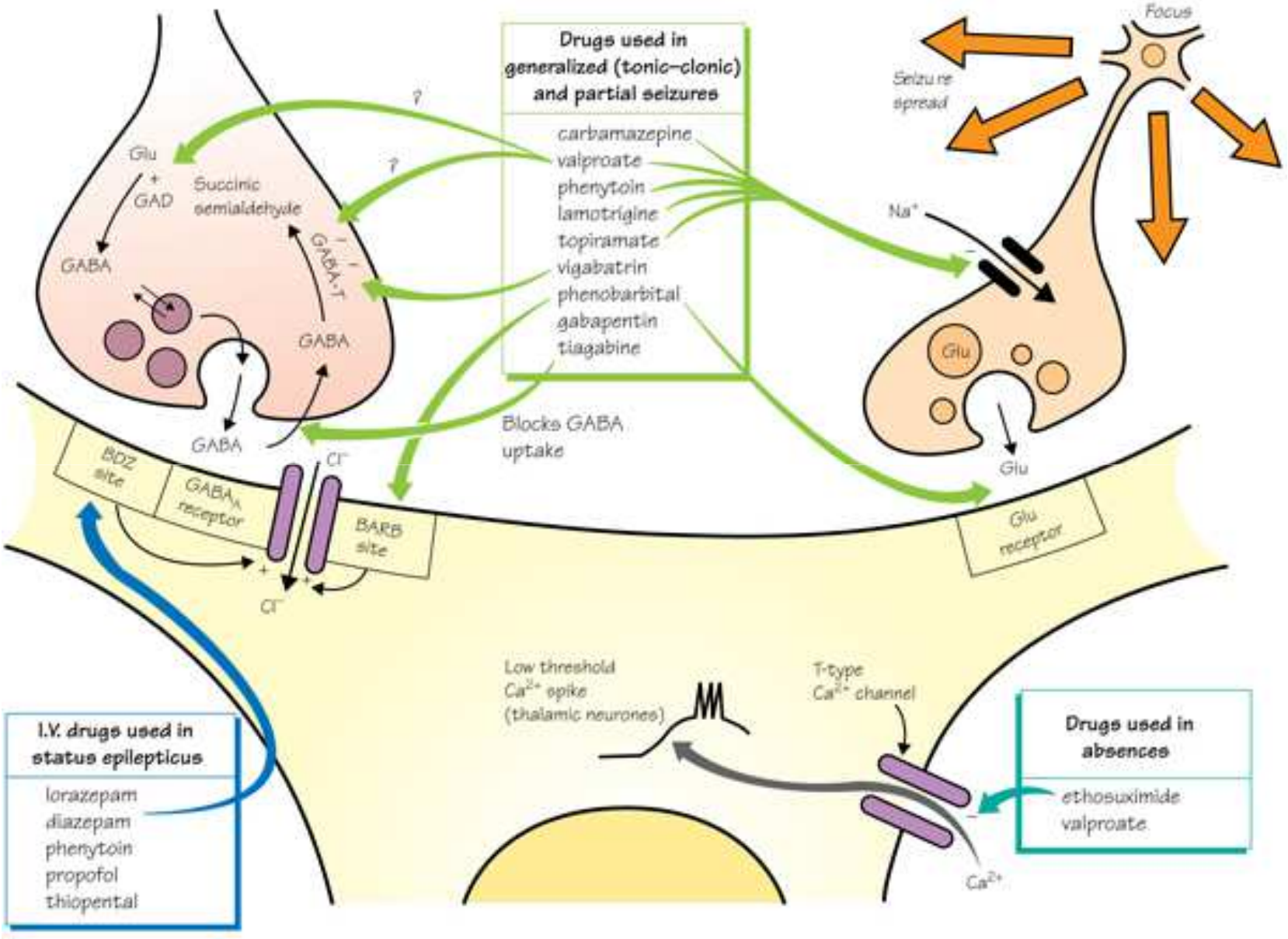
Sevoflurane



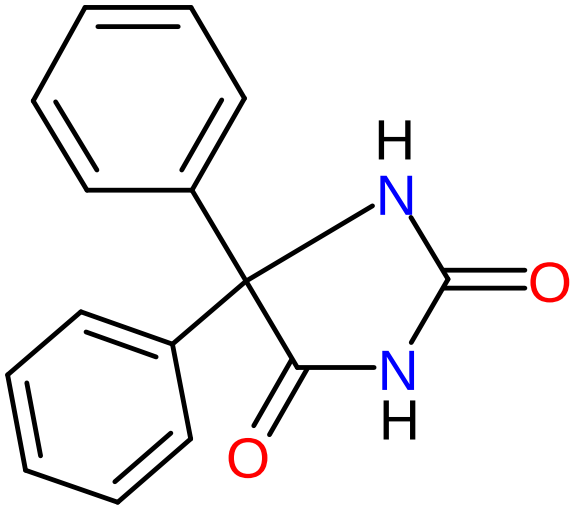
B. intravenous anaesthetics

Propofol
Thiopental
Midazolam
Ketamine **(ketamine is classified as an NMDA receptor antagonist)**

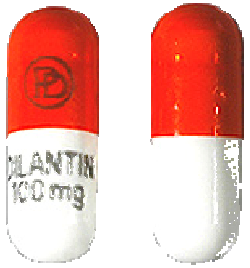
Anticonvulsant drugs:



Anticonvulsant drugs:

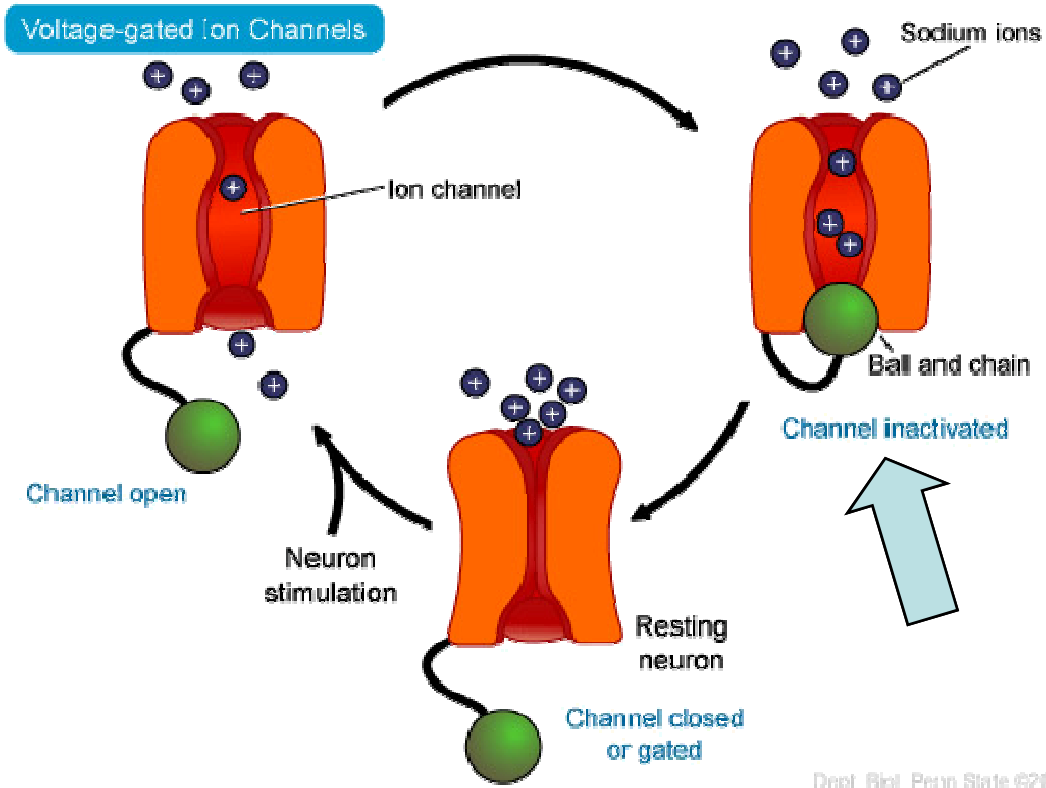


5,5-diphenylimidazolidine-2,4-dione



Phenytoin log P = 2.5

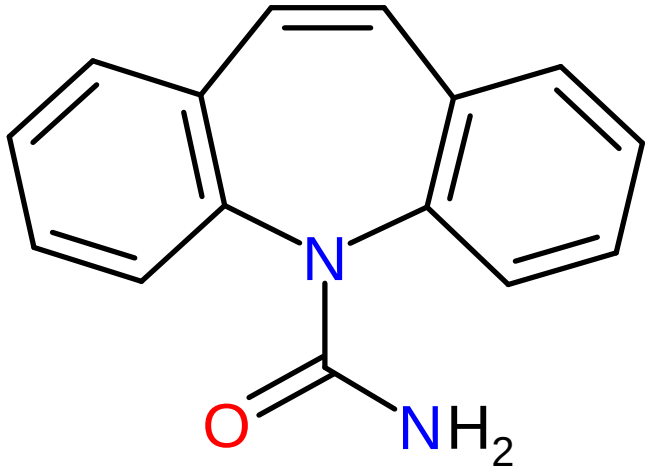
Since 1938, **Phenytoin** is a first-line anticonvulsant drug which can be useful in the treatment of epilepsy. The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Phenytoin is primarily metabolized by CYP2C9.



Phenytoin is believed to protect against seizures by causing voltage-dependent block of voltage-gated sodium channels. Phenytoin produces its anticonvulsant activity through blocking sustained high frequency repetitive firing of action potentials.

Phenytoin binds preferentially to the inactive form of the sodium channel. Because it takes time for the bound drug to dissociate from the inactive channel, there is a time dependent block of the channel. Since the fraction of inactive channels is increased by membrane depolarization as well as by repetitive firing, the binding to the inactive state by phenytoin sodium can produce voltage-dependent, use-dependent and time-dependent block of sodium-dependent action potentials

Anticonvulsant drugs:

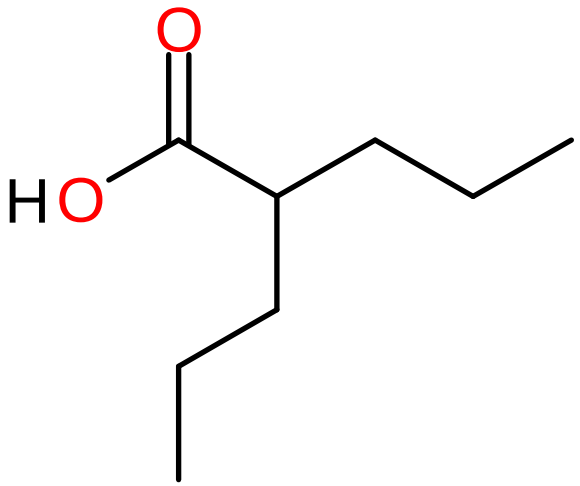


Carbamazepine log P = 2.4

5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide

Carbamazepine (**CBZ**) (Tegretol) is an **anticonvulsant** and **mood-stabilizing** drug used primarily in the treatment of **epilepsy** and **bipolar disorder**, as well as trigeminal neuralgia. Off-label uses, include attention-deficit hyperactivity disorder (ADHD), schizophrenia, phantom limb syndrome, complex regional pain syndrome, borderline personality disorder, and post-traumatic stress disorder.

Anticonvulsant drugs:



Valproic acid log P = 2.7

2-Propylpentanoic acid

Valproic acid (VPA, valproate), an acidic chemical compound, has found clinical use as an **anticonvulsant** and **mood-stabilizing drug**, primarily in the treatment of **epilepsy**, **bipolar disorder** and prevention of **migraine headaches**. *VPA is a liquid at room temperature, but it can be reacted with a base such as sodium hydroxide to form the salt sodium valproate, which is a solid.*

The mechanism of action of sodium valproate is not fully known. Its anticonvulsant effect is attributed to the blockade of voltage-dependent sodium channels and increased brain levels of gamma-aminobutyric acid (GABA). The GABA-ergic effect is also believed to contribute towards the anti-manic properties of sodium valproate.

2. Depression and antidepressant drugs

Herbal treatments

Certain herbs are reputed to have anxiolytic properties, including the following:

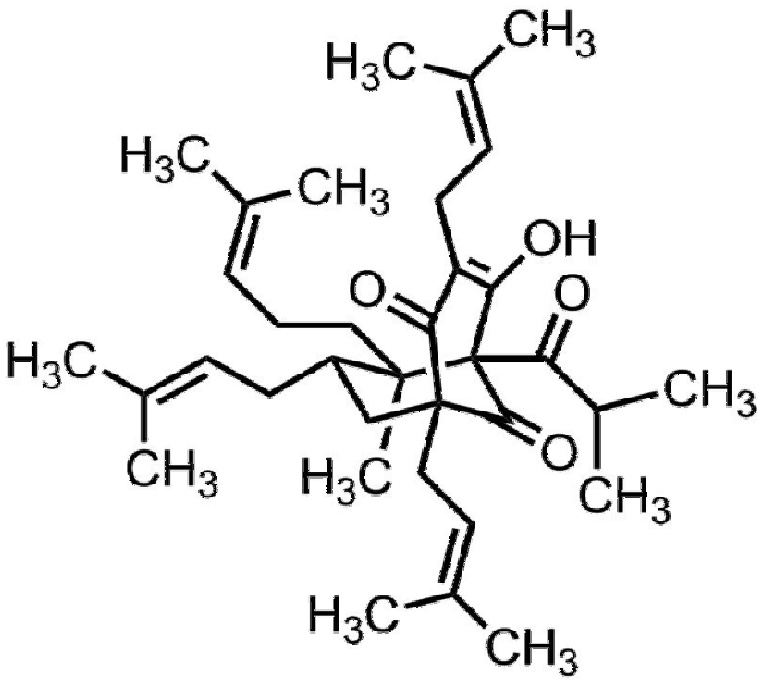
Rhodiola rosea (Arctic Weed/Golden Root)
Bacopa monnieri (Brahmi)
***Hypericum perforatum* (St. John's Wort)**
Matricaria recutita (German Chamomile)
Mitragyna speciosa (Kratom)
Nepeta persica (Catnip-Catmint)
Piper methysticum (Kava)
Sceletium tortuosum (Kanna)
Scutellaria spp. (Skullcap)
***Valeriana officinalis* (Valerian)**

2. Depression and antidepressant drugs

Herbal treatments

Hypericum perforatum (St. John's Wort)

Hyperforin is a phytochemical produced by some of the members of the plant genus Hypericum, notably Hypericum perforatum (St John's wort).



Hyperforin acts as a "reuptake inhibitor" and increases the levels of these neurotransmitters in the brain, which further improves mood and restore emotional balance. Hyperforin also inhibits the reuptake of GABA which is a neurotransmitter associated with increasing relaxation and reducing anxiety.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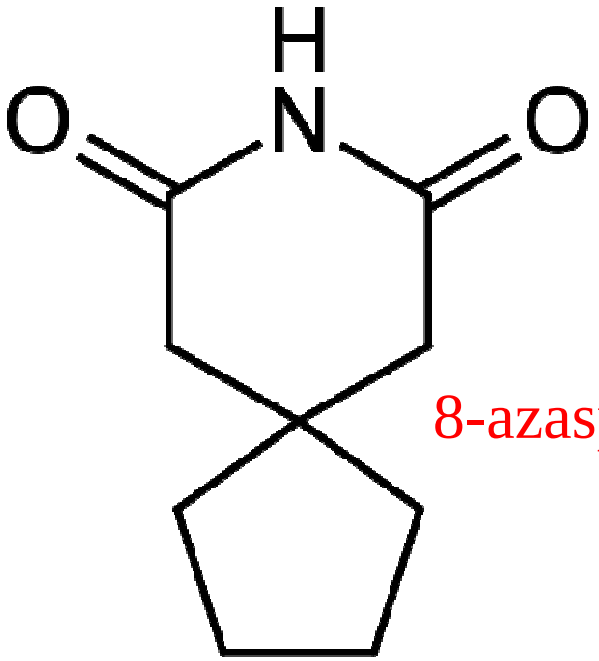
TAKE

2. Anxiety and anxiolytic drugs

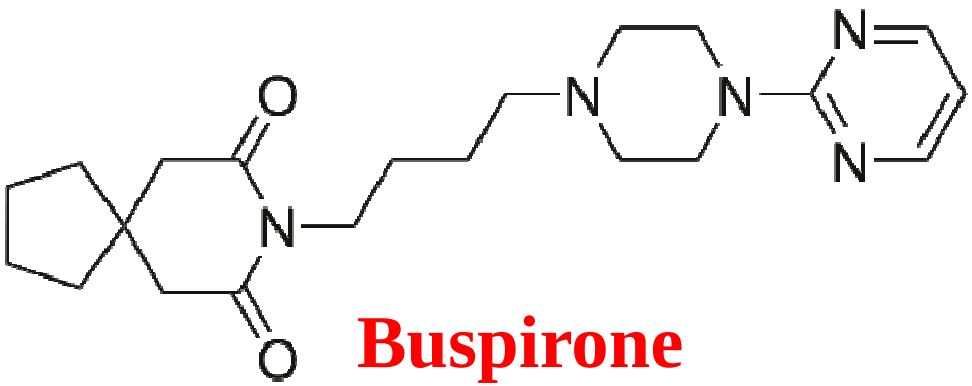
2.6 Azapirones

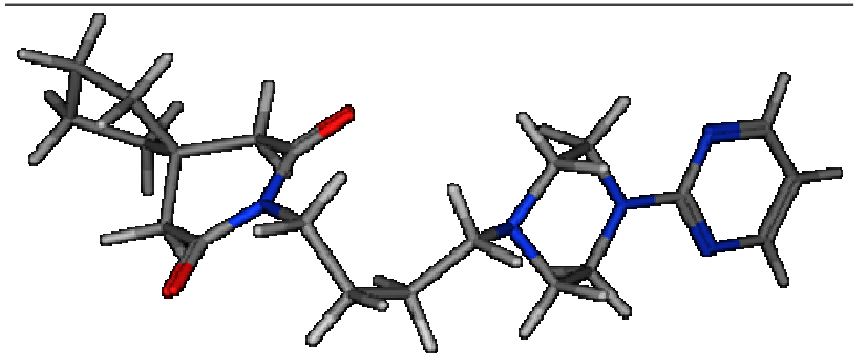


8-azaspiro[4.5]decane-7,9-dione

Azapirones are a class of 5-HT1A receptor agonists. They lack the sedation and the dependence associated with benzodiazepines and cause much less cognitive impairment. They may be less effective than benzodiazepines in patients who have been previously treated with benzodiazepines as they do not provide the sedation that these patients may expect or equate with anxiety relief. Currently approved azapirones include ***buspirone*** (Buspar) and ***tandospirone*** (Sediel). ***Gepirone*** (Ariza, Variza) is also in clinical development.

2. Anxiety and anxiolytic drugs





Buspirone **logP = 2.3**

8-[4-(4-pyrimidin-2-ylpiperazin-1-yl)butyl]-8-azaspiro[4.5]decane-7,9-dione

Buspirone's chemical structure and mechanism of action are completely unrelated to those of the benzodiazepines, but it purportedly has an efficacy comparable to that of diazepam (Valium) in treating of anxiety disorders. The main disadvantage of buspirone is that it may take several weeks before its anxiolytic effects become noticeable.

Buspirone functions as a serotonin ***5-HT1A receptor partial agonist***. It is this action that is thought to mediate its anxiolytic and antidepressant effects. Additionally, it functions as a dopamine D2, as well as α1, and α2-adrenergic receptor antagonist to a lesser degree, though these properties are generally undesirable in an anxiolytic and likely only contribute to side effects.