Al-Azhar University-Gaza

Pharmaceutical Chemistry and Pharmacognosy Department

Sedative and Hypnotics

MedChem-III

Prof. Ihab Almasri

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Defination

- A *sedative* drug decreases activity and excitement of the patient and calms anxiety by producing mild *depression of CNS* without causing drowsiness or sleep

- A *hypnotic* drug produces drowsiness, forcing the patient to sleep by *depressing the CNS*, particularly the reticular activity which influences wakefulness

Dose dependent activity

- All sedative, hypnotic and GA depress the CNS
- The observed effect depends on the dose given to patient
- Small dose cause sedation (calmness)
- Medium dose cause hypnosis (sleepy)
- Larger dose causes surgical anesthesia

Utility

Sedatives counter various types of anxiety such as:

- Obsessive-compulsive disorder (OCD)
- Post-traumatic stress disorder (PTSD)
- Social anxiety disorder
- Specific phobias

Hypnotics is for insomnia. Insomnia is a condition where person is not able to fall sleep

Ideal properties of hypnotics

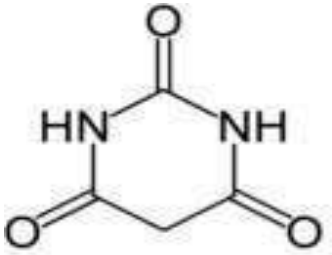
1. Cause a temporary decrease in the level of consciousness for the purpose of falling asleep without any alteration to sleep cycle
2. Must not decrease or arrest respiration, even at high doses
3. Cause no addiction, tolerance or dependence

Drug classification

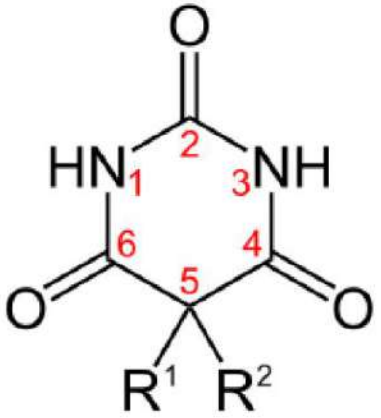
1. Barbiturates :Phenobarbitone
2. Benzodiazepines:

Alprazolam, Diazepam, Nitrazepam, Lorazepam

3. Non-Benzodiazepines: zolpidem, zopiclone
4. Others: paraldehyde, Glutethimide, Chloral Hydrate
5. Herbal sedatives: Ashwagandha, Valerian and passiflora



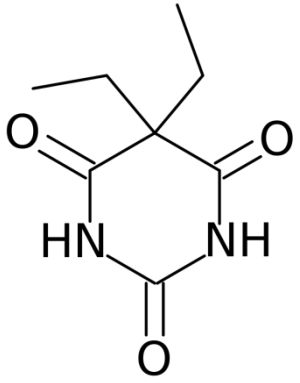
Barbiturates

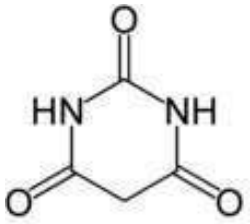


- All derivatives of Barbituric acid
- They are CNS depressants. They are effective as anxiolytics, hypnotics, anticonvulsants and analgesics.
- They have addiction potential, both physical and psychological.
- Thus Benzodiazipines have largely replaced them in term of sedative-hypnotic

Types

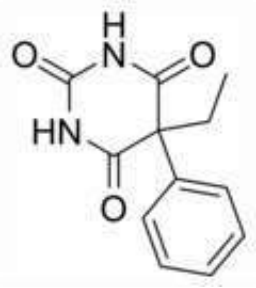
Barbital





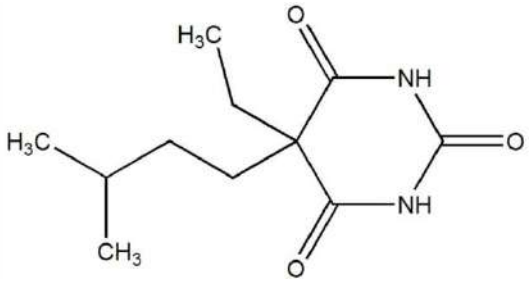
Barbituric Acid

Long-Acting



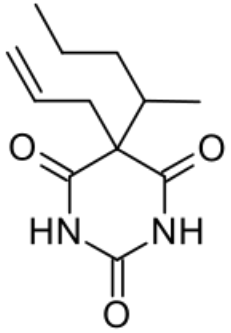
Phenobarbital

Intermediate acting



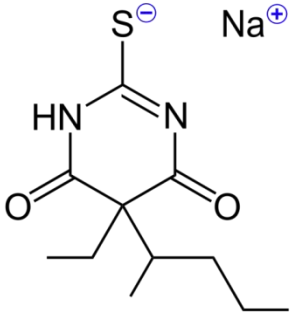
Amobarbital

Short acting

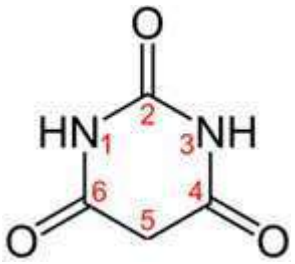


Secobarbital

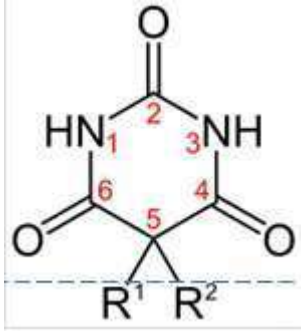
Ultra shortacting



Thiopental sodium



Structure-Activity Relationship



- Barbituric acid itself does not possess any hypnotic properties.
- Activity requires a balance of acidic and lipophilic properties.

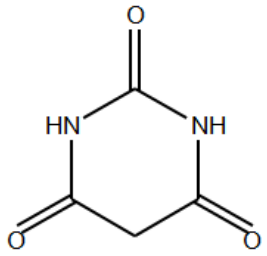
❖To make the drug sufficiently acidic, both or at least one of the two nitrogen must be unsubstituted

❖To make drug sufficiently lipophilic, the two hydrogen atoms at position 5:5 must have the appropriate substituent (*e.g., alkyl or aryl groups)*

The type of substituent's control 2 aspects of the drug

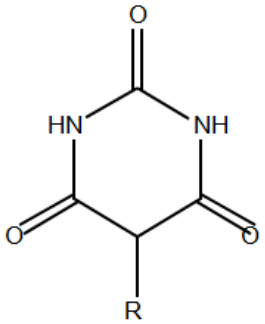
❖Potency

❖Duration of Action.

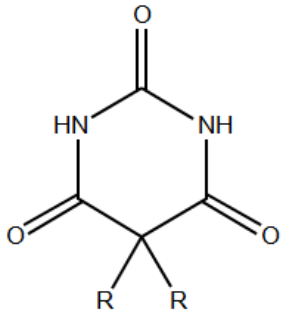


Barbituric acid

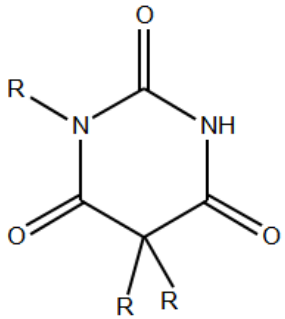
Inactive inactive coz not lipophilic enough



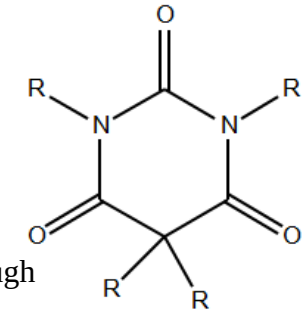
inactive
coz not lipophilic enough



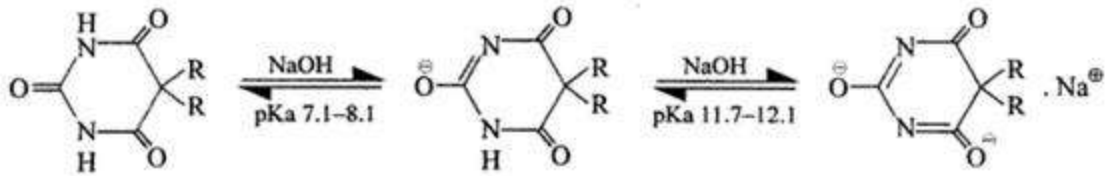
active



active



Inactive coz not acidic enough



SAR of barbiturates

- Both hydrogen atoms at the 5-position of barbituric acid must be replaced.
- Beginning with lower alkyls, there is an increase in onset and a decrease in duration of action with increasing hydrocarbon content up to about 7 to 9 total carbon atoms substituted on the 5-position.
- Increase the lipid/water partition coefficient generally increase the rate of metabolism, except with extremely high partition coefficient.
- N-methylation decreases duration of action by increasing the conc. of lipid-soluble free acid.
- 2-thiobarbiturates have a very short duration of action since they are highly lipophilic which cause depotization.
- Oral absorption is good.
- They are used as hypnotic, sedative, for induction of anesthesia, and as anticonvulsants.

- The total number of carbon atoms present in the two groups at carbon 5 must not be less than 4 and not more than 9 and influences onset of action and duration

Total carbon	Duration of action
7-9	Rapid onset and shorter duration
5-7	Intermediate duration of action
4	Slowest onset and longest duration of action

Classification :

Depending upon the duration of action barbiturates are divided into four classes like

(1) Long acting barbiturates (6 hours or more)

(2) Intermediate acting (3-6 hours)

(3) Short acting (less than 3 hours)

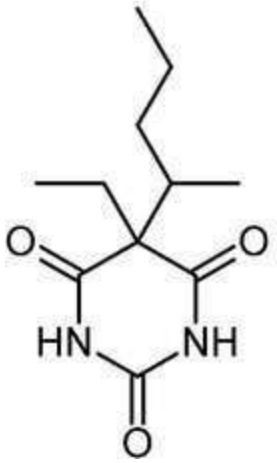
(4) Ultra-short acting (I.V.)

- Only one of the substituent groups at position 5 may be a cyclic group.

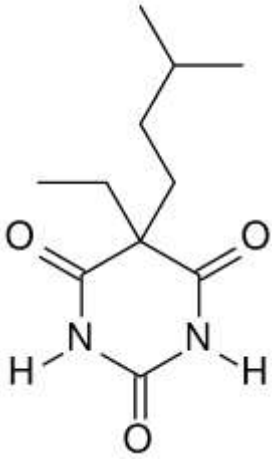
➢**The branched chain isomer exhibits** <u>greater activity</u> but **shorter duration.** The greater the branching, the more potent is the drug (e.g., pentobarbital > amobarbital).

➢This Branched, cyclic or unsaturated alkyl groups reduce duration of action due to increased ease of metabolic inactivation (Double bonds in the alkyl substituent groups produce compounds more readily vulnerable to oxidation)

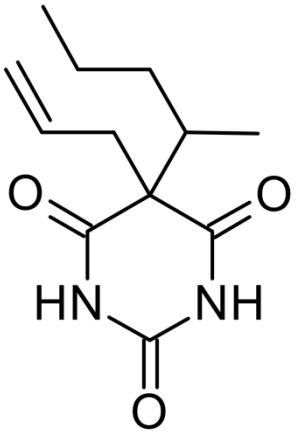
➢Aromatic and alicyclic moieties exert greater potency than the corresponding aliphatic moiety having the same number of carbon atoms.



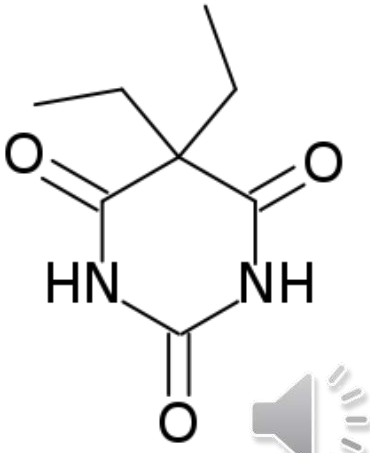
Pentobarbital



Amobarbital



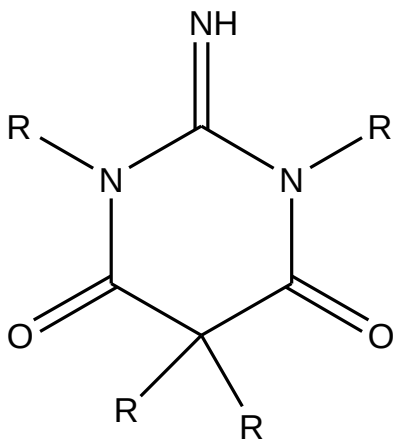
Secobarbital



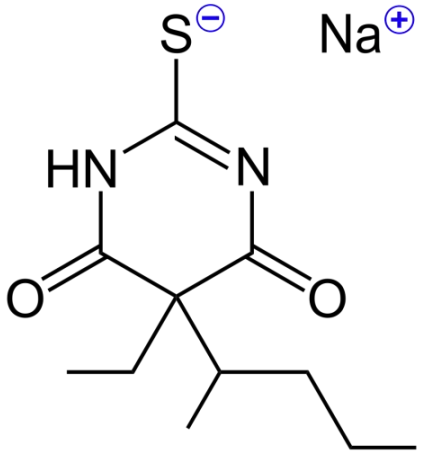
barbital

➢The replacement of O-atom with an S-atom, at C-2 position of the barbiturates significantly enhances the lipid solubility. Exert a rapid onset of action by virtue of the fact that they attain maximal thiobarbiturate-brain levels. Therefore, such drugs as ‘thiopental sodium ’find their profuse and abundant application as ‘intravenous anaesthetics.’

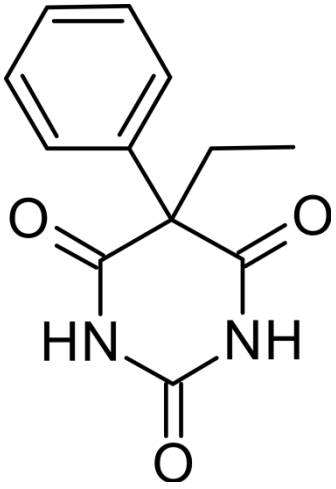
➢Inclusion of more sulphur atoms (at C-2 and C-6) decreases activity. Likewise replacement of Oxygen with Nitrogen abolishes activity



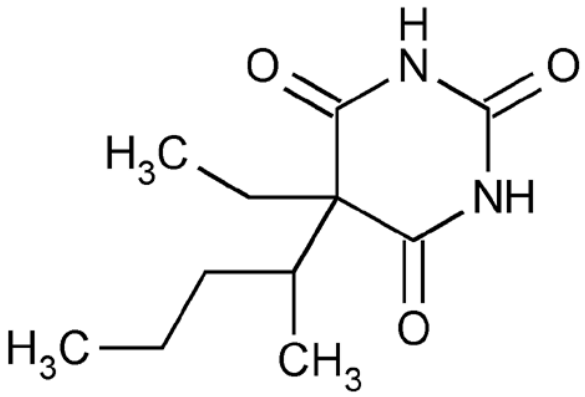
Inactive



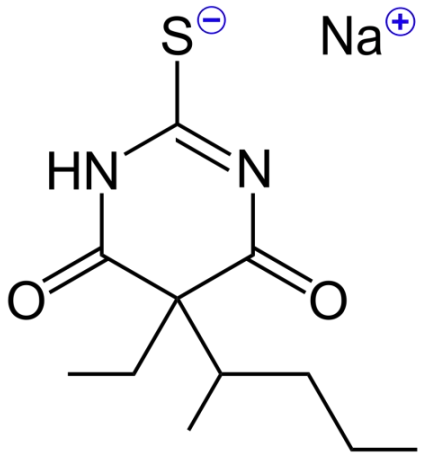
Thiopental sodium



Phenobarbital



Pentobarbital

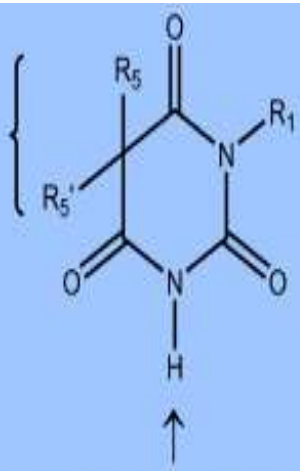


Thiopental

Factors effecting Duration of action as by the SAR	
Phenobarbital	Thiopental Sodium
	Branched R group
Short ethyl chain (Total carbon = 2 not counting aromatic)	Long chain of R group Total C= 7
	Additional improvements to Thiopental Sodium to further decrease duration of action •N methylation (potency also inc) •Unsaturated R group

Summary of barbiturates SAR

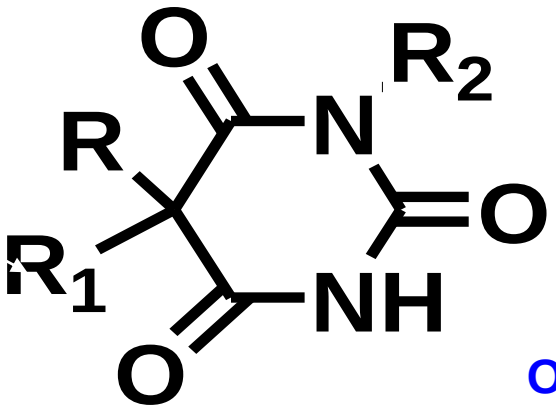
5,5-disubstitutents are important for activity and duration of action



R_1 = alkyl→↑ lipophilicity → quicker onset & shorter duration of action

O →S →↑ lipophilicity → rapid onset

must be a weak acid



R_2: CH_3

fast action

If R (R_1) = H, no activity;

it needs to be 2-5 carbon chains or 1 phenyl group

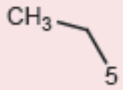
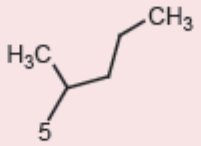
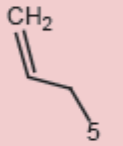
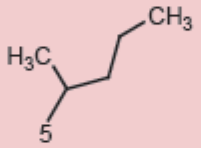
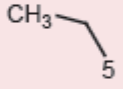
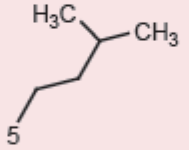
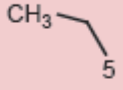
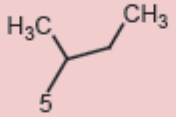
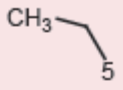
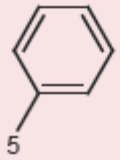
O: replace with S

fast action

The sum of R and R_1 needs to be 4-8

Note the correlation between the lipophilicity (logP) and the onset and duration of action for each drug.

TABLE 15.1 Pharmacokinetic Parameters of Barbiturates Approved for Sedative-Hypnotic Use

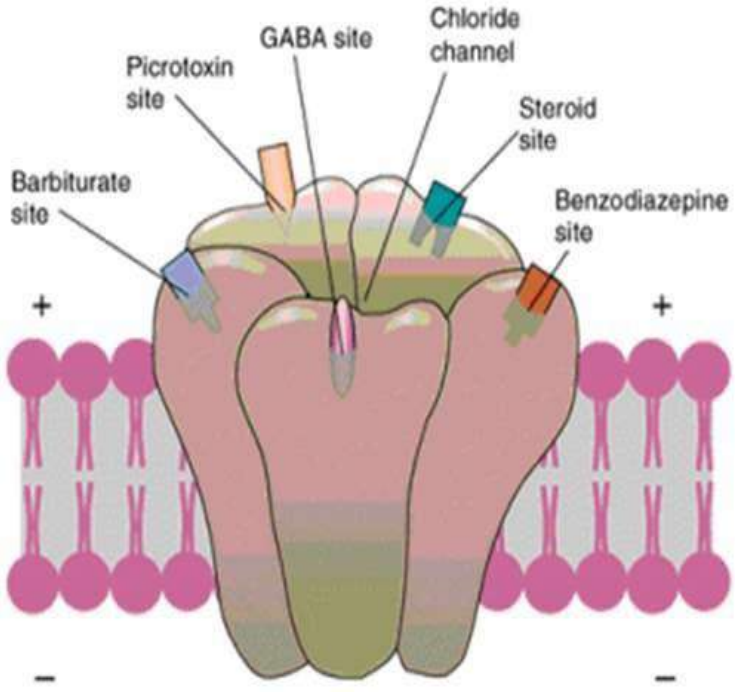
Barbiturate	R1	R2	LogP	Onset Time (min)[d]	Duration of action (hour)	Classification
Pentobarbital			2.10[a]	10–15	3–4	Short-acting
Secobarbital			2.36[b]	10–15	3–4	Short-acting
Amobarbital			2.07[d]	45–60	6–8	Intermediate acting
Butabarbital			1.60[b]	45–60	6–8	Intermediate acting
Phenobarbital			1.46[b]	30–60	10–16	Long-acting

Mode of action of barbiturates

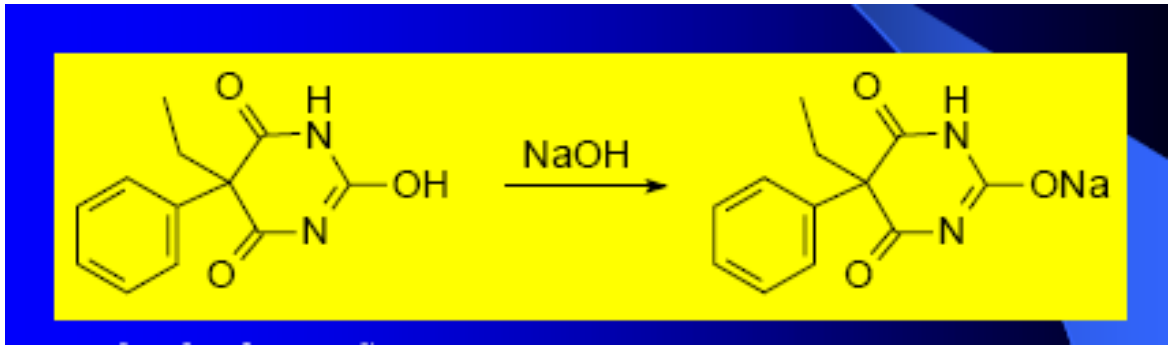
1. They have positive allosteric effect at GABA receptor. They bind at a different site than GABA or Benzodiazepines and stimulate the pharmacologic action of GABA which is the principal inhibitory neurotransmitter in the CNS

2. They inhibit AMPA receptor, which binds **glutamate** which is principal *excitatory* neurotransmitter in the CNS

3. At higher does they inhibit Ca^{+2} dependent release of neurotransmitters

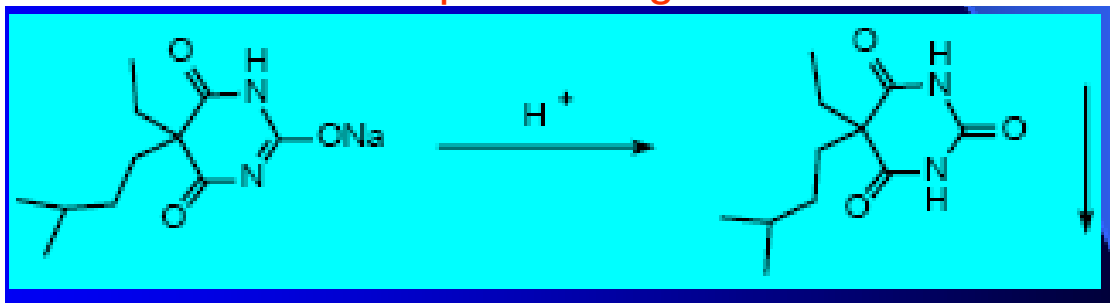


When it dissolves in sodium-containing basic solutions, it becomes sodium salt. Amobarbital sodium is used as injections.



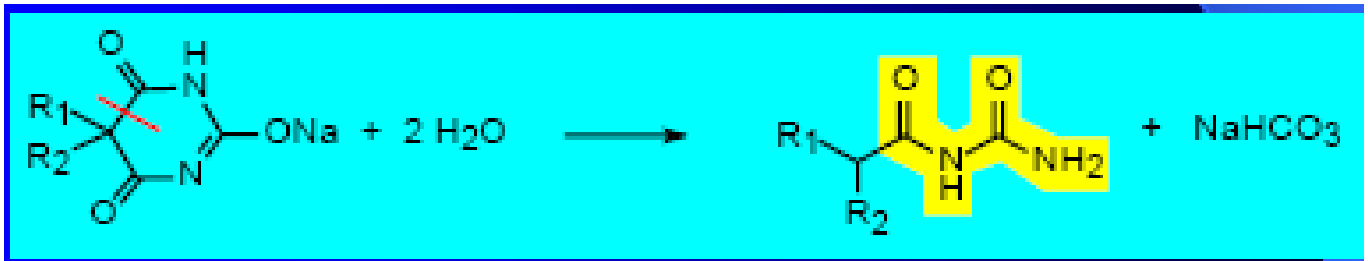
The sodium solution absorbs CO_2 and the free drug precipitates from the solution,

Suggestion: it cannot be exposed long in the air.



The sodium solution absorbs water and decomposes

Suggestion: it cannot be left long in the air.



When 10% sodium solution is placed at 35°C, 22% of the drug decomposes in one month.

If it is stored at 1°C for two month, the drug is basically stable.

Be caution if the injection is used

In order to avoid the invalidation of

the injections, be careful the following

- ★ **Avoid pre-formulation, sterilization by heating**
- ★ **should be made in powder-injection, dissolved before used**

Intravenous Anesthetics

Ultrashort-acting barbiturates:

- Administered IV. In aqueous solutions for the induction of anesthesia

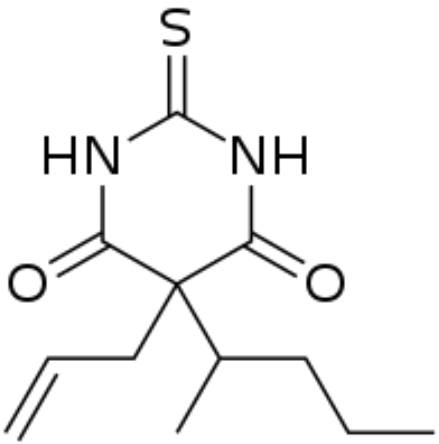
- Respiratory depression is marked at anesthetic doses therefore they are not used to maintain surgical anesthesia

Act within seconds and last for 30 minutes

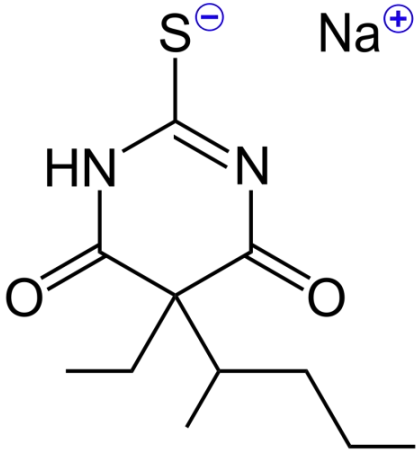
- This is due to high lipid/water partition coefficient, so fast penetration from the blood to the site of action in the brain lead to rapid onset of action.

- The short duration of action due to fast distribution to the well perfused tissues in the peripheral organs and subsequently to fat tissue

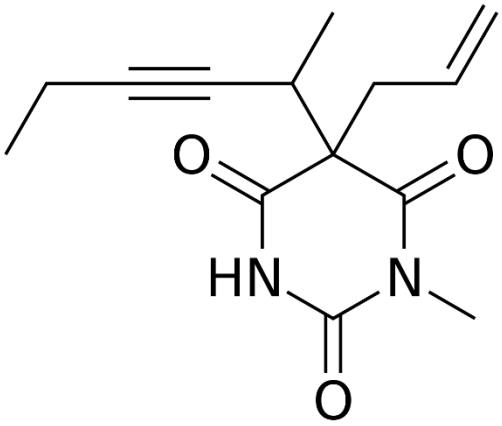
Thiamylal sodium



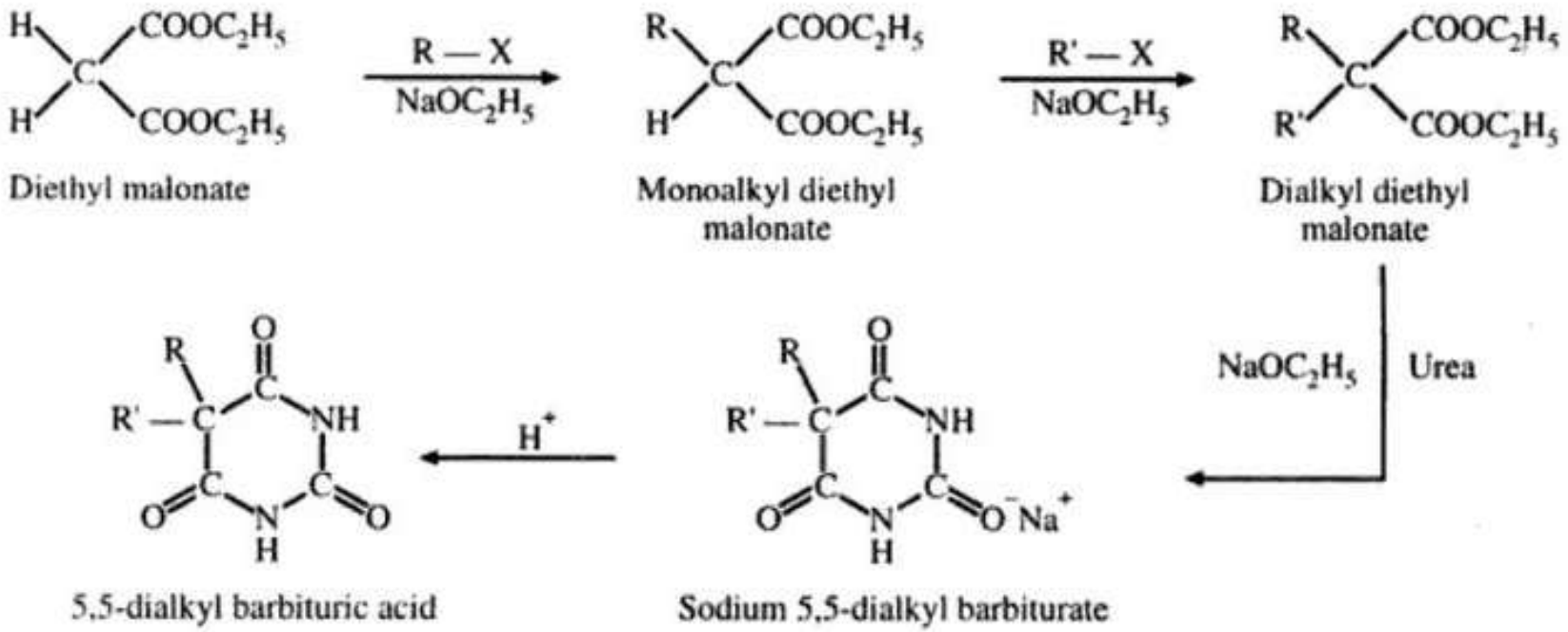
Thiopental sodium



Methohexital



General scheme for synthesis of Barbiturate :



Al-Azhar University-Gaza

Pharmaceutical Chemistry and Pharmacognosy Department

Sedative and Hypnotics

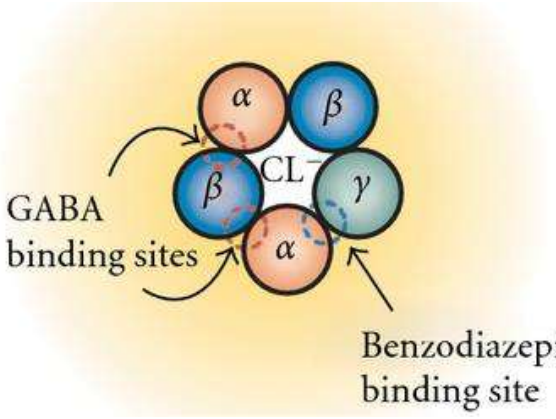
MedChem-III

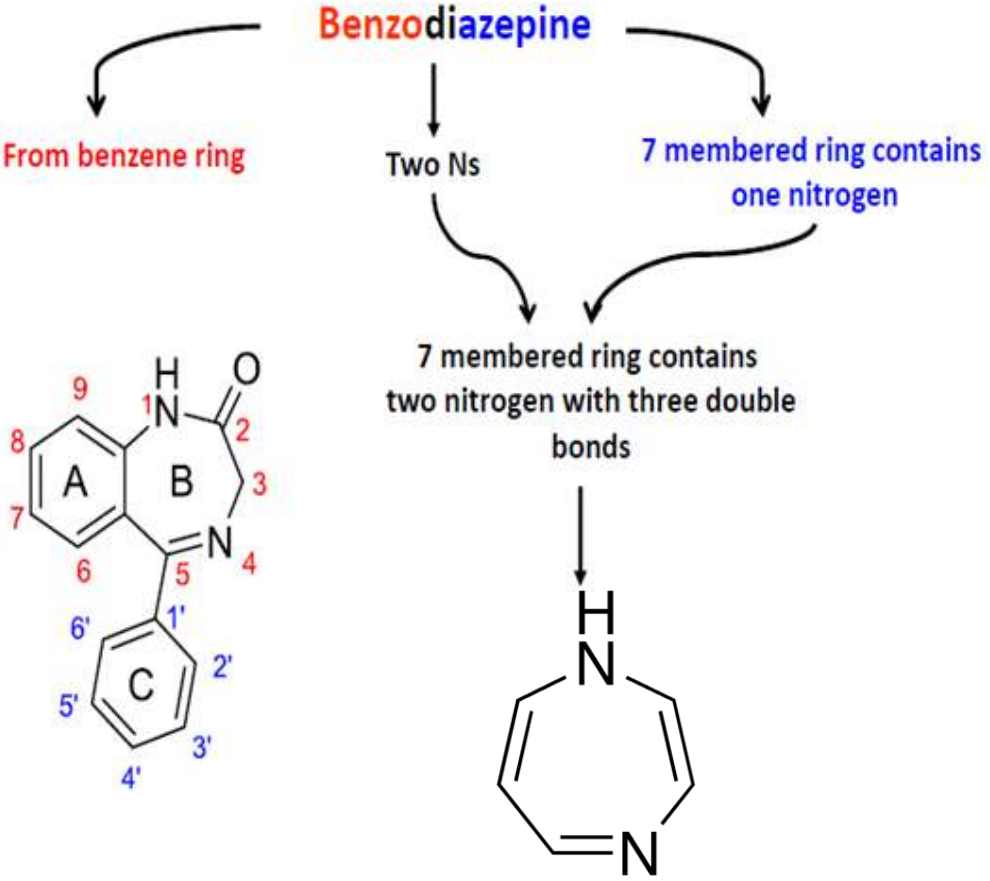
Prof. Ihab Almasri

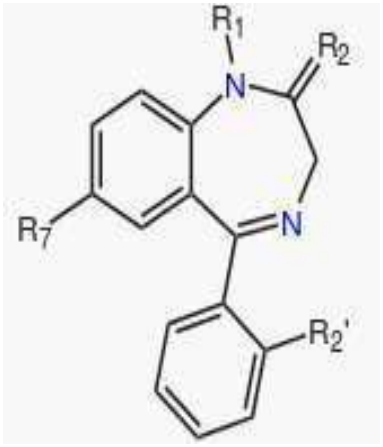
2020-2021

Anxiolytic, Sedative and hypnotic agents

1,4-Benzodiazepines







- Chemically they are a fusion of a benzene ring and a diazepine ring
- The subunit combinations and the benzodiazepine structure determine the pharmacological response.
- Are safer than barbiturate and not addictive

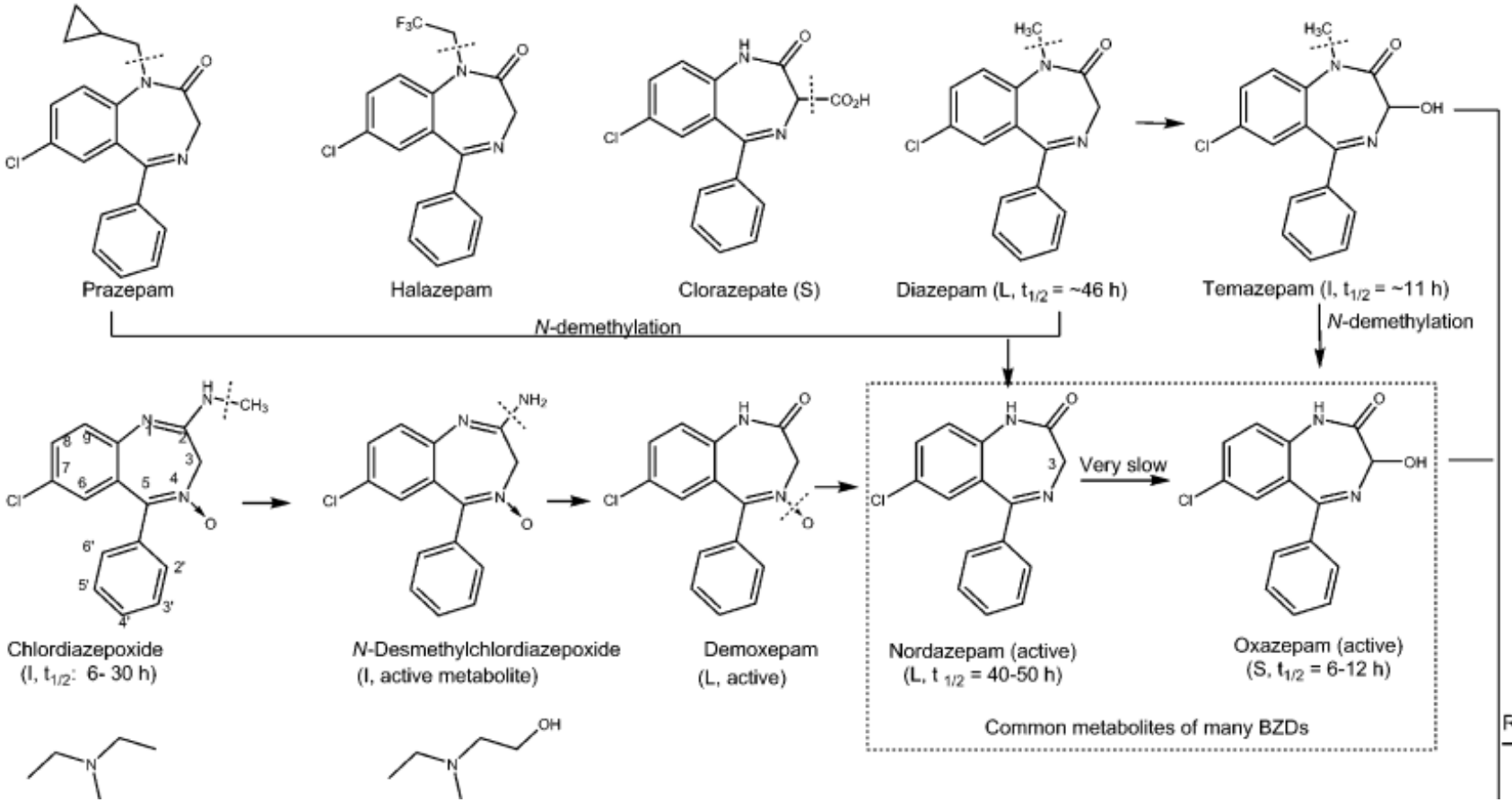
MOA of benzodiazepines

1. They have positive allosteric effect at GABA receptor. They bind at a different site than GABA or barbiturates and stimulate the pharmacologic action of **GABA**

2. They block reuptake of Adenosine which is sedating neurotransmitter, thus promoting its sedative action.

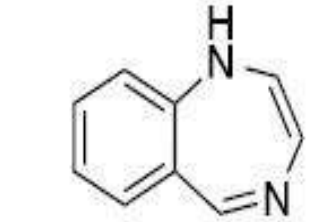
3. Attach to and directly block the Acetylcholine (Ach) receptors in the hippocampus thus causing amnesia . (Hippocampus is where memory is stored and processed).

Benzodiazepines Metabolism



The structure–activity relationship:

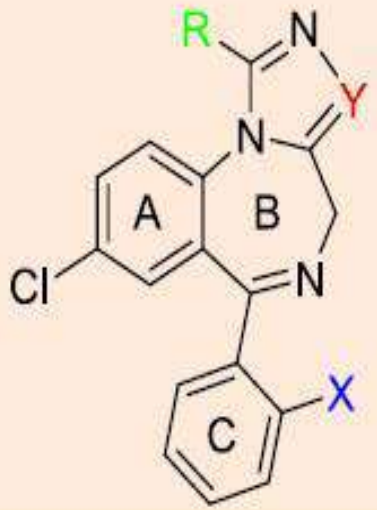
*There are **two** classes of BNZs*



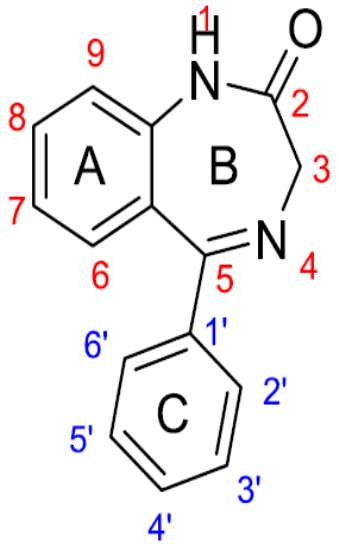
benzo-1,4-diazepine

Class **A** general structure is:

Class **B** general structure is:



the 5-phenyl-1,4-benzodiazepine-2-one backbone required for $GABA_A$ activity.



Ring A:

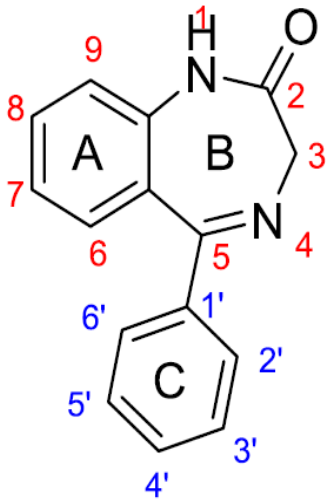
• The minimum requirement for binding of 5-phenyl-1,4-benzodiazepin-2-one derivatives to the BZR includes an ***aromatic*** or ***heteroaromatic*** ring (ring A), which is believed to participate in ***π-π*** stacking with aromatic amino acid residues of the receptor.

• Heteroaromatic rings are **less** active compared to phenyl-substituted analogs.

• Electronegative ***substituents*** on ring A (e.g., halogen or nitro) at the ***7-position*** markedly increases functional anxiolytic activity. For Sedative-hypnotic action it is a ***7- chloro***.

• Positions 6,8,9 should not be substituted..

Ring B:



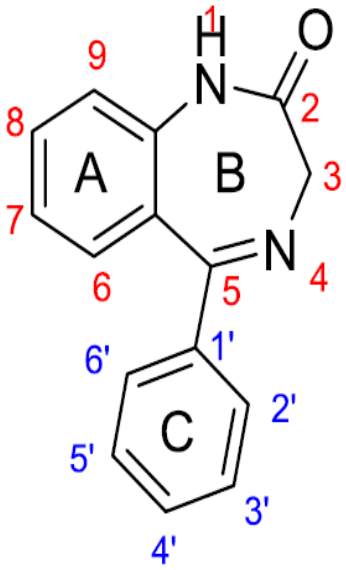
- Substituents at ***N1*** that are bulky reduce the activity while linear long chain do not much reduce the activity.
- A ***HBA*** group is a structural requirement for interactions with a histidine residue in the $GABA_A$ α1 subunit. optimal affinity occurs when it is on the ***2-position*** (i.e., the carbonyl moiety) and ***coplanar*** with the aromatic ring A.

Substitution of ***sulfur*** for oxygen at the 2-position may affect selectivity for binding to GABA BZR subpopulations, but anxiolytic activity is maintained.

• Derivatives substituted with a ***3-hydroxy*** moiety have comparable potency to nonhydroxylated analogs and are excreted faster.

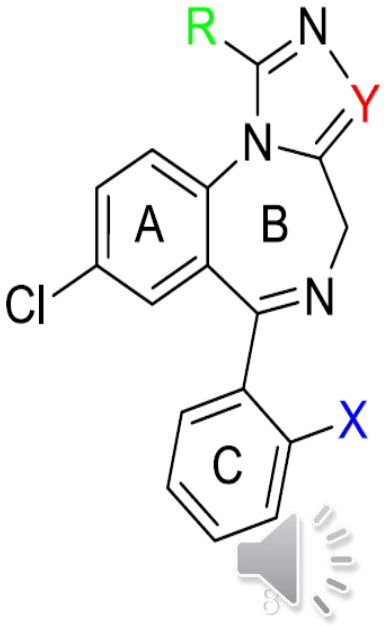
• Neither the ***4,5-double*** bond nor the ***4-position nitrogen*** in ring B is required for in vivo anxiolytic activity ?.

Ring C:



- The 5-phenyl ring C is required for in vivo agonism. It may contribute ***favorable hydrophobic*** or ***steric*** interactions to receptor binding, however, its relationship to ring A planarity may be important.
- If the phenyl group is ortho or diortho substituted with electron-attracting substituents, activity is increased. While Para substitution decreases activity greatly.

Ring fusion:



• Annelating the 1,2-bond of ring B with an additional "electron-rich" (i.e., proton acceptor) ring, such as ***triazole or imidazole***, also results in pharmacologically active benzodiazepine derivatives with high affinity for the BZR.

• Triazolam and Estazolam used as Sedative-hypnotics considered ***triazolo*** derivatives.

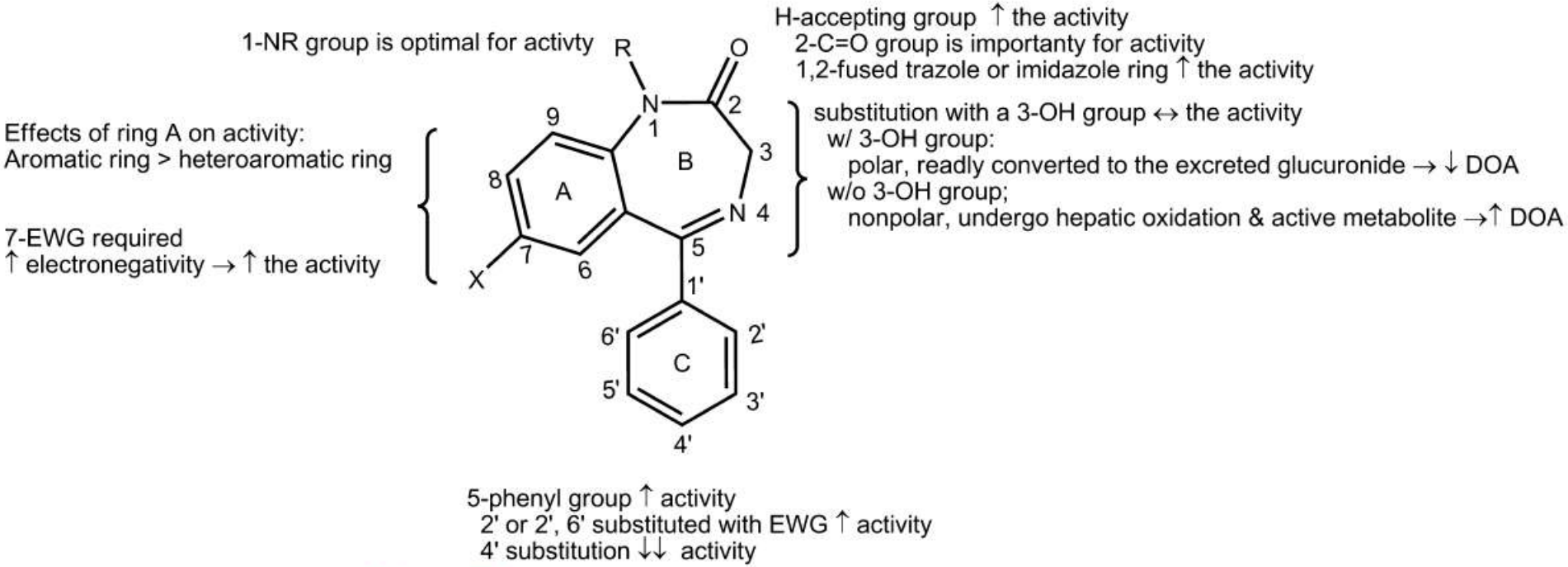


Figure 12.1 ● General structure and SAR of benzodiazepines.

Types of benzodiazepines

Based on drug elimination (metabolism + kidney filtration), 3 categories of benzodiazepines exist

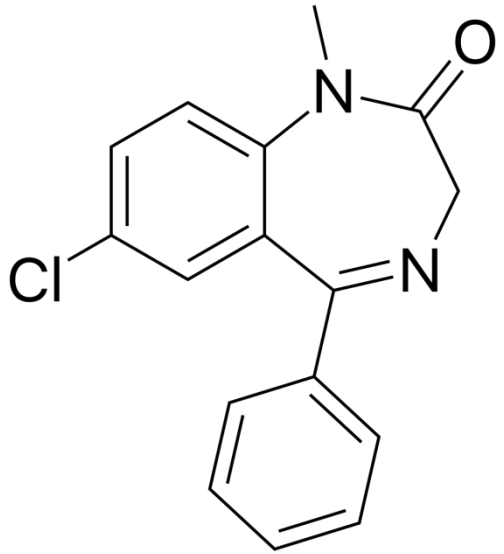
	Half life	example
Long acting	>24 hrs	Diazepam,Nitrazepam chlordiazepoxide, flurazepam
Intermediate acting	12-24 hrs	alprazolam, lorazepam clonazepam, flunitrazepam،
Short acting	< 12 hrs	midazolam and triazolam.

longer-acting benzodiazepines are recommended for the treatment of anxiety

Short- and intermediate-acting are preferred for the treatment of insomnia

Diazepam

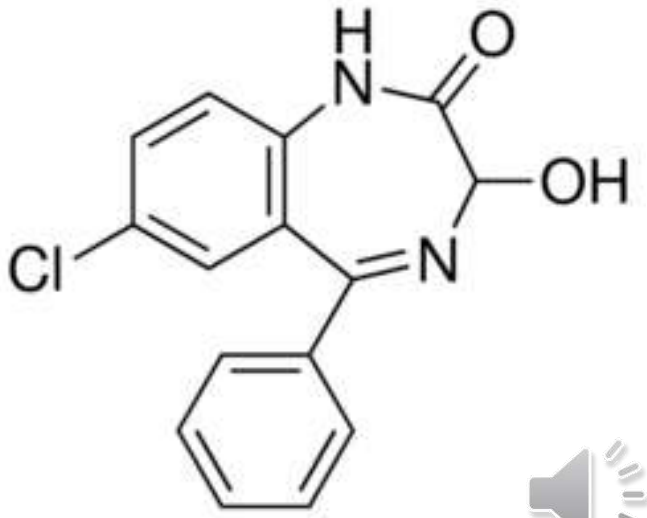
- Rapidly absorbed.
- It is widely used for several anti anxiety states and has an additional wide range of uses e.g. anticonvulsant, premedication in anesthesiology, and various spastic disorders.



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

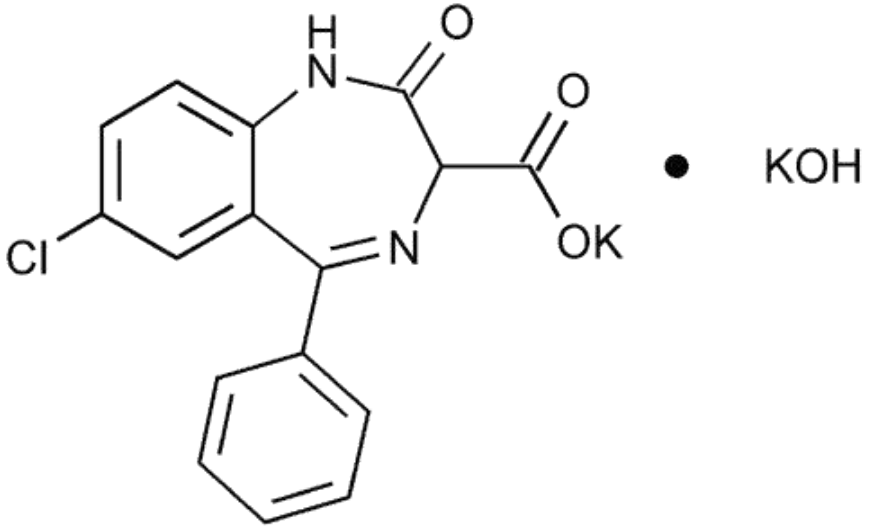
Oxazepam

- A prototype of the 3-hydroxy compounds much more polar than diazepam.
- Short duration of action.



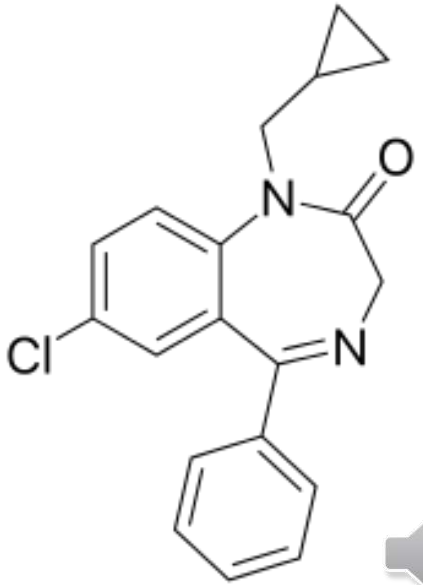
Clorazepate Dipotassium

- Can be considered a prodrug. it undergoes rapid loss of water and decarboxylation to nordazepam, which has a long half life and undergoes hepatic conversion to oxazepam.



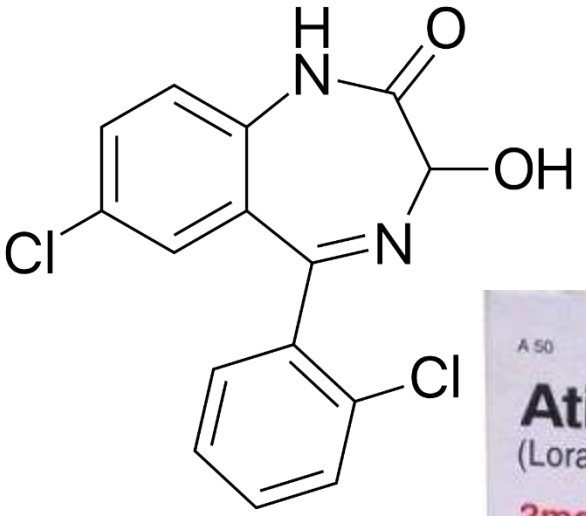
Prazepam

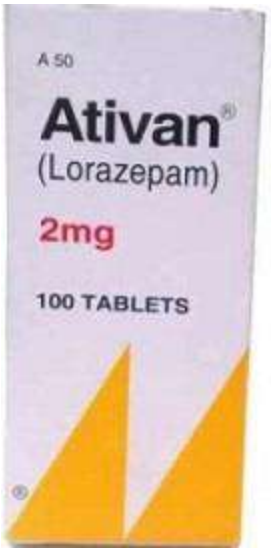
- Extensive N-dealkylation occurs to yield nordazepam.
- Overall long half life.



Lorazepam

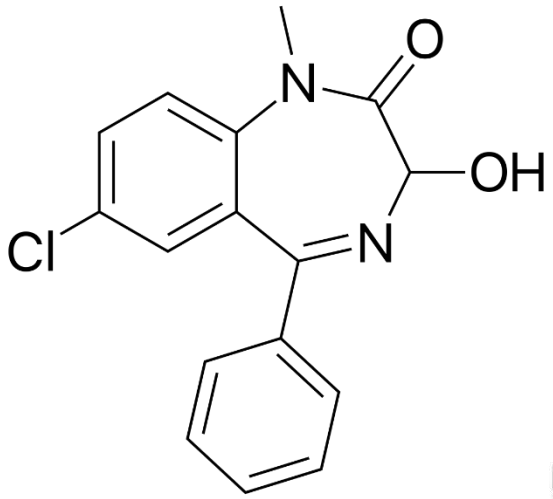
- 2’ –chloro substituted analouge of oxazepam but more active.
- Metabolism is rapid.





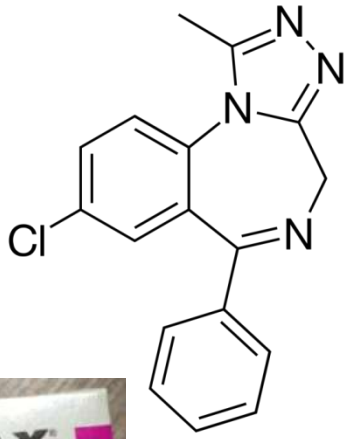
Temazepam

- The duration of action is short.
- Marketed as a hypnotic with little or no residual effects.



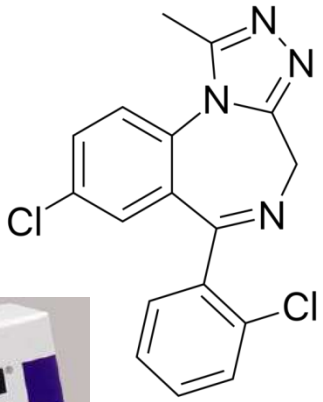
Alprazolam

- Rapidly absorbed.
- Short duration of action (oxidation of the methyl group to methyl alcohol).
- Highly potent as anxiolytic on a milligram basis.



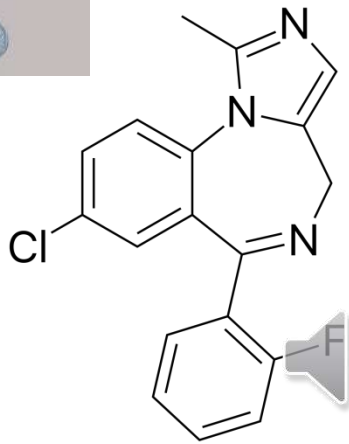
Triazolam

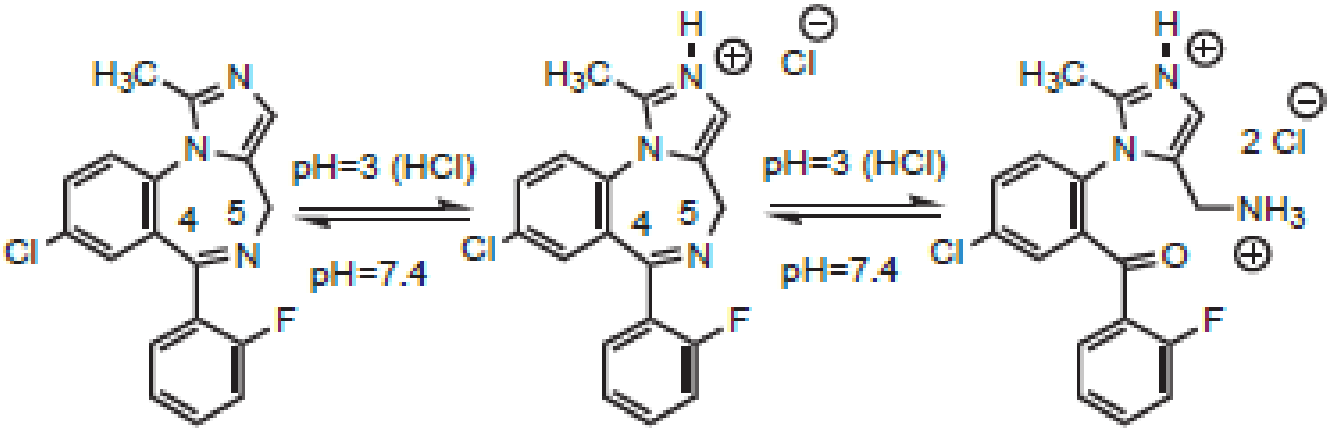
- It is marketed as sedative-hypnotic drug said to produce little, if any, daytime impairment of function.
- Short duration of action.



Midazolam

- Potent full agonist used I.V. as a sedative-hypnotic and induce anesthesia .





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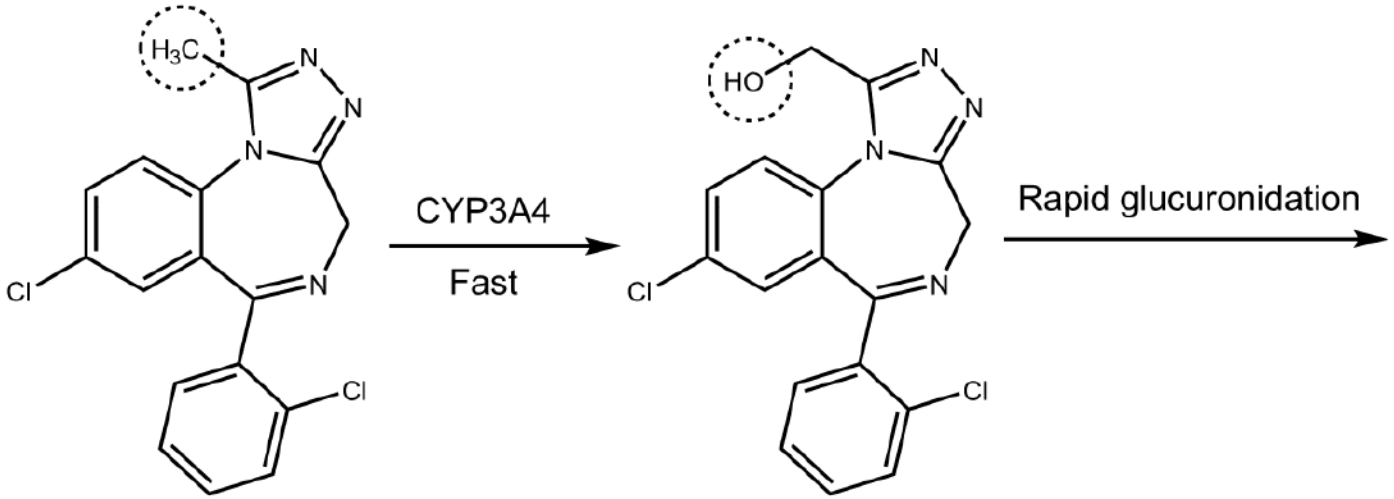

Triazolam
Fast metabolism
$t_{1/2}$ = ~ 4 h
short-acting
Less daytime sedation

An α-hydroxylated metabolite
Eliminated as *O*-glucuronides

Barbiturates vs Benzodiazepines

Barbiturates	Benzodiazepines
They cause high physiological and psychological dependence	They cause very less physiological and psychological dependence
Long term use avoided due to toxicity	Long term use is relatively safe
Sleep induced by it causes hangover effect after waking up	Sleep induced by it is just like natural sleep and is refreshing to wake up
Increase duration of GABA Cl channel opening	Increase frequency of GABA Cl channel opening
High Respiratory depression	Manageable Respiratory depression

Al-Azhar University-Gaza

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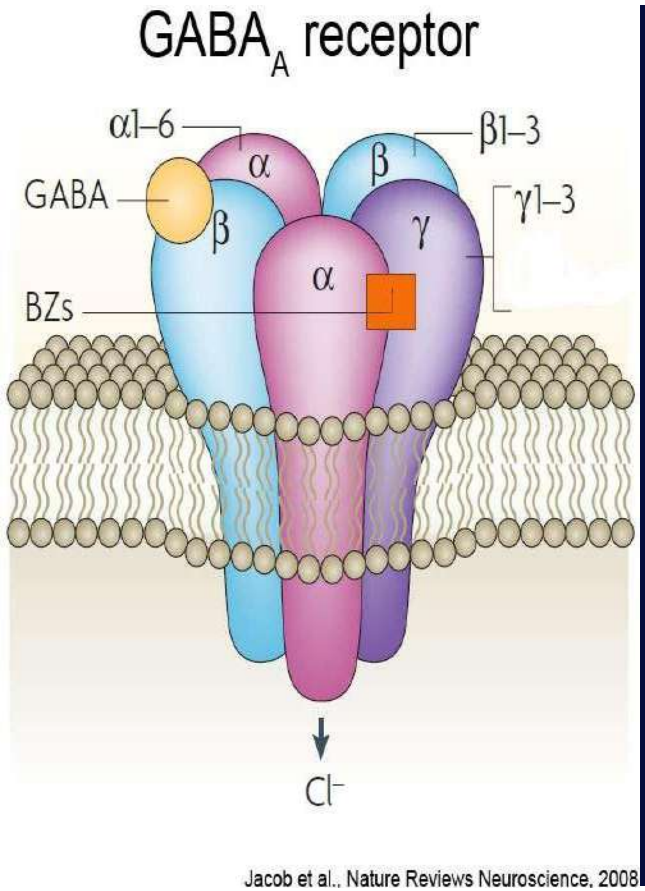
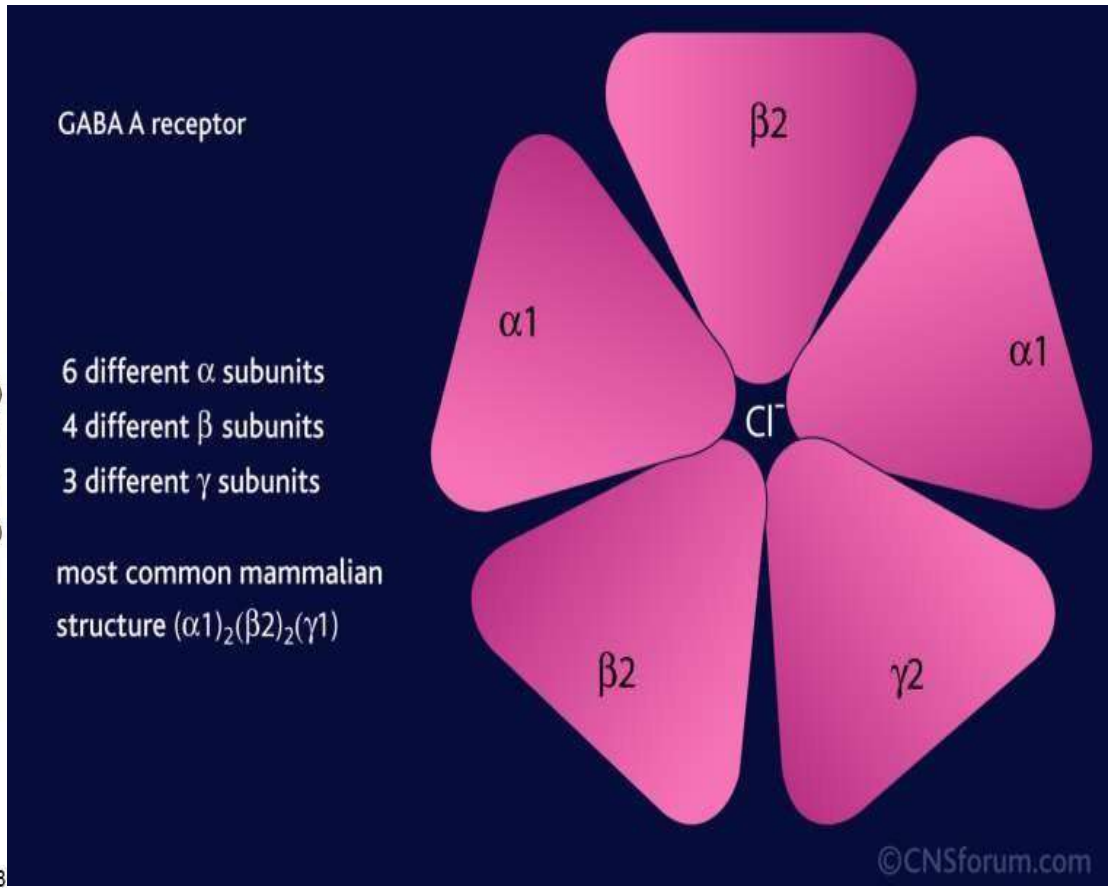
Nonbenzodiazepine $GABA_A$ Agonists

Different alpha units of $GABA_A$ have different effects

GABA A receptors containing alpha 1 subunits are involved in sleep.

GABA A receptors containing alpha 2 or alpha 3 subunits are involved in anxiety.





$GABA_A$ Alpha 1 Selective Hypnotics

- The $GABA_A$ receptor contain 6 different alpha subunits
- Benzodiazepines bind to four of $GABA_A$ 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.
- The hypnotics **zaleplon** and **zolpidem** bind selectively to GABA-A receptors that contain the **alpha 1 subunit (sleep**)

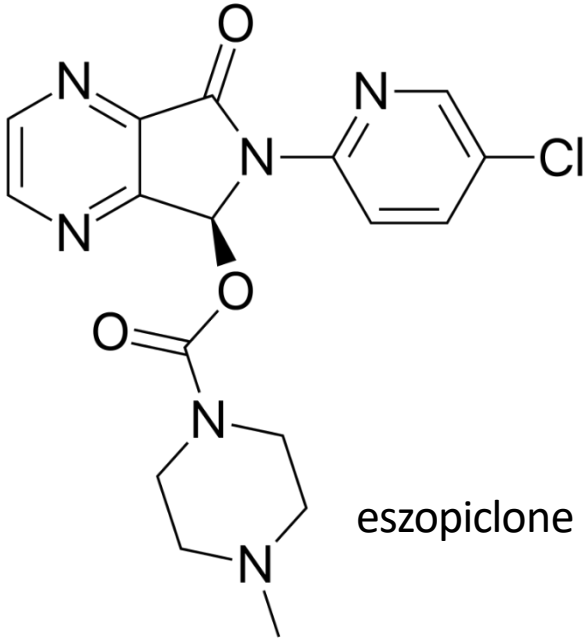
Nonbenzodiazepine Agonists at the Benzodiazepine Receptor

Z-Drugs

Advantages over benzodiazepines

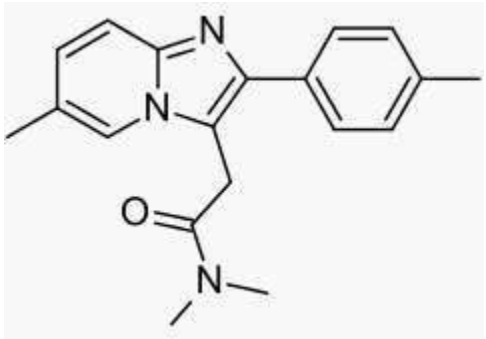
- A relatively short half life so one does not wake up with a "hangover" the following day
- Having little effect on sleep staging, allowing the individual to obtain approximately the same amount of time in each stage of sleep as one would without the medications
- Less likely to cause addiction, withdrawal, or tolerance relative to older sleeping medications.

- These drugs are very lipophilic which increases absorption into brain
- They are metabolized by liver into water soluble metabolites which is rapidly cleared out in urine and thus avoid accumulation



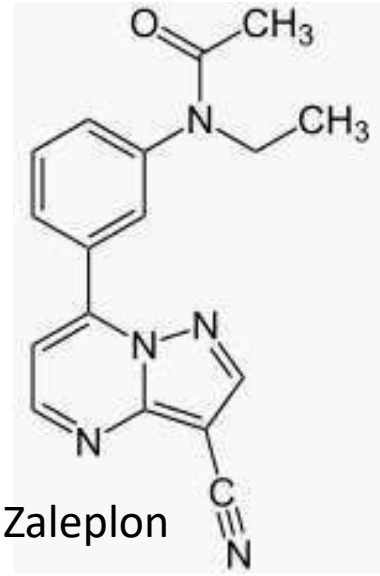
eszopiclone

Cyclopyrolone



Zolpidem

Imidazopyridine



Zaleplon

pyrazolopyrimidine

S-enantiomer (eszopiclone) has **50 fold greater** binding affinity than R-enantiomer .

- S-enantiomer is safer to be used (less hangover).

Zolpidem SAR

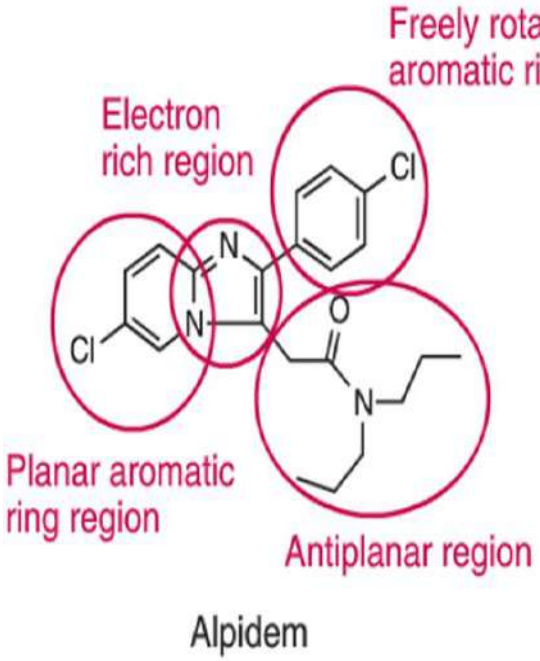
•Zolpidem is α1-selective imidazopyridine derivative.

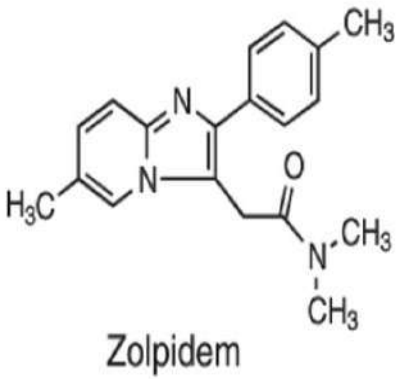
•Alpidem is non α1-selective (anxiolytic used as a reference for zolpidem SAR).

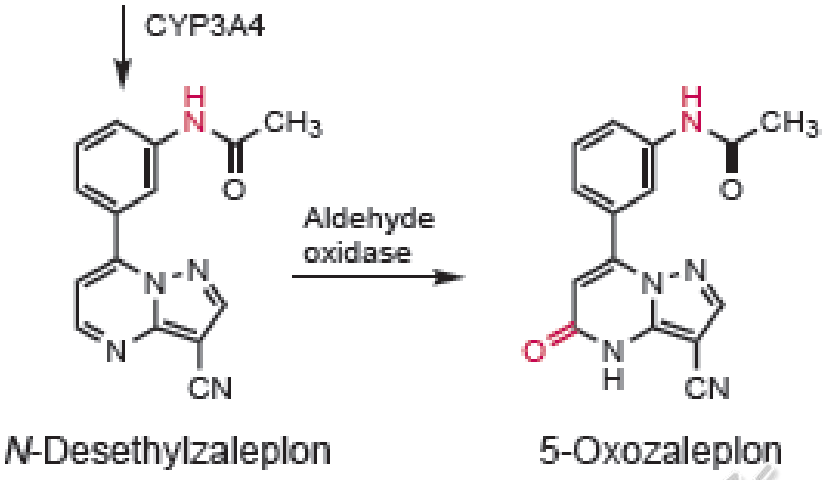
•Nitrogens of imidazole are essential as H-bond acceptors, can not be changed into H-bond donors (results in loss of selectivity on α1-receptor).

•Replacements of Cl by CH_3 leads to selectivity on α1-receptor.

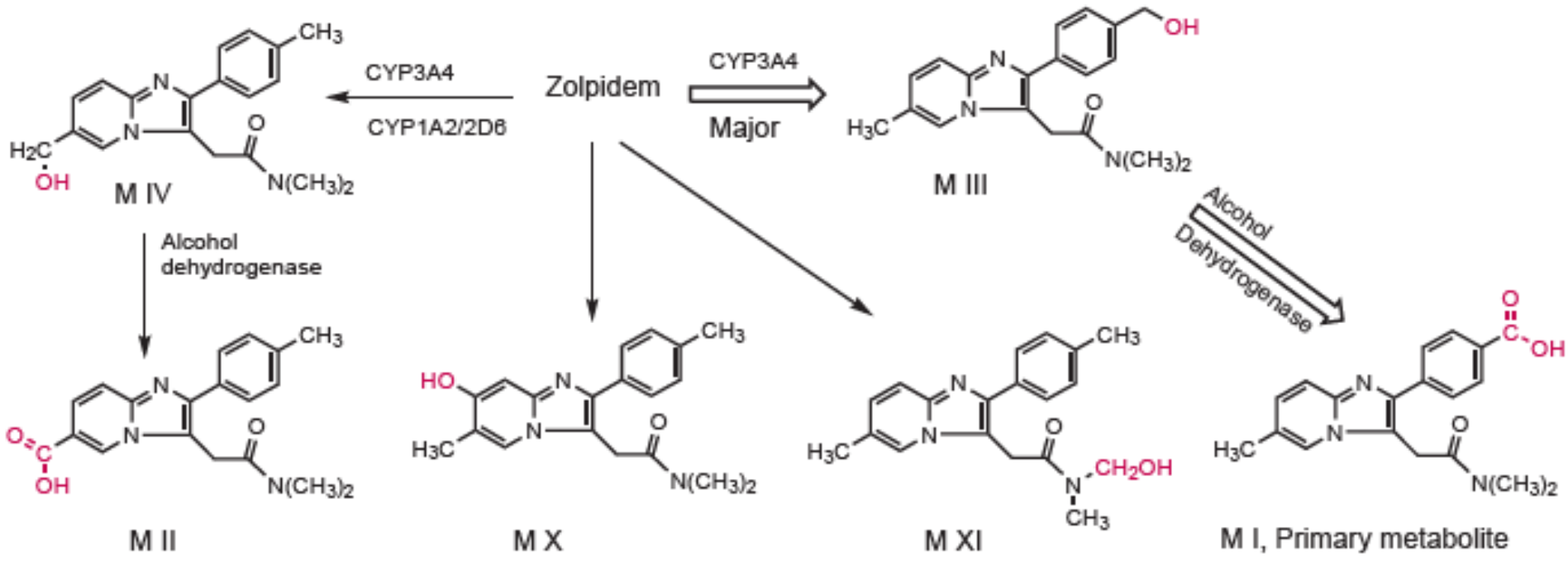
•Bulkier alkyl groups on the amide results in loss of selectivity.





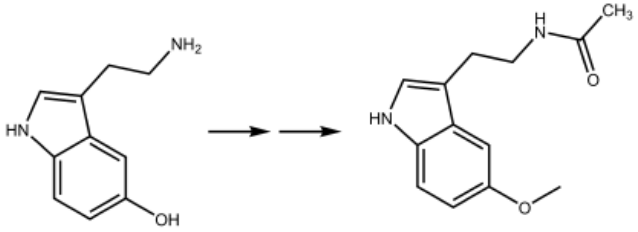


Zolpidem Metabolism



2-Melatonin Receptor Agonists

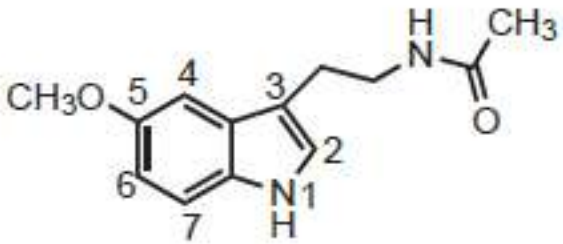
- Melatonin is a neurohormone that is primarily synthesized in the pineal gland from its precursor serotonin.
- The sleep-promoting and circadian effects of melatonin are due to agonism of both MT1 and MT2 receptors.
- Ramelteon, is a sleep agent medication that selectively binds to the MT1 and MT2 receptors in the suprachiasmatic nucleus (SCN), instead of binding to GABAA receptors, such as with drugs like zolpidem.
- It appears to speed the onset of sleep and alter the total amount of sleep a person gets. It is approved by the US Food and Drug Administration (FDA) for long-term use.



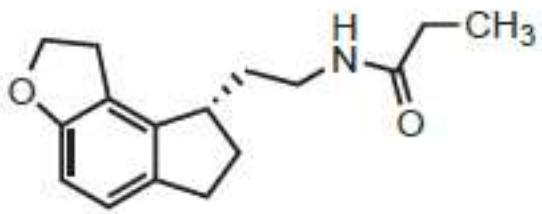
Serotonin
Precursor of melatonin

Melatonin
An endogenous
sleeping neurohormone

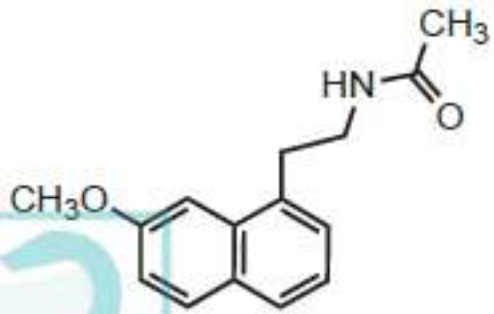
Ramelteon (Rozerem)
A marketed drug



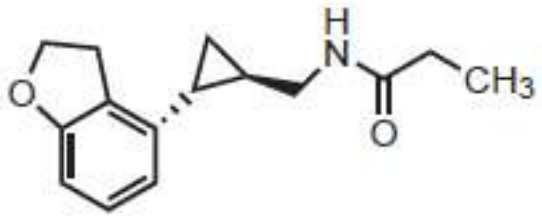
Melatonin



(*S*)-Ramelteon



Agomelatine

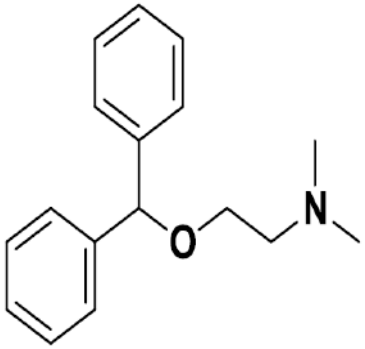


Tasimelteon

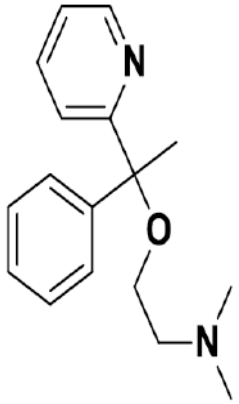
Agomelatine is an atypical antidepressant used to treat major depressive disorder

3 Histamine H_1 receptor antagonists

- The first generation of ethanolamine ether histamine H_1 receptor antagonists that cross BBB are used as sedative-hypnotics. ***Diphenhydramine*** and ***Doxylamine***.
- They are considered OTC sedatives.
- Their use associated with nest day drowsiness, tolerance and low cognition.



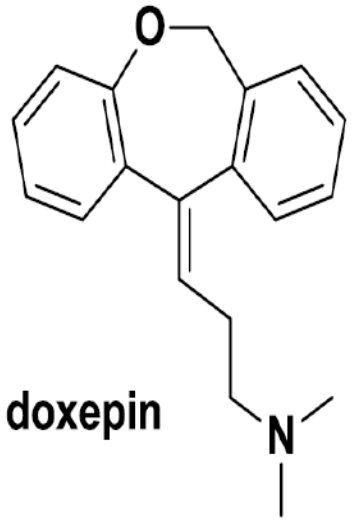
Diphenhydramine



Doxylamine

Doxepin

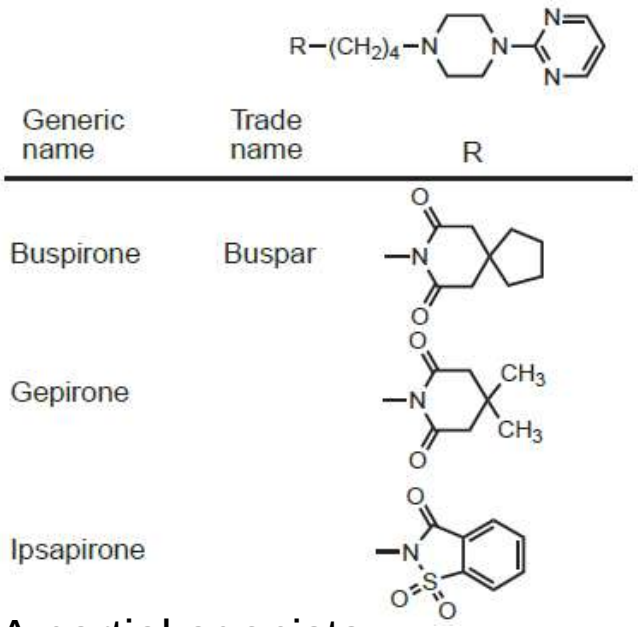
Tricyclic antidepressant

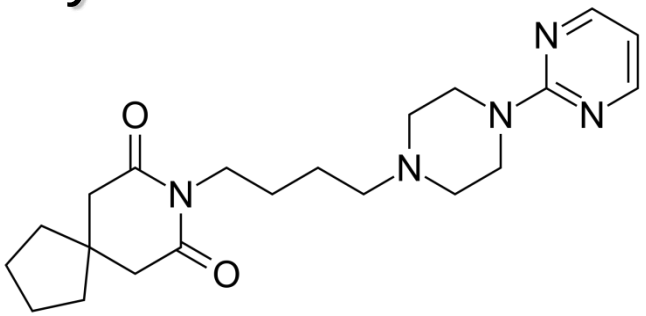


- Used as hypnotic at lower doses than those for depression
- Acts as H_1 histamine receptor antagonist in the hypthalamus

Miscellaneous Anxiolytic Agents
5HT-1A Agonists and partial agonists

- **Azapirones (pyrimidinylbutylpiperazines)**
- **Buspirone**
- Anxiolytic and antidepressant .
- It acts as a partial agonist of serotonin at 5-HT1A receptors. Has anti-dopaminergic activity.





Azapirone-type 5-HT1A partial agonists.

Pharmacokinetic Properties and Clinical Uses of Sedative-Hypnotic and Anxiolytic Drugs

Drug	Onset of Action*	Duration of Action*	Active Metabolites	Major Clinical Uses
Benzodiazepines				
Alprazolam	Fast	Medium	Yes	Anxiety, including panic disorder
Chlordiazepoxide	Fast; very fast (IV)	Long	Yes	Alcohol detoxification; anxiety
Clonazepam	Fast	Medium	No	Anxiety, including panic disorder; seizure disorders
Diazepam	Fast; very fast (IV)	Long	Yes	Alcohol detoxification; anxiety; muscle spasm; seizure disorders; spasticity
Estazolam	Fast	Medium	Yes	Insomnia
Flurazepam	Fast	Long	Yes	Insomnia
Lorazepam	Fast; very fast (IV)	Medium	No	Anxiety; seizure disorders
Midazolam	Very fast (IV)	Short (IV)	Yes	Anesthesia
Oxazepam	Fast	Short	No	Anxiety
Temazepam	Fast	Medium	No	Insomnia
Triazolam	Fast	Short	Yes	Insomnia
Barbiturates				
Amobarbital	Fast	Medium	No	Insomnia
Pentobarbital	Fast	Short	No	Insomnia
Phenobarbital	Slow	Long	No	Seizure disorders
Thiopental	Very fast (IV)	Short (IV)	No	Induction of anesthesia
Antihistamines				
Diphenhydramine	Fast	Medium	No	Insomnia
Hydroxyzine	Fast	Long	No	Anxiety; sedation
Other sedative-hypnotic drugs				
Zolpidem	Fast	Short	No	Insomnia
Zaleplon	Fast	Very short	No	Insomnia; mid-sleep awakenings
Eszopiclone	Fast	Short	No	Insomnia
Ramelteon	Slow	Short	Yes	Sleep-onset insomnia
Nonsedating Anxiolytic Drugs				
Buspirone	Very slow	Long	No	Chronic anxiety
Propranolol	Fast	Medium	Yes	Situational or performance anxiety

*Unless onset and duration of action are specifically indicated for intravenous (IV) administration, they are for oral administration. Very fast = <15 minutes; fast = 15–59 minutes; slow = 1–4 hours; very slow = 3–4 weeks; short = 1–6 hours; medium = 7–12 hours; and long = >12 hours.