Unit-4
Medicinal Chemistry-I

B.Pharma 4th Sem Notes

Unit: 4

Drugs acting on Central Nervous System

1. Sedatives and Hypnotics

Benzodiazepines:

- SAR of Benzodiazepines, Chlordiazepoxide, Diazepam*, Oxazepam, Chlorazepate, Lorazepam, Alprazolam, Zolpidem

Barbiturtes:

- SAR of barbiturates, Barbital*, Phenobarbital, Mephobarbital, Amobarbital, Butabarbital, Pentobarbital, Secobarbital

Miscelleneous:

- Amides & imides: Glutethmide.
- Alcohol & their carbamate derivatives: Meprobomate, Ethchlorvynol.
- Aldehyde & their derivatives: Triclofos sodium, Paraldehyde.

2. Antipsychotics
Phenothiazeines:

- SAR of Phenothiazeines – Promazine hydrochloride, Chlorpromazine hydrochloride*,
- Triflupromazine, Thioridazine hydrochloride, Piperacetazine hydrochloride,
- Prochlorperazine maleate, Trifluoperazine hydrochloride.

Ring Analogues of Phenothiazeines:

- Chlorprothixene, Thiothixene, Loxapine succinate, Clozapine.
- **Fluro buterophenones:** Haloperidol, Droperidol, Risperidone.

Beta amino ketones: Molindone hydrochloride.

Benzamides: Sulpieride.

3. Anticonvulsants:

SAR of Anticonvulsants, mechanism of anticonvulsant action

- **Barbiturates:** Phenobarbitone, Methabarbital.
- **Hydantoins:** Phenytoin*, Mephenytoin, Ethotoin
- **Oxazolidine diones:** Trimethadione, Paramethadione
- **Succinimides:** Phensuximide, Methsuximide, Ethosuximide*
- **Urea and monoacylureas:** Phenacemide, Carbamazepine*
- **Benzodiazepines:** Clonazepam
- **Miscellaneous:** Primidone, Valproic acid , Gabapentin, Felbamate

1. Sedatives and Hypnotics

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- Aldehyde & their derivatives: Triclofos sodium, Paraldehyde.

1. Sedatives and Hypnotics:

Sedatives and hypnotics are a class of drugs primarily used to induce sedation, reduce anxiety, promote relaxation, and facilitate sleep.

- **Sedative** refers to a substance that moderates activity and excitement while inducing a calming effect, while
- **Hypnotic** refers to a substance that causes drowsiness and facilitates the onset and maintenance of natural sleep.

Classification of Sedatives and Hypnotics:

Benzodiazepines:

- Chlordiazepoxide, Diazepam*, Oxazepam, Chlorazepate, Lorazepam, Alprazolam, Zolpidem

Barbiturtes:

- Barbital*, Phenobarbital, Mephobarbital, Amobarbital, Butabarbital, Pentobarbital, Secobarbital

Miscelleneous:

- **Amides & imides:** Glutethmide.
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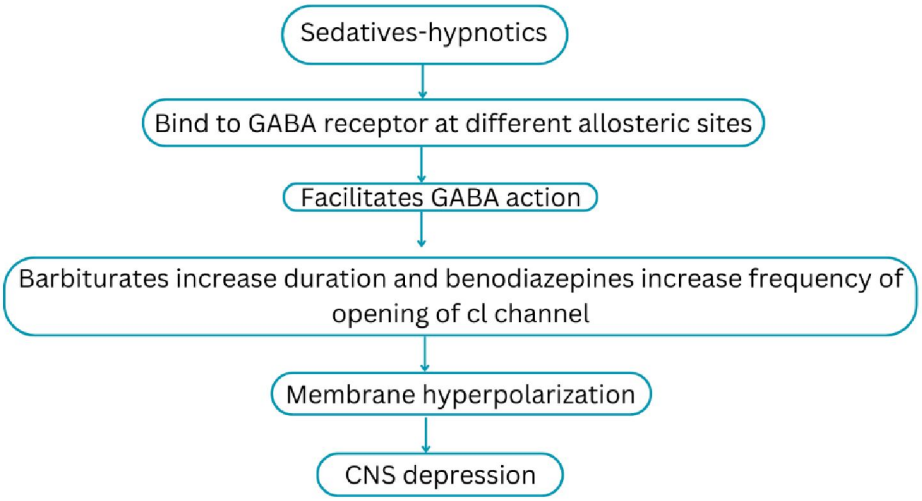
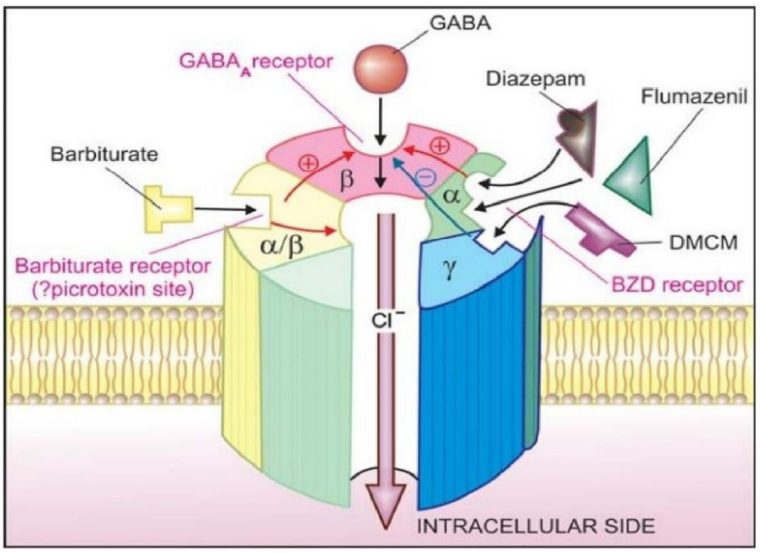
- **Aldehyde & their derivatives:** Triclofos sodium, Paraldehyde.

Mode of Action of Sedative and Hypnotics:

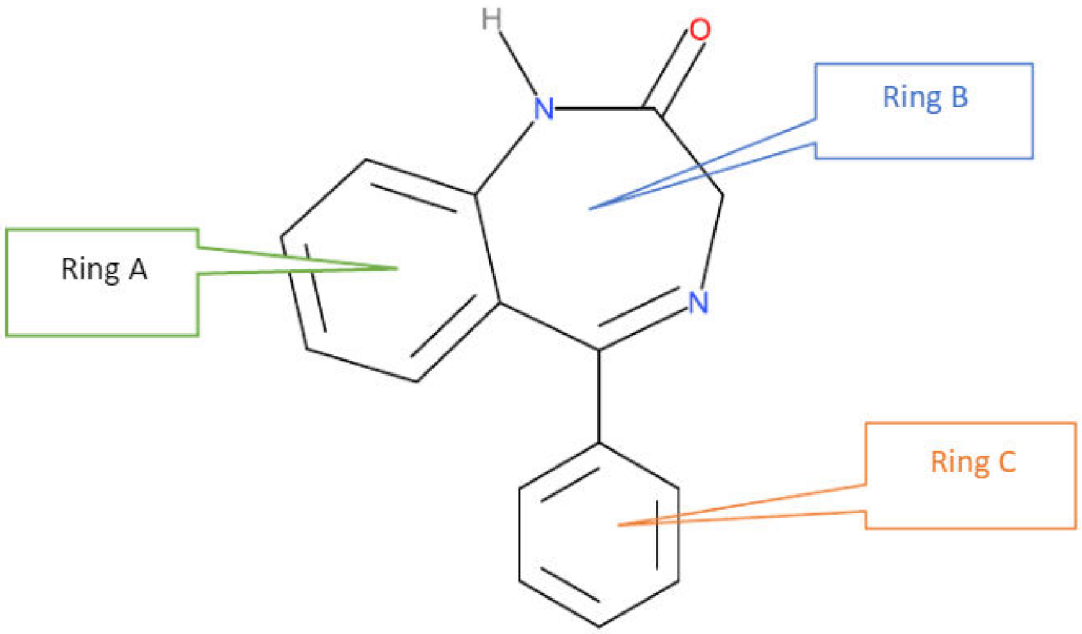




Benzodiazepines:

- Benzodiazepine is an sedative and hypnotic drugs, They work by enhancing the action of the neurotransmitter gamma-aminobutyric acid (GABA), which has calming effects on the brain. Common examples of benzodiazepines include Chlordiazepoxide, Diazepam*, Oxazepam, Chlorazepate, Lorazepam, Alprazolam, Zolpidem.

SAR of Benzodiazepines:



Ring A:

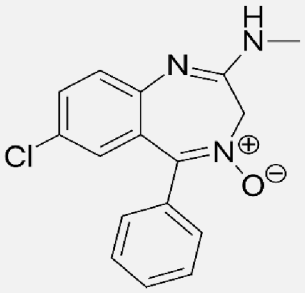
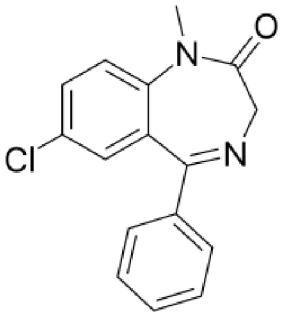
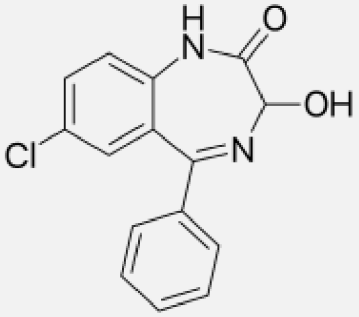
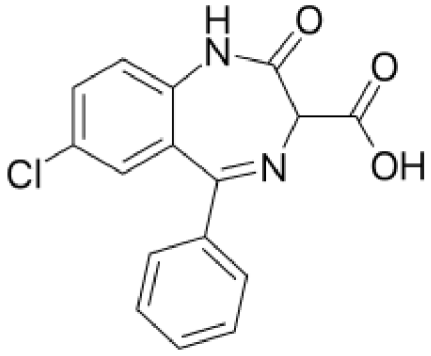
- In ring A at 7th position attachement of an electron withdrawing group like –cl, -Br, -No2 or CN will increase the activity eg: flurazepam.
- If we add any substitute at position 6th, 8th and 9th in ring A the activity decrease.

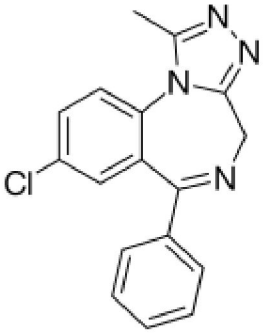
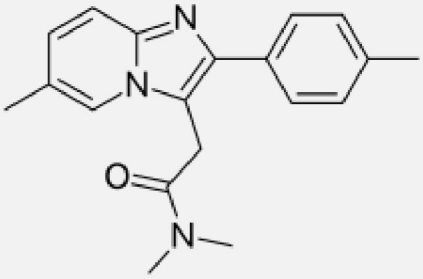
Ring B:

- In ring B substitution of alkyl group like –CH3 or –C2H5 at position 1st on Nitrogen will increase activity (essential) eg. Flurazepam.
- Carbonyl group present at position 2nd is essential and good for activity.
- Replacement of this carbonyl function with two hydrogen atom gives medazepam which is less effective (activity decrease)
- By replacing one of the hydrogen with OH group at position 3rd lowers the activity and facilitates elimination.
- Attachment of carbonyl group at position 3rd increase duration of action and form water soluble salts.
- At position 4th and 5th double bond is good for activity, saturation of this reduce potency decrease.

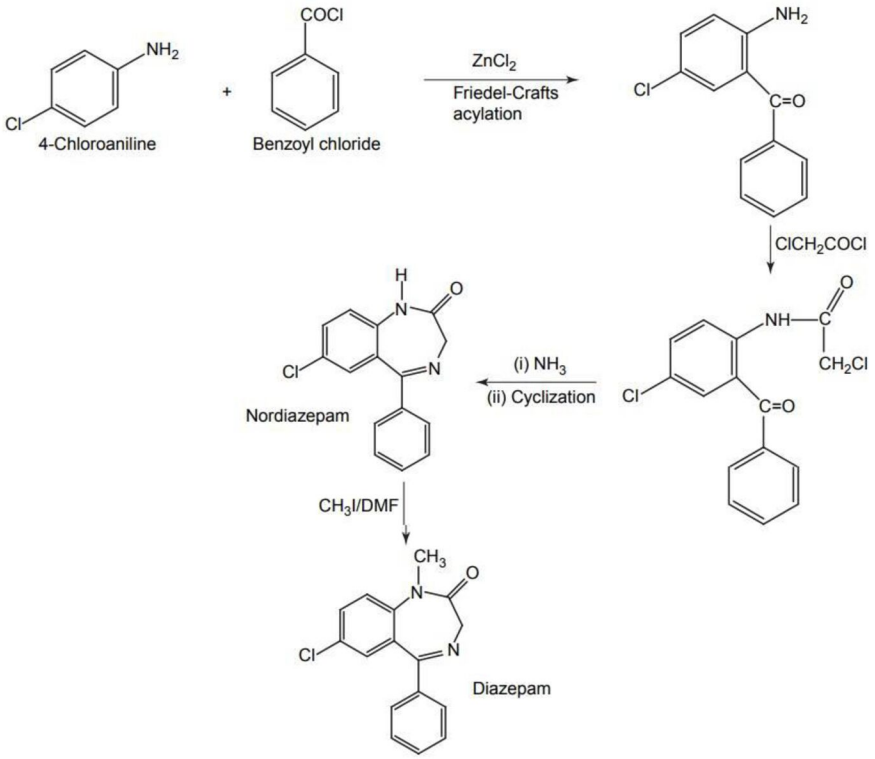
Ring C:

- Phenyl substitution at position is increase activity.
- Attachement of an electronegative substitution like –cl and –f at ortho and di-ortho position will increase activity.
- By replacing this benzene ring with aromatic heterocyclic ring (eg. pyrazole) increase anxiolytic properties eg. Ripazepam etc.

Drug	Uses	Mechanism of Action	Structure
Chlordiazepoxide	Anxiety, alcohol withdrawal	Enhances GABA neurotransmission	
Diazepam*	Anxiety, insomnia, seizures, muscle spasms	Enhances GABA neurotransmission	
Oxazepam	Anxiety	Enhances GABA neurotransmission	
Chlorazepate	Anxiety	Enhances GABA neurotransmission	

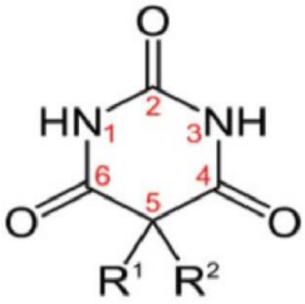
Lorazepam	Anxiety, seizures, status epilepticus	Enhances GABA neurotransmission	
Alprazolam	Anxiety, panic disorder	Enhances GABA neurotransmission	
Zolpidem	Insomnia	Modulates GABA receptors	

Diazepam Synthesis:

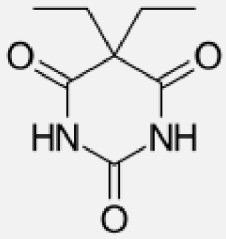
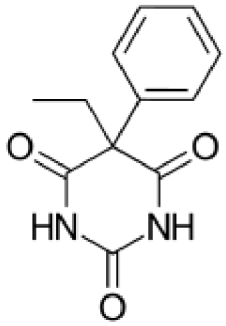


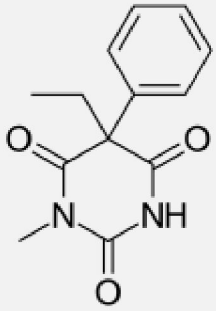
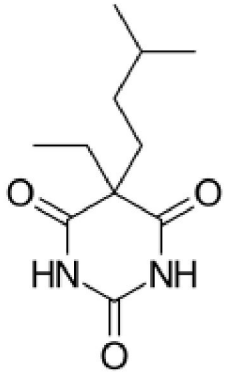
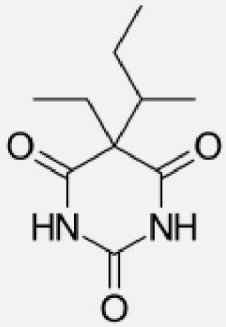
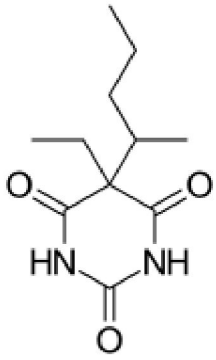
Barbiturtes:

SAR of barbiturates:



1. Both hydrogen atoms in position 5 of barbituric acid must be replaced for maximal activity.
2. Increasing the length of an alkyl chain in the 5 position enhances potency up to 5 or 6 carbon atoms.
3. Branched, cyclic or unsaturated in the 5 position generally produce a briefer duration of action than do normal saturated chains containing the same number of carbon atoms.
4. Compounds with alkyl groups in the 1 or 3 position may have a shorter onset & duration of action.
5. Replacement of oxygen by sulfur on the 2 carbon shortens onset & duration of action.

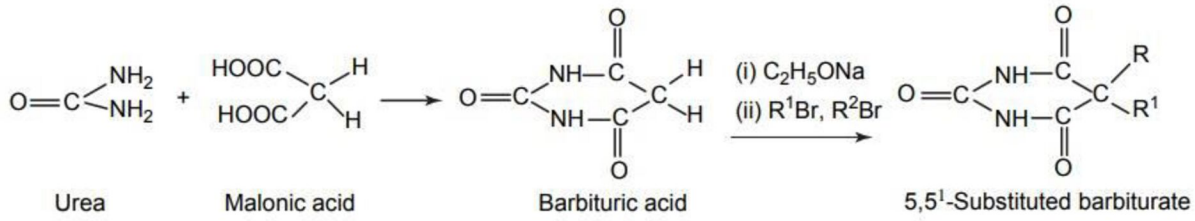
Drug	Primary Use(s)	Mechanism of Action	Structure
Barbital*	Sedative, Hypnotic (sleep medication)	Enhances GABA neurotransmission	
Phenobarbital	Epilepsy, seizures	Enhances GABA neurotransmission and stabilizes neuronal membranes	

Mephobarbital (Methylphenobarbital)	Epilepsy	Similar to Phenobarbital	
Amobarbital	Sedative, Hypnotic, Anxiety	Similar to Phenobarbital	
Butabarbital	Anxiety, Insomnia	Similar to Phenobarbital	
Pentobarbital	Hypnotic, Anesthesia	Similar to Phenobarbital	

Secobarbital	Hypnotic, Anesthesia	Similar to Phenobarbital	

Synthesis of Barbital:

From urea and malonic acid:



Miscelleneous:

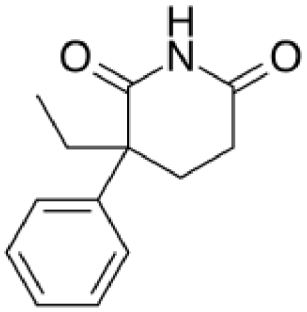
- Amides & imides: Glutethmide.
- Alcohol & their carbamate derivatives: Meprobomate, Ethchlorvynol.
- Aldehyde & their derivatives: Triclofos sodium, Paraldehyde.

Amides & imides:

- Heterocyclic compound which have amide linkage.

Glutethmide:

- **Glutethimide** was previously used as a **hypnotic sedative** to treat insomnia.



Uses:

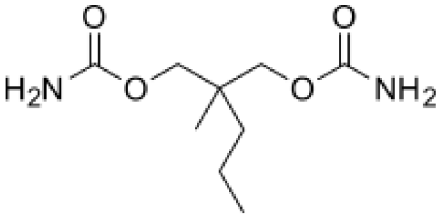
- Treatment of **insomnia**.

Mechanism of Action:

- The exact mechanism of action **enhancing the effects of the neurotransmitter GABA** in the brain. GABA has calming and sleep-promoting effects.

Alcohol & their carbamate derivatives:

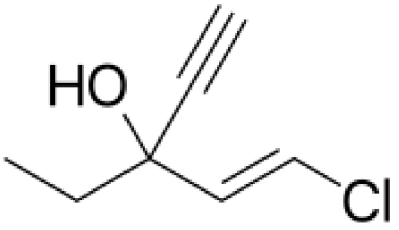
Meprobomate:



Use:

- Used as hypnotic, sedative, anti-anxiety, muscle relaxant and anticonvulsant.

Ethchlorvynol.

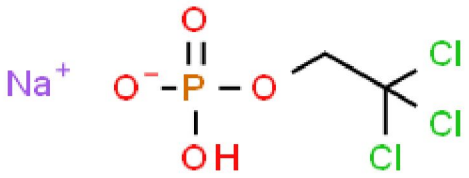


Uses:

- Ethchlorvynol is used to treat insomnia (trouble in sleeping).

Aldehyde & their derivatives:

Triclofos sodium:



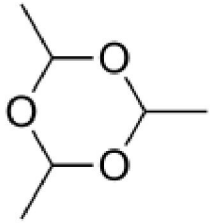
MoA:

- It rapidly hydrolysed to trichloroethanol which act on brain and produce sleep.

Uses:

- Used to treat insomnia

Paraldehyde:



Uses:

- Used to treat insomnia.
- Anticonvulsants.

2. Antipsychotics:

Phenothiazeines:

- SAR of Phenothiazeines – Promazine hydrochloride, Chlorpromazine hydrochloride*, Triflupromazine, Thioridazine hydrochloride, Piperacetazine hydrochloride, Prochlorperazine maleate, Trifluoperazine hydrochloride.

Ring Analogues of Phenothiazeines:

- Chlorprothixene, Thiothixene, Loxapine succinate, Clozapine.
- **Fluro buterophenones:** Haloperidol, Droperidol, Risperidone.

Beta amino ketones: Molindone hydrochloride.

Benzamides: Sulpieride.

Antipsychotics:

- Antipsychotics are psychiatric medications that are available by prescription to treat psychosis.
- Psychosis: A mental disorder characterized by a disconnection from reality.

Symptoms:

- Confusion
- Aggression
- Anxiety
- Hallucination

Antipsychotic drugs are not curative they do not eliminate this disorder they only decrease the symptoms and make person comfortable to function in a supportive environment.

Classification of Antipsychotics:

Phenothiazeines:

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Beta amino ketones: Molindone hydrochloride.

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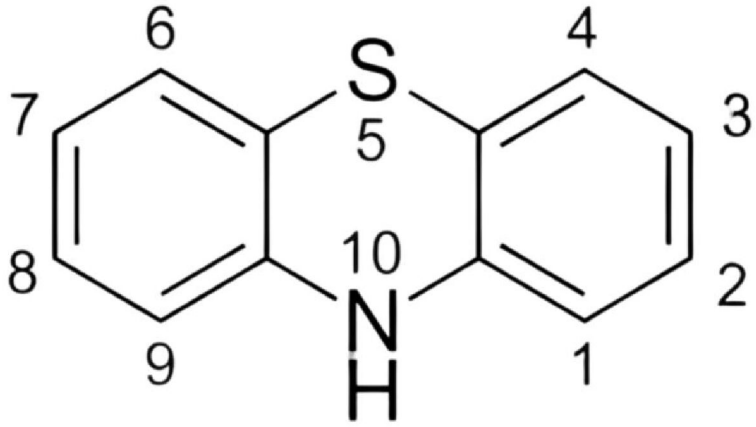
Phenothiazeines:

- These are used for treating severe mental and emotional disorder such as schizophrenia and other psychotic disorders.

SAR of Phenothiazeines:

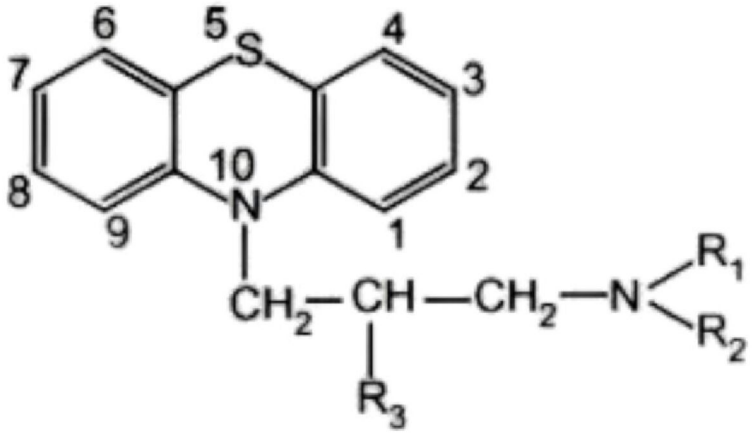


Structurally, substitution (modification) is possible on:-

Position 2nd – C-2

Position 10th – N-10

Unsubstituted phenothiazines has no activity so, substitution at C-2 and N-10 is essential for activity.



Also N and S is essential for activity.

Position 2nd:

At position 2nd addition of e- withdrawing group such as cl will increase the activity.

Activity increase in the following order at position 2nd.

$$OH<H<CH_3<C_2H_5CO<CH_3COCL<SCH_3<CL<Cf_3$$

Position 10th:

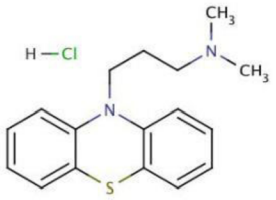
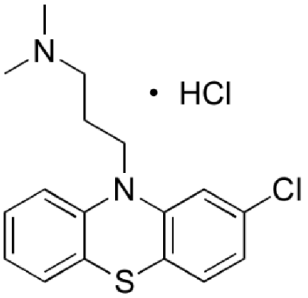
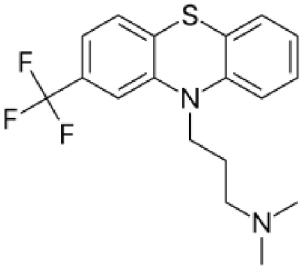
At position 10 aliphatic chain (terminal amino substituent) is essential for activity.

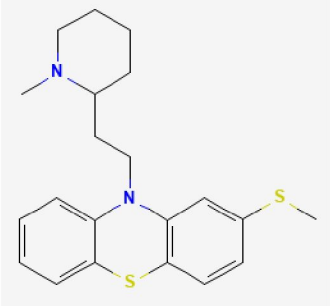
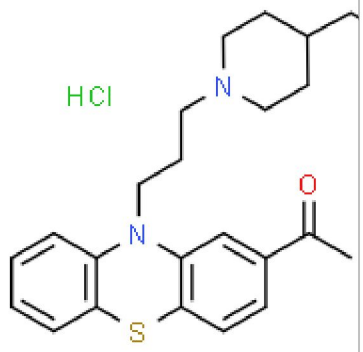
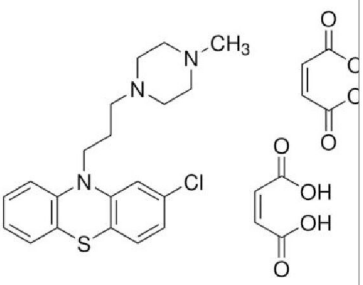
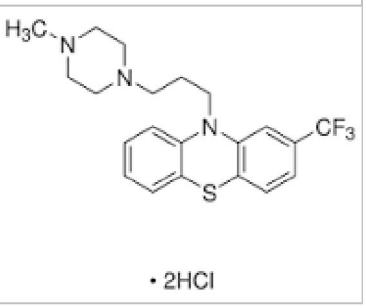
By branching the β-position of the side chain (aliphatic chain) with small methyl group, decrease in antipsychotic activity but increase in antihistamine activity.

There are three methylene unit i.e. $-CH_2-CH_2-CH_2-$. Reduction in these carbon number reduces the activity.

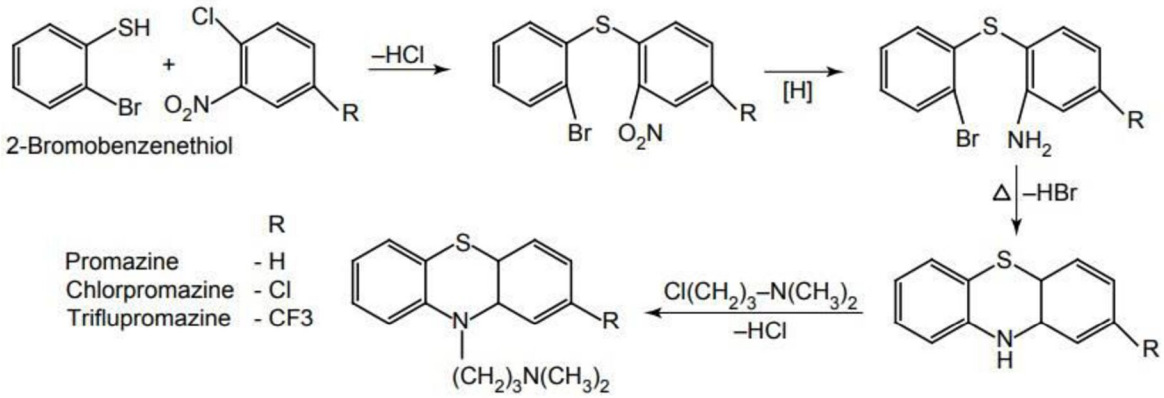
The 10th position>N-CH_2 can be replaced isosterically by ethylidene group to form various thioxanthenes (ring analogues). These are more potent than the parent drugs eg Chloroprothixene and thiothixene etc.

If we increase the chain length at "N" on aliphatic chain (at last), then Lipophilicity ↑ and their duration of action increase.

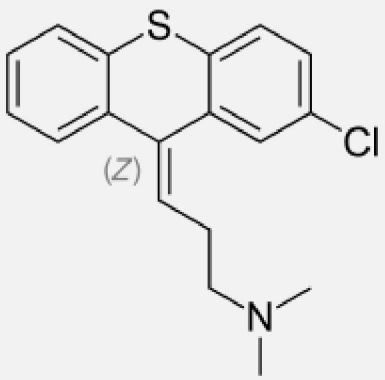
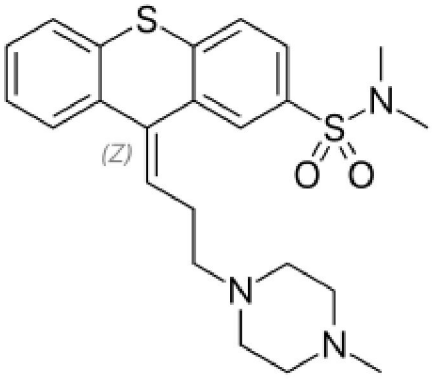
Drug	Uses	Mechanism of Action	Structure
Promazine hydrochloride	Schizophrenia, Psychosis	Blocks dopamine and other neurotransmitters in the brain	
Chlorpromazine hydrochloride*	Schizophrenia, Psychosis	Blocks dopamine and other neurotransmitters in the brain	
Triflupromazine	Schizophrenia, Psychosis	Blocks dopamine and other neurotransmitters in the brain	

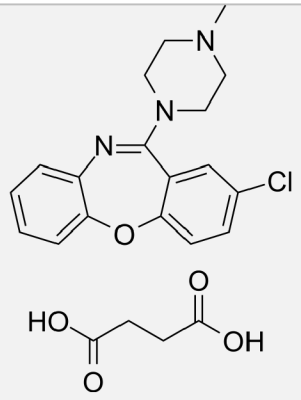
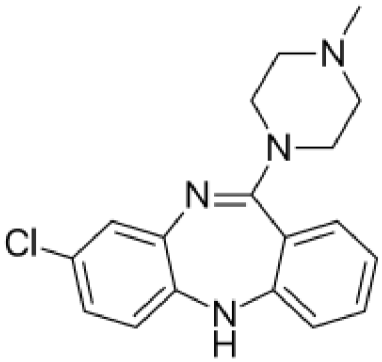
Thioridazine hydrochloride	Schizophrenia, Psychosis	Blocks dopamine and other neurotransmitters in brain	
Piperacetazine hydrochloride	Schizophrenia, Psychosis	Blocks dopamine and other neurotransmitters in the brain	
Prochlorperazine maleate	Nausea and vomiting	Primarily blocks dopamine receptors in a different brain region than for psychosis	
Trifluoperazine hydrochloride	Schizophrenia, Psychosis	Blocks dopamine and other neurotransmitters in the brain	

Synthesis of Chlorpromazine hydrochloride:

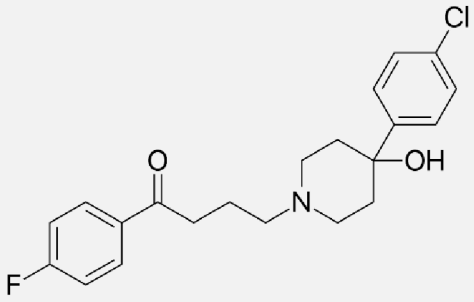
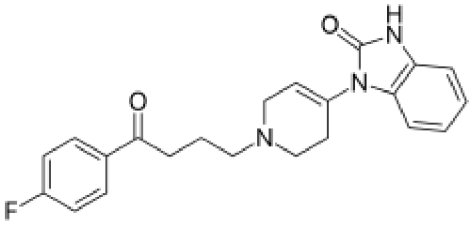


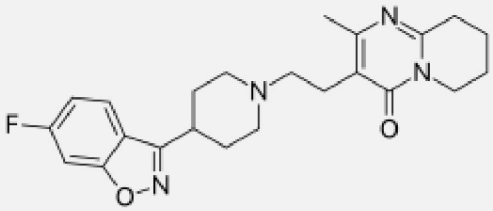
Ring Analogues of Phenothiazeines:

Drug	Primary Use(s)	Mechanism of Action	Structure
Chlorprothixene	Schizophrenia, Psychosis	Blocks dopamine and other neurotransmitters in the brain	
Thiothixene	Schizophrenia, Psychosis	Blocks dopamine and other neurotransmitters in the brain	

Loxapine succinate	Schizophrenia, Psychosis, Agitation	Blocks dopamine and other neurotransmitters in the brain	
Clozapine	Schizophrenia, Treatment-resistant Schizophrenia	Blocks dopamine and other neurotransmitters in the brain, with unique effects on serotonin	

Fluro buterophenones: Haloperidol, Droperidol, Risperidone.

Drug	Primary Use(s)	Mechanism of Action	Structure
Haloperidol	Schizophrenia, Tourette Syndrome, Tardive Dyskinesia, Psychosis	Primarily blocks dopamine D2 receptors in the brain	
Droperidol	Nausea and vomiting (postoperative)	Primarily blocks dopamine D2 receptors in the brain, with additional effects	

		on serotonin receptors	
Risperidone	Schizophrenia, Schizoaffective Disorder, Bipolar Disorder	Blocks dopamine D2 receptors and serotonin 5-HT2A receptors in the brain	

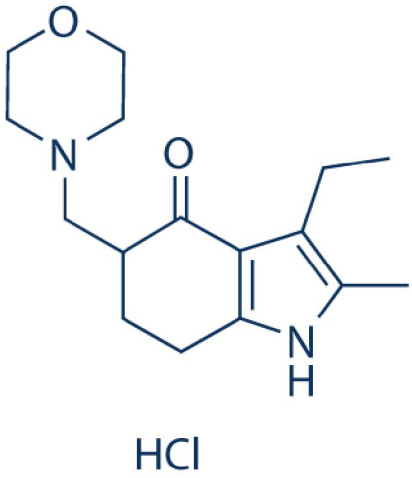
Beta amino ketones:

Molindone hydrochloride:

MOA: Blocks dopamine D2

Uses: Schizophrenia, Schizoaffective Disorder, Bipolar Disorder

Structure:

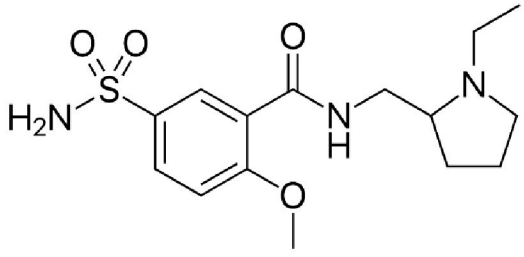


HCl

Benzamides:

Sulpieride.

Use: Used in Schizophrenia



3. Anticonvulsants:

SAR of Anticonvulsants, mechanism of anticonvulsant action

- **Barbiturates:** Phenobarbitone, Methabarbital.
- **Hydantoins:** Phenytoin*, Mephenytoin, Ethotoin
- **Oxazolidine diones:** Trimethadione, Paramethadione
- **Succinimides:** Phensuximide, Methsuximide, Ethosuximide*
- **Urea and monoacylureas:** Phenacemide, Carbamazepine*
- **Benzodiazepines:** Clonazepam
- **Miscellaneous:** Primidone, Valproic acid , Gabapentin, Felbamate

Anticonvulsants:

- Anticonvulsants, also known as antiepileptic drugs (AEDs) or antiseizure medications, are a diverse group of medications used to treat and prevent seizures.
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Classification of Anticonvulsants:

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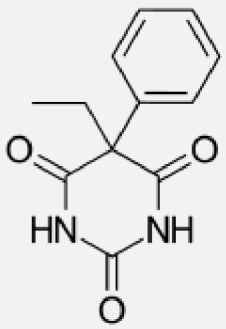
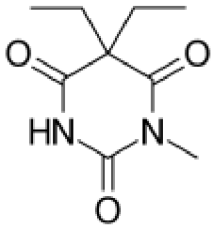
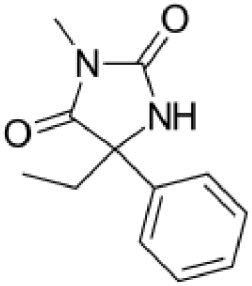
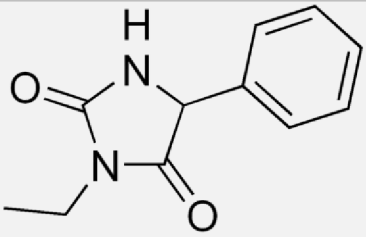
Barbiturates: Phenobarbitone, Methabarbital

Drug	Use	Mechanism of Action	Structure
Phenobarbital	• **Partial seizures (less preferred due to side effects)** • **Generalized tonic-clonic seizures (grand mal seizures)** • **Febrile seizures (in children)** • **Status epilepticus**	**It block Na^+ channel or increase the GABA function.**	

Metharbital	**- Primarily used for myoclonic seizures and absence seizures (petit mal seizures)**	**Binds to the voltage-gated sodium channels, blocking their activation and reducing neuronal firing.**	

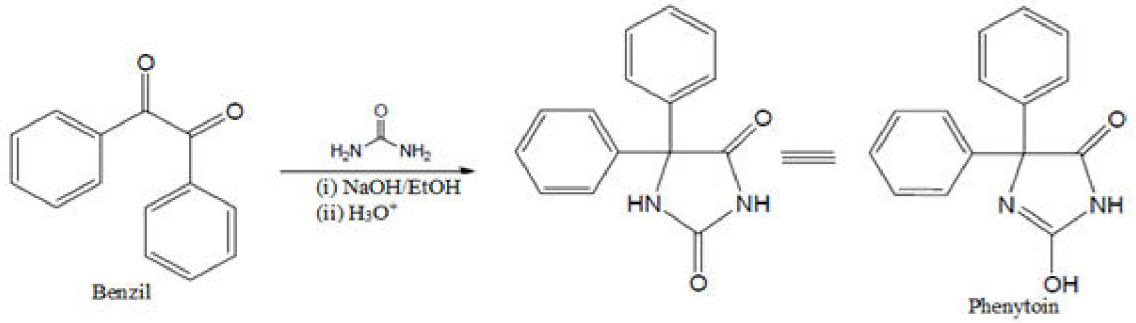
Hydantoins: Phenytoin*, Mephenytoin, Ethotoin

Drug	Use	Structure	Mechanism of Action
Phenytoin (Dilantin)	**Partial seizures (first-line reatment)** **Generalized tonic-clonic seizures (grand mal seizures)** **Status epilepticus**		**Blocking voltage-gated sodium channels, reducing neuronal firing.** **Inhibiting glutamate release, an excitatory neurotransmitter.**
Mephenytoin	**- Primarily used for partial seizures, especially those not controlled by other medications**		**Blocking voltage-gated sodium channels, similar to phenytoin.** **Stabilizing neuronal membranes.**
Ethotoin	**- Partial seizures (less preferred due to lower effectiveness and potential side effects)**		**Blocking voltage-gated sodium channels.** **Inhibiting glutamate release.**

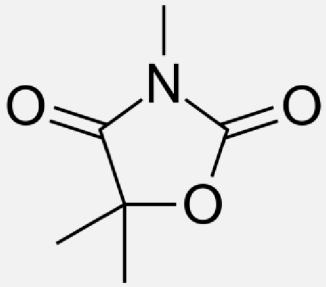
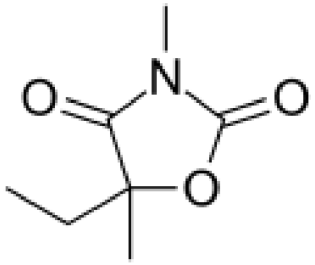
SAR of Phenytoin:

- For the activity of the drug, a phenyl or other aromatic substituent is necessary.
- Substitution with an alkyl group at position 5 will result in the sedative properties of drug.
- Some hydantoins may also exhibit properties against chemically induced convulsions.
- Many hydantoins are ineffective against electroshock induced convulsions.

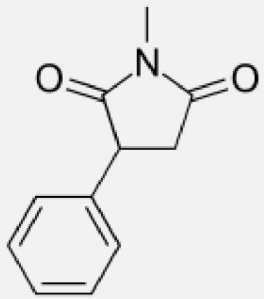
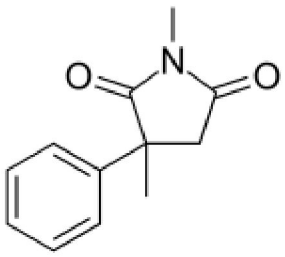
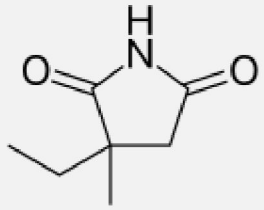
Synthesis of Phenytoin:



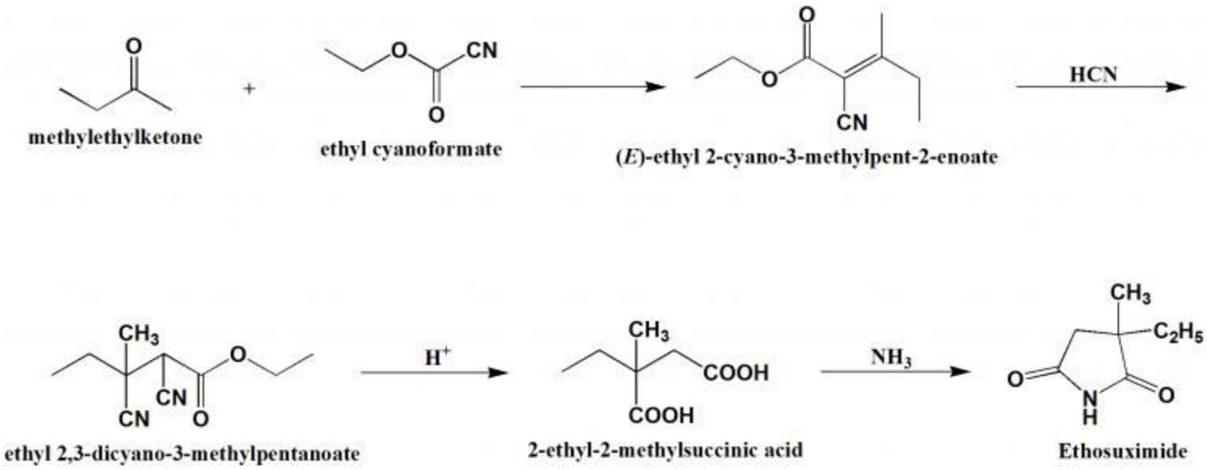
Oxazolidine diones: Trimethadione, Paramethadione

Drug	Use	Mechanism of Action
Trimethadione 	**Absence seizures (petit mal seizures) refractory to other medications**	• **Reduces T-type calcium currents in thalamic neurons, specifically in the thalamic reticular nucleus.** • **Inhibits corticothalamic transmission.** • **Raises the threshold for repetitive activity in the thalamus.** • **Dampens the abnormal thalamocortical rhythmicity associated with absence seizures.**
Paramethadione 	**- Previously used for absence seizures, but replaced by safer and more effective medications**	• **Similar to trimethadione, it acts on thalamic neurons, reducing T-type calcium currents and affecting thalamocortical activity to suppress absence seizures.**

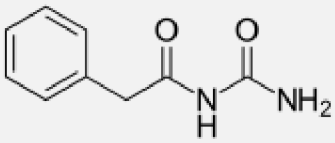
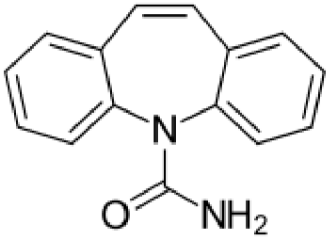
Succinimides: Phensuximide, Methsuximide, Ethosuximide*

Drug	Use	Mechanism of Action
Phensuximide 	**- Primarily for absence seizures (petit mal seizures)**	**Suppress the proximal cycle and wave EFG patter in case of absence seizure** **Inhibit accumulation of cAMP and cGMP in the brain.**
Methsuximide 	**- Primarily for absence seizures (petit mal seizures)**	**Increase threshold of seizures and also suppress the proximal cycle.**
Ethosuximide 	**- Absence seizures (petit mal seizures)**	**Blocking T-type calcium channels in thalamic neurons, thereby suppressing thalamocortical oscillations associated with absence seizures.**

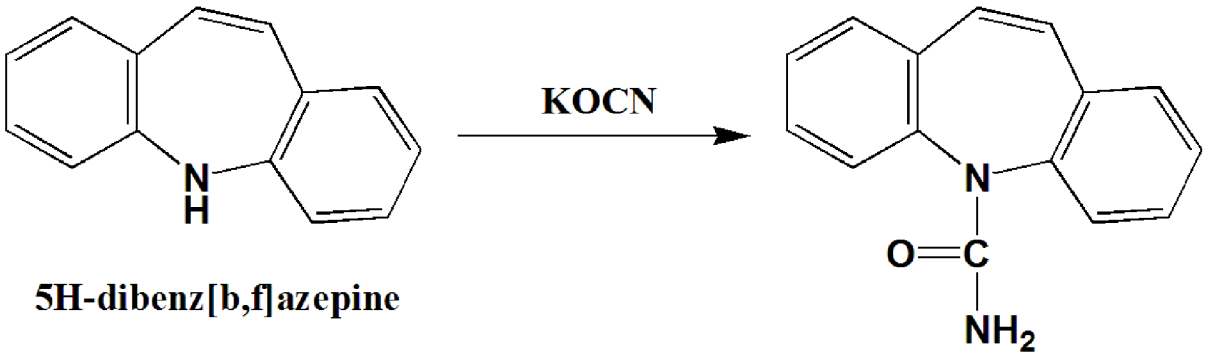
Synthesis of Ethosuximide:



Urea and monoacylureas: Phenacemide, Carbamazepine*

Drug	Use	Mechanism of Action
Phenacemide 	- Absence seizures (petit mal seizures)	**- Blocking neuronal sodium channel or voltage sensitive calcium channel which suppress neuronal depolarization. Increase threshold for electroshock convulsions.**
Carbamazepine 	Partial seizures (first-line treatment) Bipolar disorder	**- Blocking voltage-gated sodium channels**, inhibiting neuronal firing. **- Inhibiting glutamate release**, an excitatory neurotransmitter. **- Stabilizing neuronal membranes**.

Synthesis of Carbamazepine:

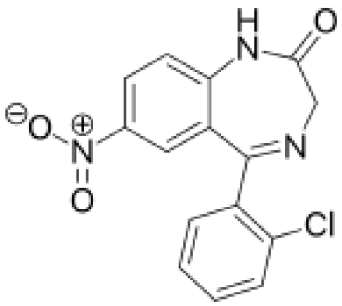


5H-dibenz[b,f]azepine

Carbamazepine

Benzodiazepines:

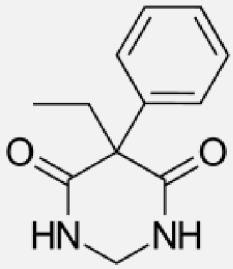
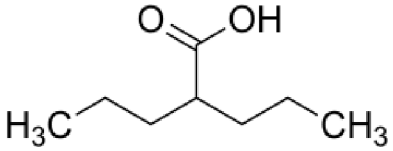
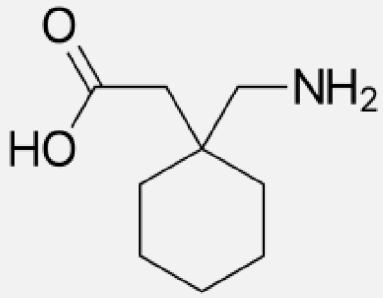
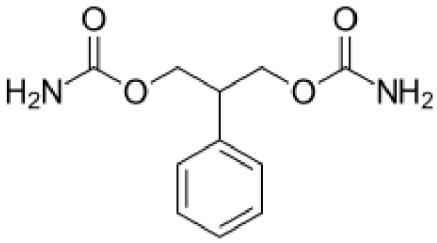
Clonazepam:



MOA: Stimulate GABA

Use: Epilepsy and sedative & hypnotics

Miscellaneous: Primidone, Valproic acid , Gabapentin, Felbamate

Drug	Use	Mechanism of Action
Primidone 	- Partial seizures	**Direct effects** on voltage-gated sodium and calcium channels, although less understood.
Valproic Acid 	- Partial seizures -Bipolar disorder	**Enhancing GABAergic inhibition** by increasing GABA levels and potentiating GABA receptors. - **Blocking sodium channels** to a lesser extent. - **Modulating other neurotransmitters** like glutamate and dopamine, but the exact effects are unclear.
Gabapentin 	- **Neuropathic pain** (primary use) - Partial seizures (adjunctive therapy)	- **Modulating calcium channels** in the central nervous system, affecting neuronal excitability. - **Interacting with GABAergic transmission**, although the exact nature of this interaction is unclear.
Felbamate 	- **Refractory Lennox-Gastaut syndrome** (a severe form of childhood epilepsy)	- **Blocking NMDA (N-methyl-D-aspartate) glutamate receptors**, reducing excitatory neurotransmission. - **Modulating voltage-gated sodium channels**.