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UNIT-4 (Topic-2)

Antipsychotics

Antipsychotic agents, which have also been called major Tranquilizers, Neuroleptics & ataractics, produce calm or neurosedation in severly disturbed psychiartric patients.

→ primarily used for the treatment of symptoms of mental Syndromes. They cause sedation.

→ They are essentially used in the treatment of psychoses such as Schizophrenia & Organic psychoses.

→ They act mainly on the lower brain area to produce emotional Calmness & relaxation without significant sedation, hypnosis motor impairment or Euphoria.

→ These donot cause dependence, only inhibits the psychotic manifestations without treating the underlying disease.

→ These drugs have in common the pharmacological property of antagonising the actions of dopamine, ~~and~~

The most imp types of psychosis are :-

i) Schizophrenic affective disorders E.g. depression, mania
organic psychoses

Neuroleptics drugs are effective in the treatment of Schizophrenia.

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* Delusions, hallucinations, thought disorders withdrawal from social contacts and flattening of emotional responses.

Mechanism:—

- The MOA of antipsychotics is not clear.
- However it is believed that they are antagonist of dopamine and dopaminomimetics

  these drugs causes blockage of dopamine D receptors which results in changes of behavioral reasons.
- It is also possible that they block serotonin receptors and muxcarinic choline receptors.
- Antipsychotic drugs are competetively bind with dopamine receptors and block the action of dopamine on the corresponding receptor sites & hence lowers the psychotic activity.

  Central dopaminergic receptors are subdivided into D_1, D_2, D_3.

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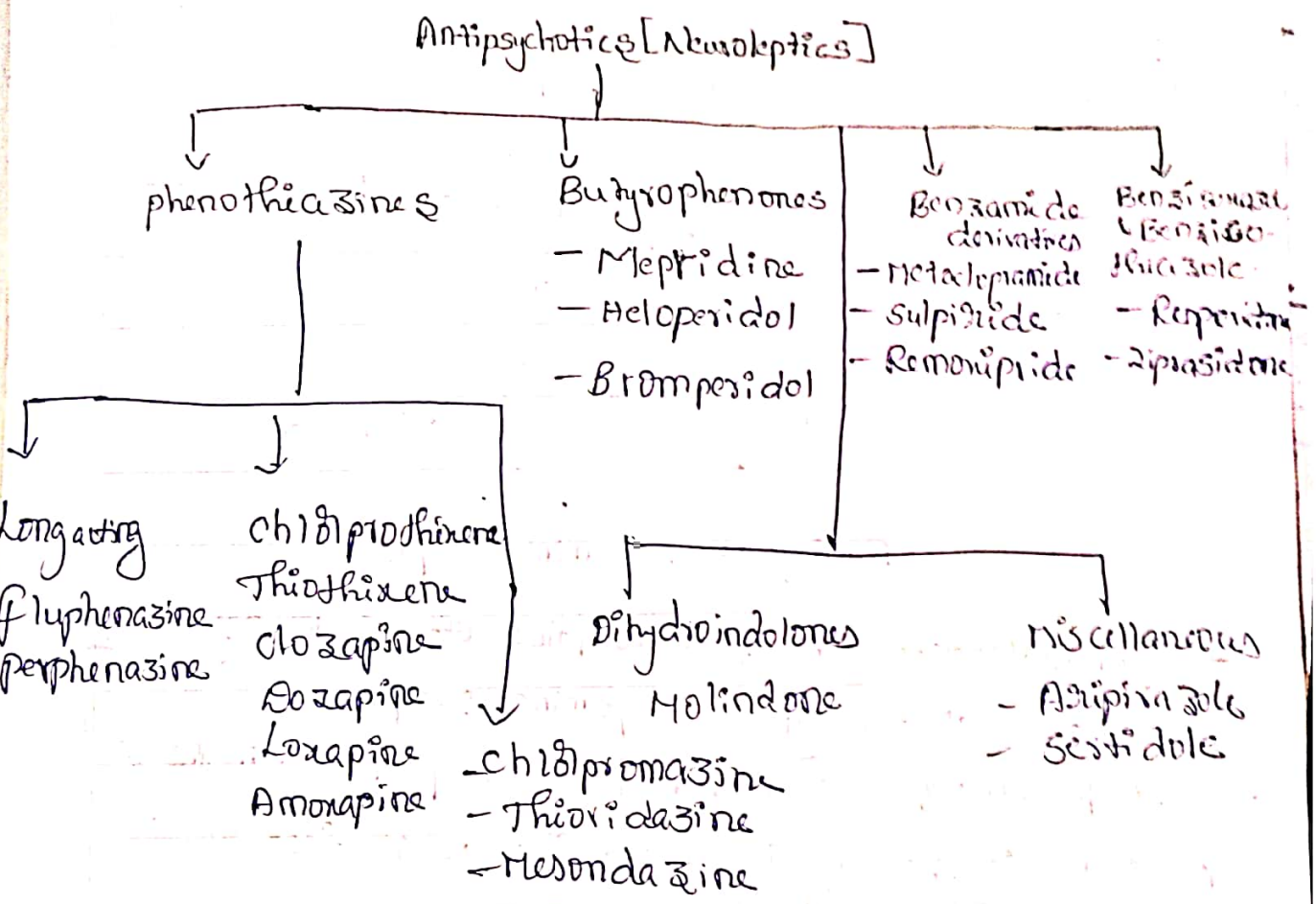
classification



Syllabus:-

phenothiazines:- promazine Hydrochloride, chlorpromazine Hydrochloride, Trifluopromazine, Thioridazine HCl, piperacetazine HCl, prochlorperazine maleate, Trifluperazine HCl.

Ring analogues of phenothiazines:- chlorprothixene, Thiothixene, Loxapine Succinate, clozapine.

fluorobutyrophenones:- Haloperidol, Droperidol, Risperidone.

Beta amino ketones:- Molindone HCl,

Benzamide :- Sulpieride.

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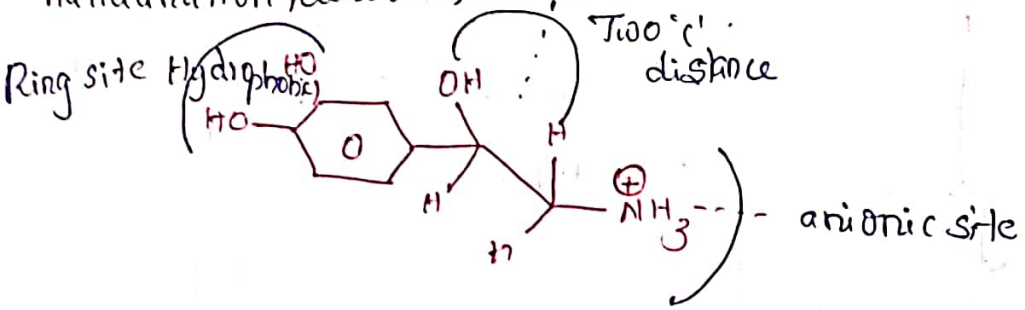
phenothiazines :—

- phenothiazine is a tricyclic ring of thiazine type.
- phenothiazine act on specific post-synaptic receptor and block the post synaptic dopamine receptor.
- They work on positive symptoms on psychosis such as hallucination, delusion, loss of association and bizarre behaviour.



Binding of Dopamine receptor.

-> phenothiazine shows neuroleptics effects mainly through interaction at D_2 type of dopamine receptor.

-> The presence of e⁻ withdrawing group(chloro) in the 2nd position of the ring is an imp structural feature for neuroleptic property.

-> The chloro group in the 2nd position tilts the protonated side chain towards the ring. This allows the favourable Vander waal's force of attraction of side chain with chloro substituent. The resulting conformation permits the superimposition of dopamine. Even though phenothiazine contains 3 'c' chains, two carbon chains, two carbon distances is attained through the molecular bonding of the side chain towards ring. phenyl ring interact with flat hydrophobic area of ring.

Date :

Name of the Experiment :

Phenothiazine Derivatives

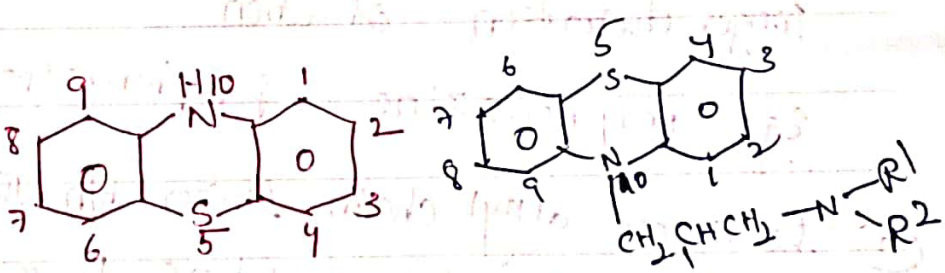
These are non-selective, competitive antagonists of D_1 & D_2 receptors and hence blocks dopamine activity on these receptor sites.

a) Phenothiazine with an aliphatic side chain — Chlorpromazine, promazine, Triflupromazine

b) Piperazine derivatives — Acetophenazine, fluphenazine, perphenazine, difluoperazine.

c) Piperidines — Mesoridaine, thioridazine

SAR :—



Basic structure of phenothiazine.

(1) Unsubstituted phenothiazines has no activity but has good lipophilicity for brain penetration. Substitution at C-2 & N-10 is required for activity.

(2) C-2 must have an electron withdrawing group and a terminal amino substituent must be present at N-10. It can be piperazine piperidine / aliphatic chain.

Eg: chlorpromazine & prochlorperazine.

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(3) Substituent 3rd position shows significant activity when compared to unsubstituted compound but not as significant as substituent at 2nd position.

(4) Substitution at 1st & 4th has a deleterious effect on antipsychotic activity.

(5) Oxidation of ring sulphur to sulphoxide or sulphone ↓es neuroleptic activity.

(6) 4th position of the piperizine ring system can be substituted by 2-OH methyl group to give drugs with longer duration of action.

Eg: perphenazine & fluphenazine.

(7) The linear alkyl chain linker b/n the core ring and the terminal amino ring must have three methylene units $-CH_2-CH_2-CH_2-$; shortening of the sidechain ↓es activity.

(8) At N-10 the terminal amino substituent can be a part of piperidine nucleus and substituent at C-2 can be methylthio (CH_3S-) or its oxidized form (CH_3SO-).

for eg: thioridazine & mesoridazine.

(9) The 10th position $-N-CH_2$ can be replaced isosterically by ethylidene group to form various thioxanthenes. These are more potent than the parent drug.

Eg: chlorprothixene & thiothixene.

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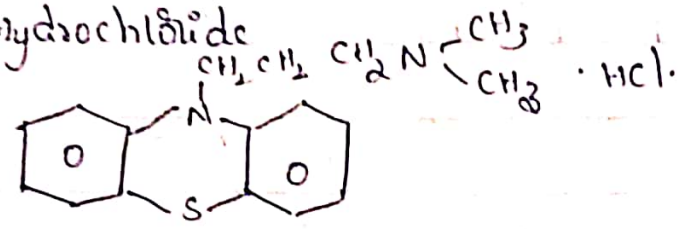
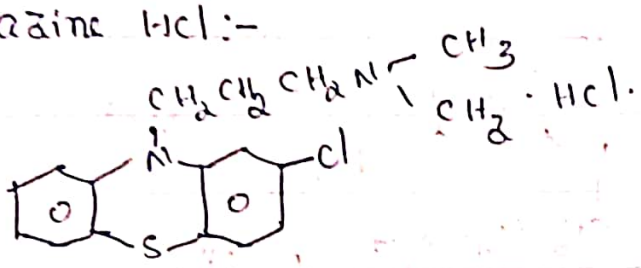
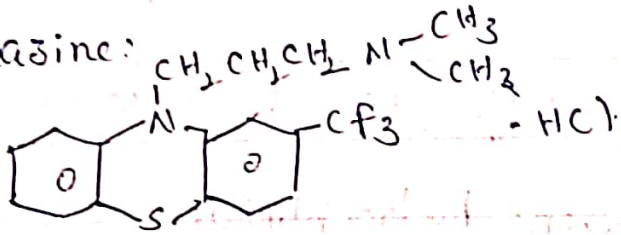
① promazine Hydrochloride



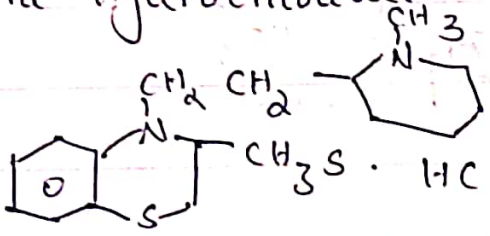
② Chlorpromazine HCl :-



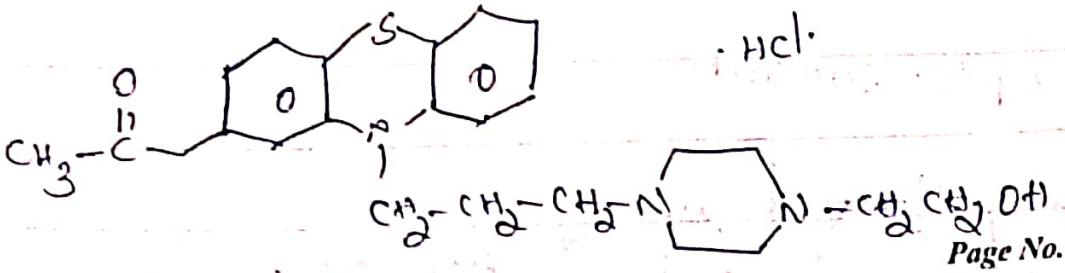
③ Triflupromazine :



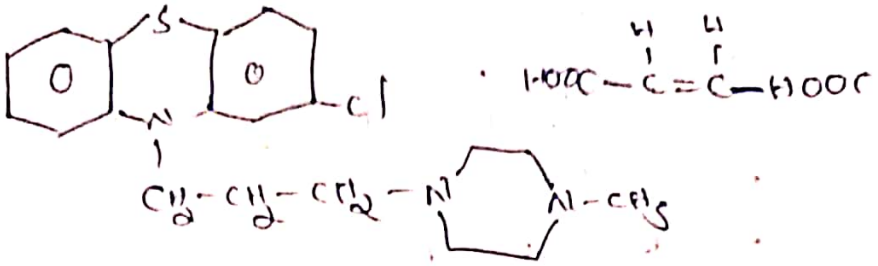
④ Thioridazine Hydrochloride :-



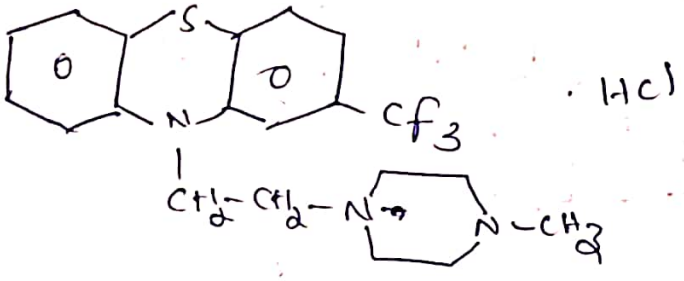
⑤ Piperacetazine Hydrochloride



⑥ prochlorperazine Maleate:-

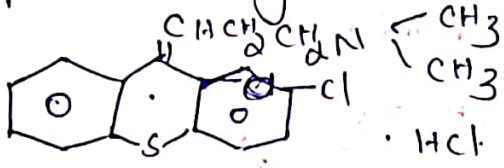


⑦ Trifluoperazine Hydrochloride:

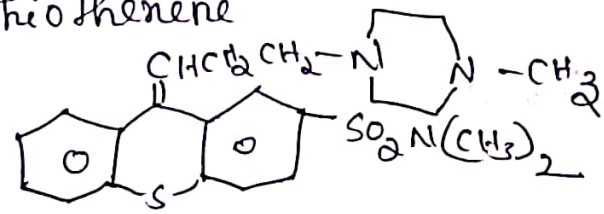


. Ring analogues of phenothiazines:-

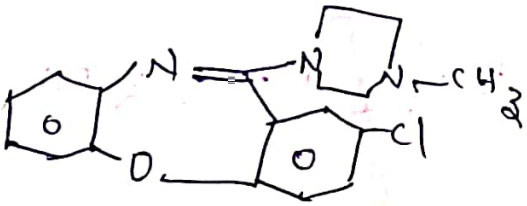
① chlorprothixene hydrochloride



② Thiothenene



③ Loxapine succinate.



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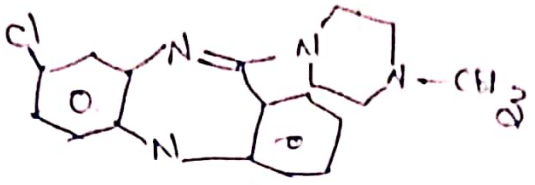
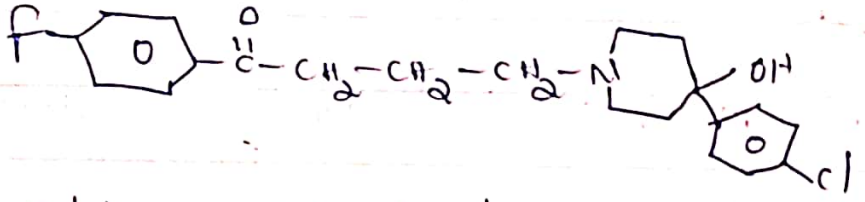
④ Clozapine :-

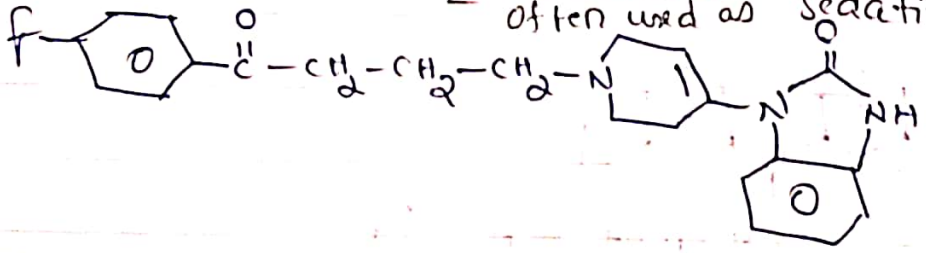


Butyrophenones :-

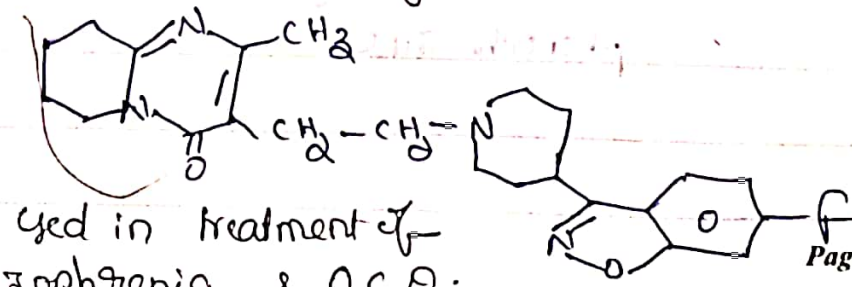
① Haloperidol



② Droperidol use :- used as an antipsychotic, antiemetic often used as Sedative.



③ Risperidone MOA :- act as antagonist of dopamine, serotonin, α, adrenergic & H, histamine receptors.



use :- used in treatment of Schizophrenia & OCD.

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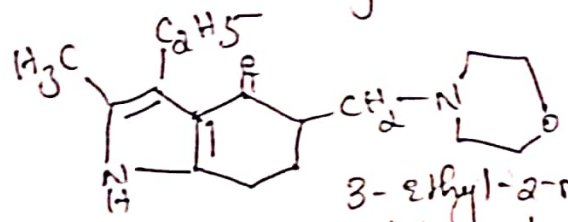
C. Beta Amino Ketones:-

MOA:- D_2 receptor ↓ dopamine activity.

① Molindone Hydrochloride.



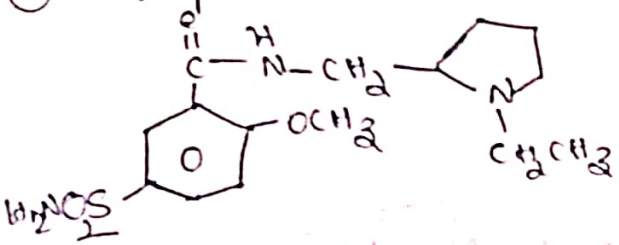
Use:- psychotic disorders Schizophrenia.

3-ethyl-2-methyl-5-morpholin-4yl-methyl)1,5,6,7 tetrahydro-4H-indol-4-one hydrochloride.

D. Benzamides:-

MOA:- selective ↓ act as D_2 receptor antagonist.

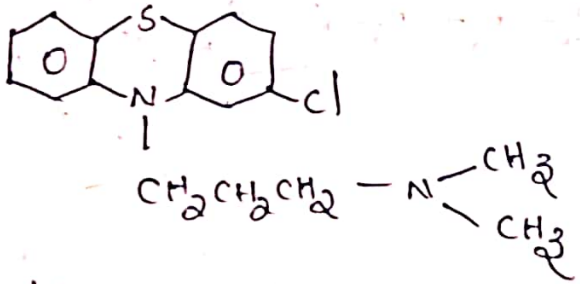
① Sulpiride



Use:- mainly used in the treatment of Schizophrenia.

(RS) - 5-sulphamoyl-N-(1-ethyl pyrrolidin-2-yl) methyl-2-methoxy benzamide

* Chlorpromazine.



2 chloro - 10-[3-(dimethyl amino) propyl] phenothiazine.

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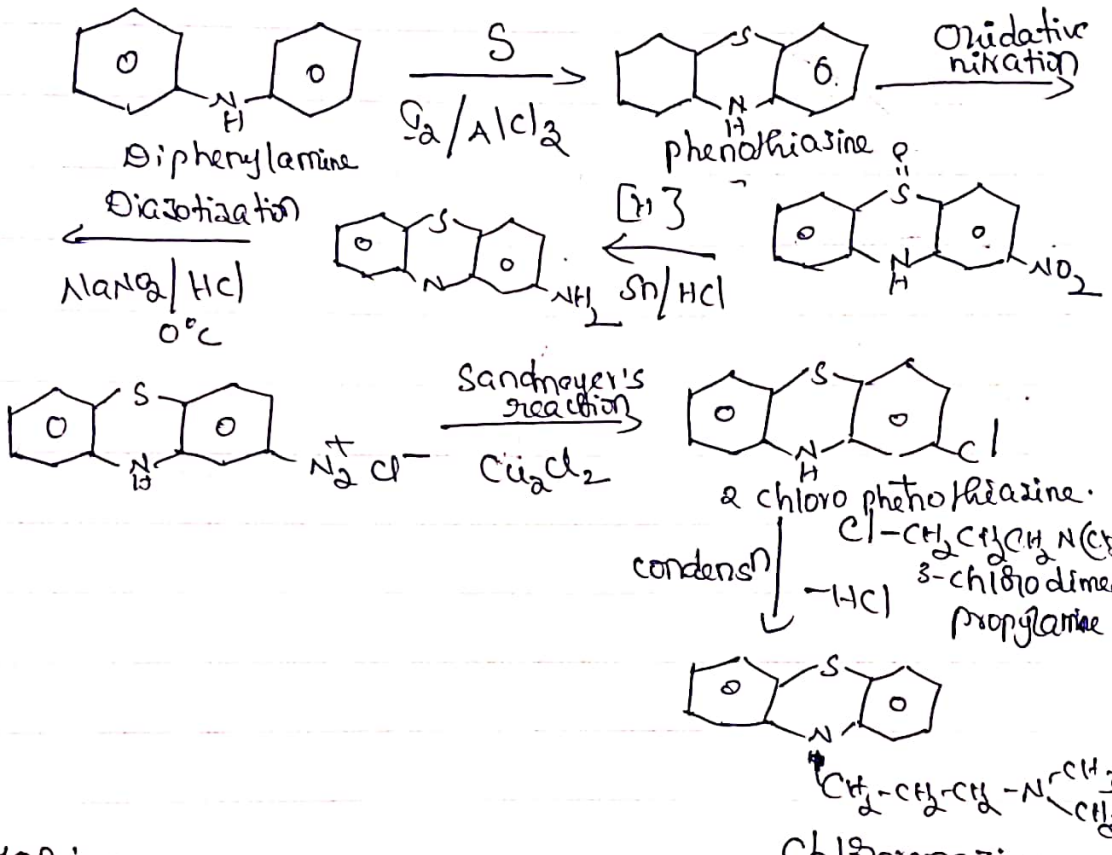
Synthesis :—



MOA :—

It acts as an antagonist of Dopamine, serotonin, Histamine Adrenergic & muscarinic receptors.

Uses :— used in the treatment of Schizophrenia.

management of manifestation of psychotic disorders, depressive illness

- also used as an antiemetic to control nausea & vomitting.
- occassionally used for treatment of migraine.

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Name of the Experiment : UNIT 4 (Topic-3) Date :

Anticonvulsants/Antiepileptics.

Introduction:-

Epilepsy is a chronic disorder characterized by paroxysmal brain dysfunction due to excessive neuronal discharge and usually associated with some alteration of consciousness.

epilepsy drived from greek

epi- upon, at, close upon

Leptos- Seizure.

Antiepileptics are drugs, which decrease the frequency and or selectivity of seizures in people with epilepsy.

A seizure is a physical findings/changes in behaviour that occur after an episode of abnormal electrical activity in the brain.

Seizures can be classified into :-

partial - Simplex & Complex

Generalized seizure- Absence/petitmal,

Tonic-clonic/grandmal)

myoclonic.

Seizures are generated in the epileptogenic centre of the brain and involves shaking of the extremities i.e body parts.

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Classification, Symptoms & Silent features of Seizures.

Simple partial seizures without impairment of consciousness.

- Motor symptoms
- Special sensory or
- Somato sensory symptoms
- Autonomic symptoms
- Psychic symptoms.

complex partial seizures with impairement of consciousness.

progress to impairement of consciousness with no other features with features as in simple partial seizures. with automatisms.

with impairement consciousness at onset with no other features with features as in simple partial seizures with automatisms

Generalized seizures.

- Absence
  - typical
  - Atypical
- 1. Myoclonic
- 2. clonic
- 3. Tonic
- 4. Tonic/cl
- 5. Atonic

Petit mal - Abse
Grandmal - Tonic

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Classification of Anticonvulsant drugs.

(based on structure).

- **Barbiturates**
  - phenobarbitol
  - methabarbital
- **Hydantoins**
  - phenytoin
  - mephenytoin
  - ethotoin.
- **Oxazolidine diones**
  - Trimethadione
  - paramethadione
- **Succinimides**
  - phensuximide
  - methsuximide
  - ethosuximide
- **Miscellaneous**
  - primidone
  - valproic acid
  - gabapentin
  - felbamate.
- **Benzodiazepines**
  - clonazepam.
- **Urea & monocyclic ureas**
  - phenacemide
  - carbamazepine

2. Based on MOA :-

Sodium channel blockers — phenytoin, carbamazepine, oxcarbazepine, lamotrigine, zonisamide, Lacosamide.

Ca^{+2} channel blocks :- Topiramate, lamotrigine, Ethosuximide.

GABA enhancers :- BZD's, Tiagabine, Vigabatrine, phenobarbital

Glutamate receptor antagonists - Eg: Topiramate, felbamate.

GABA pentenoids Eg: gabapentic, pregabalin.

Diuretics Eg: Butetanide, Acetazolamide.

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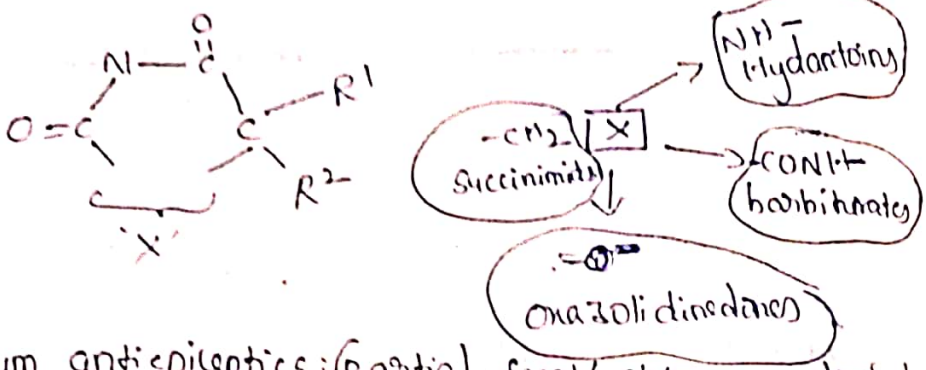
Structures common to anticonvulsant drugs.



① Narrow spectrum antiepileptics: (partial, focal/ absence, myoclonic)
Eg: phenytoin, phenobarbitone, carbamazepine, oxcarbazine, gabapentin, pregabalin, lacosamide, vigabatrin.

② Broad spectrum:- (partial plus absence or myoclonic seizures).
Eg: valproic acid, lamotrigine, topiramate, zonisamide, levetiracetam, clonazepam, rufinamide.

Drugs used in treatment of diff. kinds of epilepsy:—

a) Grandmal — phenytoin, carbamazepine, phenobarbitone, valproic acid.

b) partial — phenytoin, carbamazepine, barbiturates

c) petitmal/ absence — valproic acid, Ethosuximide, clonazepam

d) myoclonic — valproic acid, clonazepam.

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Mechanism of Action :-

The mechanism of antiepileptic drugs are not clear since the etiology of epilepsy is not yet completely understood.

1) Some drugs block Na^+ channel :-

Both Na^+ & Cl^- ions are present at higher conc. outside the cell, where as K^+ charged proteins & org. cations are more abundantly available inside the cell.

epileptic seizures causes Na^+ ion accumulation with in the contral neuron, which initiates enhanced synaptic nerve transmissions following presynaptic stimulation.

These drugs ↓es Na^+ intracellular ion by activating biochemical process that normally extrudes Na^+ ion from neurons.

prolongation of this inactive state with prolongation of the refractory period is the principle of mech.

2. Some drugs block Ca^{2+} channel :- A low threshold Ca^{2+} current govern oscillatory response in thalamic neuron.

3. Some drugs affect synaptic transmission :- Enhanced GABA mediated ⊗n.

4. Some drugs act on GABA :- ↓ing reuptake or ↓ing metabolism of GABA.

5. Some drugs block glutamate-target receptors.

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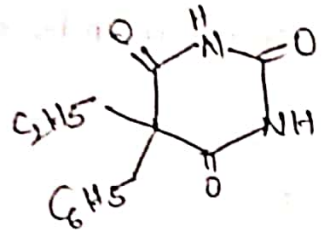
I. Barbiturates:-

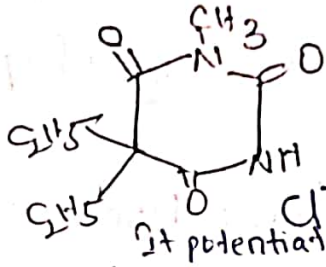
① phenobarbitone



MOA:- Block Na^+ channels or ↑ GABA function.

Use:- used in treatment of grandmal epilepsy. Also used as a hypnotic & sedative. Also used to ↓ the level of bilirubin in neonatal jaundice.

② Methabarbitone.



MOA:- Binds to the GABA receptor & ↑ the duration of time for the Cl^- channels opening. It potentiates the inhibitory action of GABA

Use:- Used in treatment of Grandmal epilepsy.

II. Hydantoins:-

③ phenytoin

MOA:- Blocking the voltage gated Na^+ channel.

Use:- used as an antiepileptic drug. also used in trigeminal neuralgia.

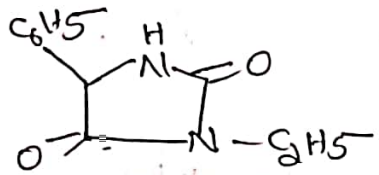
④ Mephenytoin

MOA: It promotes Na^+ efflux from neurons & causes stabilization of threshold against hyper-excitability caused by excessive stimulation or environmental changes. It reduces maximum activity of brainstem centres which causes tonic phase of tonic-clonic seizures.

Use:- Used in treatment of tonic-clonic seizure

Used to control partial seizure

⑤ Ethotoin:-



MOA: Block Na^+ channels or ↑ GABA function.

Use: used in treatment of tonic clonic seizures

- combination ∈ another anticonvulsants.

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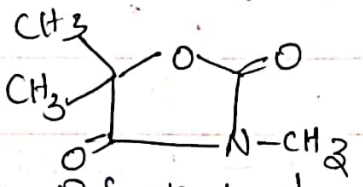
(iii). Oxazolidine diones :-

(6) Trimethadione



MOA :- ⊗ Ca^{+2} chanel.

Use :- Used in treatment of absence seizures.

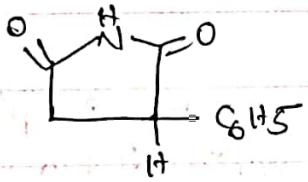
(7) paramethadione.

Use :- Used to treat absense seisures

MOA :- It acts on CNS and reduce the absence seisures by blocking Ca^{+2} channels.

(iv). Succinimides :-

(8) phensuximide

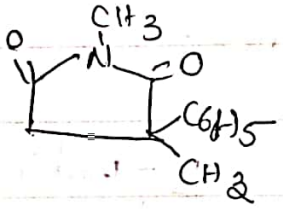


MOA :- It supresses the paroxysmal cells & wave & spike pattern in case of absence seizures.

It also inhibits accumulation of cAMP & cGMP in the brain.

Use :- used in treatment of petitmal seisure.

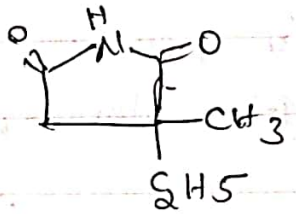
(9) methosuximide



MOA : Alters the chemical mediated neurotransmission

use :- used in the treatment of absense seisures.

(10) Ethosuximide.



MOA : Blocks Ca^{+2} channel. It leads to ↓ burst firing of neuron wh causes stabilizn of nerves.

uses :- used to treat seizures.

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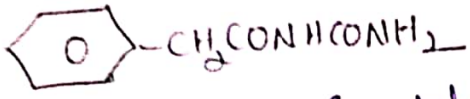
(vi) Ureas & monoacyl ureas:-

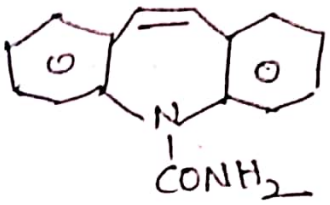
(12) phenacemide:-



MOA:- Raises the threshold for electroshock convulsion & eliminates the tonic phase of seizures.

Use:- used in treatment of tonic-clonic seizures, absence seizures.

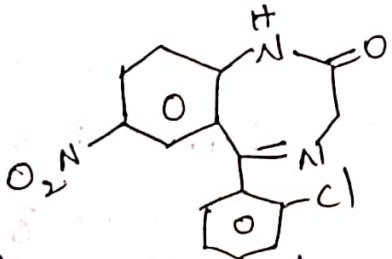
* (13) Carbamazepine



MOA:- Block Na^{+2} channels. and binds to voltage gated Na channels & prevents repetitive and sustained firing of AP.

(vii). Benzodiazepines:-

(13). Clonazepam:-

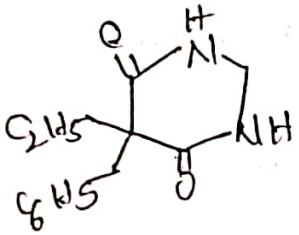


Use:- used in treatment of all types of epilepsy. used in mangement of panic disorders. used in alcohol withdrawl syndrome. also used in management of acute mania.

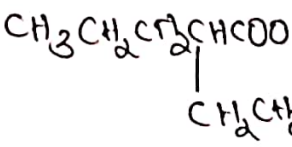
MOA:- operates through GABAergic mech. It potentiates actions of GABA

(viii). Miscellaneous.

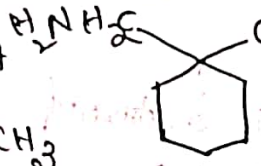
(14) primidone



(15) valproic acid



(16) Gabapentin



Use:- treatment of absence, myoclonic seizures.

(17) Felbamate: