

# MEDICINAL CHEMISTRY-I

## UNIT 4 NOTES

### DRUGS ACTING ON CNS

- SEDATIVE AND HYPNOTICS
- ANTIPSYCHOTICS
- ANTICONVULSANTS



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# DRUGS ACTING ON CNS

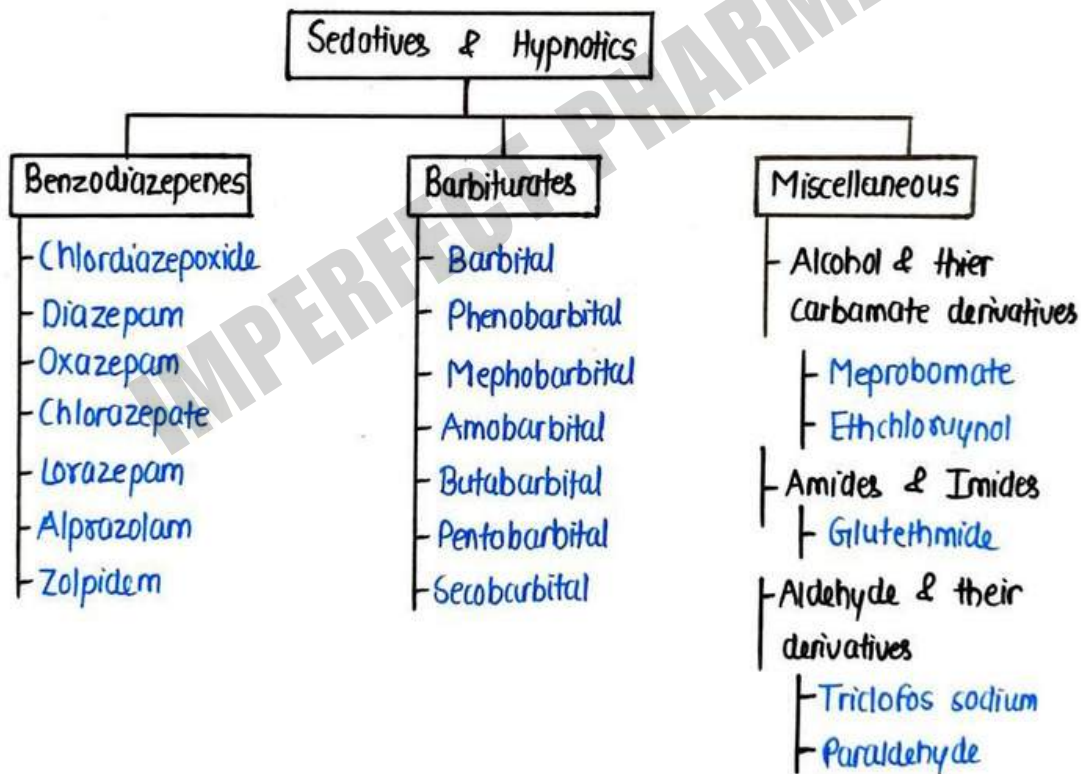
- Drugs Acting on CNS refers to pharmacological agents that particularly acts on Brain & spinal cord.
- These drugs modify mental activity, consciousness, mood or behaviour and are used to treat various neurological & psychiatric disorders.
- Some most common CNS agents include :
  - Sedative & Hypnotics
  - Antipsychotics
  - Antidepressants
  - Antiepileptics (Anticonvulsants)
  - Anti parkinsonian Drugs

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# SEDATIVES & HYPNOTICS

- Sedatives are drugs / medicines that help calm you down or make you feel relaxed.
- Hypnotics are medicines that help you fall asleep.
- Both are often used to treat anxiety or sleep problems.
- Hypnosis are strong depression of CNS, cause sleep & used in insomnia.

## CLASSIFICATION



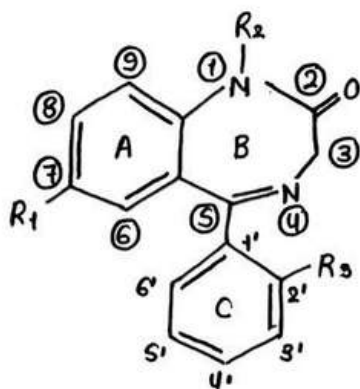
## BENZODIAZEPINES

- Benzodiazepines are drugs that help reduce anxiety, relax muscles, and make it easier to sleep.
- They work by calming the brain.
- They were accidentally synthesized in 1961.
- They include:
  - ① Chlordiazepoxide
  - ② Diazepam\*
  - ③ Oxazepam
  - ④ Chlorazepate
  - ⑤ Lorazepam
  - ⑥ Alprazolam
  - ⑦ Zolpidem

## MECHANISM OF ACTION

- Benzodiazepines work by increasing the effect of a brain chemical GABA, which calms down brain activity.
- This helps reduce anxiety, relax muscles, and cause sleepiness.

## SAR OF BENZODIAZEPENES



### ① RING A

- It is essential for proper binding to the GABA-A receptor
- Electron withdrawing substituent at position 7 enhances activity.
- Substitution at 6, 8 & 9<sup>th</sup> position generally reduce potency.

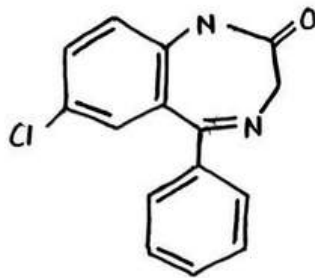
### ② RING B

- It is a diazepine ring with two 'N' atoms.
- Substitution at N<sub>1</sub> by alkyl, halo alkyl or amino alkyl increases activity.
- Hydroxy group at position 3 increases water solubility, improves metabolism but shortens duration of action.
- Phenyl group at position 5 is essential for activity.

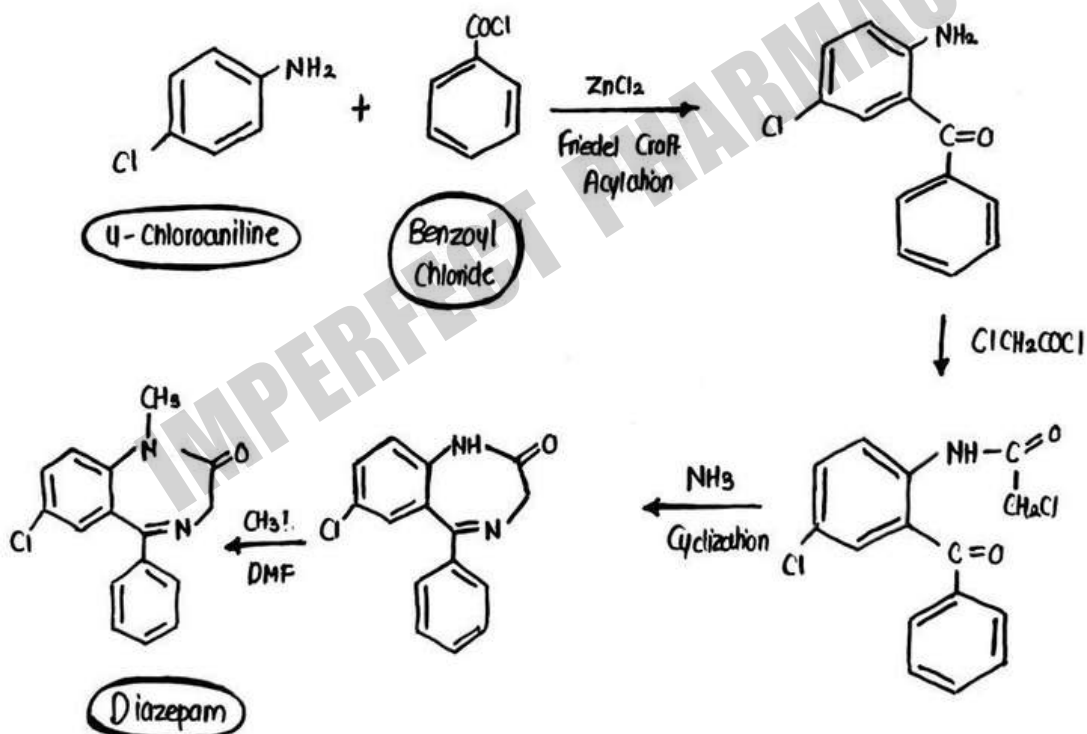
### ③ RING C

- Important for binding affinity to GABA-A receptor.
- Substituents at ortho position (2') increases potency (e.g. electron withdrawing groups)
- Para substitution (4') typically reduces activity.

## ① DIAZEPAM\*



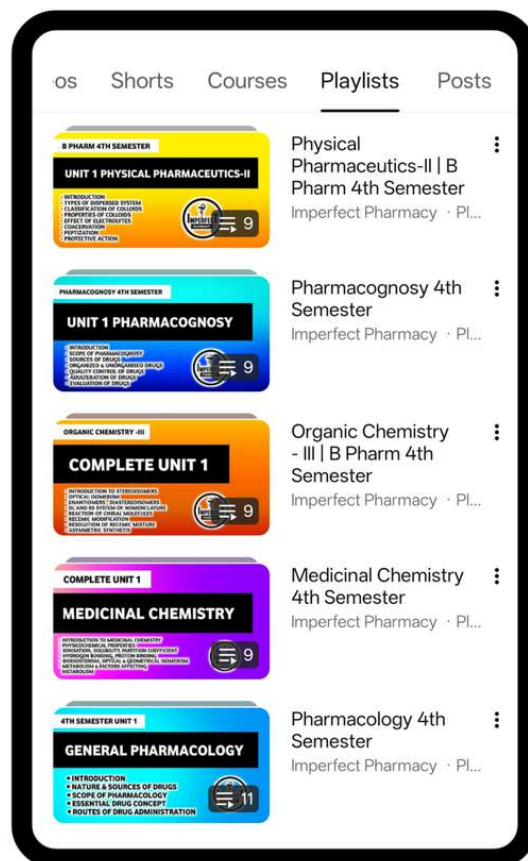
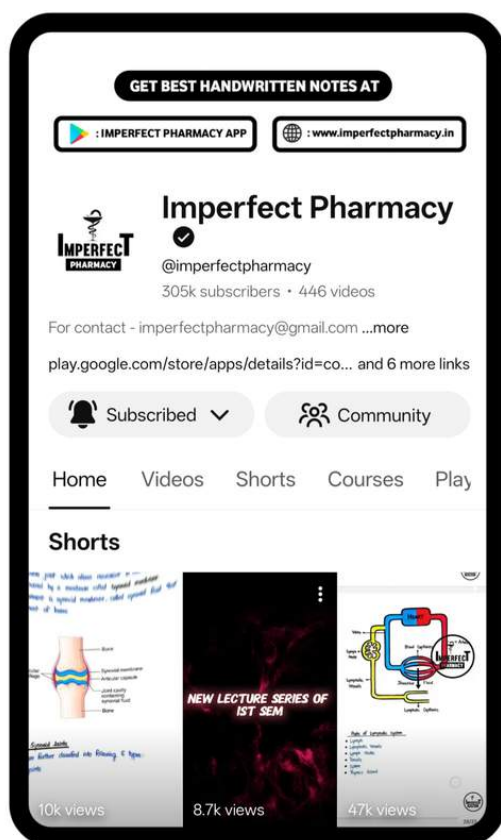
### SYNTHESIS



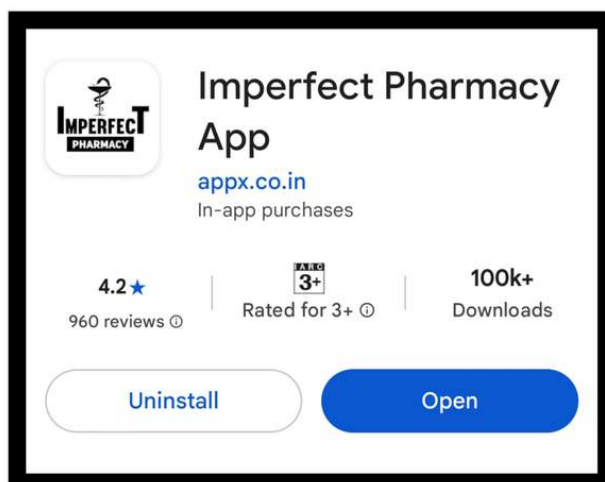
### Uses

- Anxiety
- Insomnia
- Musclespasm

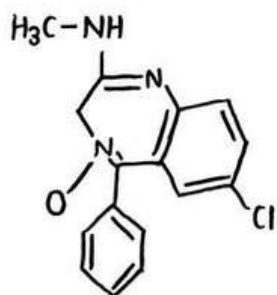
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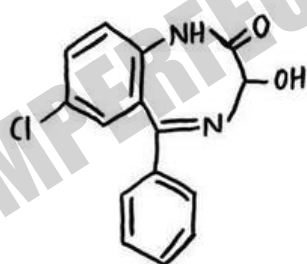
## CHLORDIAZEPOXIDE



Uses:

- Used in treatment of anxiety & insomnia.
- Used in treatment of withdrawal symptom from Alcohol (Nausea, Muscle spasm) etc.

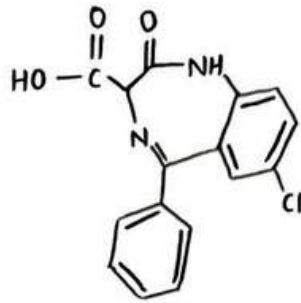
# Oxazepam



Uses:

- Used in treatment of insomnia & anxiety disorder.

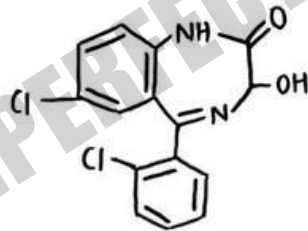
## CHLORAZEPATE



### Uses

- Used in treatment of insomnia & anxiety.
- Used as muscle relaxant.

## LORAZEPAM



### Uses

- Used as hypnotics in treatment of anxiety.
- Used in treatment of anticonvulsant.

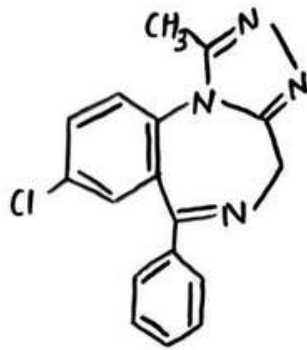
## **BARBITURATES**

- Barbiturates are potent CNS depressants.
- They are medicines that slow down brain or CNS activity.
- They can be very strong and risky if not used carefully.
- They are used to treat anxiety, sleep problems and seizures etc.
- They includes :
  - ① Barbitol \*
  - ② Phenobarbital
  - ③ Mephobarbital
  - ④ Amobarbital
  - ⑤ Butobarbital
  - ⑥ Pentobarbital
  - ⑦ Secobarbital

### MECHANISM OF ACTION

- Barbiturates work by increasing the effect of GABA, a calming chemical of brain and slows down brain activity, helping to cause sleep, reduce anxiety and stop seizures.
- They bind on allosteric site (other than benzodiazepine site)
- At high concentration they can directly open the channels.

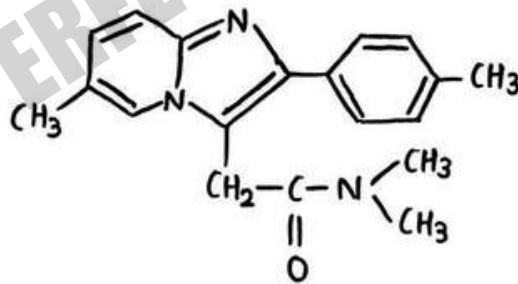
## ALPRAZOLAM



### Uses

- Used as anti-anxiety, sedative, hypnotic.

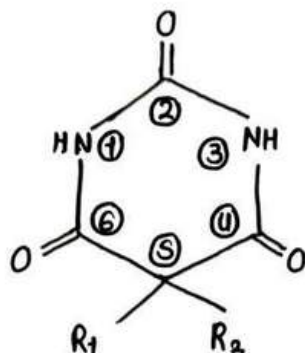
## ZOLPIDEM



### Uses

- Used in treatment of insomnia.

## SAR OF BARBITURATES



- They are derivative of barbituric acid & having a cyclic structure with two nitrogen atoms & three carbonyl groups.

### ① C5 Substitution

- It is most critical for activity.
- Dialkyl or Aryl / Alkyl substitution at C5 increase lipid solubility & CNS activity.
- Aryl groups tend to prolong the action duration and enhance anticonvulsant activity.

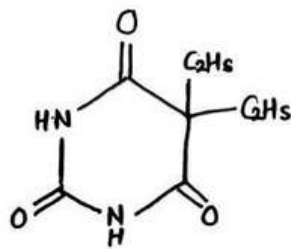
### ② N1 & N3 Substitution

- Alkylation of nitrogen reduces polarity, increasing lipophilicity.
- In general substitution at N-1 or N-3 reduces anticonvulsant activity but may enhance hypnotic activity.

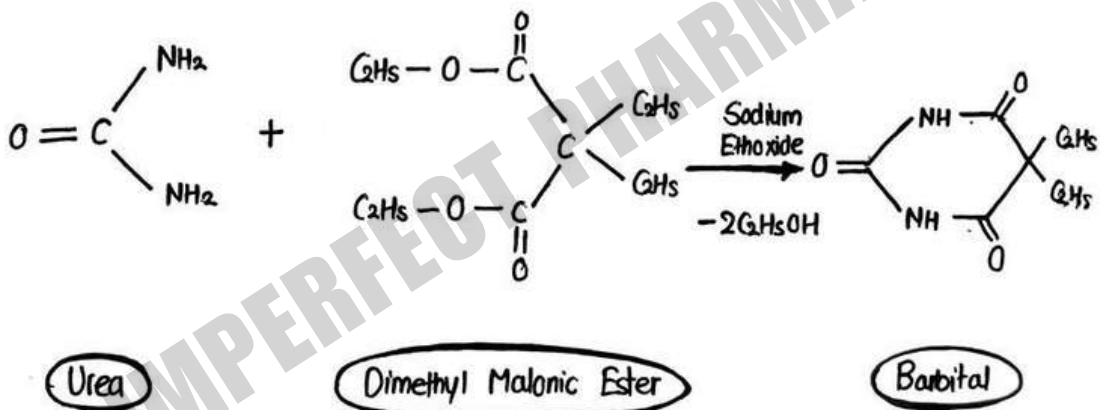
### ③ Unsaturation or Aromaticity

- Introducing double bonds or Aromatic ring increased lipid solubility.

## BARBITAL\*



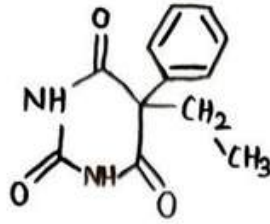
### SYNTHESIS



### Uses

- Epilepsy
- Sedative & Hypnotics

## PHENOBARBITAL



### Uses

- Used both as sedative & hypnotic.
- Also has anticonvulsant effect.

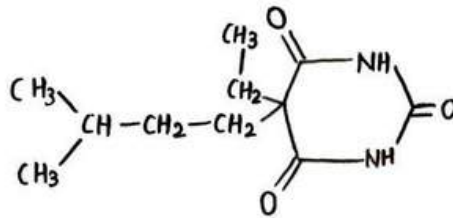
## MEPHOBARBITAL



### Uses

- Used to treat anxiety, excitement & also anticonvulsant agent.

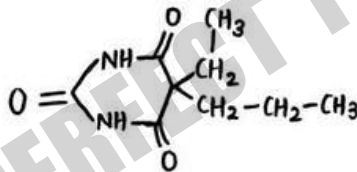
## AMOBARBITAL



### Uses

- Used to treat anxiety, epilepsy and insomnia.

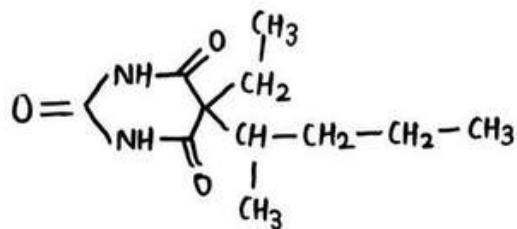
## BUTABARBITAL



### Uses

- Used to treat severe insomnia due to fast onset of action.
- Also used to relieve anxiety before surgical procedure.

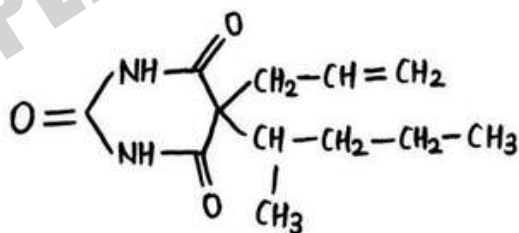
## PENTOBARBITAL



### Uses

- Used as sedative & hypnotic for short term preanesthetic procedure.
- Used as anticonvulsant in emergency condition.
- Used to reduce intracranial pressure in Reye's syndrome.

## SECOBARBITAL



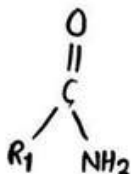
### Uses

- Used as sedative & hypnotic in severe insomnia.
- Also used as anesthetic and anxiolytic.

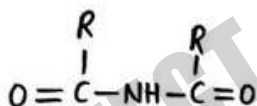
## MISCELLANEOUS

### ① AMIDES AND IMIDES

- Amide is a functional group in which a nitrogen is attached to only C=O via single sigma bond.



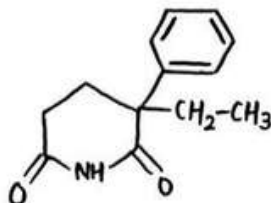
- Imide is a functional group in which nitrogen is attached to two C=O groups via single sigma bond.



### MOA

Amides and Imides are drugs that often work by blocking (Na<sup>+</sup>) sodium channels in nerves. This stops pain signals or nerve activity, helping in pain relief or controlling seizures.

### GLUTETHIMIDE



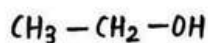
### Uses

- Used in treatment of insomnia.

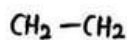
## ② ALCOHOL AND THEIR CARBAMATE DERIVATIVES

- General formula :  $R-OH$ .
- Alcohols can be further categorised by mono, di & the trihydric alcohols, based on the presence of one, two & three hydroxyl group in their molecules.

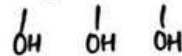
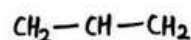
Examples:



Ethylalcohol



ethane-1,2-diol

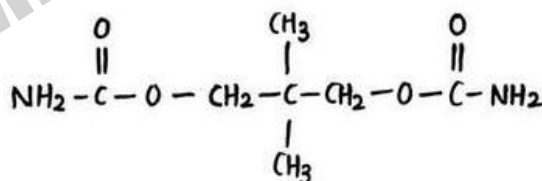


Propane-1,2,3,- triol

### MOA

- They work by enhancing effect of GABA in CNS and calming the brain & nerves activity.

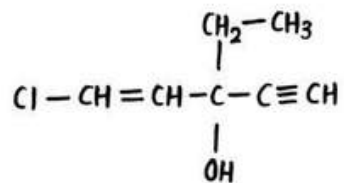
### MEPROBAMATE



### Uses

- Used as hypnotic, sedative, antianxiety, muscle-relaxant etc.

## ETHCHLORVYNOL



### Uses

- Used as sedative & insomnia, hypnotic in treatment of short term insomnia.

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### ③ ALDEHYDE AND THEIR DERIVATIVES

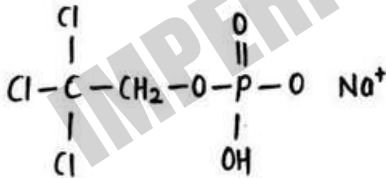
- A carbon atom shares a double bond with an oxygen atom, a single bond with a hydrogen atom & single bond with another atom or group of atom.



#### MOA

- They work by enhancing calming effect of GABA in the brain or CNS, and help to reduce anxiety and cause sleep by slowing down brain activity.

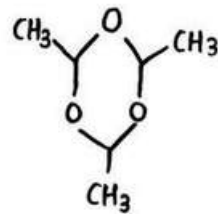
#### TRICLOFOS SODIUM



#### Uses

- Used as a sedative & hypnotic to treat insomnia.

#### PARALDEHYDE



#### Uses

- Used as expectorant in some cough medicines.
- Used as hypnotic, sedative, anti-convulsants etc.

## ANTIPSYCHOTICS

- Antipsychotics are the drug that have specific sedative effect and which improves the attitude and calm behaviour of psychotic patient.
- They are also called as neuroleptic or major tranquilizers.
- They do not eliminate the disorder they only decrease the symptoms.

### PSYCHOSIS

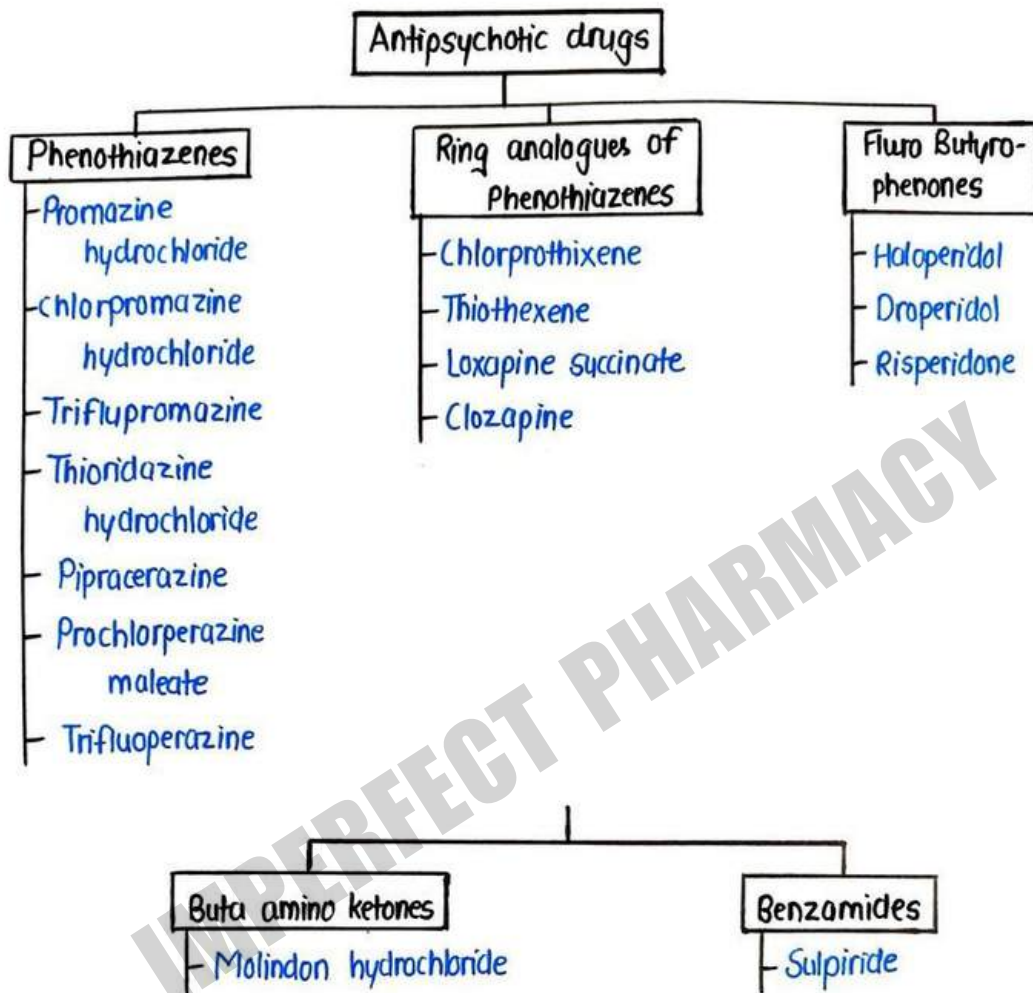
A mental disorder characterized by a disconnection from reality.

#### Types of psychotic disorder

Psychosis occurred due to :

- Schizophrenia
- Bipolar disorder
- Psychotic depression
- Schizoaffective disorder
- Drug induced psychosis

## CLASSIFICATION



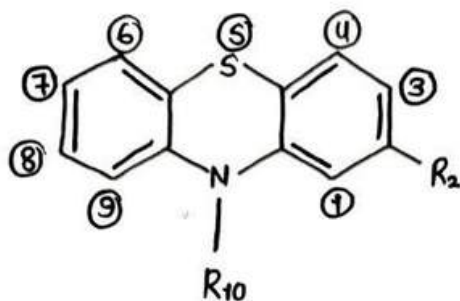
## PHENOTHIAZINES

- They are non-selective, competitive antagonist of D<sub>1</sub> and D<sub>2</sub> receptors and blocks dopamine activity on this receptor site.
- These drugs are also known as Tricyclic antipsychotics.
- These acts on the CNS by causing moderate sedative and antiemetic effect.
- These includes :
  - ① Promazine hydrochloride
  - ② Chlorpromazine hydrochloride
  - ③ Trifluoperazine
  - ④ Thioridazine hydrochloride
  - ⑤ Piperacerazone
  - ⑥ Prochlorperazine maleate
  - ⑦ Trifluoperazine

## MECHANISM OF ACTION

They work by blocking dopamine (D<sub>1</sub> & D<sub>2</sub>) receptors in the brain or CNS and help reduce symptoms like hallucinations, delusions and agitation, making them help to treat mental health conditions like schizophrenia.

## SAR OF PHENOTHIAZINES



### ① Tricyclic Ring System

- The phenothiazine nucleus is essential for activity.
- It consists of two benzene rings linked by a central ring containing sulfur & nitrogen atom.

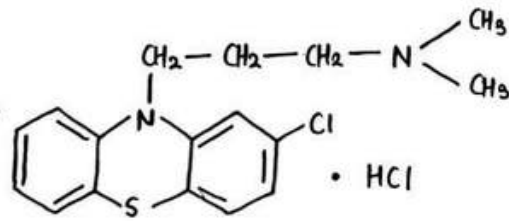
### ② Substitution at Position 2

- A Cl or other electron-withdrawing group at position 2 increases potency by enhancing receptor binding.

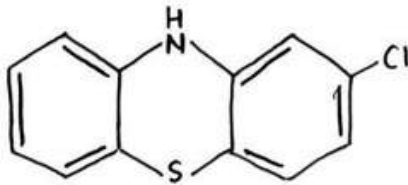
### ③ Side Chain at Nitrogen

- The nitrogen at position 10 is typically substituted with a 3-carbon side chain ending in a terminal amine.
- The nature of the side chain determines the type of phenothiazines & receptor binding affinity.

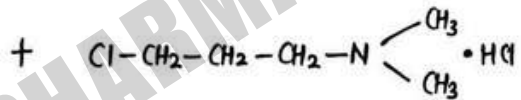
## CHLORPROMAZINE HYDROCHLORIDE \*



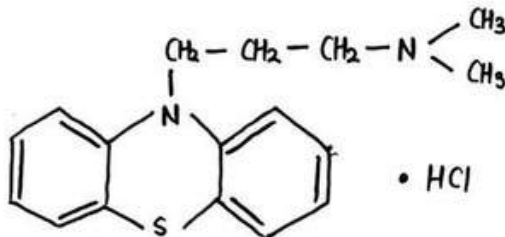
### SYNTHESIS



2-Chlorophenothiazine



3-Chloropropyl-diethylamine  
Hydrochloride

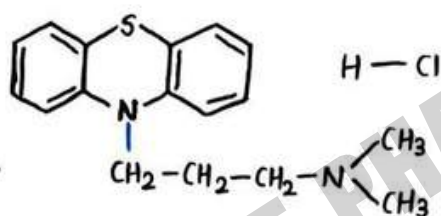


Chlorpromazine  
Hydrochloride

### Uses

- Treatment of Schizophrenia.
- Sedative Agent

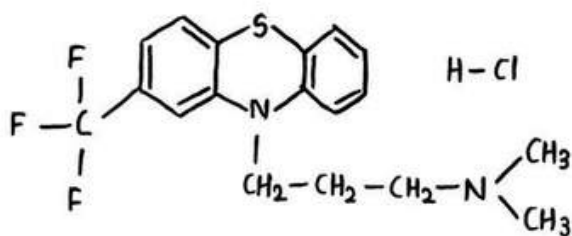
## PROMAZINE HYDROCHLORIDE



### Uses

Used for short term treatment of disturbed and agitated behaviour.  
Used as an antiemetic.

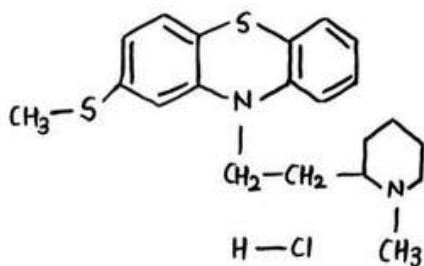
## TRIFLUPROMAZINE



### Uses

Used in treatment of psychotic disorder.  
Also used to control nausea & vomiting.

## THIORIDAZINE HYDROCHLORIDE



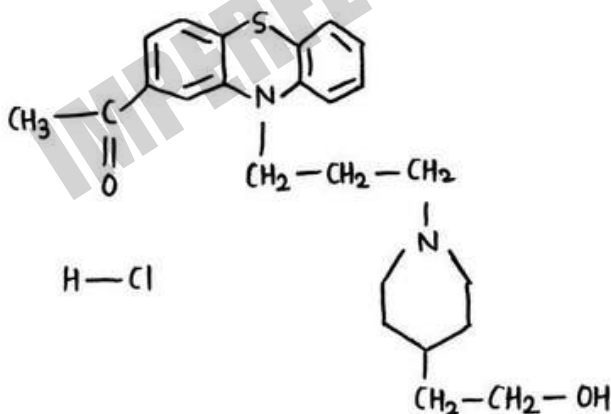
### Uses

Treatment of psychosis.

Antiemetic.

Used to control disturbed & agitated behaviour.

## PIPERACERAZINE HYDROCHLORIDE

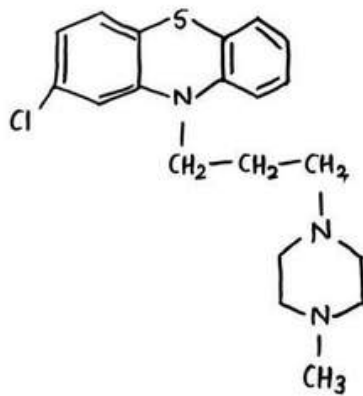


### Uses

Used as tranquilizer.

Used in treatment of psychosis.

## PROCHLORPERAZINE MALEATE

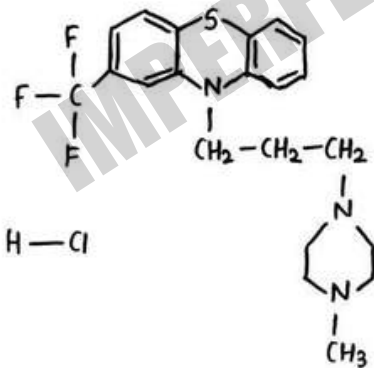


### Uses

Used as antipsychotic and antiemetics.

Used in treatment of migraine headaches.

## TRIFLUOPERAZINE HYDROCHLORIDE



### Uses

Used in treatment of schizophrenia and acute mania disorder.

Used as antiemetics.

Treatment of anxiety.

## RING ANALOGUES OF PHENOTHIAZINES

Ring analogues are chemical compounds that have a similar three-ring structure to phenothiazines but with slight changes in the atoms or arrangement within the rings.

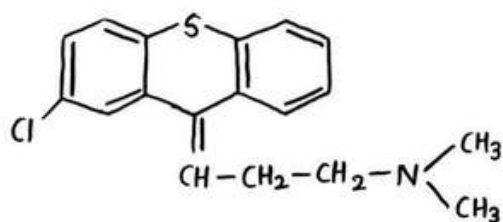
## MECHANISM OF ACTION

- They are mainly work by blocking Dopamine ( $D_1$  &  $D_2$ ) receptors in the brain, and helps reduce symptoms like schizophrenia.
- Some analogues are may also blocks other receptors like serotonin or histamine, affecting mood, sleep or movement.

## CLASSIFICATION

- ① Chlorpromazine
- ② Thioridazine
- ③ Loxapine succinate
- ④ Clozapine

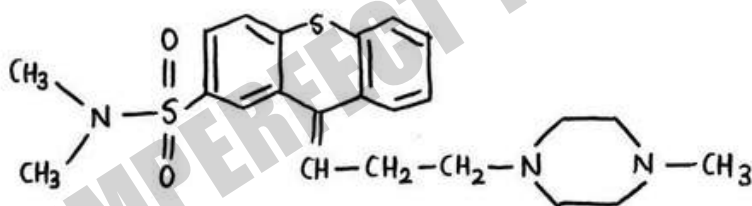
## CHLORPROTHIXENE



### Uses

- Used in treatment of schizophrenia & acute mania disorder.
- Used to treat anxiety and insomnia.

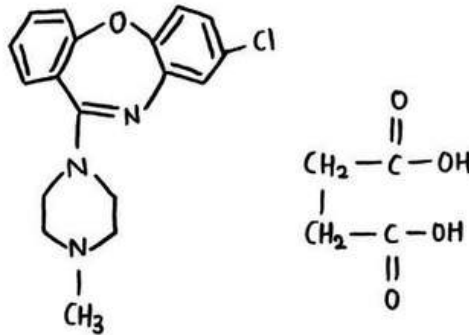
## THIOTHIXENE



### Uses

- Used to treat schizophrenia and bipolar mania.
- Reduce aggression and the desire to hurt yourself and others.
- Help to decrease hallucinations.

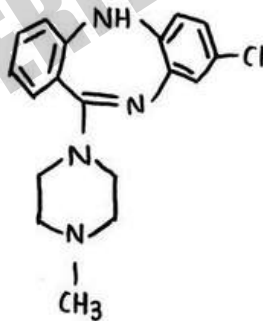
## LOXAPINE SUCCINATE



### Uses

- Used for managing the symptoms of psychotic disorder like schizophrenia.

## CLOZAPINE



### Uses

- Used for those patient who are responsive and intolerant to other anti-psychotic drugs.
- Used in the treatment of schizophrenia.

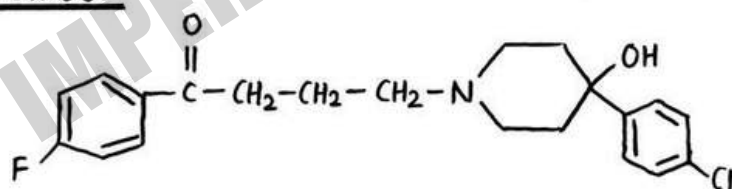
## FLURO BUTEROPHENONES

- Fluoro Buterophenones are a group of drugs with a chemical structure that includes a fluorine atom and a butyrophenone base.
- They are mainly used as antipsychotics to treat mental disorders by blocking dopamine receptors in brain.
- They includes :
  - ① Haloperidol
  - ② Droperidol
  - ③ Risperidone

## MECHANISM OF ACTION

They work by blocking Dopamine D<sub>2</sub> receptors and help to reduce symptoms of psychosis, like hallucinations and delusions, in conditions such as schizophrenia.

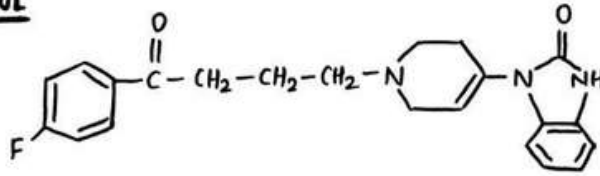
## HALOPERIDOL



## Uses

- Used in management of severe anxiety and also used as antiemetic.
- Used in treatment of schizophrenia and psychotic disorder.

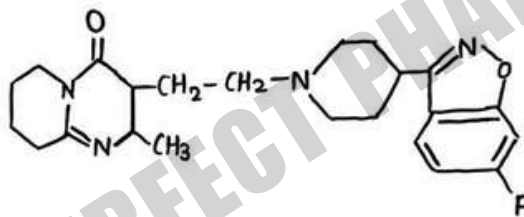
## DROPERIDOL



### Uses

- Used as antipsychotic and antiemetics.
- Used as sedative in intensive care treatment (it depressed CNS).

## RISPERIDONE



### Uses

- Used to treat mood disorder (bipolar disorder and mood swings).
- Used in treatment of schizophrenia and psychosis disorders.

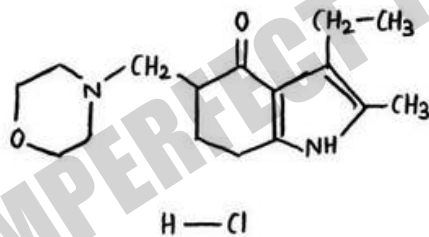
## BETA AMINO KETONES

- Beta amino ketones are chemical compounds that have a ketone group ( $C=O$ ) and an amino group ( $-NH_2$ ) separated by two carbon atoms.
- They include:
  - Molindone Hydrochloride

## MECHANISM OF ACTION

- They work by affecting the brain's chemical messengers, like dopamine and norepinephrine.
- They usually increase the levels of these messengers, which can help improve alertness, mood or focus, depending on the specific drug.

## MOLINDONE HYDROCHLORIDE



## Uses

- Antidepressant
- ADHD

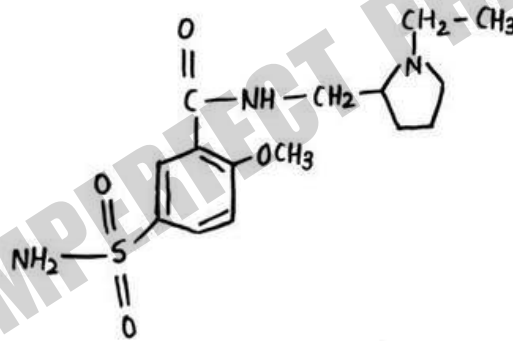
## BENZAMIDES

- Benzamides are group of chemical compounds made from benzoic acid and an amine.
  - Some benzamides are used to especially to treat mental or stomach disorders.
  - They include:
- ① Sulpiride

## MECHANISM OF ACTION

- They work by blocking Dopamine D<sub>2</sub> receptors in the brain and gut.

## SULPIRIDE



## Uses

- Mainly used in the treatment of schizophrenia.

## ANTICONVULSANT DRUGS

- Anticonvulsants, also known as Antiepileptic drugs, are medications used to prevent or reduce the severity & frequency of seizures in various types of Epilepsy.
- They mainly act by
  - Inhibiting excitatory signals
  - Enhancing Inhibitory signals
  - Interfering with ion channels

IMPERFECT PHARMACY

# EPILEPSY

- Epilepsy is one of the most common chronic neurological disorder characterised by recurrent & unpredictable seizures due to disorder of brain cells.
- Seizures occurs due to sudden, uncontrolled electrical disturbances in brain that can cause changes in behaviour, movement, sensation & loss of consciousness.
- It is an Paroxysmal Disorder.
- It often occurs due to too much excitation or too low inhibition.

## TYPES OF EPILEPSY

It is of mainly two types :

- ① Generalised Epilepsy
- ② Focal Epilepsy

## GENERALISED EPILEPSY

- A Generalised Epilepsy is a type of seizure that involves abnormal electrical activity throughout the entire brain.
  - It affects both Hemispheres.
  - It is further subdivided as follows :
- ① Tonic Clonic Seizure
  - ② Absence Seizure
  - ③ Tonic Seizure
  - ④ Clonic Seizure
  - ⑤ Atonic Seizure
  - ⑥ Myoclonic Seizure

- ① **Tonic - Clonic** : • It is also known as Grand-Mal Seizure.  
• It is characterised by loss of consciousness, stiffening of muscles (Tonic Phase) & jerking movements (Clonic Phase)  
• It leads to Post Seizure Depression.
- ② **Absence** : • It is also known as Petit-Mal Seizures.  
• It is characterised by sudden loss of consciousness (For 30-60 seconds) in middle of an activity.  
• In this patient shows absent minded behaviour & typically occurs in children
- ③ **Tonic** : • Tonic seizure involves sustained muscle stiffness/rigidity.  
• It usually affects muscles in back, arms & legs.
- ④ **Clonic** : • It is characterised by repeated jerking movement of muscles.  
• It usually affects neck, face & arms.
- ⑤ **Atonic** : • It involves sudden loss of muscle control, leading to collapse or fall.
- ⑥ **Myoclonic** : • These seizure involves sudden brief muscle contraction.  
• It can occur in specific muscle group or involve in entire body

## FOCAL EPILEPSY

- It is also known as Partial Epilepsy.
  - In this only a single / specific part of brain is affected
  - It is further subclassified into two types
- ① Simple Partial Seizure
  - ② Complex Partial Seizure

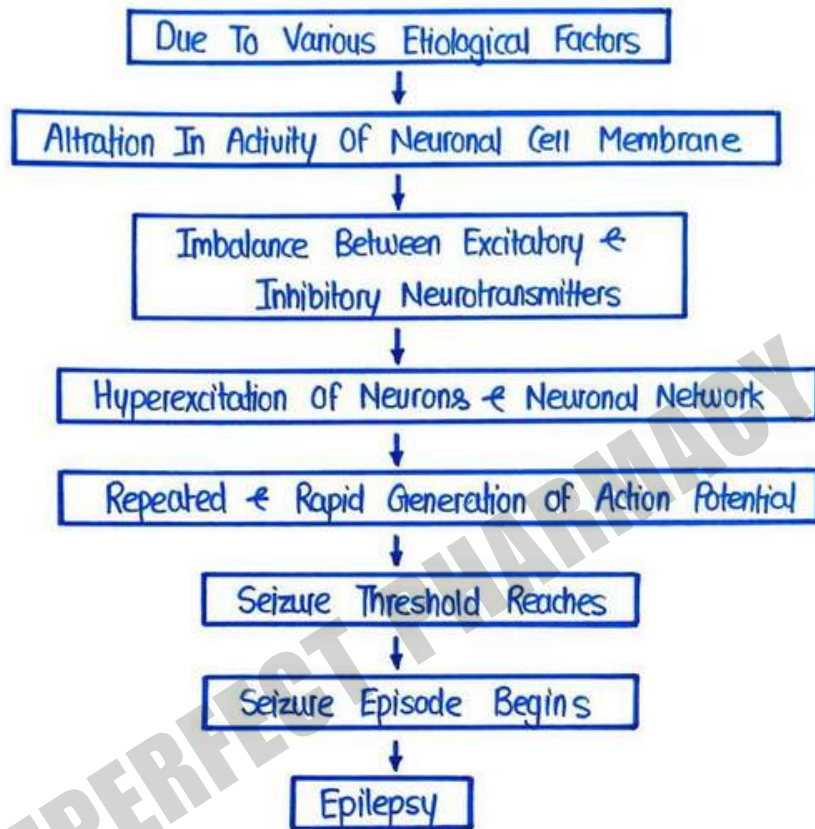
- ① **Simple Partial** :
  - These seizures do not cause loss of consciousness.
  - They may cause localised symptoms such as tingling, changes in emotion, sensation & perception.
- ② **Complex Partial** :
  - These seizures involves loss of consciousness accompanied by unusual behaviour or automatism.
  - The person may not remember seizure afterwards.

## CAUSES / ETIOLOGY

- Genetic Factors
- Head Injury
- Brain Tumour
- Meningitis
- Alzheimer's Disease
- Stroke
- Hypoglycemia
- Idiopathic Reasons
- Certain Medications

## PATHOGENESIS

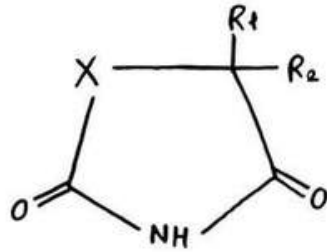
The pathogenesis of Epilepsy can be explained as follows :



## SYMPTOMS

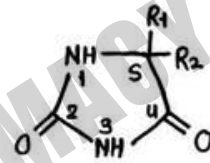
- Temporary Confusion
- Muscle Contraction
- Muscle Stiffening
- Loss Of Consciousness
- Uncontrolled Jerking
- Sudden rapid eye movement
- Sudden Mood Changes

## SAR OF ANTICONVULSANTS



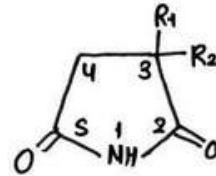
### ① Hydantoin Derivative

- Obtain by substitution of  $\text{—NH—}$  at X
- Substitution at position S is crucial for activity  
N1 & N3 should be unsubstituted



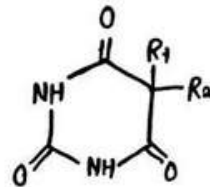
### ② Succinimides

- Substitution of  $\text{—CH}_2\text{—}$  yields succinimides
- Substitution of  $R_1$  by aryl group forms active form e.g. Phenyloximide



### ③ Barbiturates

- Substitution of  $\text{—NH—C(=O)—}$  yields Barbiturates
- SAR already discussed in Sedative & Hypnotics



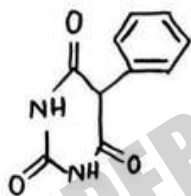
### ④ Benzodiazepines

- SAR discussed in Sedative & Hypnotics

## BARBITURATES

- Barbiturates are group of drugs that act as central nervous system depressants.
- They slow down brain activity and are used to treat seizures, anxiety, insomnia and to include anesthesia.
- They includes:
  - ① Phenobarbitone
  - ② Methobarbital

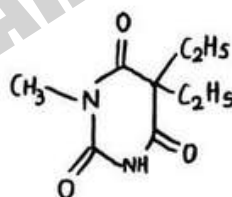
### PHENOBARBITONE



#### Uses

- Used in treatment of grand mal epilepsy.
- Used as sedatives & hypnotics.

### METHABARBITAL



#### Uses

- Used as anticonvulsant, sedative & hypnotics.

## HYDANTOINS

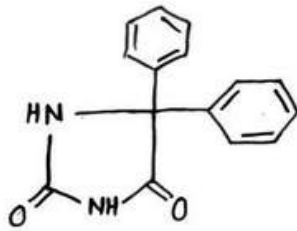
- Hydantoins are class of drugs that used as anticonvulsants (antiepileptic).
- They help to control seizures by stabilizing nerve activity in the brain.
- They includes :
  - ① Phenytoin
  - ② Mephenytoin
  - ③ Ethotoin

## MECHANISM OF ACTION

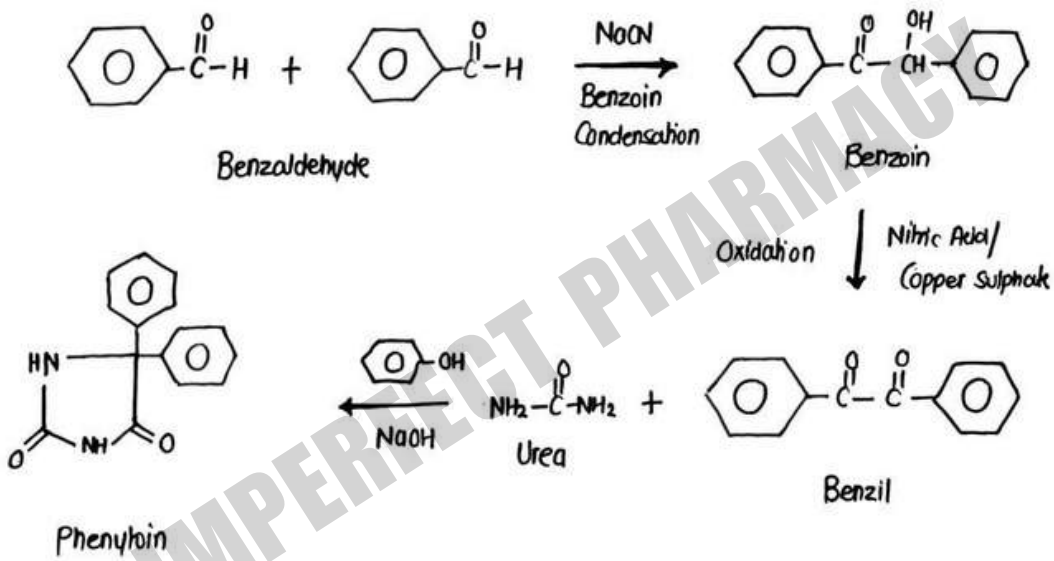
- They blocks sodium ( $\text{Na}^+$ ) channels in brain cells, and stop to rapid & repeating fire of nerves, which prevents seizures from happening.

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## PHENUTOIN



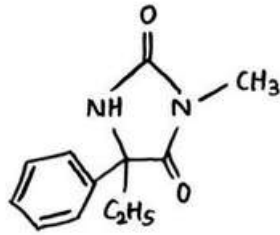
## SYNTHESIS



## Uses

- Treatment of seizures

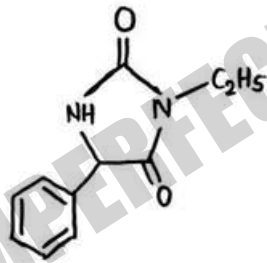
## MEDPHENYTOIN



### Uses

- Used in the treatment of tonic-clonic seizures.

## ETHOTOIN



### Uses

- Mostly used in combination with other anticonvulsants.
- Used in tonic-clonic and partial seizures.

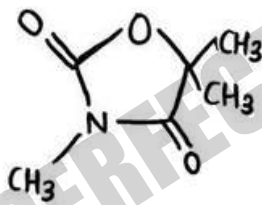
## OXAZOLIDINE DIONES

They are class chemical compounds used to treat mainly seizures.

### MECHANISM OF ACTION

They reduce the activity of nerves by blocking calcium channels in brain.

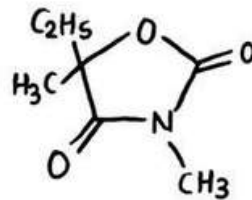
#### TRIMETHADIONE



##### Uses

- Used in the treatment of absence seizures, when other drugs not work.

#### PARAMETHADIONE



##### Uses

- Used as anticonvulsants.

## SUCCINIMIDES

It is a five membered ring containing two carbonyl group & 1 nitrogen atom

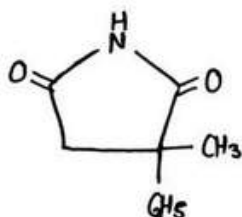
### MOA

- Succinimides reduce the frequency of seizures by inhibiting T-type calcium channels, which are believed to play a role in absence seizures.

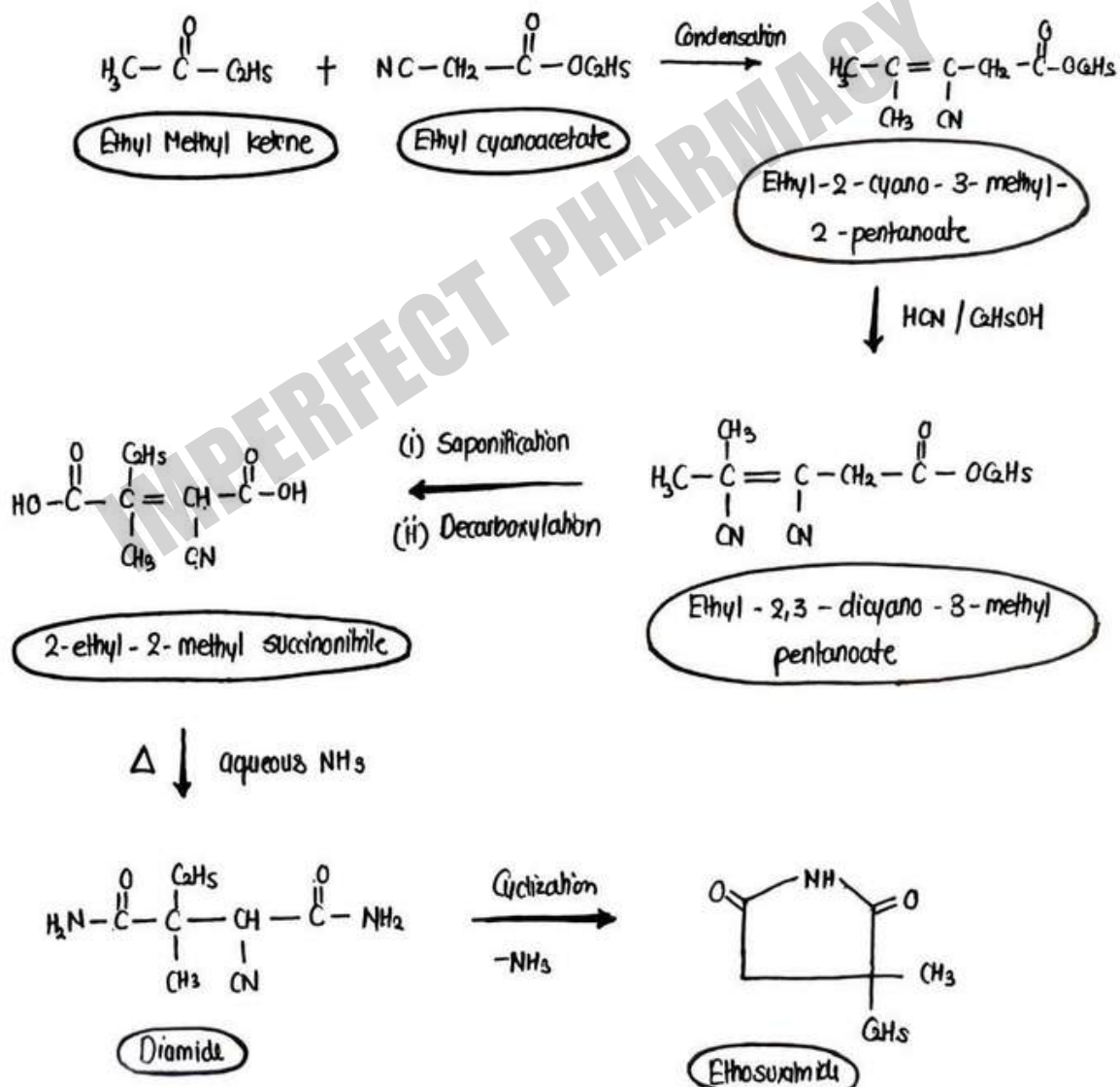
### Drugs

- ① Ethosuximide \*
- ② Phenytoin
- ③ Methusuximide

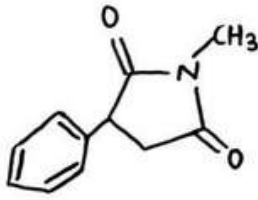
## ETHOSUXIMIDE



### SYNTHESIS



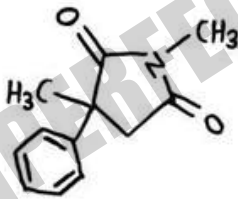
## PHENSUXIMIDE



### Uses

- Used as an anticonvulsant (antiepileptic)
- Reduce the risk of attack.

## METHSUXIMIDE



### Uses

- Prevent seizures
- Treatment of absence seizures.

## UREA AND MONOCYUREAS

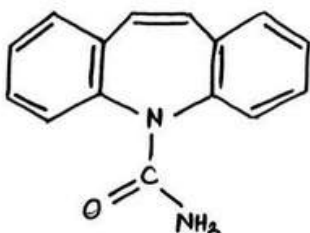
- Urea and Monocylureas are chemical compounds used in medicines, where ureas contain two nitrogen atoms bonded to carbonyl group, and monocylureas are ureas with one acyl (carbon-based) group attached.

## MECHANISM OF ACTION

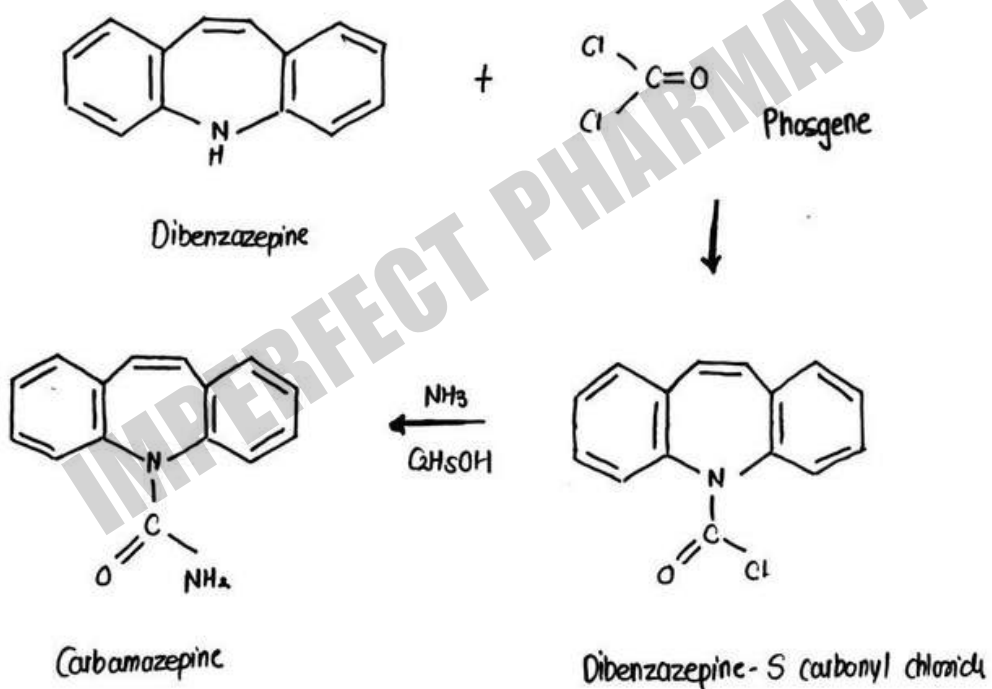
They work by calming overreactive brain signals, often by blocking  $\text{Na}^+$  sodium channels or enhancing GABA activity, helping to seizures prevention.

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## CARBAMAZEPINE



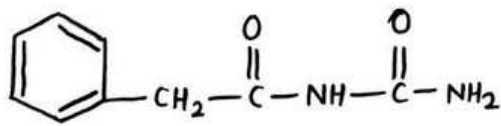
### Synthesis



### Uses

- Epilepsy | Seizures

## PHENACEMIDE



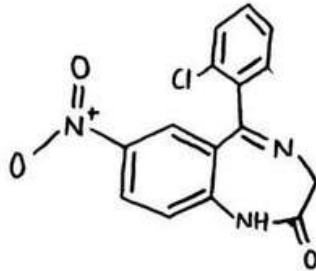
### Uses

- Used in treatment of generalised tonic-clonic, absence & mixed seizures.

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## BENZODIAZEPINES

### CLONAZEPAM

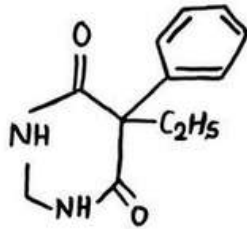


#### Uses

- Used in treatment of all types of epilepsy.
- Used as Hypnotics & Sedatives.

## MISCELLANEOUS

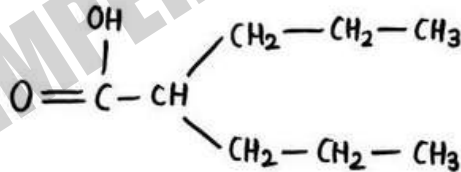
### ① PRIMIDONE



#### Uses

- Management of psychosis.

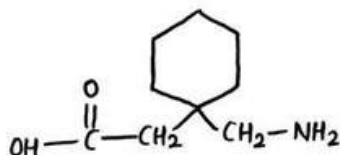
### ② VALPROIC ACID



#### Uses

- Used in treatment of absence and tonic-clonic seizures.

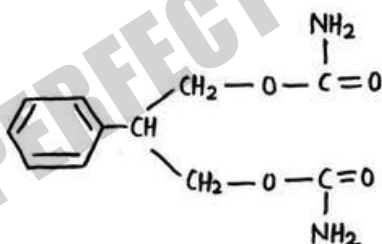
### ③ GABAPENTIN



#### Uses

- Used in the treatment of epilepsy.
- Used as analgesic, anti-anxiety, antimanic and antiparkinson, also used to treat neuralgia.

### ④ FELBAMATE



#### Uses

- Used in treatment of partial seizures, when not treated by other drugs.  
Used as anticonvulsant / antiepileptic.

# THANK YOU

FOR CHOOSING IMPERFECT PHARMACY AS YOUR STUDY PARTNER



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