Unit-IV

Sedative Hypnotics

Prepared By Chinmaya Chidananda Behera, Lecturer, UDPS, Utkal University, Vani Vihar, Bhubaneswar, Odisha-751004

Sedative hypnotics definition:

Sedative, Hypnotic, and Anxiolytic-Related Disorders. Definition. Sedatives, hypnotics, and anxiolytics are often prescribed for a number of physical and psychological medical conditions. These substances that **reduce arousal and stimulation in various areas of the brain.**

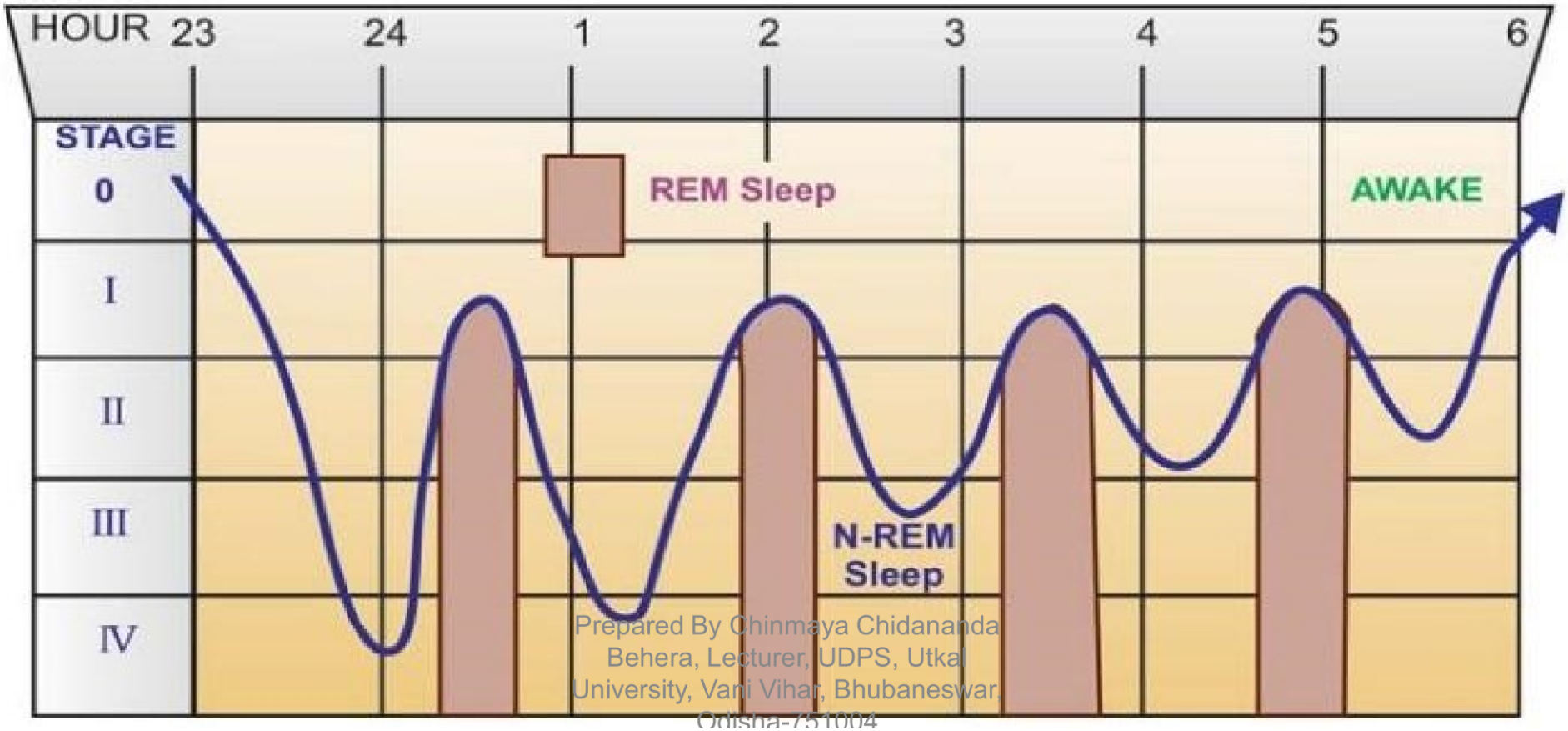
SEDATIVE : Drugs that clam the patient and reduce anxiety without inducing normal sleep.

- Site of action is on the limbic system which regulates thought and mental function.

HYPNOTICS : Drugs that initiate and maintain the normal sleep.

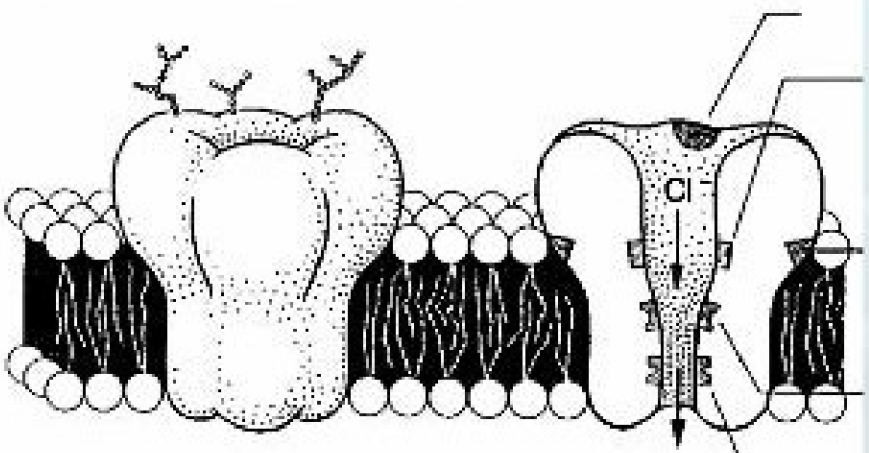
- Site of action is on the midbrain and ascending RAS which maintain wakefulness.

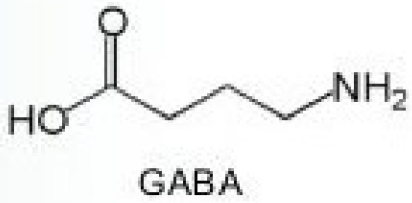
The sedatives and hypnotics are more or less general CNS depressants with somewhat differing time action and dose action relationships. Those with quicker onset, shorter duration and steeper dose-response curves are preferred as *hypnotics* while more slowly acting drugs with flatter dose-response curves are employed as *sedatives*. However, there is considerable overlap; a hypnotic at lower dose may act as sedative. Thus, sedation—hypnosis—general anaesthesia may be regarded as increasing grades of CNS depression. Hypnotics given in high doses can produce general anaesthesia. However, benzodiazepines (BZDs) cannot be considered nonselective or general CNS depressants like barbiturates and others.



Mechanism of Action

Barbiturates potentiate the effect of GABA at the GABA-A receptor. The GABA-A receptor is a ligand gated ion channel membrane receptor that allows for the flow of Cl through the membrane in neurons. GABA is the principle neurotransmitter for this receptor which upon binding causes the channel to open and creates a negative charge in the transmembrane potential. This makes it an Inhibitory neurotransmitter





GABA

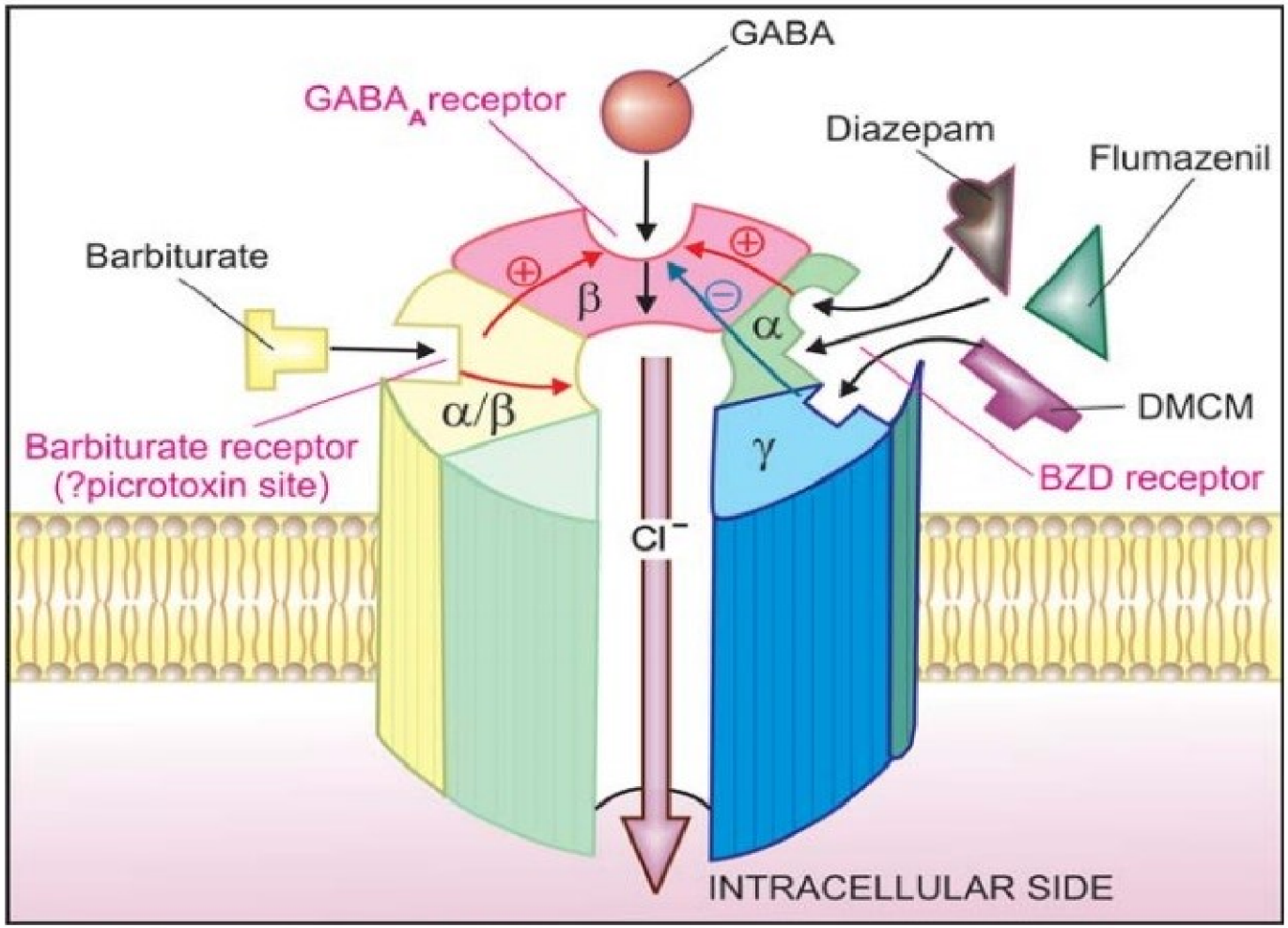


Fig. 29.3: Schematic depiction of $GABA_A$-benzodiazepine receptor-chloride channel complex

The chloride channel is gated by the primary ligand GABA acting on $GABA_A$ receptor located on the β subunit. The benzodiazepine (BZD) receptor located on the interface of α and γ subunits modulates $GABA_A$ receptor in either direction: agonists like diazepam facilitate, while inverse agonists like DMCM hinder GABA mediated Cl^- channel opening, and BZD antagonist flumazenil blocks the action of both. The barbiturate receptor, located either on α or β subunit also facilitates GABA and is capable of opening Cl^- channel directly as well. Bicuculline blocks $GABA_A$ receptor, while picrotoxine blocks the Cl^- channel directly

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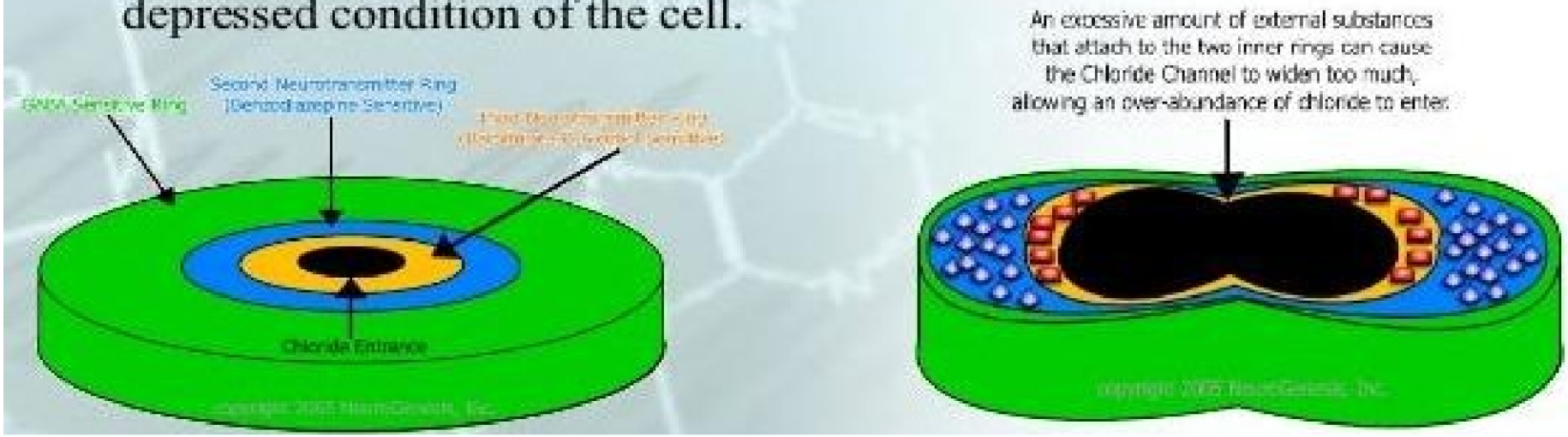
Mechanism of Action

Barbiturates potentiate the effect of GABA by binding to the GABA-A receptor at a nearby site and increasing the chloride flow through the channel. Barbiturates also block the AMPA (2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid) receptor which is sensitive to glutamate, the excitatory neurotransmitter. Glutamate performs the opposite effect from GABA restricting ion flow and increasing the transmembrane action potential of the neuron. By blocking this action Barbiturates serve to increase the duration of the receptor response to GABA and extend the depressed condition of the cell.



Barbiturates also target nicotinic acetyicholine receptors at concentrations that are achieved with clinical use of these drugs. Barbiturates bind to both open and closed states of the AChR and block the flow of ions through the channel. They also block sodium channels and inhibit the neurotransmission.

1. Barbiturates

Long acting	*Short acting*	*Ultra-short acting*
Phenobarbitone	Butobarbitone	Thiopentone
	Pentobarbitone	Methohexitone

2. Benzodiazepines

Hypnotic	*Antianxiety*	*Anticonvulsant*
Diazepam	Diazepam	Diazepam
Flurazepam	Chlordiazepoxide	Lorazepam
Nitrazepam	Oxazepam	Clonazepam
Alprazolam	Lorazepam	Clobazam
Temazepam	Alprazolam	
Triazolam		

3. Newer nonbenzodiazepine hypnotics

Zopiclone, Zolpidem Zaleplon

Chloral hydrate, Triclophos, Paraldehyde, Glutethimide, Methylprilone, Methaqualone and Meprobamate are historical sedative hypnotics no longer used. In addition some antihistaminics (promethazine, diphenhydramine), some neuroleptic/antidepressants (chlorpromazine, amitriptyline), some anticholinergic (hyoscine) and opioids (morphine, pethidine) have significant sedative action, but are not reliable for treatment of insomnia.

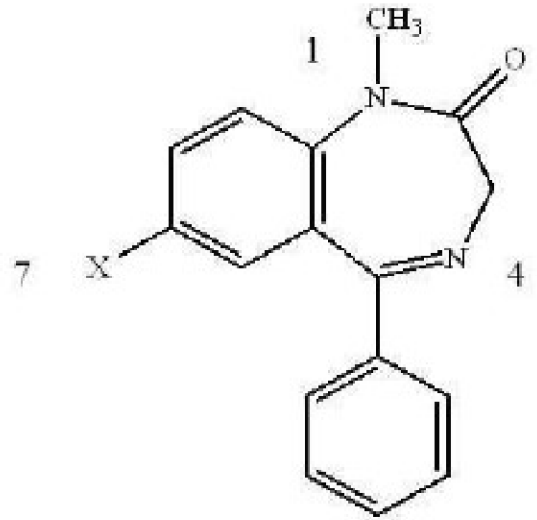
Benzodiazepines

Classification of Benzodiazepines:

Based on duration of action:

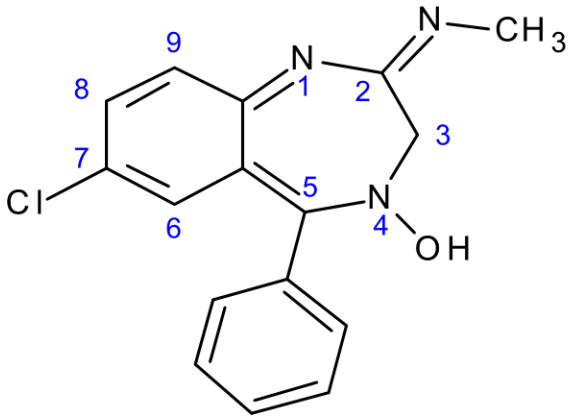
- Ø A long duration of action: (1-3 days) e.g: Diazepam, Nitrazepam
- Ø An intermediate of action: (10-20 hours) e.g: Alprazolam, Lorazepam.
- Ø A short duration of action: (3-8 hours) e.g: Oxazepam, Triazolam

SAR of benzodiazepines



1. The presence of an electron attracting substituent at position 7 is required for activity
2. Position 6,8 and 9 should not be substituted.
3. A phenyl group at the 5 position promotes activity if this group is ortho or di ortho substituted with electron attracting groups , activity is increased.
4. On the other hand, para substitution decreases activity greatly.
5. The 2 carbonyl function is optimal for activity as in the nitrogen atom at 1 position.
6. The N-substituent should be small.

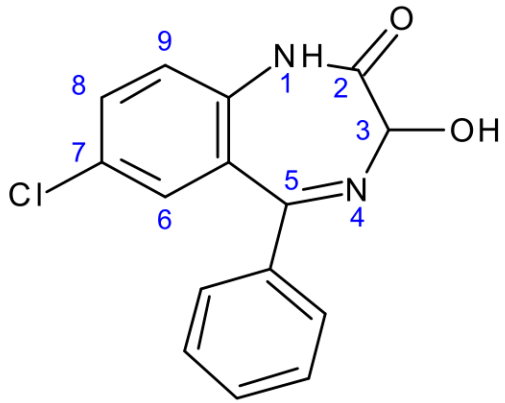
Chlordiazepoxide:



7-chloro-4-hydroxy-N-methyl-5-phenyl-3H-1,4-benzodiazepin-2-imine

Uses: Chlordiazepoxide has antianxiety, sedative, appetite-stimulating and weak analgesic actions. The drug seems to block EEG arousal from stimulation in the brain stem reticular formation. The drug has been studied extensively in many species of animals and these studies are suggestive of action on the limbic system of the brain, which recent evidence indicates is involved in emotional responses.

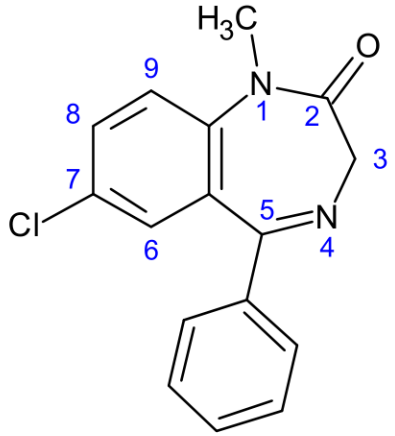
Oxazepam:



7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-one

Uses: Oxazepam stimulates GABA receptors in the ascending reticular activating system. Since GABA is inhibitory, receptor stimulation increases inhibition and blocks both cortical and limbic arousal following stimulation of the brain stem reticular formation.

Diazepam

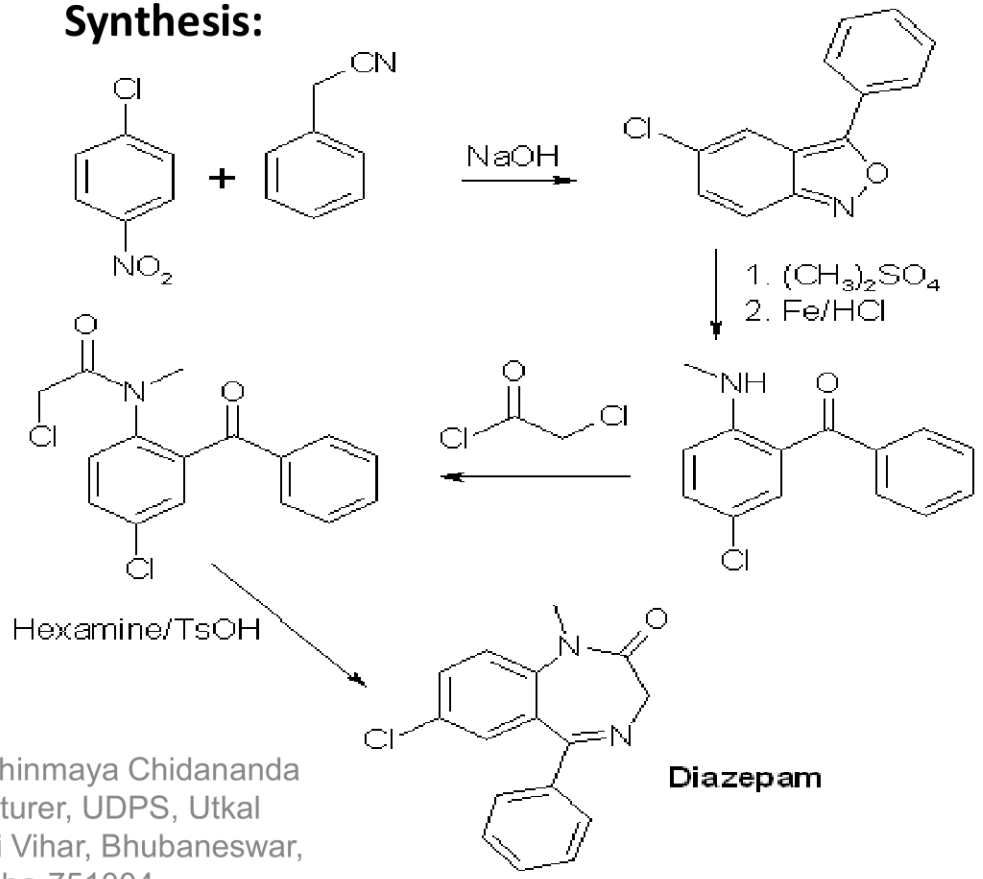


7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2-one

Uses:

Diazepam, a benzodiazepine, generates the same active metabolite as chlordiazepoxide and clorazepate. In animals, diazepam appears to act on parts of the limbic system, the thalamus and hypothalamus, and induces calming effects. Diazepam, unlike chlorpromazine and reserpine, has no demonstrable peripheral autonomic blocking action, nor does it produce extrapyramidal side effects.

Synthesis:



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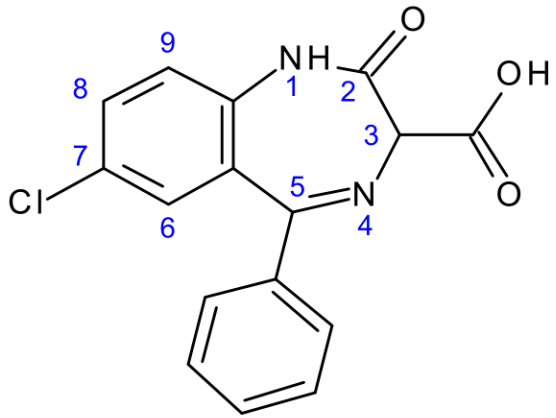
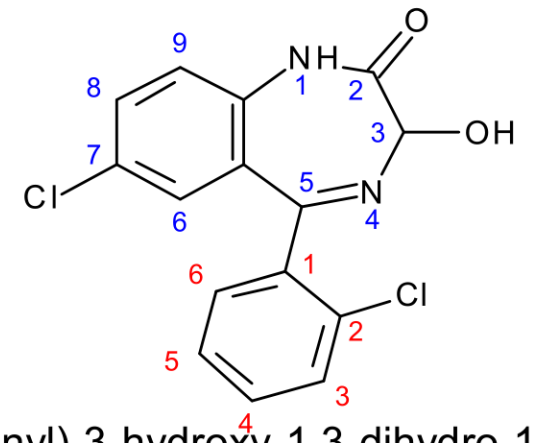
Chlorazepate:



7-chloro-2-oxo-5-phenyl-1,3-dihydro-1,4-benzodiazepine-3-carboxylic acid

Uses: It has depressant effects on the central nervous system. Studies in healthy men have shown that clorazenate has depressant effects on the central nervous system. Since orally administered clorazepate dipotassium is rapidly decarboxylated to form nordiazepam, there is essentially no circulating parent drug.

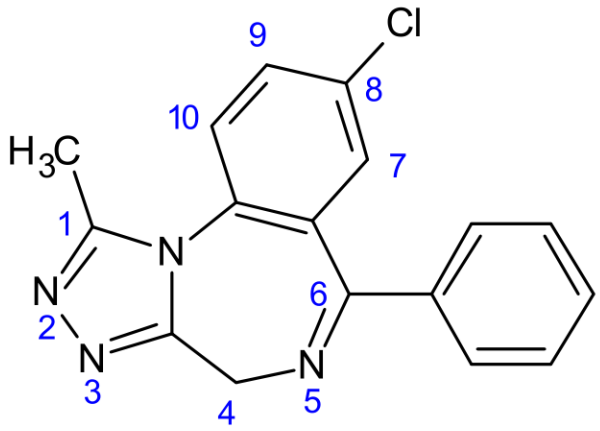
Lorazepam:



7-chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-1,4-benzodiazepin-2-one

Uses: Lorazepam is a benzodiazepine with anxiolytic, anti-anxiety, anticonvulsant, anti-emetic and sedative properties. Lorazepam enhances the effect of the inhibitory neurotransmitter by binding to the GABA receptors causing hyperpolarization, and eventually inhibition of the transmission of nerve signals, thereby decreasing nervous excitation.

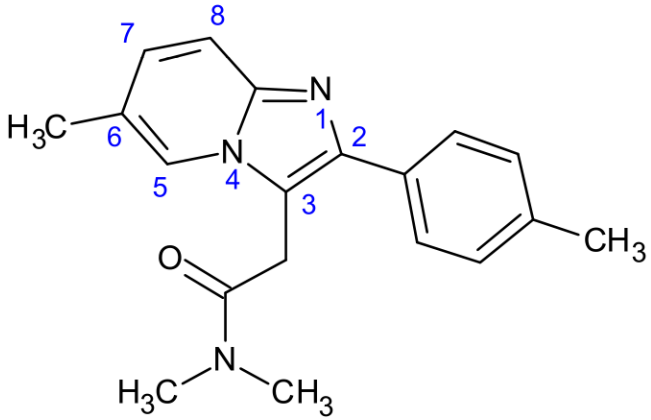
Alprazolam:



8-chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

Uses: Alprazolam, a benzodiazepine, is used to treat panic disorder and anxiety disorder. Unlike chlordiazepoxide, clorazepate, and prazepam, alprazolam has a shorter half-life and metabolites with minimal activity.

Zolpidem:



N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide

Uses: Zolpidem is a sedative or hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties. It interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which non-selectively bind to and activate all three alpha receptor subtypes, zolpidem in vitro binds the (alpha1) receptor preferentially.

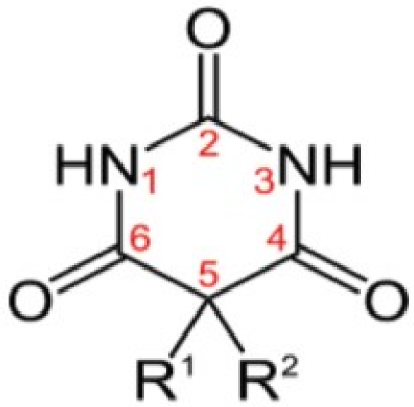
Barbiturtes:

Classification of Barbiturates:

Based on duration of action:

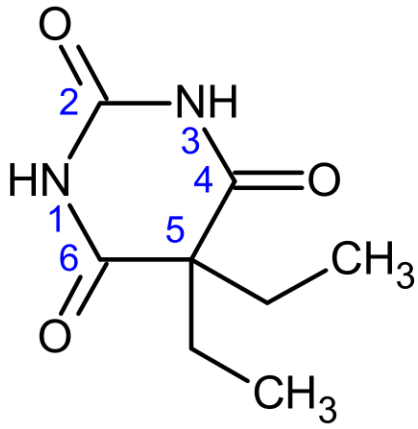
- Ø A long duration of action: (6 hours or more) e.g: Barbital, Phenobarbital.
- Ø An intermediate duration of action: (3 to 6 hours) e.g: Amobarbital, Talbutal.
- Ø A short duration of action: (less than 3 hours) e.g: Pentobarbital, Secobarbital.

Structure Activity Relationship (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.

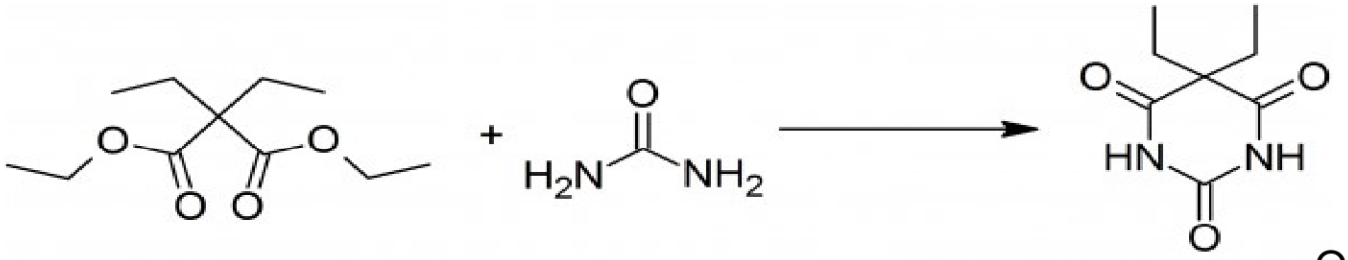
Barbital



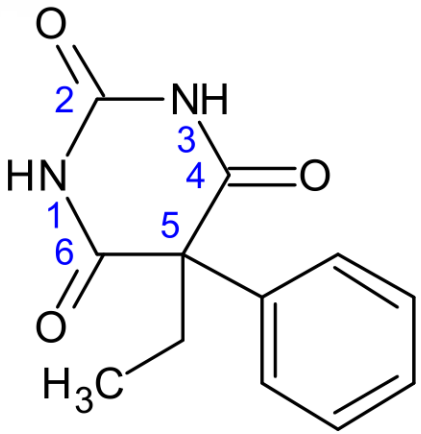
Nomenclature:5,5-diethyl-1,3-diazinane-2,4,6-trione

Uses: Act to prolong the duration of channel opening; and a site at which some steroids may act. GENERAL ANESTHETICS probably act at least partly by potentiating GABAergic responses.

Synthesis:



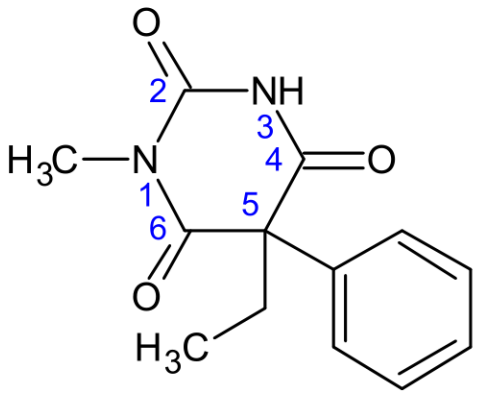
Phenobarbital



Nomenclature:5-ethyl-5-phenylpyrimidine-2,4,6(1H,3H,5H)-trione

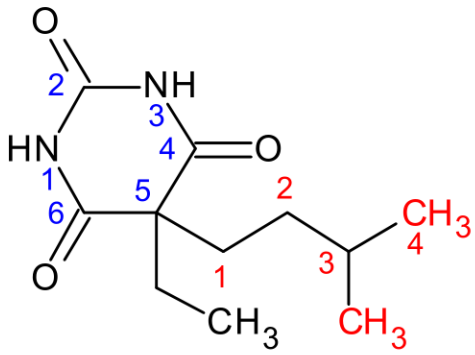
Uses: Phenobarbital, the longest-acting barbiturate, is used for its anticonvulsant and sedative-hypnotic properties in the management of all seizure disorders except absence (petit mal), act by (GABA)-A receptor and synaptic inhibition by hyperpolarization.

Mephobarbital



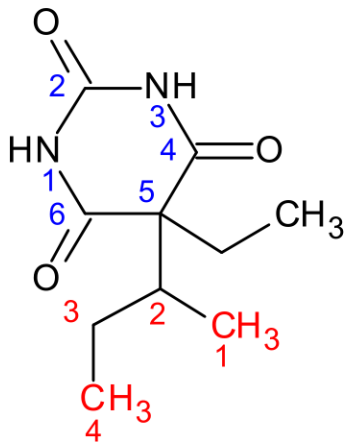
Nomenclature:5-ethyl-1-methyl-5-phenyl-1,3-diazinane-2,4,6-trione
Uses: Methylphenobarbital, a barbiturate, is used in combination with acetaminophen or aspirin and caffeine for its sedative and relaxant effects in the treatment of tension headaches, migraines, and pain.

Amobarbital



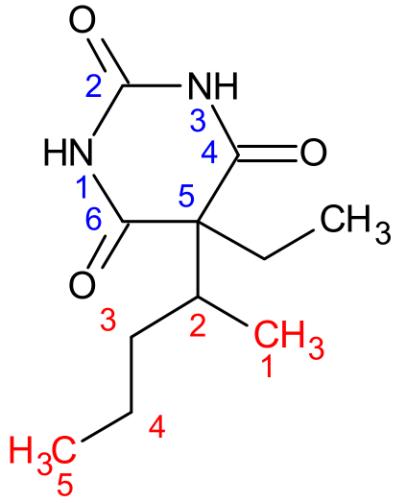
Nomenclature:5-ethyl-5-(3-methylbutyl)-1,3-diazinane-2,4,6-trione
Uses: It induce GABA mediated drowsiness or sleep and reduce psychological excitement or anxiety.

Butabarbital



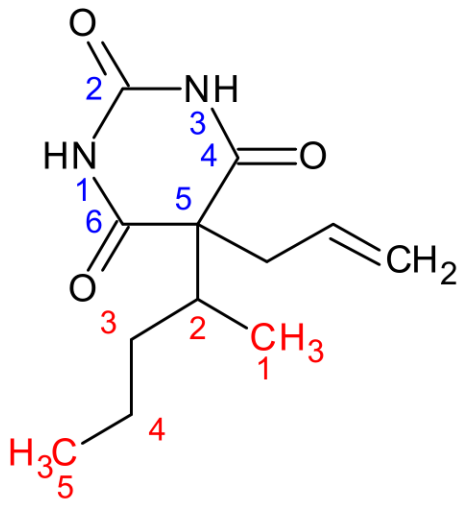
Nomenclature:5-butan-2-yl-5-ethyl-1,3-diazinane-2,4,6-trione
Uses: Butabarbital, a barbiturate, is used for the treatment of short term insomnia. It belongs to a group of medicines called central nervous system (CNS) depressants that induce drowsiness and relieve tension or nervousness.

Pentobarbital



Nomenclature:5-ethyl-5-pentan-2-yl-1,3-diazinane-2,4,6-trione
Uses: Pentobarbital, a barbiturate, is used for the treatment of short term insomnia. It belongs to a group of medicines called central nervous system (CNS) depressants that induce drowsiness and relieve tension or nervousness.

Secobarbital



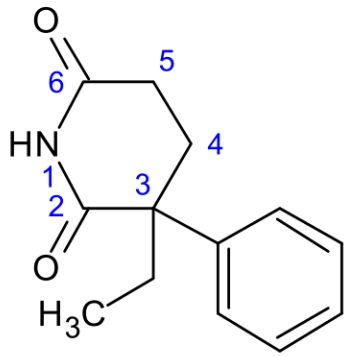
Nomenclature:5-pentan-2-yl-5-prop-2-enyl-1,3-diazinane-2,4,6-trione

Uses: Secobarbital, a barbiturate, is used for the induction of anesthesia prior to the use of other general anesthetic agents and for induction of anesthesia for short surgical, diagnostic, or therapeutic procedures associated with minimal painful stimuli.

Prepared By Chinmaya Chidananda Behera, Lecturer, UDPS, Utkal University, Vani Vihar, Bhubaneswar, Odisha-751004

Miscelleneous:

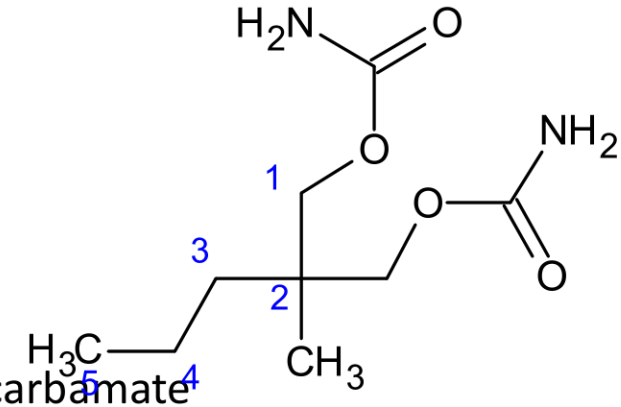
Amides & imides: Glutethmide



Nomenclature:3-ethyl-3-phenylpiperidine-2,6-dione

Uses: Glutethimide is a hypnotic sedative that was introduced in 1954 as a safe alternative to barbiturates to treat insomnia. However, it had become clear that glutethimide was just as likely to cause addiction and caused similarly severe withdrawal symptoms.

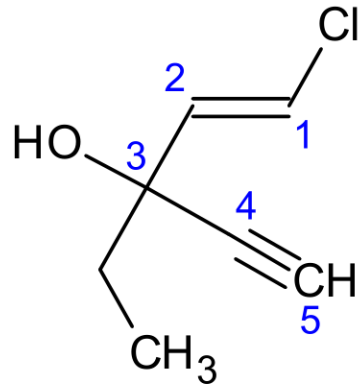
Alcohol & their Carbamate derivatives: Meprobomate



Nomenclature:[2-(carbamoyloxymethyl)-2-methylpentyl] carbamate

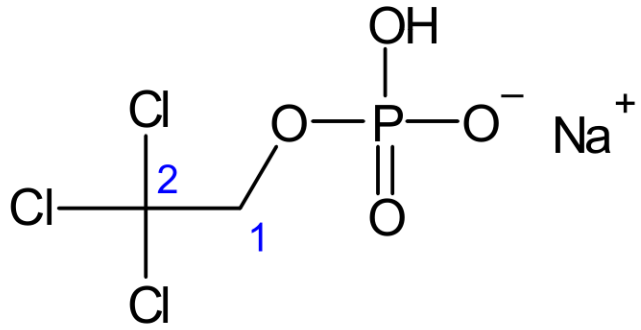
Uses: Meprobamate is an anxiolytic drug. It was the best selling minor tranquilizer for a time but has largely been replaced by benzodiazepines. Meprobamate has most of the pharmacological effects and dangers of the barbiturates (though it was marketed as being safer). However, it is less sedating at effective doses.

Ethchlorvynol



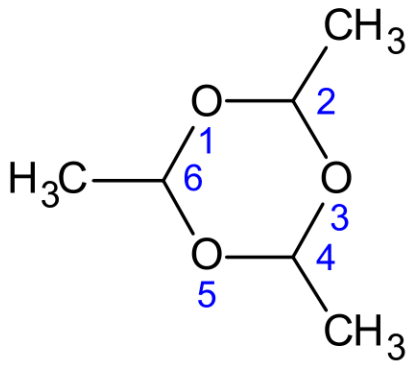
Nomenclature:(*E*)-1-chloro-3-ethylpent-1-en-4-yn-3-ol
Uses: Ethchlorvynol is a sedative drug and schedule IV (USA) controlled substance. It produces cerebral depression, by GABA-mediated Hyperpolarization.

Aldehyde & their derivatives: Triclofos sodium



Nomenclature: Sodium;2,2,2-trichloroethyl hydrogen phosphate
Uses: Triclofos is a prodrug which is metabolized in the liver into the active drug trichloroethanol. This delayed action means that the half-life of triclofos is fairly long and it may cause drowsiness the next day. Trichloroethanol is a sedative drug used rarely for treating insomnia, usually as a second-line treatment after other drugs have failed but may cause liver damage and triclofos should not be used for extended periods.

Paraldehyde



Nomenclature:2,4,6-trimethyl-1,3,5-trioxane

Uses: used to induce drowsiness or sleep or to reduce psychological excitement or anxiety but less frequently practiced now a days.

Prepared By Chinmaya Chidananda Behera, Lecturer, UDPS, Utkal University, Vani Vihar, Bhubaneswar, Odisha-751004

Antipsychotics

Prepared By Chinmaya Chidananda Behera, Lecturer, UDPS, Utkal University, Vani Vihar, Bhubaneswar, Odisha-751004

Phenothiazeines

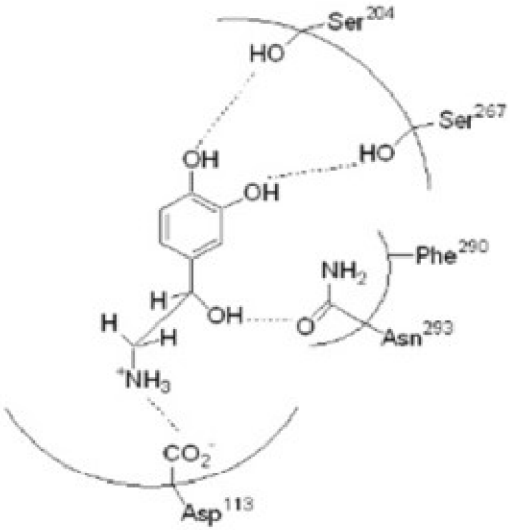
Mechanism of Action:

DOPAMINE RECEPTOR

Anionic site on receptor to interact with the protonated nitrogen of dopamine

A flat, hydrophobic area that interacts with the phenyl ring and hydrogen bonding at specific areas around the phenyl ring to accommodate the ring hydroxyls

A two carbon distance between the anionic site and the ring site



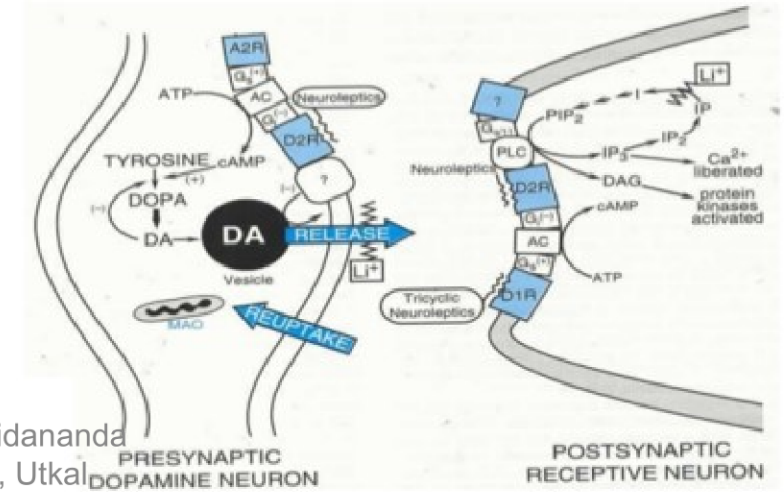
PHENOTHIAZINE BINDING TO D_2 RECEPTOR

Protonatable nitrogen that can interact with the anionic site on the receptor

A phenyl ring to interact with the flat hydrophobic area of the receptor

The two carbon distance is attained through molecular bending of the side chain, which contains a three carbon bridge, toward one of the phenyl rings to approximate a two carbon distance

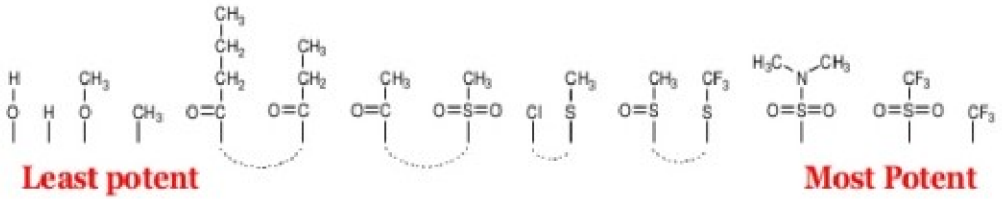
Ring geometry is also important in the binding of phenothiazines to their receptor



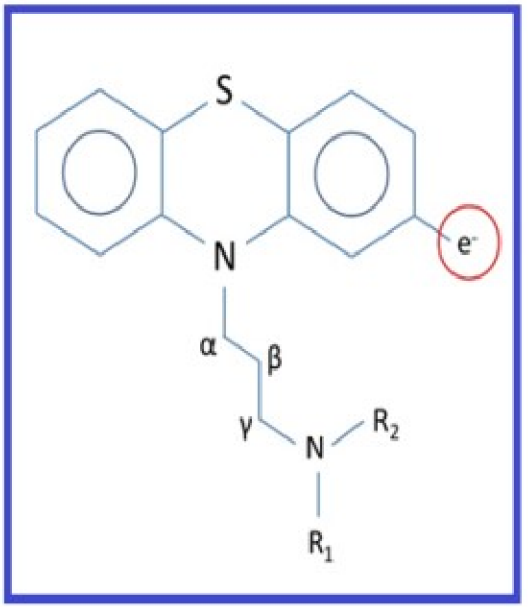
SAR of Phenothiazines

Electron withdrawing group at C2 Increases potency

The most potent position for the electron withdrawing group is C2 which may help bending the side chain N through H bond to form dopamine-like conformation



Least potent — Most Potent



The rank order of potency is position 2>3>4>1

Substitution at C1 has deleterious effect on antipsychotic activity (which may interfere the bending as in 1) as does (to a lesser extent) substitution at C4 which may interfere S binding to receptor

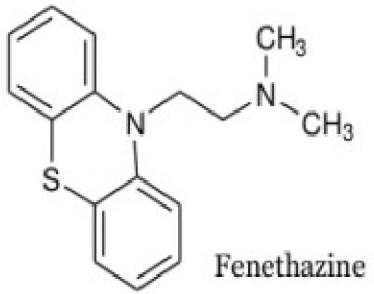
Stronger electron withdrawers are more potent

More than one substitution on the ring system decreases potency

Oxidizing the ring-sulfur to sulfoxide or sulfone reduces potency

ALKYL SIDE CHAIN

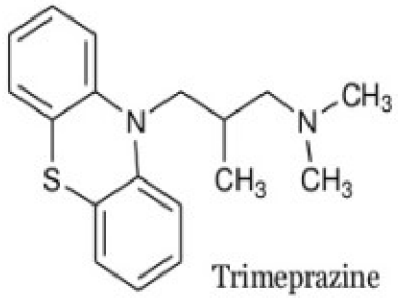
Increasing or decreasing the **length** from 3 carbons decreases the potency. The further from 3 the less potent. Two carbon side chains increase H1 antagonism (Fenethazine)



Fenethazine

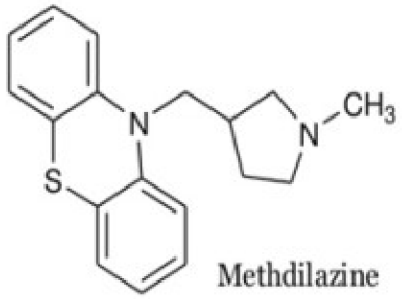
Substitutions on the α carbon decrease potency

A methyl substituent on the β carbon decrease dopamine antagonism (Trimeprazine)



Trimeprazine

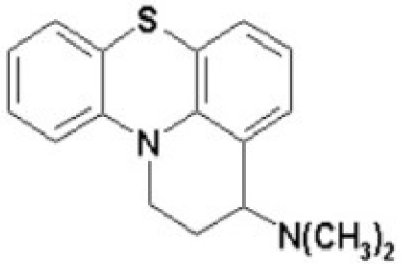
A methyl substituent on the β carbon increases H_1 antagonism. Substituents that are larger than methyl decrease antihistaminic activity unless they are part of a heterocycle (Methdilazine)

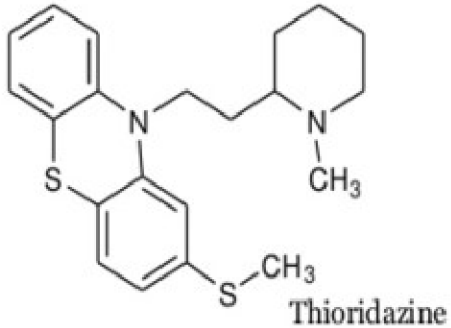


Methdilazine

Substituents on the γ carbon decrease dopamine antagonism but increase anticholinergic activity. These would be expected to produce less extrapyramidal side effects. All the piperidines fit this category

Bridging of position γ of the side chain to position 1 the phenothiazine significantly reduces neuroleptic activity





Thioridazine

SUBSTITUENTS ON THE γ NITROGEN

There are three classes of phenothiazines based on the nature of this substituent

1. N,N-Dimethyl (aliphatic) 2. Piperazine 3. Piperidine

BASIC AMINO GROUP

Maximum neuroleptic potency is observed in aminoalkylated phenothiazines having a tertiary amino group.
In general, alkylation of the basic amino group with groups larger than methyl decreases the neuroleptic potency.

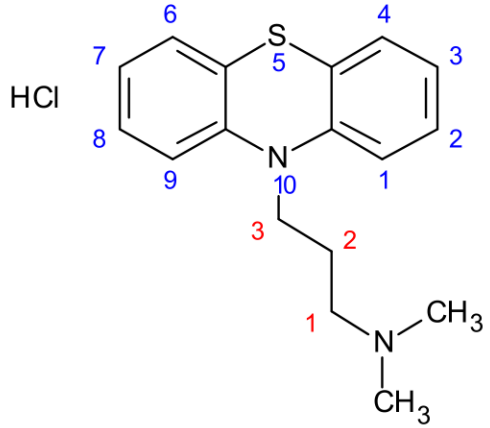
Quaternization of the terminal nitrogen result in loss of activity due to inability of these polar compounds to cross the BBB.

POTENCY COMPARISON

Potency at the D_2 receptors:

Given equal C_2 substituents, ranked from most potent to least potent - Piperazine > Aliphatic > Piperidine

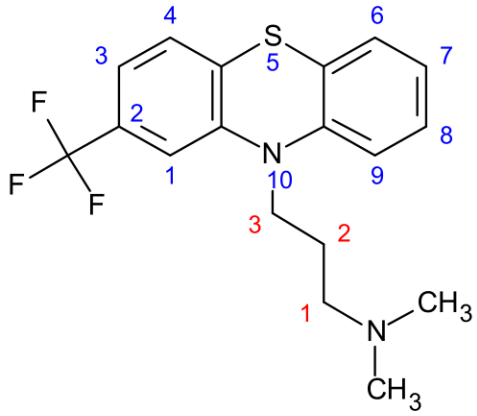
Promazine hydrochloride:



N,N-dimethyl-3-phenothiazin-10-ylpropan-1-amine;hydrochloride

Uses: It has antipsychotic and antiemetic properties. Promazine hydrochloride blocks postsynaptic dopamine receptors D1 and D2 in the mesolimbic and medullary chemoreceptor trigger zone (CTZ), thereby decreasing stimulation of the vomiting center in the brain and psychotic effects, such as hallucinations and delusions.

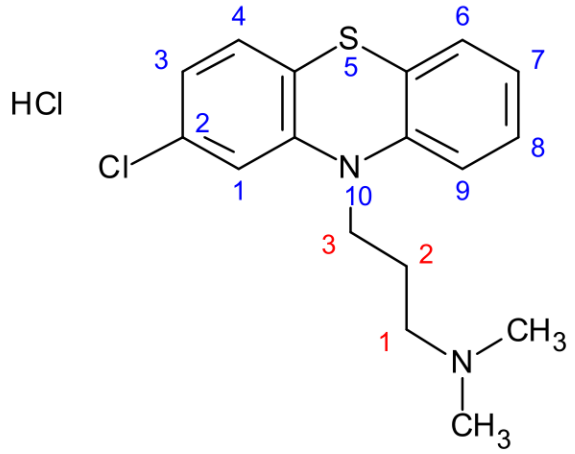
Trifluprom azine:



N,*N*-dimethyl-3-[2-(trifluoromethyl)phenothiazin-10-yl]propan-1-amine

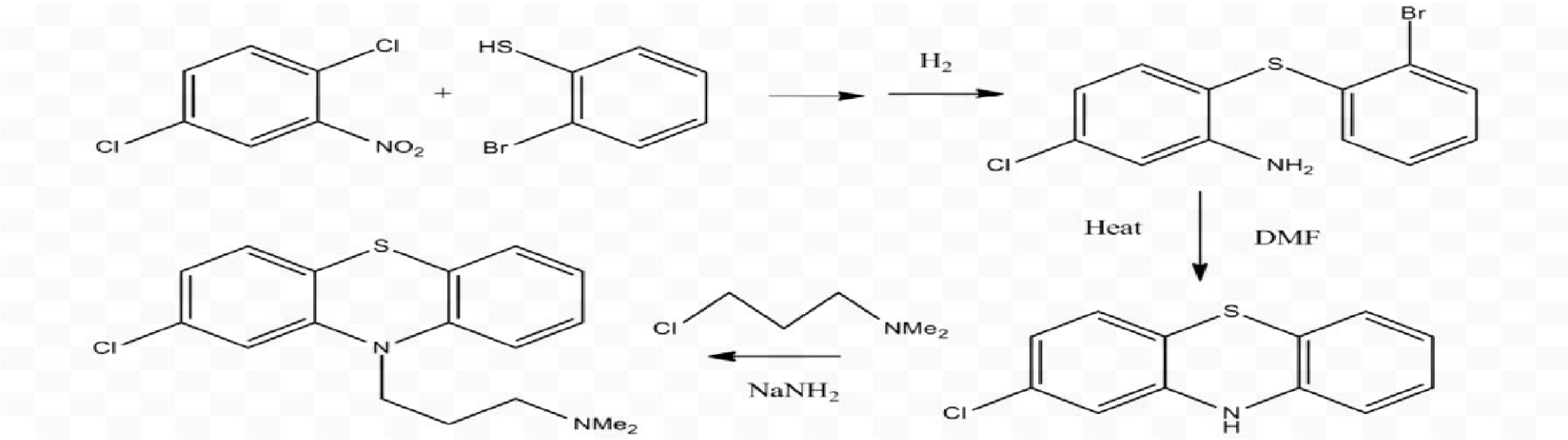
Uses: It reduces anxiety, emotional withdrawal, hallucinations, disorganized thoughts, blunted mood, and suspiciousness. Trifluprom azine is used particularly to control violent behavior during acute episodes of psychotic disorders. It can also be used to control severe nausea and vomiting, severe hiccups, and moderate to severe pain in some hospitalized patients.

Chlorpromazine hydrochloride:



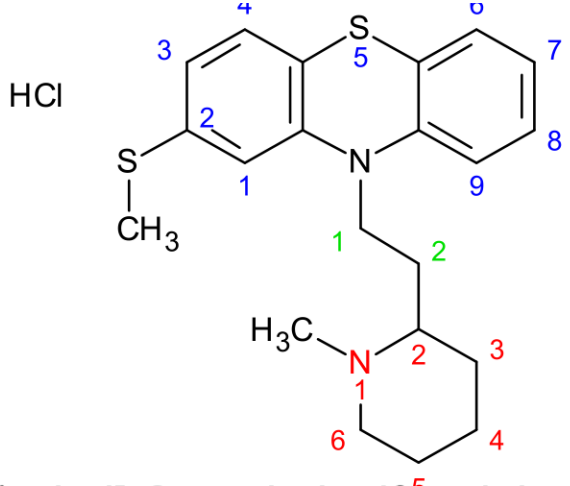
3-(2-chlorophenothiazin-10-yl)-*N*,*N*-dimethylpropan-1-amine;hydrochloride

Synthesis:



Uses: Chlorpromazine hydrochloride exerts its antipsychotic effect by blocking postsynaptic dopamine receptors in cortical and limbic areas of the brain, thereby preventing the excess of dopamine in the brain. Chlorpromazine hydrochloride appears to exert its anti-emetic activity by blocking the dopamine receptors in the chemical trigger zone (CTZ) in the brain, thereby relieving nausea and vomiting.

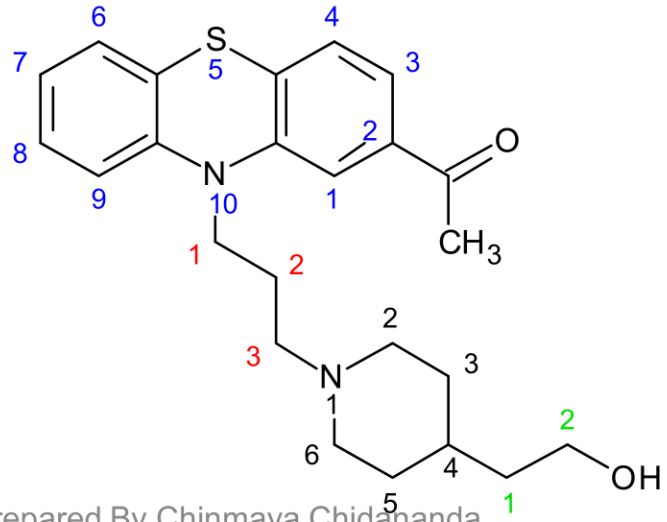
Thioridazine hydrochloride:



10-[2-(1-methylpiperidin-2-yl)ethyl]-2-methylsulfanylphenothiazine;hydrochloride

Uses: Thioridazine hydrochloride binds to mesolimbic postsynaptic dopamine receptor D2, thereby decreasing dopamine activity leading to decreased psychotic effects, such as hallucinations and delusions.

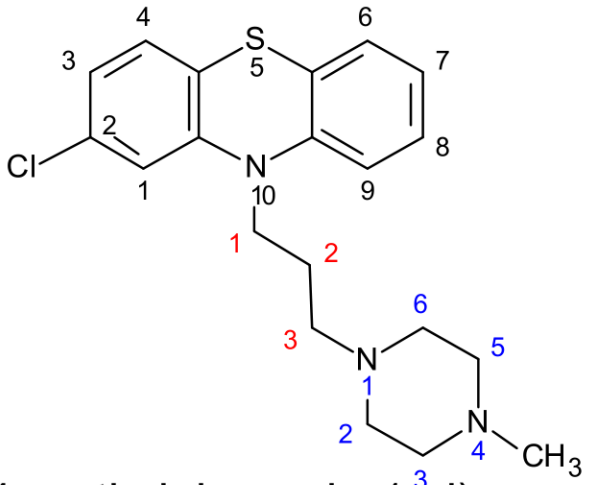
Piperacetazine hydrochloride:



1-[10-[3-[4-(2-hydroxyethyl)piperidin-1-yl]propyl]phenothiazin-2-yl]ethanone

Uses: Piperacetazine (Quide) is an antipsychotic prodrug, most notably used for schizophrenia..

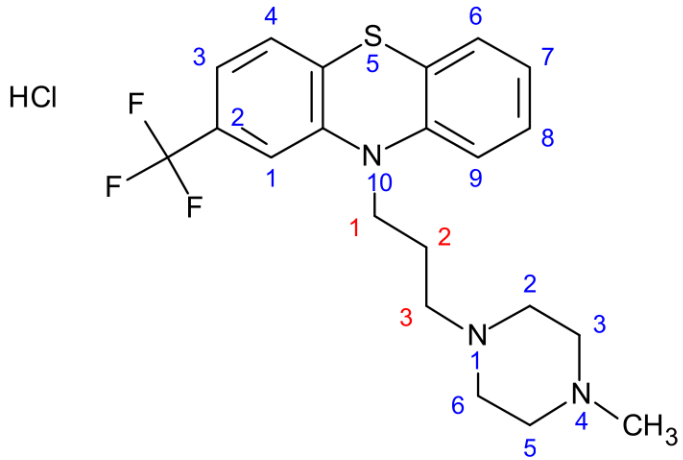
Prochlorperazine maleate:



2-chloro-10-[3-(4-methylpiperazin-1-yl)propyl]phenothiazine

Uses: It is a high-potency neuroleptics with with antiemetic, antipsychotic, antihistaminic, and anticholinergic activities. Prochlorperazine antagonizes the dopamine D2-receptor in the chemoreceptor trigger zone (CTZ) of the brain and may prevent chemotherapy-induced emesis.

Trifluoperazine hydrochloride:

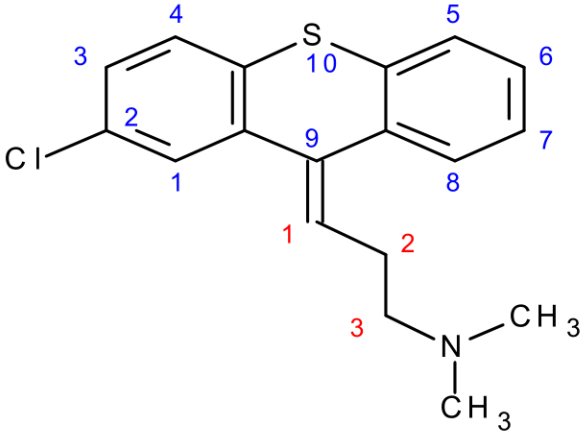


10-[3-(4-methylpiperazin-1-yl)propyl]-2-(trifluoromethyl)phenothiazine;hydrochloride

Uses: It is a dopamine, alpha-adrenergic, and anticholinergic antagonist with antipsychotic, anxiolytic, and antiemetic activities. Trifluoperazine blocks central dopamine receptors, which may prevent or mitigate delusions and hallucinations caused by an excess of dopamine.

Ring Analogues of Phenothiazeines:

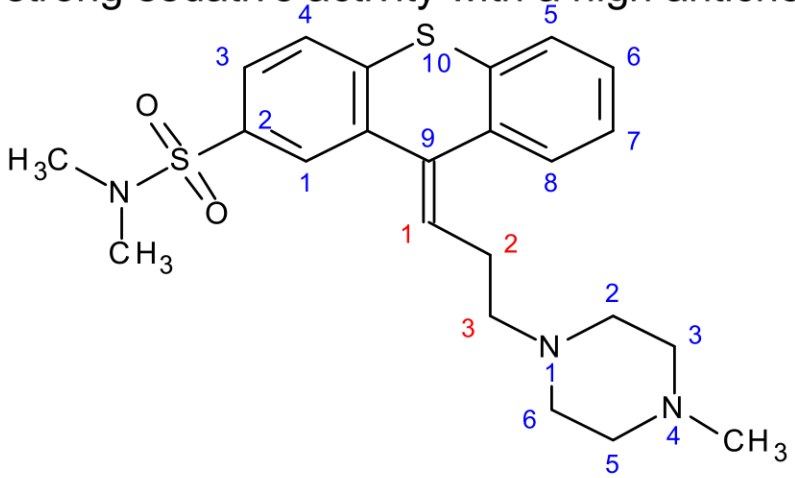
Chlorprothixene:



3-(2-chlorothioxanthen-9-ylidene)-*N*,*N*-dimethylpropan-1-amine

Uses: It is used in the treatment of nervous, mental, and emotional conditions. Improvement in such conditions is thought to result from the effect of the medicine on nerve pathways in specific areas of the brain. It has a strong sedative activity with a high anticholinergic side-effects

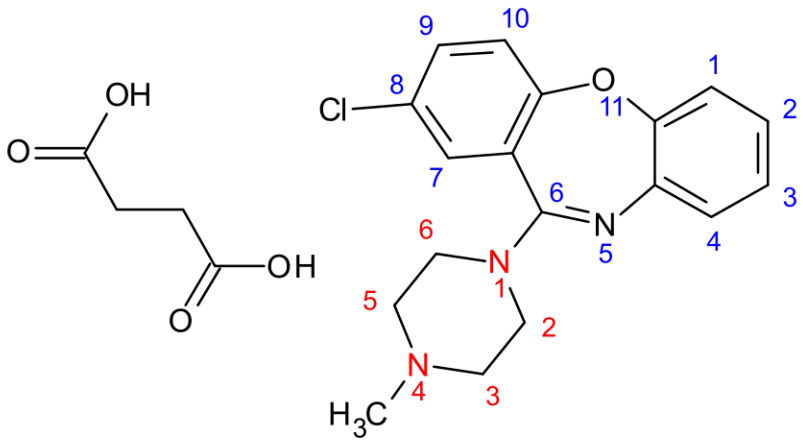
Thiothixene :



N,*N*-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]thioxanthene-2-sulfonamide

Uses: Thiothixeneblocks postsynaptic dopamine receptors in the mesolimbic system and medullary chemoreceptor trigger zone, thereby decreasing dopamine activity leading to decreased stimulation of the vomiting center and psychotic effects, such as hallucinations and delusions.

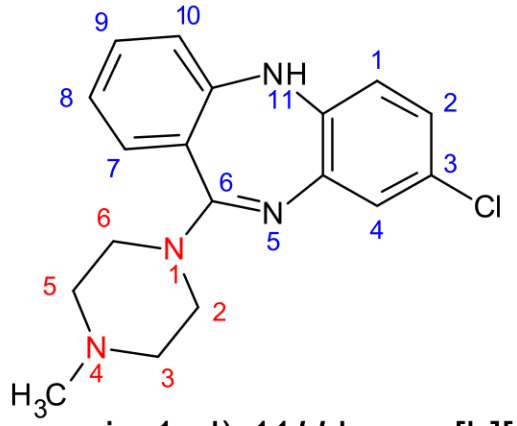
Loxapine succinate:



Butanedioic acid;8-chloro-6-(4-methylpiperazin-1-yl)benzo[b][1,4]benzoxazepine

Uses: It is a tricyclic dibenzoxazepine antipsychotic agent with antiemetic, sedative, anticholinergic, and antiadrenergic actions. Loxapine succinate exerts its actions by blocking the dopamine receptors at postsynaptic receptor sites in the limbic system, cortical system and basal ganglia, thereby reducing the hallucinations and delusions that are associated with schizophrenia.

Clozapine:

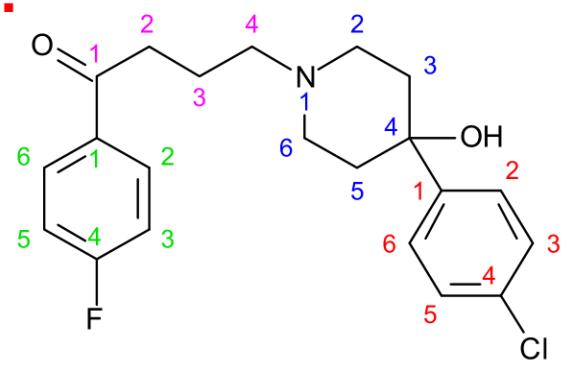


3-chloro-6-(4-methylpiperazin-1-yl)-11*H*-benzo[b][1,4]benzodiazepine

Uses: Clozapine is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives and is indicated for the treatment of schizophrenia. Clozapine is a selective monoaminergic antagonist with high affinity for the serotonin Type 2 (5HT2), dopamine Type 2 (D2), 1 and 2 adrenergic, and H1 histaminergic receptors. Clozapine acts as an antagonist at other receptors, but with lower potency.

Fluro buterophenones:

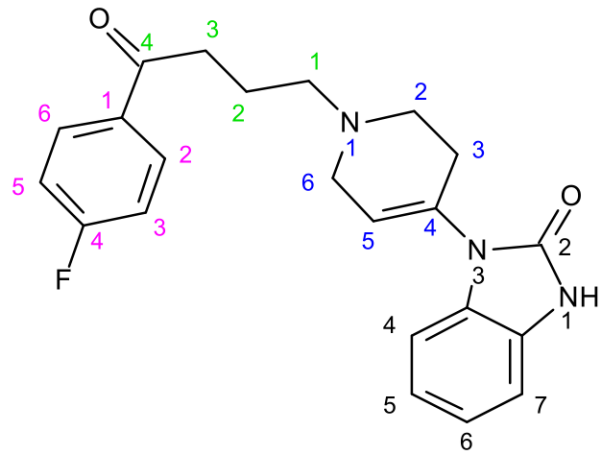
Haloperidol:



4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one

Uses: Haloperidol is a psychotropic agent. The drug has action at all levels of the central nervous system-primarily at subcortical levels-as well as on several organ systems. Haloperidol has potent neuroleptic antiadrenergic activity and weak peripheral anticholinergic activity, as well as minor ganglionic binding ability.

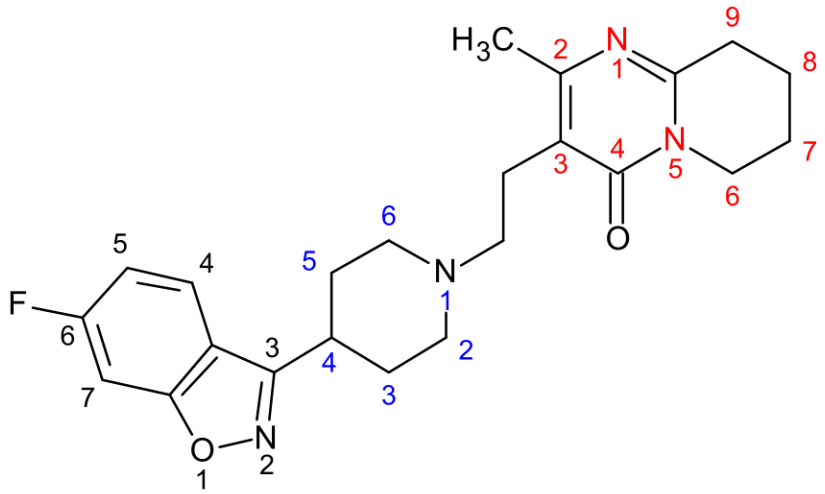
Droperidol:



3-[1-[4-(4-fluorophenyl)-4-oxobutyl]-3,6-dihydro-2*H*-pyridin-4-yl]-1*H*-benzimidazol-2-one

Uses: Droperidol produces an antiemetic effect as evidenced by the antagonism of apomorphine in dogs. It lowers the incidence of nausea and vomiting during surgical procedures and provides antiemetic protection in the postoperative period. Droperidol potentiates other CNS depressants.

Risperidone:



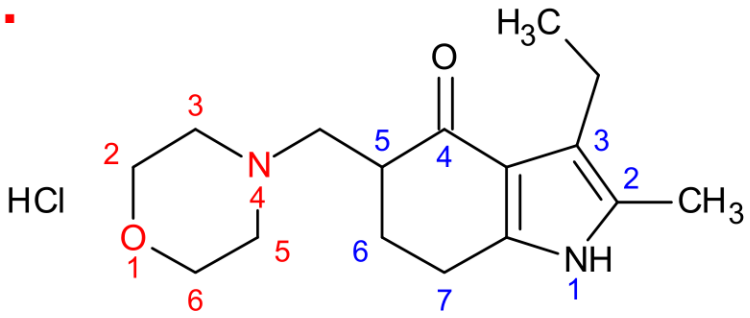
3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidin-4-one

Uses: Risperidone has high affinity binding to serotonergic 5-HT2A receptors versus dopaminergic D2 receptors in the brain. Risperidone binds the D2 receptors with lower affinity than the traditional, first generation antipsychotic drugs, which bind with very high affinity.

Prepared By Chinmaya Chidananda Behera, Lecturer, UDPS, Utkal University, Vani Vihar, Bhubaneswar, Odisha-751004

Beta amino ketones:

Molindone hydrochloride:

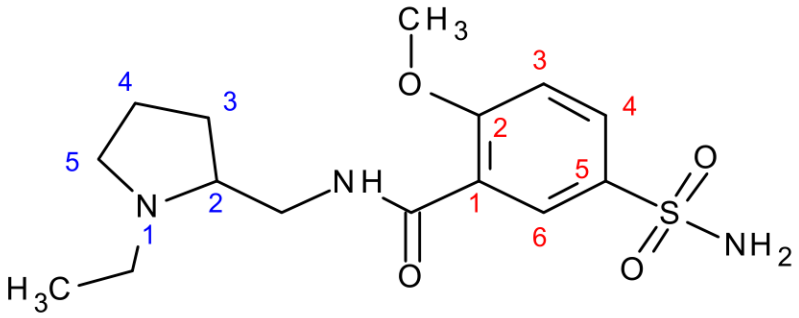


3-ethyl-2-methyl-5-(morpholin-4-ylmethyl)-1,5,6,7-tetrahydroindol-4-one;hydrochloride

Uses: Molindone hydrochloride exerts its effect by blocking dopamine receptors, probably D2 and D3, in the reticular activating and limbic systems, thereby decreasing dopamine excess in the brain. This leads to a reduction of spontaneous locomotion and aggressiveness, suppression of conditioned response, antagonism of stereotyped behavior and hyperactivity induced by amphetamines.

Benzamides:

Sulpieride:

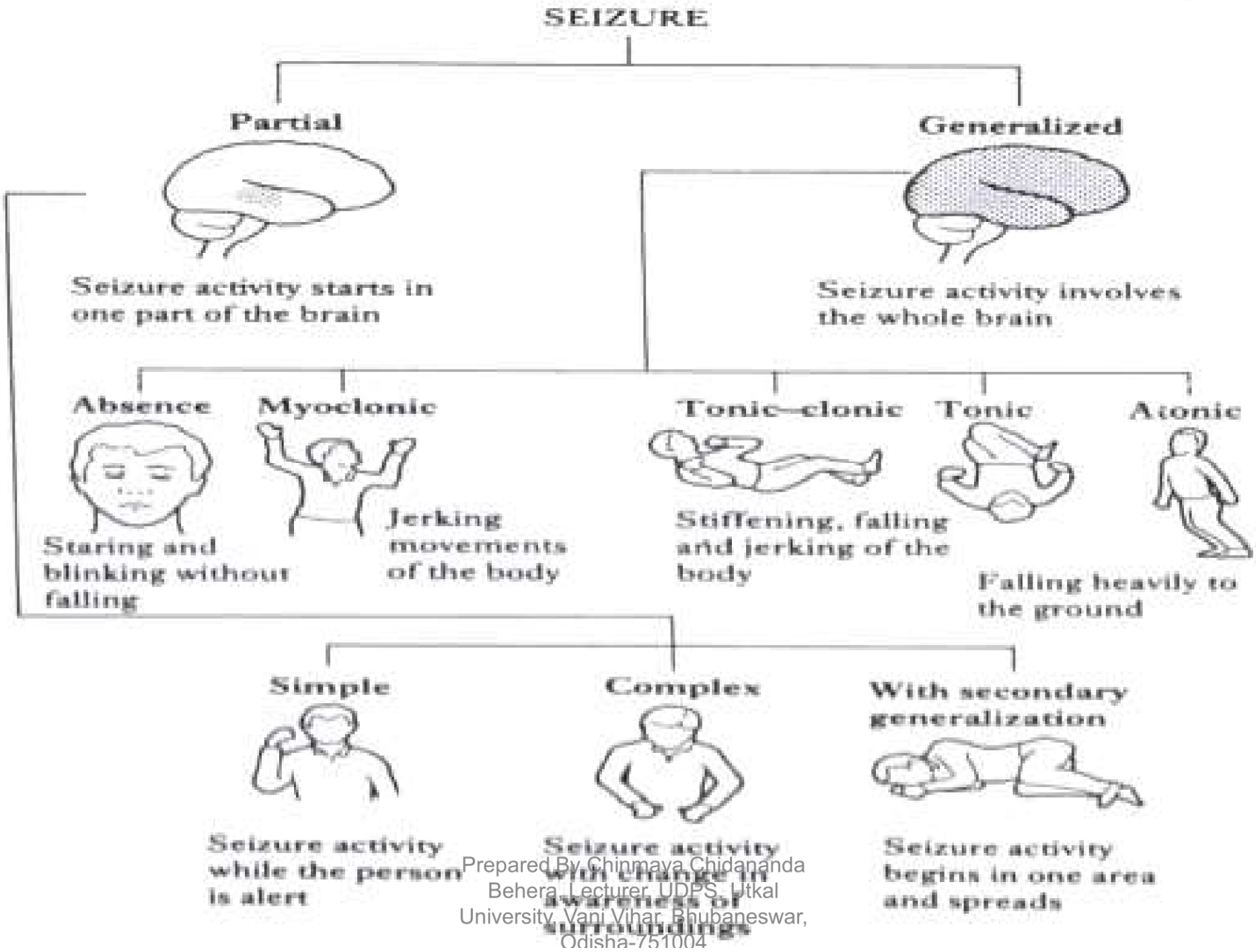


N-[(1-ethylpyrrolidin-2-yl)methyl]-2-methoxy-5-sulfamoylbenzamide

Uses: It is used in schizophrenia; senile dementia; transient psychosis following surgery; or myocardial infarction; etc.

Anticonvulsants

Prepared By Chinmaya Chidananda Behera, Lecturer, UDPS, Utkal University, Vani Vihar, Bhubaneswar, Odisha-751004



MECHANISM OF ACTION OF ANTIEPILEPTIC DRUGS

Three main mechanisms –

- Enhancement of GABA action
- Inhibition of sodium channel function
- Inhibition of calcium channel function.

Other mechanisms include -

- Inhibition of glutamate release and
- Block of glutamate receptors.

Classification Based on Mechanism of Action

Action on Ion Channels	Enhance GABA Transmission	Inhibit EAA Transmission
Na^+:	Benzodiazepines	Felbamate
Phenytoin,	(diazepam,	Topiramate
Carbamazepine,	clonazepam)	
Lamotrigine	Barbiturates	
Topiramate	(phenobarbital)	
Valproic acid	Valproic acid	
Ca^{++}:	Gabapentin	
Ethosuximide	Vigabatrin	
Valproic acid	Topiramate	
	Felbamate	

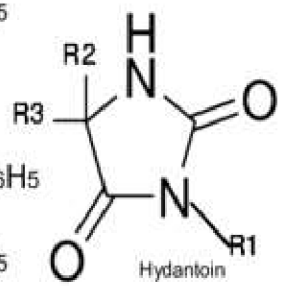
- **Phenytoin, Carbamazepine, felbamate, lamotrigine,** Block voltage-dependent sodium channels at high firing frequencies.
- **Barbiturates** Prolong GABA-mediated chloride channel openings
- **Benzodiazepines** Increase frequency of GABAmediated chloride channel openings
- **Valproic acid** May enhance GABA transmission in specific circuits, Blocks voltage-dependent sodium channels and Blocks T-type calcium currents.
- **Ethosuximide** Blocks slow, threshold, “transient” (T-type) calcium channels in thalamic neurons

Prepared By Chinmaya Chidananda Behera, Lecturer, UDPS, Utkal University, Vani Vihar, Bhubaneswar, Odisha-751004

SAR of Anticonvulsants or Antiepileptics

Hydantoins

- Phenylethylhydation
  $R_1 = H \quad R_2 = C_2H_5 \quad R_3 = C_6H_5$
- Phenytoin
  $R_1 = H \quad R_2 = R_3 = C_6H_5$
- Mephenytoin
  $R_1 = CH_3 \quad R_2 = C_2H_5 \quad R_3 = C_6H_5$
- Ethotoin
  $R_1 = C_2H_5 \quad R_5 = H \quad R_5 = C_6H_5$

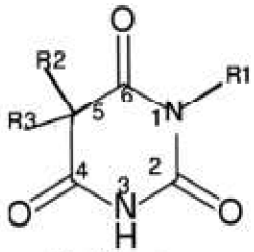


Hydantoin

- A phenyl or other aromatic substituents at C_5 is essential for the activity.
- Alkyl substituents at position 5 may contribute to sedation, a property absent in phenytoin. Hydantoin
- 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.

Barbiturates

- Phenobarbitone
  $R_1 = H \quad R_2 = C_2H_5 \quad R_3 = C_6H_5$
- Mephobarbitone
  $R_1 = CH_3 \quad R_2 = C_2H_5 \quad R_3 = C_6H_5$
- Metharbital
  $R_1 = CH_3 \quad R_2 = C_2H_5 \quad R_3 = C_2H_5$

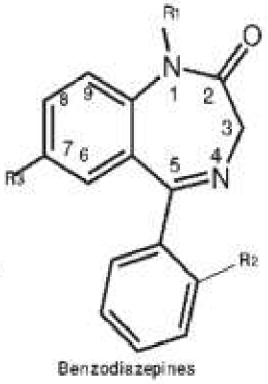


Barbiturates

- Optimum activity is observed when one of the substituents at C_5 is phenyl.
- The 5, 5-diphenyl derivatives have less activity than phenobarbitone.
- N2 and N3 substituents, in some cases also results in an increased activity.
- 5, 5-dibenzyl barbituric acid causes convulsions.

Benzodiazepines

- Diazepam
  $R_1 = CH_3 \quad R_2 = H \quad R_3 = Cl$
- Nitrazepam
  $R_1 = H \quad R_2 = H \quad R_3 = NO_2$
- Clonazepam
  $R_1 = H \quad R_2 = Cl \quad R_3 = NO_2$

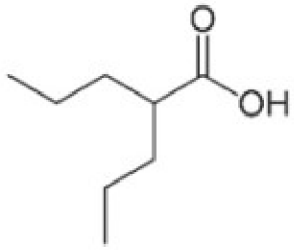


Benzodiazepines

- The electron withdrawing atom or group at position 7 increases the anti-epileptic activity while electron donating substituents at 7, 8 or 9 positions decrease it.
- A phenyl group at position 5 is necessary for activity. But only halogen substituents are allowed in the ortho position.
- The electron withdrawing groups at ortho or diortho positions at 5-phenyl increase the activity while any substituents on meta or para position at 5-phenyl decreases the activity.
- Methyl substitution at position 1 confirms high activity.

SAR of Anticonvulsants or Antiepileptics

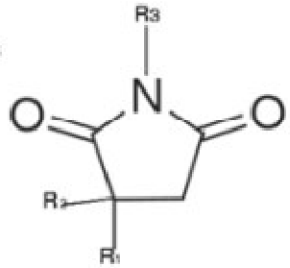
Valproic Acid



- Among other relatives of valproic acid, 3, 3, 4-trimethyl pentanoic acid is also as active as valproic acid.
- The anticonvulsant activity increases with increased chain length.
- Introduction of a double bond decreases the activity.

Succinamide

- Phensuximide
  $R_1 = C_6H_5$ $R_2 = H$ $R_3 = CH_3$
- Methsuximide
  $R_1 = C_6H_5$ $R_2 = R_3 = CH_3$
- Ethosuximide
  $R = C_2H_5$ $R_2 = CH_3$ $R_3 = H$

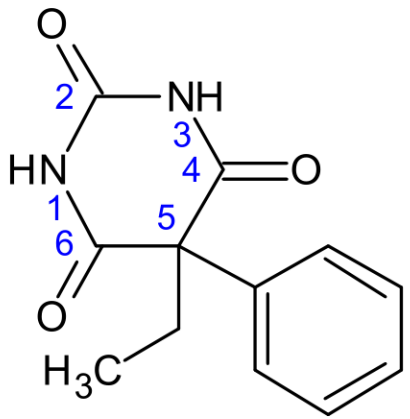


- Methsuximide and phensuximide have phenyl substituents which makes them active against electrically induced convulsion.
- N-Methylation decreases activity against electroshock seizures and impart more activity against chemically induced convulsion.

Prepared By Chinmaya Chidananda Behera, Lecturer, UDPS, Utkal University, Vani Vihar, Bhubaneswar, Odisha-751004

Barbiturates:

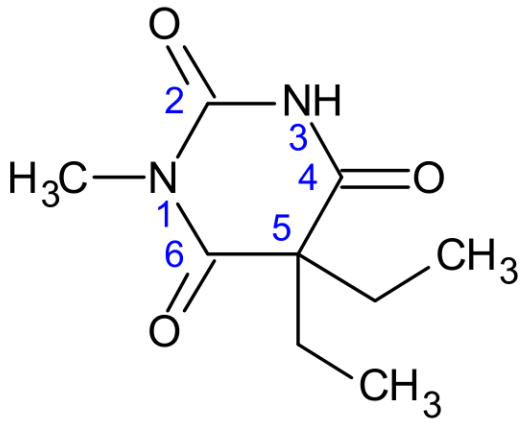
Phenobarbital



5-ethyl-5-phenylpyrimidine-2,4,6(1H,3H,5H)-trione

Uses: Phenobarbital, the longest-acting barbiturate, is used for its anticonvulsant and sedative-hypnotic properties in the management of all seizure disorders except absence (petit mal), act by (GABA)-A receptor and synaptic inhibition by hyperpolarization.

Methabarbital:

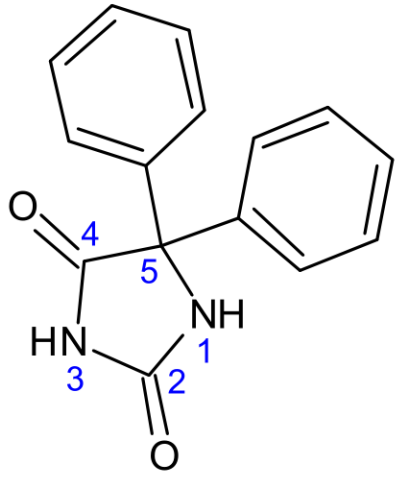


5,5-diethyl-1-methyl-1,3-diazinane-2,4,6-trione

Uses: Metharbital, a barbiturate, is used for the treatment of short term insomnia. Little analgesia is conferred by barbiturates; their use in the presence of pain may result in excitation.

Hydantoins:

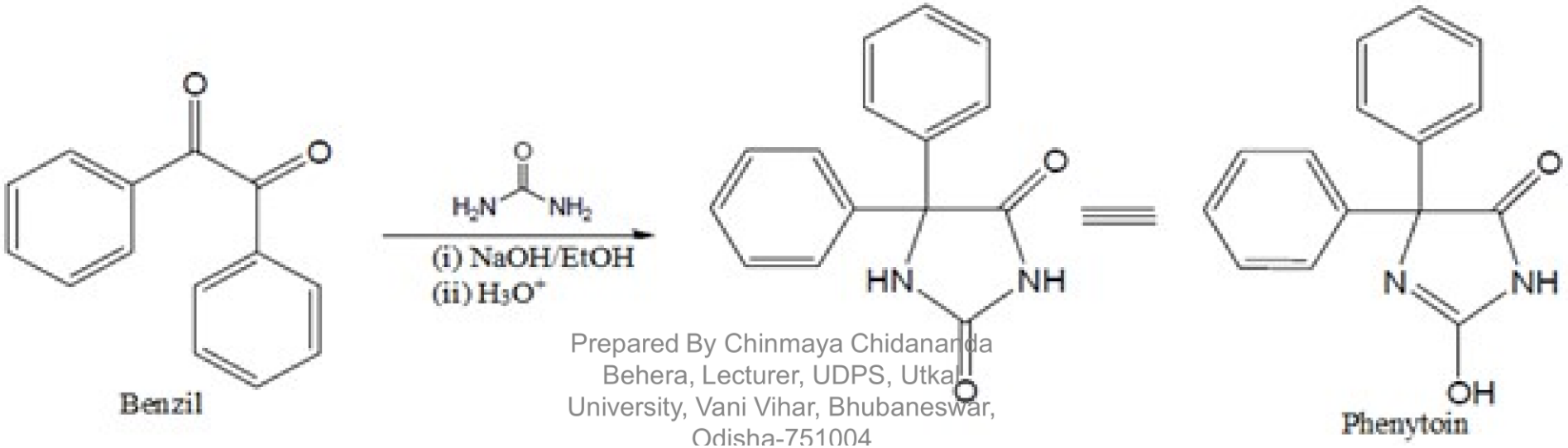
Phenytoin:



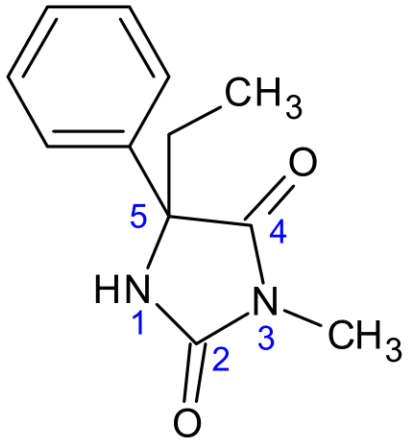
IUPAC Name: 5,5-diphenylimidazolidine-2,4-dione

Uses: Phenytoin is a hydantoin derivative and a non-sedative antiepileptic agent with anticonvulsant activity. Phenytoin potentially acts by promoting sodium efflux from neurons located in the motor cortex reducing post-tetanic potentiation at synapses. The reduction of potentiation prevents cortical seizure foci spreading to adjacent areas, stabilizing the threshold against hyperexcitability. In addition, this agent appears to reduce sensitivity of muscle spindles to stretch causing muscle relaxation..

Svnthesis:



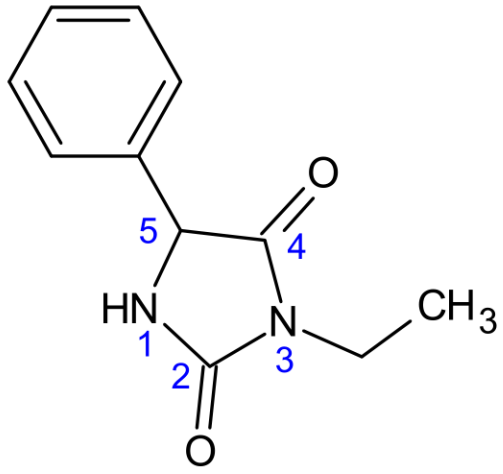
Mephenytoin:



5-ethyl-3-methyl-5-phenylimidazolidine-2,4-dione

Uses: Mephenytoin is a heterocyclic organic compound with anticonvulsant property. Although the mechanism of action is not well established, mephenytoin potentially promotes sodium efflux from neurons in motor cortex, and stabilizes the threshold against hyperexcitability caused by excessive stimulation. Thus this agent reduces the membrane sodium gradient and prevents cortical seizure signal spreading.

Ethotoin:

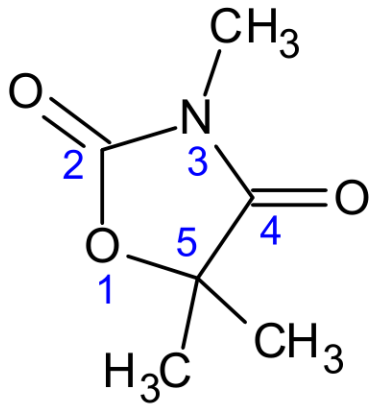


3-ethyl-5-phenylimidazolidine-2,4-dione

Uses: Ethotoin is a hydantoin derivative and anticonvulsant. Ethotoin exerts an antiepileptic effect without causing general central nervous system depression. The mechanism of action is probably very similar to that of phenytoin.

Oxazolidine diones:

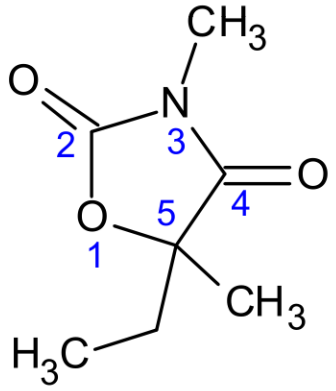
Trimethadione:



3,5,5-trimethyl-1,3-oxazolidine-2,4-dione

Uses: Trimethadione is a dione-type anticonvulsant with antiepileptic activity. Trimethadione reduces T-type calcium currents in thalamic neurons, thereby stabilizing neuronal membranes, raising the threshold for repetitive activities in the thalamus and inhibiting corticothalamic transmission. This decreases absence (petit mal) seizures.

Paramethadione:

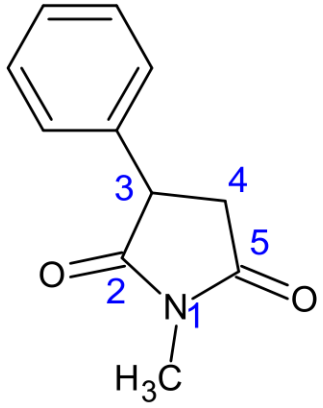


5-ethyl-3,5-dimethyl-1,3-oxazolidine-2,4-dione

Uses: Paramethadione is an oxazolidinedione anticonvulsant similar to trimethadione that acts on the central nervous system (CNS) to reduce the number of absence seizures (often seen in epileptics). Absence seizures involve an interruption to consciousness where the person experiencing the seizure seems to become vacant and unresponsive for a short period of time (usually up to 30 seconds).

Succinimides:

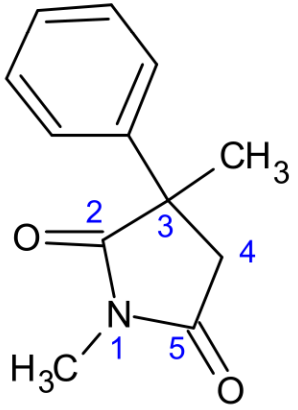
Phensuximide:



1-methyl-3-phenylpyrrolidine-2,5-dione

Uses: Phensuximide suppresses the paroxysmal three cycle per second spike and wave EEG pattern associated with lapses of consciousness in absence (petit mal) seizures. The frequency of attacks is reduced by depression of nerve transmission in the motor cortex.

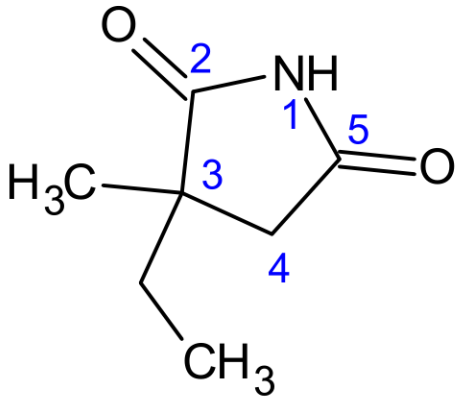
Methsuximide:



1,3-dimethyl-3-phenylpyrrolidine-2,5-dione

Uses: Used in the treatment of epilepsy. Methsuximide suppresses the paroxysmal three cycle per second spike and wave activity associated with lapses of consciousness which is common in absence (petit mal) seizures. The frequency of epileptiform attacks is reduced, apparently by depression of the motor cortex and elevation of the threshold of the central nervous system to convulsive stimuli.

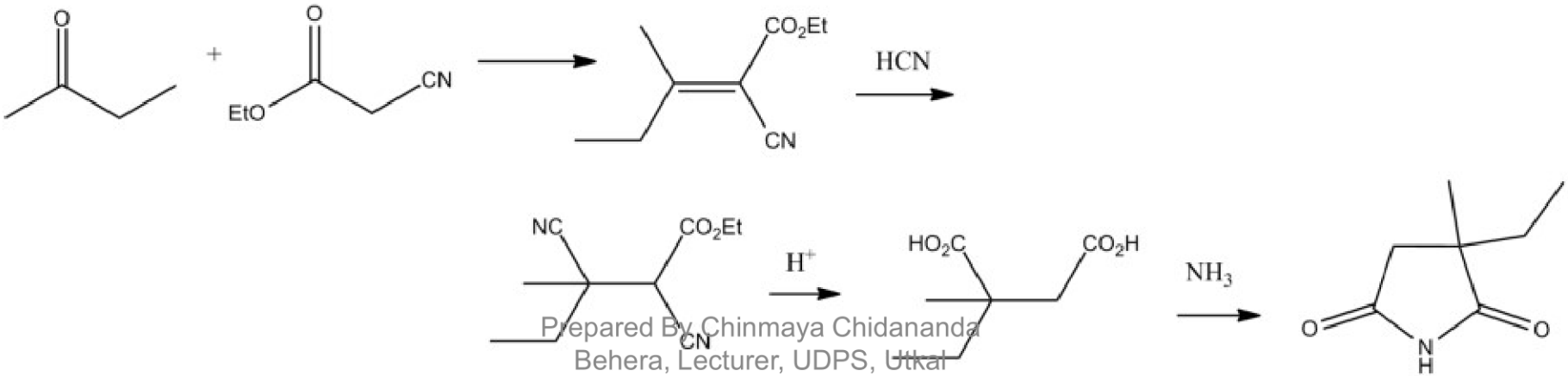
Ethosuximide:



3-ethyl-3-methylpyrrolidine-2,5-dione

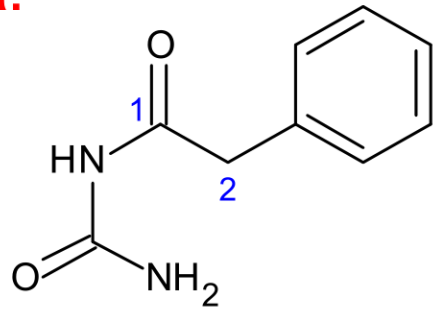
Uses: Ethosuximide is a succinimide with anticonvulsant activity. The exact mechanism of action is not entirely understood, but most likely ethosuximide exerts its effects by partial antagonism of T-type calcium channels of the thalamic neurons. This leads to a decrease in burst firing of thalamocortical neurons, which stabilizes the nerve activity in the brain and prevents seizures.

Synthesis:



Urea and Monoacylurea:

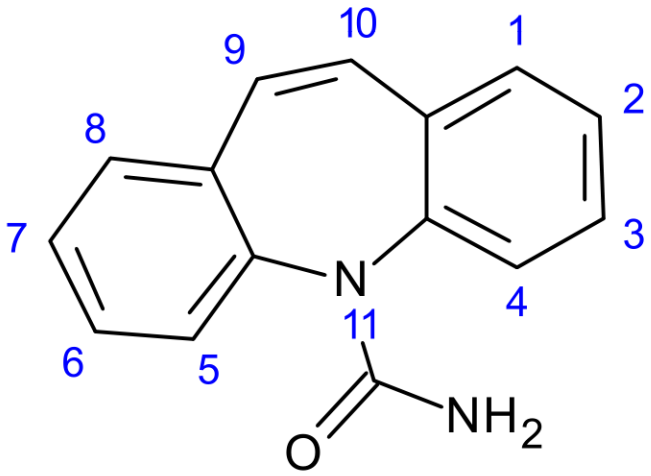
Phenacemide:



N-carbamoyl-2-phenylacetamide

Uses: Phenacemide is a ureal anticonvulsant indicated for control of severe epilepsy, particularly mixed forms of complex partial (psychomotor or temporal lobe) seizures, refractory to other anticonvulsants. Phenacemide elevates the threshold for minimal electroshock convulsions and abolishes the tonic phase of maximal electroshock seizures.

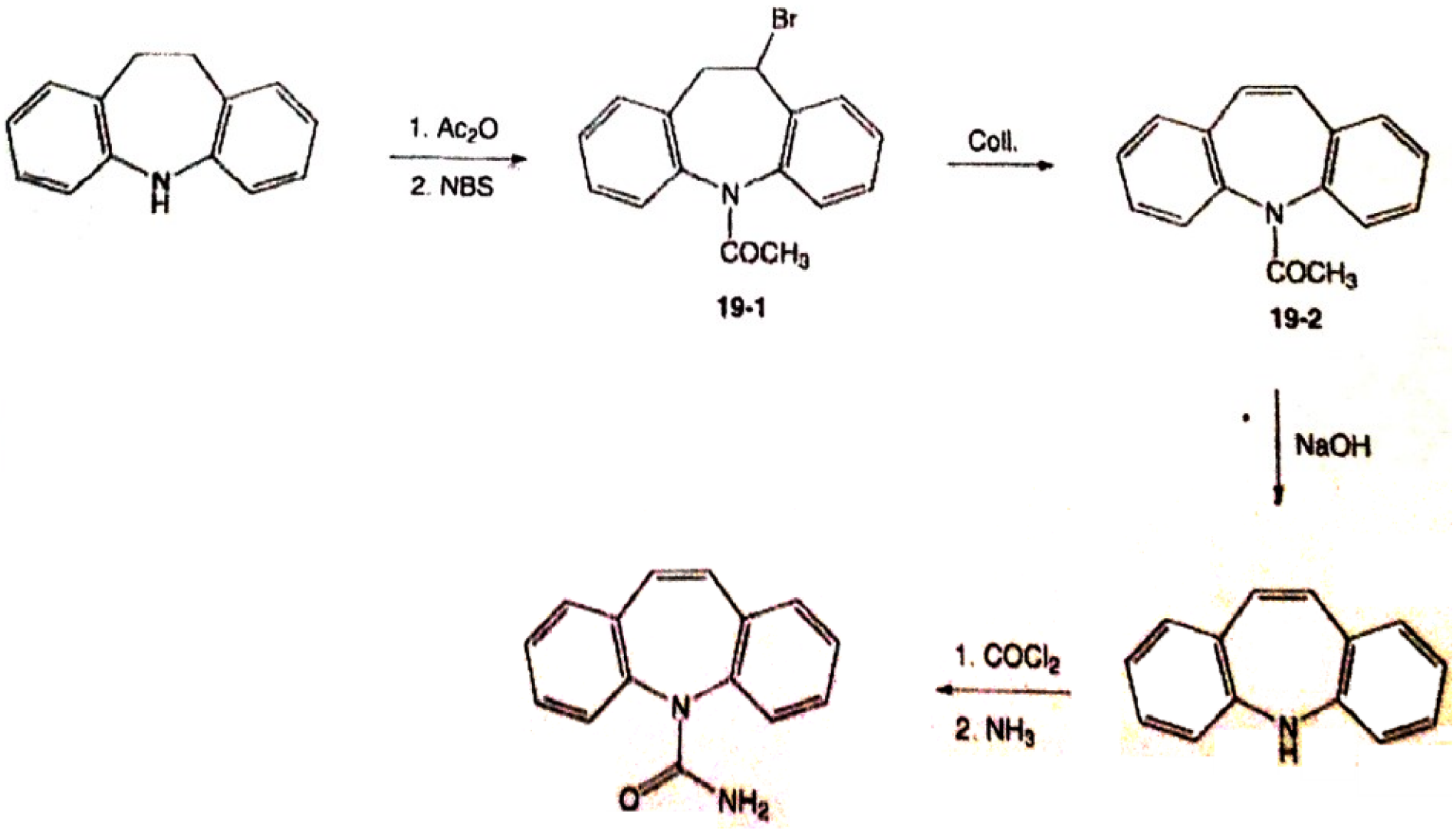
Carbamazepine:



Benzo[b][1]benzazepine-11-carboxamide

Uses: Carbamazepine is a tricyclic compound chemically related to tricyclic antidepressants (TCA) with anticonvulsant and analgesic properties. Carbamazepine exerts its anticonvulsant activity by reducing polysynaptic responses and blocking post-tetanic potentiation.

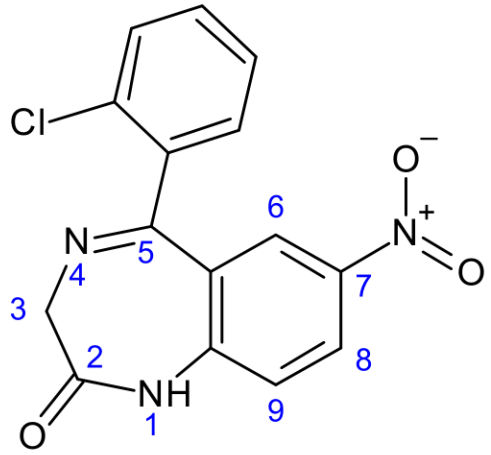
Synthesis of Carbamazepine:



Prepared By Chinmaya Chidananda Behera, Lecturer, UDPS, Utkal University, Vani Vihar, Bhubaneswar, Odisha-751004

Benzodiazepines:

Clonazepam:



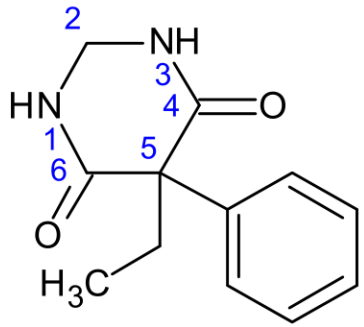
5-(2-chlorophenyl)-7-nitro-1,3-dihydro-1,4-benzodiazepin-2-one

Uses: Clonazepam is a synthetic benzodiazepine derivative used for myotonic or atonic seizures, absence seizures, and photosensitive epilepsy, anticonvulsant Clonazepam appears to enhance gamma-aminobutyric acidreceptor responses, although its mechanism of action is not clearly understood. It is seldom effective in generalized tonic-clonic or partial seizures.

Prepared By Chinmaya Chidananda Behera, Lecturer, UDPS, Utkal University, Vani Vihar, Bhubaneswar, Odisha-751004

Miscellaneous:

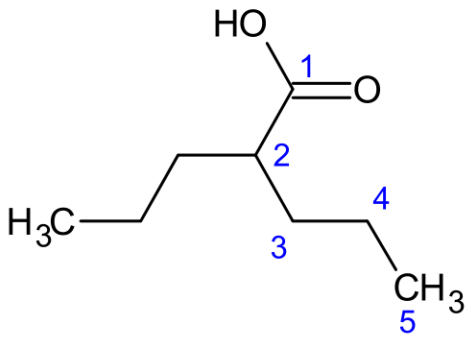
Primidone:



5-ethyl-5-phenyl-1,3-diazinane-4,6-dione

Uses: Primidone is an analog of phenobarbital with antiepileptic property. Although the mechanism of action has not been fully elucidated, primidone probably exerts its actions, in a manner similar to phenobarbital, via activation of gamma-aminobutyric acid (GABA)-A receptor/chloride ionophore complex, which leads to prolonged and increased frequency of opening of the chloride channel. This results in hyperpolarization and prevention of partial and tonic-clonic seizures.

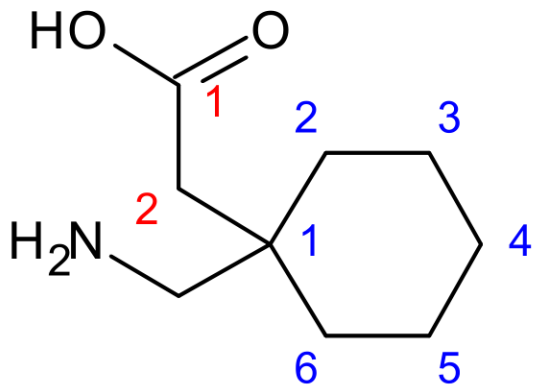
Valproic acid:



2-propylpentanoic acid

Uses: Valproic Acid is a synthetic derivative of propylpentanoic acid with antiepileptic properties and potential antineoplastic and antiangiogenesis activities. In epilepsy, valproic acid appears to act by increasing the concentration of gamma-aminobutyric acid (GABA) in the brain.

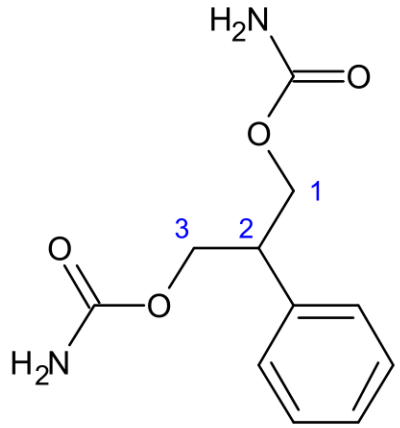
Gabapentin:



2-[1-(aminomethyl)cyclohexyl]acetic acid

Uses: Gabapentin is a synthetic analogue of the neurotransmitter gamma-aminobutyric acid with anticonvulsant activity. Although its exact mechanism of action is unknown, gabapentin appears to inhibit excitatory neuron activity. This agent also exhibits analgesic properties.

Felbamate:



(3-carbamoyloxy-2-phenylpropyl) carbamate

Uses: Felbamate is an antiepileptic indicated as monotherapy or as an adjunct to other anticonvulsants for the treatment of partial seizures resulting from epilepsy. Receptor-binding studies in vitro indicate that felbamate has weak inhibitory effects on GABA-receptor binding, benzodiazepine receptor binding, and is devoid of activity at the MK-801 receptor binding site of the NMDA receptor-ionophore complex.