

## Semester-IV

### Sub Name-medicinal chemistry-I (sub code-BP-402T)

#### Objective

Drugs acting on Central Nervous System

Sedatives and Hypnotics

- Benzodiazepines: SAR of Benzodiazepines, Chlordiazepoxide, Diazepam\*, Oxazepam, Chlorazepate, Lorazepam, Alprazolam, Zolpidem
- Barbiturates: SAR of barbiturates, Barbitol\*, Phenobarbital, Mephobarbital, Amobarbital, Butobarbital, Pentobarbital, Secobarbital

Miscellaneous

- Amides and imides: Glutethimide.
- Alcohol and their carbamate derivatives: Meprobamate, Ethchlorvynol. Aldehyde and their derivatives: Triclofos sodium, Paraldehyde.

Antipsychotics

- Phenothiazines: SAR of Phenothiazines - Promazine hydrochloride, Chlorpromazine hydrochloride\*, Triflupromazine, Thioridazine hydrochloride, Piperacetazine hydrochloride, Prochlorperazine maleate, Trifluoperazine hydrochloride.
- Ring Analogues of Phenothiazines: Chlorprothixene, Thiothixene, Loxapine succinate, Clozapine.
- Fluoro buterophenones: Haloperidol, Droperidol, Risperidone.

- Beta amino ketones: Molindone hydrochloride. Benzamides: Sulpieride.

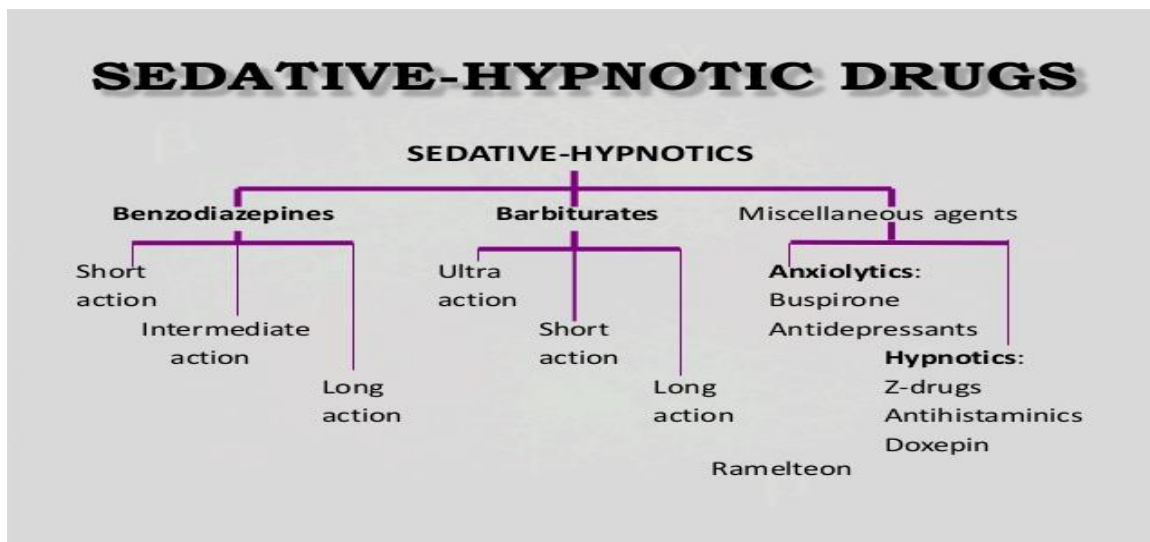
Anticonvulsants: SAR of Anticonvulsants, mechanism of anticonvulsant action

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

#### Sedative and Hypnotics

Sedative-hypnotics are a class of drugs that cause a dose-dependent depression of the CNS function, inducing sedation, sleep, and unconsciousness with increasing dose. Agents in this class of drugs include benzodiazepines and Z-drugs, barbiturates, and melatonin agonists.

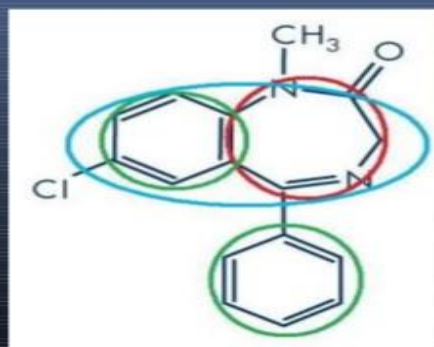
## Classification



## SAR of Benzodiazepines

### Benzodiazepines

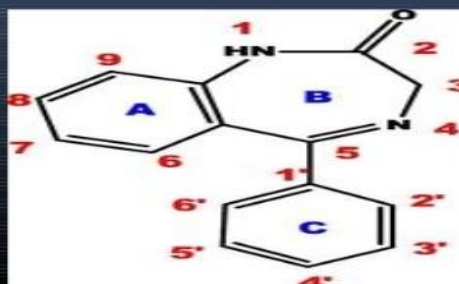
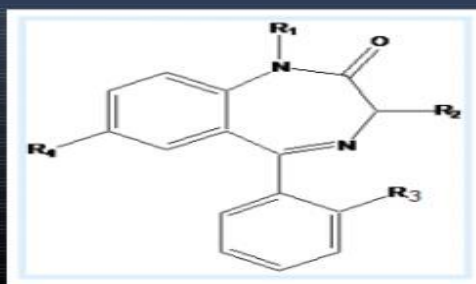
- ❑ All benzodiazepines have a benzene ring attached to a diazepine ring.
- ❑ In the green circles are benzene rings and in the red circle is a diazepine ring, with the whole 1,4-benzodiazepine system being in the blue ring (the 1 and 4 denote the position of the nitrogen atoms in the ring)



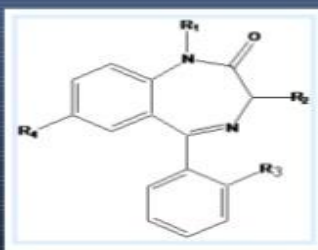
# Benzodiazepines

Different benzodiazepines have been developed through chemical substitutions at two major positions on the benzodiazepine structure

Therefore, all benzodiazepines are simply variations on the same core chemical structure.



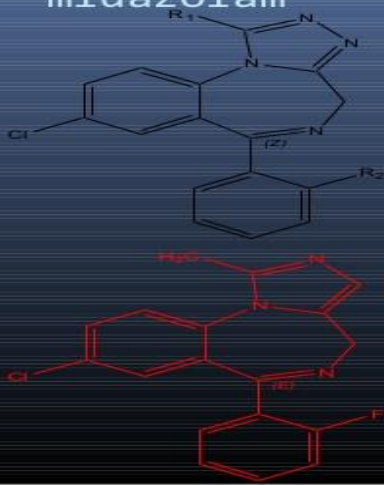
## Benzodiazepine



|   | R1              | R2 | R3 | R4              |
|---|-----------------|----|----|-----------------|
| a | CH <sub>3</sub> | H  | H  | Cl              |
| b | CH <sub>3</sub> | H  | F  | Cl              |
| c | H               | H  | H  | NO <sub>2</sub> |
| d | H               | H  | Cl | NO <sub>2</sub> |

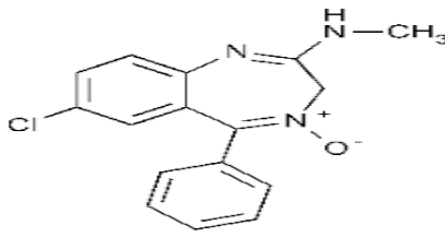
- a. diazepam    b. flutoprazepam    c. nitrazepam  
d. clonazepam

Modification: (triazole or imidazole)  
 estazolam, alprazolam, triazolam and  
 midazolam

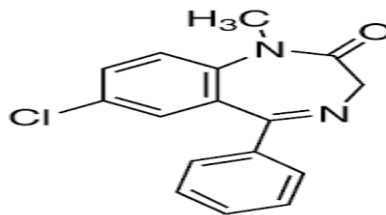


|            | R1              | R2 |
|------------|-----------------|----|
| estazolam  | H               | H  |
| alprazolam | CH <sub>3</sub> | H  |
| triazolam  | CH <sub>3</sub> | Cl |
| Midazolam  | CH <sub>3</sub> | F  |

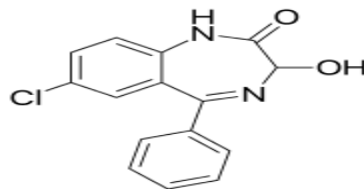
1. Chlordiazepoxide



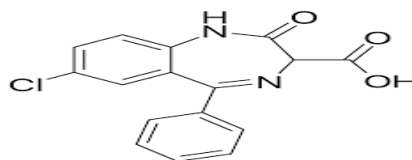
2. Diazepam



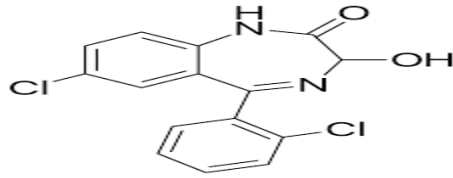
3. Oxazepam



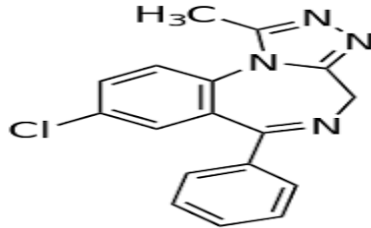
4. Chlorazepate



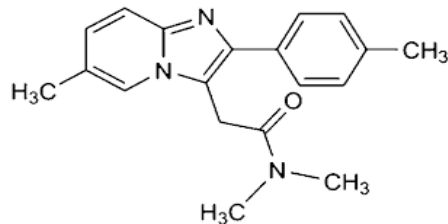
5. Lorazepam



6. Alprazolam



7. Zolpidem

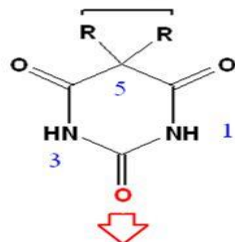


## Barbiturates:

SAR of Barbiturates

**SAR:**

**5,5,-disubstituted & 1,5,5-trisubstituted are active**



if replaced with S give thiobarbiturates

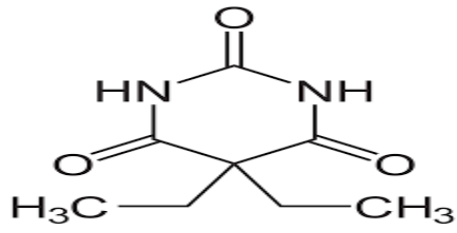
**All other substitution ► inactive**

**1,3-disubstituted or 1,3,5,5-tetrasubstituted are inactive or produce convulsions**

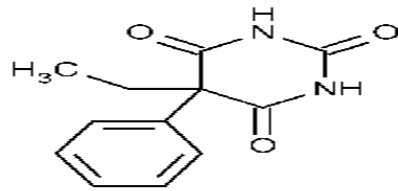
\* **Replacement of C-2 O by S** → ↑ lipid solubility. **Thiopental** used as IV anesthetics due to rapid onset & quick brain levels achieved.

\* Introduction of **more sulfur atoms** (2,4-dithio derivatives) destroys **potency**, due to **decreased hydrophilic character** beyond required limits.

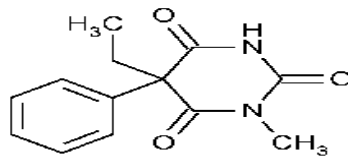
1. Barbital



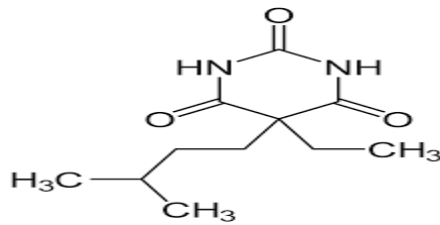
2. Phenobarbital



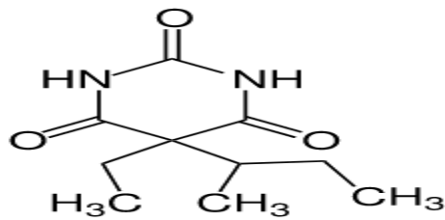
3. Mephobarbital



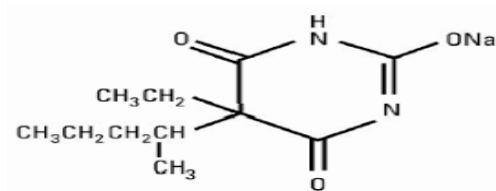
4. Amobarbital



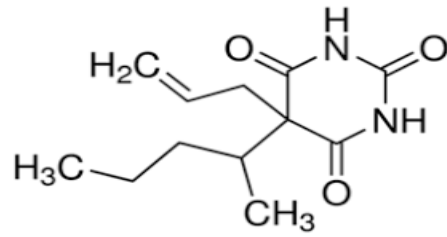
5. Butobarbital



6. Pentobarbital

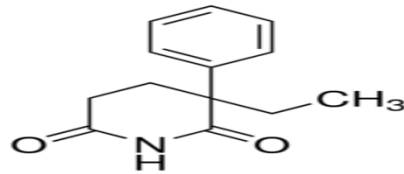


7. Secobarbital

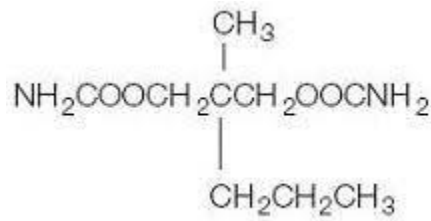


**Miscellaneous**

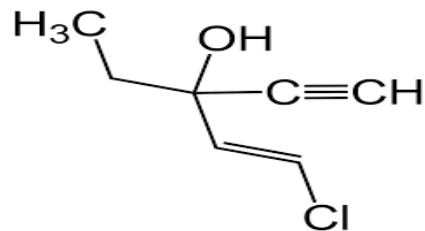
1. Glutethimide



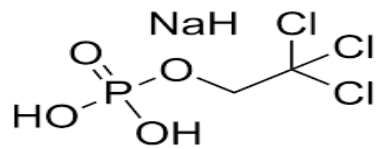
2. Meprobamate



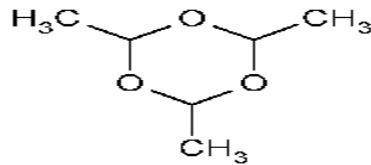
3. Ethchlorvynol



4. Triclofos sodium



## 5. Paraldehyde



### Sedative-Hypnotics: Clinical Uses

- For relief of anxiety
- For insomnia
- For sedation and amnesia before and during medical and surgical procedures
- For treatment of epilepsy and seizure states
- As a component of balanced anesthesia (intravenous administration)
- For control of ethanol or other sedative-hypnotic withdrawal states
- For muscle relaxation in specific neuromuscular disorders
- As diagnostic aids or for treatment in psychiatry

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### Adverse Effects

- Drowsiness and confusion: Most common AE
- Ataxia occurs at high doses
- Cognitive impairment (decreased long-term recall and retention of new knowledge) can occur with use of benzodiazepines.
- Benzodiazepines should be used cautiously in patients with liver disease.
- Alcohol and other CNS depressants enhance the sedative-hypnotic effects of the benzodiazepines.
- Administration in third trimester can result in “floppy-infant syndrome”





## Antipsychotics

Antipsychotics, also known as neuroleptics or major tranquilizers, are a class of medication primarily used to manage psychosis (including delusions, hallucinations, paranoia or disordered thought), principally in schizophrenia and bipolar disorder. Antipsychotics are usually effective in relieving symptoms of psychosis in the short term.

The long-term use of antipsychotics is associated with adverse effects such as involuntary movement disorders, gynecomastia, impotence, weight gain and metabolic syndrome.

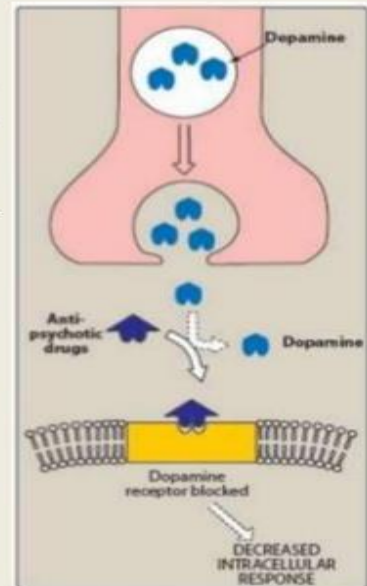
| <b>CLASSIFICATION OF ANTIPSYCHOTIC DRUGS</b>  |  |
|---|--|
| <b>Typical antipsychotics</b>   | <b>Atypical antipsychotics</b>   |
| <ul style="list-style-type: none"><li>• Phenothiazines<ul style="list-style-type: none"><li>• e.g. chlorpromazine, fluphenazine, thioridazine</li></ul></li><li>• Butyrophenones<ul style="list-style-type: none"><li>• e.g. haloperidol, droperidol</li></ul></li><li>• Thioxanthenes<ul style="list-style-type: none"><li>• e.g. chlorprotixen, thiothixene</li></ul></li></ul> | <ul style="list-style-type: none"><li>• Clozapine</li><li>• Risperidone</li><li>• Sulpiride</li><li>• Sertindole</li><li>• Seroquel</li><li>• Olanzapine</li><li>• Quetiapine.</li></ul> |

### Mechanism of action

➤ All typical antipsychotic agents currently employed clinically block post synaptic dopaminergic  $D_2$  receptors in the mesolimbic and cortex regions of the brain and act as a competitive antagonist of dopamine. The blockade of  $D_2$  receptors is thought to be responsible for decreasing the positive symptoms of schizophrenia.

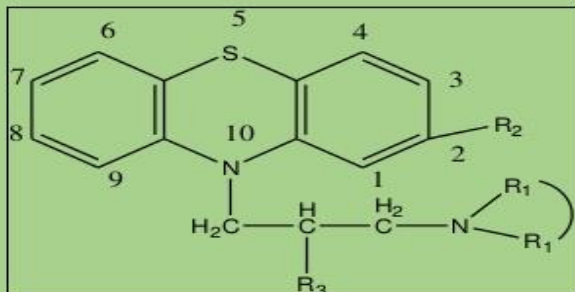
➤ Central dopamine receptors are subdivided into  $D_1$ ,  $D_2$  and according to some sources,  $D_3$  receptors. These receptors have a high affinity for dopamine, but they differ in selectivity to neuroleptics of various chemical classes.

➤ Adenyl cyclase is involved which is responsible for the conversion of adenosine triphosphate to cyclic adenosine monophosphate (cAMP).



## SAR of Phenothiazines

### Structure activity relationship of Phenothiazine...



THE NEUROLEPTIC PROPERTIES OF PHENOTHIAZINE MAY BE AFFECTED BY FOLLOWING :

- A) NATURE OF THE CHAIN IN POSITION 10
- B) NATURE OF THE AMINO GROUP
- C) R<sub>2</sub> SUBSTITUTION

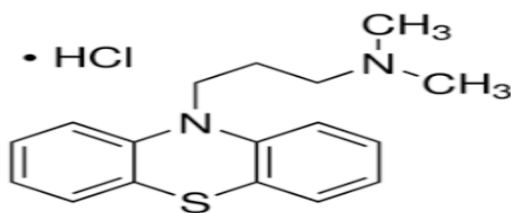
- ✓ Replacement of the h in position 2
- ✓ Substitution at position 3
- ✓ Substitution at position 1
- ✓ Three carbon chain
- ✓ Branching with larger groups
- ✓ Replacement of terminal alkyl amino group

Antipsychotic agents

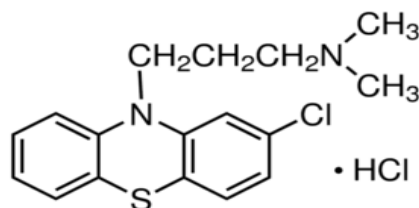
Miss Priya S Hargunani

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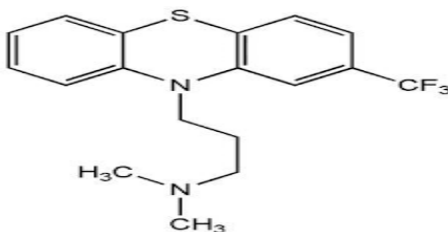
- Promazine hydrochloride



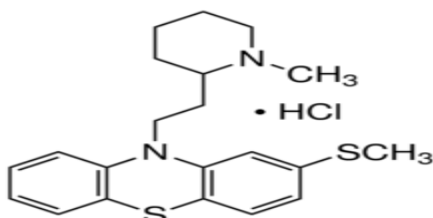
- Chlorpromazine hydrochloride



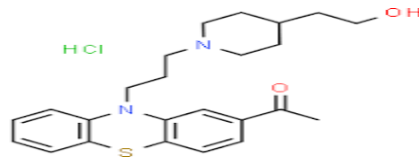
- Triflupromazine



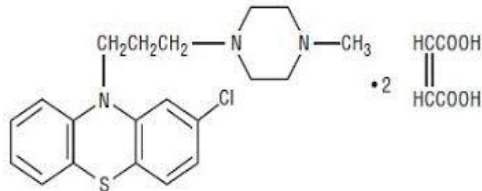
- Thioridazine hydrochloride



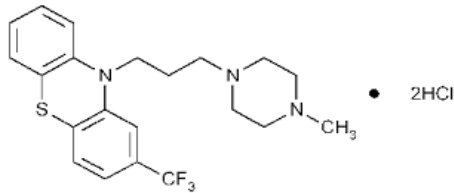
5. Piperacetazine hydrochloride



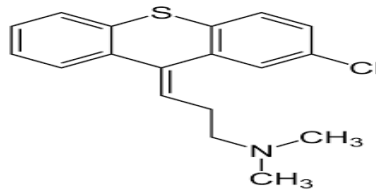
6. Prochlorperazine maleate



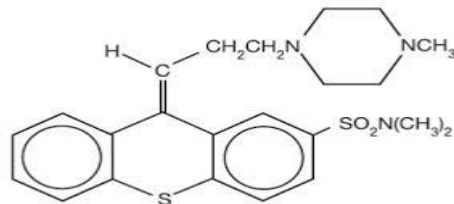
7. Trifluoperazine hydrochloride



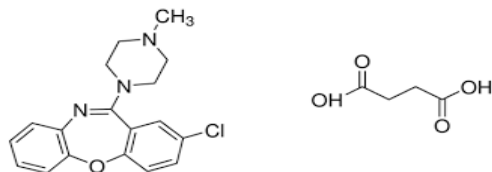
8. Chlorprothixene



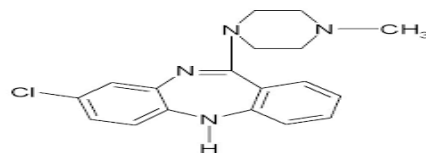
9. Thiothixene



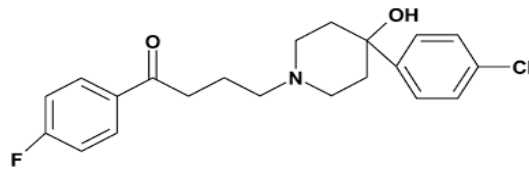
10. Loxapine succinate



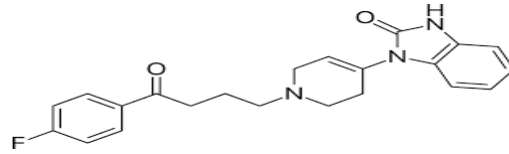
11. Clozapine



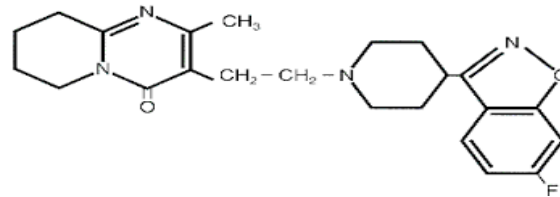
12. Haloperidol



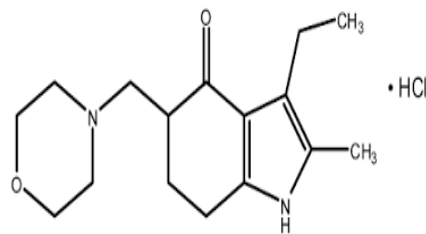
13. Droperidol



14. Risperidone



15. Molindone hydrochloride

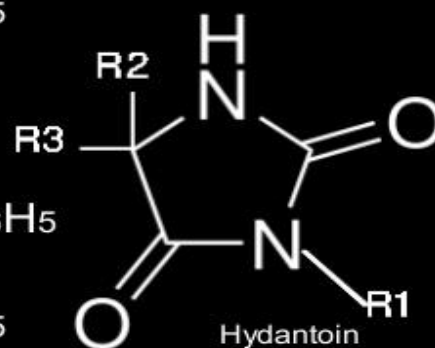


**Anticonvulsants:**

Anticonvulsants are a diverse group of pharmacological agents used in the treatment of epileptic seizures. Anticonvulsants are also increasingly being used in the treatment of bipolar disorder and borderline personality disorder, since many seem to act as mood stabilizers, and for the treatment of neuropathic pain.

# 1. Hydantoins

- Phenylethylhydantoin  
 $R_1 = H$   $R_2 = C_2H_5$   $R_3 = C_6H_5$
- Phenytoin  
 $R_1 = H$   $R_2 = R_3 = C_6H_5$
- Mephentytoin  
 $R_1 = CH_3$   $R_2 = C_2H_5$   $R_3 = C_6H_5$
- Ethotoin  
 $R_1 = C_2H_5$   $R_2 = H$   $R_3 = C_6H_5$



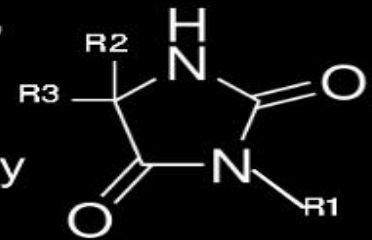
## Contd..

- A phenyl or other aromatic substituents at C<sub>5</sub> is essential for the activity.
- Alkyl substituents at position 5 may contribute to sedation, a property absent in phenytoin. Hydantoin



Contd..

- Among other hydantoins, like spirohydantoins, thiohydantoins, dithiohydantoins, and 1, 3-disubstituted hydantoins, some exhibit activity against chemically induced convulsions.
- While remaining are ineffective against electroshock induced convulsions.



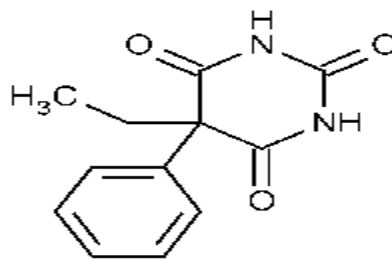
Hydantoin



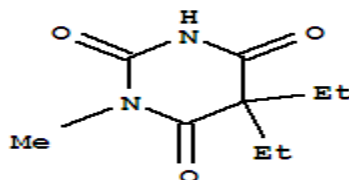
### Mechanism of Action

Anticonvulsants suppress the excessive rapid firing of neurons during seizures. Anticonvulsants also prevent the spread of the seizure within the brain. Conventional antiepileptic drugs may block sodium channels or enhance  $\gamma$ -aminobutyric acid (GABA) function.

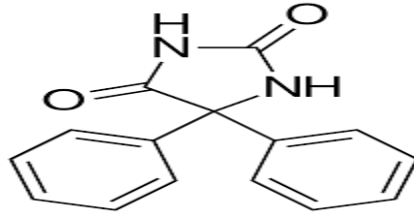
1. Phenobarbitone



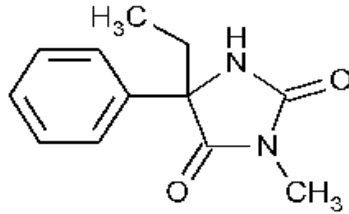
2. Methabarbital



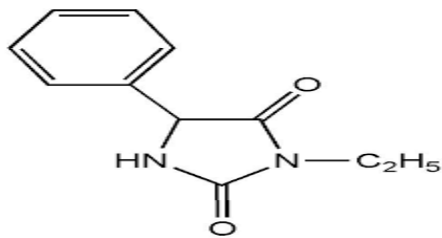
3. Phenytoin



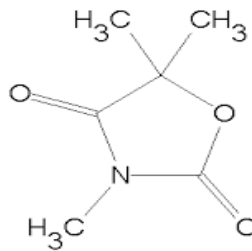
4. Mephénytoin



5. Ethotoin



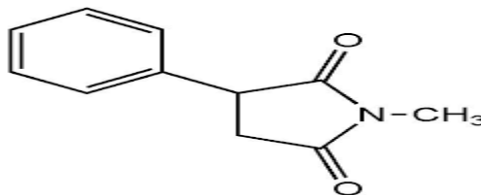
6. Trimethadione



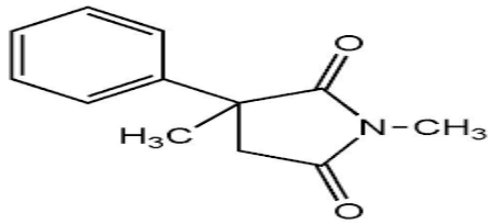
7. Paramethadione



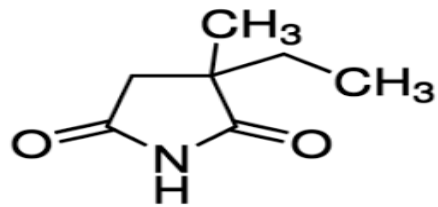
8. Phensuximide



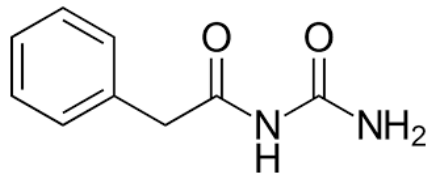
9. Methsuximide



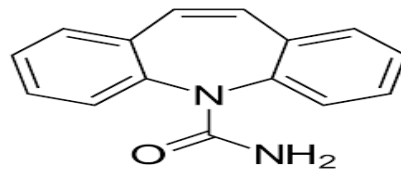
10. Ethosuximide



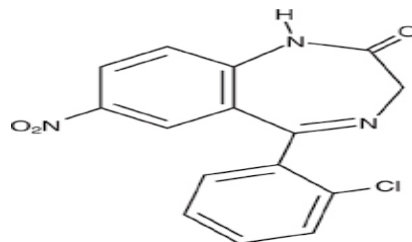
11. Phenacemide



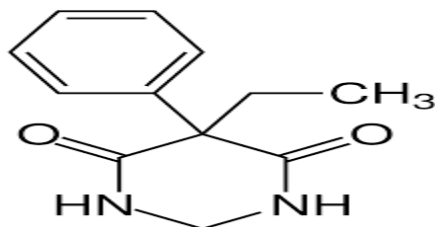
12. Carbamazepine



13. Clonazepam

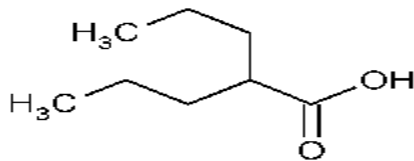


14. Primidone

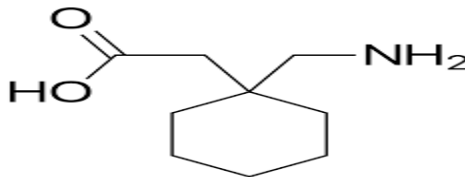




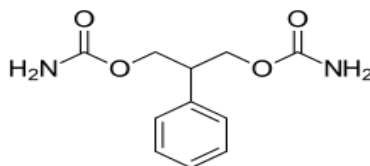
15. Valproic acid



16. Gabapentin



17. Felbamate



### Uses of Anticonvulsants

- Anticonvulsants work by calming hyperactivity in the brain in various ways.
- For this reason, some of these drugs are used to treat epilepsy, prevent migraines, and treat other brain disorders.
- They are often prescribed for people who have rapid cycling -- four or more episodes of mania and depression in a year.

### Adverse effects of Anticonvulsants

- Dizziness.
- Drowsiness.
- Fatigue.
- Nausea.
- Tremor.
- Rash.
- Weight gain

### Learning outcomes

- Know the structural activity relationship (SAR) of different class of drugs.