Medicinal Chemistry

Chapter 16

ANTIEPILEPTIC DRUGS

Contents

INTRODUCTION

- Antiepileptic Drugs are drugs that are used to arrest convulsions or seizures caused in epilepsy. The term epilepsy, based on the Greek word epilambian (meaning to seize), has been first mentioned by Hippocrates.

- Approximately 1% of world's population has epilepsy, the second most common neurological disorder after stroke. Up to 1990, approximately 16 antiseizure drugs were available and 13 of them can be classified into five similar chemical groups, that is, barbiturates, hydantoins, oxazolidinediones, succinamides, and acetyl ureas.

- These groups have a common and similar heterocyclic ring structure with a variety of substituents for the drugs with this basic structure; the substituents on this heterocyclic ring determine the pharmacological class, either antimaximal electro shock or antipentylenetetrazole.

Causes of seizure

- Sleep deprivation
- Flickering lights, (sunlight, TV, computers etc)
- Arterio-venous malformation (AVM)
- Head injury may cause non-epileptic post-traumatic seizures or post-traumatic epilepsy, in which the seizures chronically recur.
- Intoxication with drugs, for example aminophylline or local anesthetics.
- Normal doses of certain drugs that lower the seizure threshold, such as tricyclic antidepressants.

- Infection, such as encephalitis or meningitis
- Fever leading to febrile convulsions
- Metabolic disturbances
- Withdrawal from drugs (anticonvulsants, antidepressants, and sedatives such as alcohol, barbiturates, and benzodiazepines,)
- Space-occupying lesions in the brain (abscesses, tumors)
- Seizures during (or shortly after) pregnancy can be a sign of eclampsia.
- Haemorrhagic stroke

Disorders that mimic epilepsy

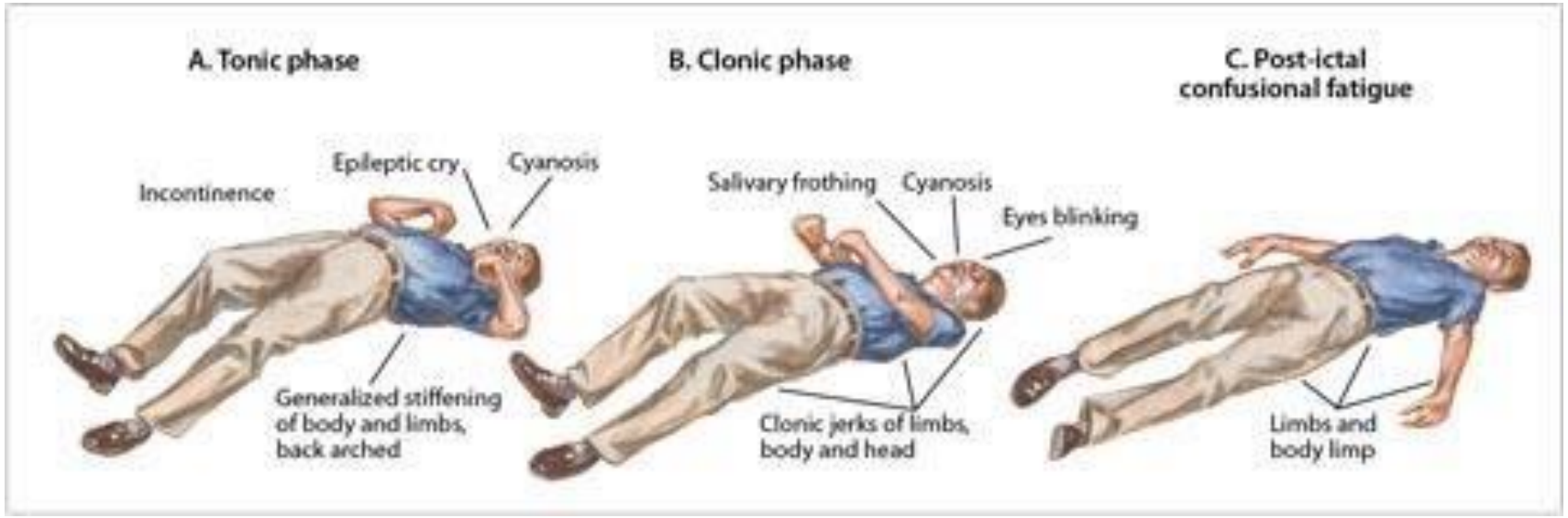
- Gastro-oesophageal reflux
- Migraine
- Cardiovascular events (cardiac arrhythmias)
- Psychological disorders (panic or hyperventilation attacks)
- Breath holding spells
- Sleep disorders
- Movement disorders (shuddering attacks)

Diagnosis and Investigation of Epilepsy

- Clinical features – description of seizure
- EEG (electroencephalogram)
- Neurological examinations
- Blood count and plasma biochemistry
- Family history
- ECG (electrocardiogram)
- Neuroimaging

Types of Epilepsy

- Tonic: Stiffening of the body
- Clonic: Rhythmic jerking movements or convulsions (Clonic phase)



Types of Epilepsy

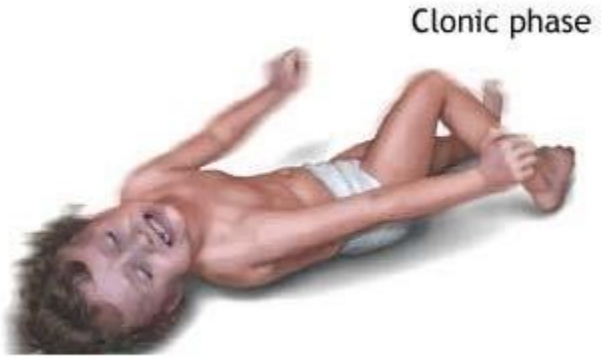
Tonic phase:

- The person will quickly lose consciousness, and the skeletal muscles will suddenly tense, often causing the extremities to be pulled towards the body or rigidly pushed away from it, which will cause the person to fall if standing.
- The tonic phase is usually the shortest part of the seizure, usually lasting only a few seconds.
- The person may also express vocalizations like a loud moan during the tonic stage, due to air forcefully expelled from the lungs.

Types of Epilepsy

Clonic phase:

- The person's muscles will start to contract and relax rapidly, causing convulsions.
- These may range from exaggerated twitches of the limbs to violent shaking or vibrating of the stiffened extremities.
- The person may roll and stretch as the seizure spreads.
- The eyes typically roll back or close and the tongue often suffers bruising sustained by strong jaw contractions. Incontinence is seen in some cases.



Classification of Seizures

- **Partial seizures:**
  - Here localized onset of the attack can be identified by clinical observation or EEG
  - **Simple partial seizures (no loss of consciousness)**
    - With motor symptoms
    - With sensory symptoms
    - With autonomic symptoms
    - Only involve one hemisphere

Dependant on which area of the brain

  - **Complex partial seizures (loss of consciousness)**
    - Simple followed by loss of consciousness
    - Involves limbic systems
    - los of memory
  - **Partial seizures secondarily generalized**

- **Unclassified:**
  - Classification not possible to problems with diagnosis – suspected

- **Generalised (affect whole brain with loss of consciousness)- grand mal seizure (generalized tonic-clonic seizure):**
  - Clonic, tonic (1min) or tonic-clonic (2-4min): muscle spasm (extensors), respiration stops, defecation, urinary incontinence, salivation, violent jerks, tongue or cheek may be bitten
  - Two types

1. **Primary generalized tonic-clonic seizure**
2. **Secondary generalized tonic-clonic seizure**

Classification of Generalized Seizures

- **Myoclonic jerking:**
  - Seizures of a muscle or group of muscles
  - This has been seen in wide variety of seizure
- **Absence (petit mal seizures):**
  - Abrupt loss of awareness of surroundings, little motor disturbance, mostly children, mild clonic jerking of the eyelid or extremities
  - It may occur 100 times a day
  - Onset is 10 seconds (maximum up to 45 seconds)

- **Atonic:**
  - loss of muscle tone/strength (postural tone), the patient may fall suddenly to the floor and may be injured
  - Many patients with this seizure wear helmet to prevent the head injury
- **Infantile spasm:**
  - It is an epileptic syndrome
  - Characterized by brief, recurrent myoclonic jerks of the body with sudden flexion or extension of the body and limbs

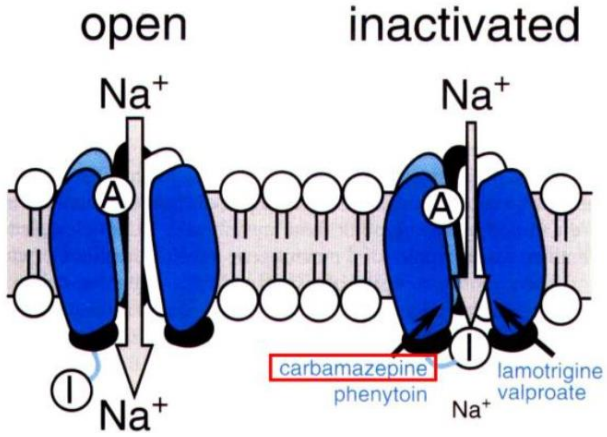
Pathological Basis of seizure

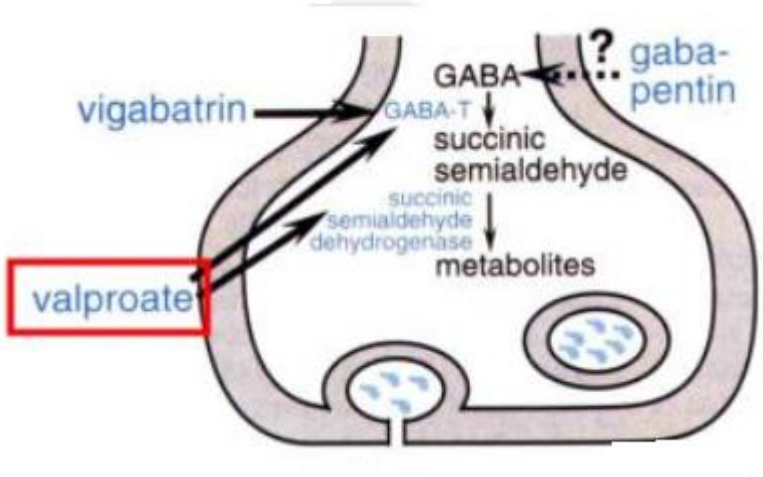
- Abnormal electrical discharge in the brain.
- Coordinated activity among neurons depends on a controlled balance between excitation and inhibition.
- Any local imbalance will lead to a seizure.
- Imbalances occur between glutamate-mediated excitatory neurotransmission and gamma-aminobutyric acid (GABA) mediated inhibitory neurotransmission.

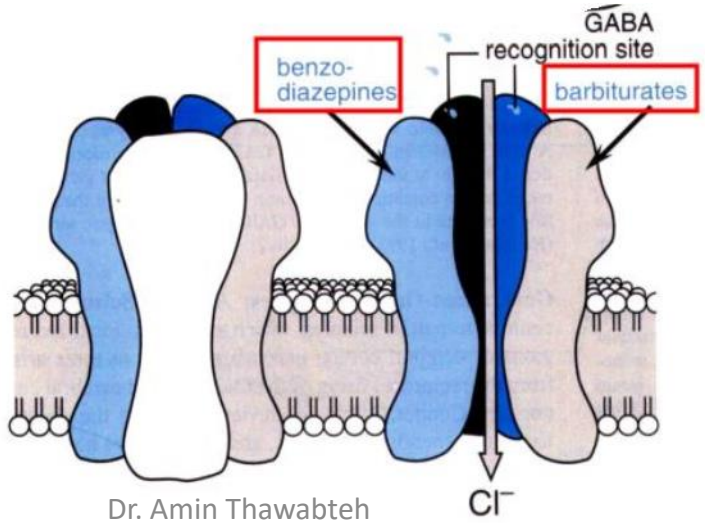
- ❑ Depolarising Na+ and Ca++ ionic current shifts are activated by glutamate receptors.
- ❑ Repolarising K+ currents are mediatedby GABA receptors
- ❑ Hyperpolarisation is mediated by GABAa receptors creating an influx of Cl- => inhibition of impulse generation.

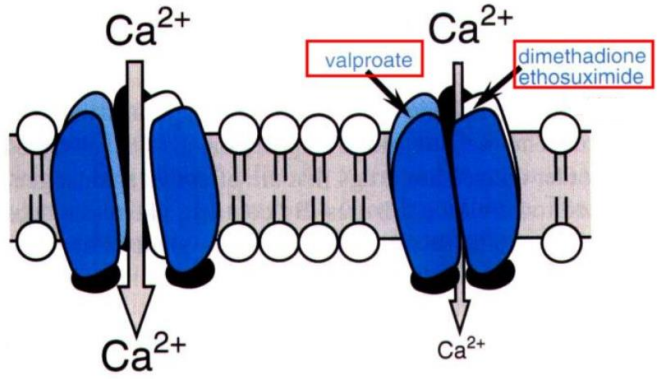
Basis of Pharmacological Mechanism

- Most anti-epileptic agents act either by blockade of depolarisation channels (Na+ and Ca++).
- Enhancing the activity of GABA (neurotransmission inhibition).
- Reduction of excitatory (glutamatergic) transmission.









Three principle types of epilepsy are found. They are as follows:

- Grand mal: In which the seizures last from 2 to 5 min, being characterized by a sudden loss of consciousness, tonic and clonic convulsions of all muscles associated with urinary incontinence.
- Petit mal: The seizures last from 5 to 30 sec, being characterized by brief attacks of unconsciousness, usually occur in children at the age of 4 to 8 years.
- Psychomotor seizures: Characterized by attacks without convulsions and lasts from 2 to 3 min.

The ideal antiepileptic drug should completely suppress seizures in doses that do not cause sedation or other undecided CNS toxicity. It should be well tolerated and highly effective against various types of seizures and devoid of undesirable side effects on vital organs and functions.

Categories of Anti-epileptic Drugs

Classification is based upon chemistry:

I. Barbiturates

eg: Phenobarbital, Mephobarbital

II. Hydantoins

eg: Phenytoin, Phenylethyl hydantoin

III. Oxazolidinedione derivatives

eg: Trimethadione, Paramethadione

IV. Succinimides

eg: Phensuximide, methsuximide

V. Phenyl acetyl ureas

eg: Phenacemide

VI. Benzodiazepines

eg: Diazepam, Clobazepam

VII. GABA analogues

eg: Vigabatrin, Tiagabin

VIII. Iminostilbenes

eg: Carbamazepine

IX. Miscellaneous

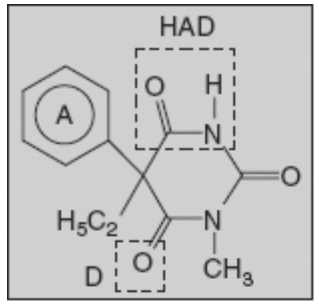
eg: Carbamazepine, Valproate

X. Newer—anticonvulsants

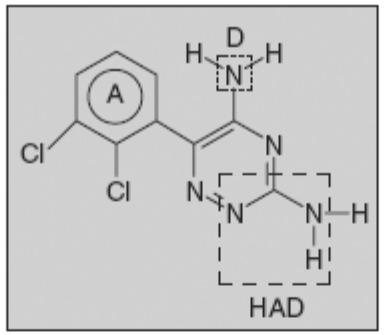
eg: Denzimol, Denzinamide

Structural requirements for anticonvulsant agents and their to structure activity relationship

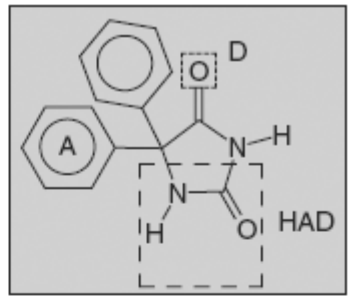
It was stated that for a compound to act as anticonvulsants, the molecule should contain at least one aryl/lipophilic unit (A), one or two hydrogen acceptor–donor atoms (HAD), and an electron-donor atom (D) in a special spatial arrangement to be recommended for anticonvulsant activity. The well-known and structurally different compounds with anticonvulsant activity—carbamazepine, gabapentin, lamotrigine, mephobarbital, phenytoin, progabide, ralitoline, and zonisamide—are represented with their structural elements as follows.



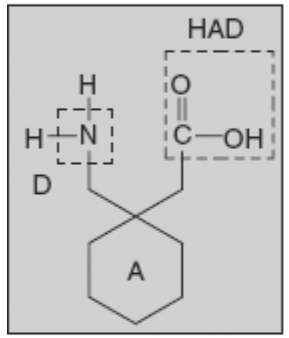
Mephobarbital



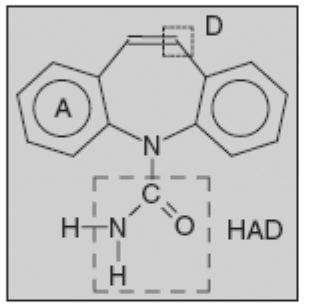
Lamotrigine



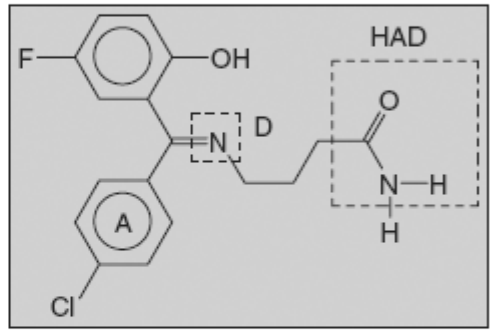
Phenytoin



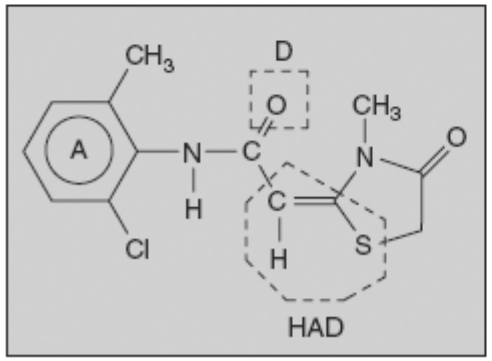
Gabapentin



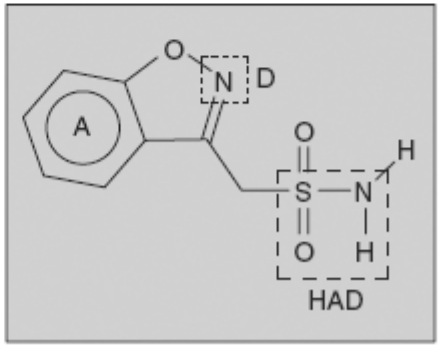
Carbamazepine



Progabide

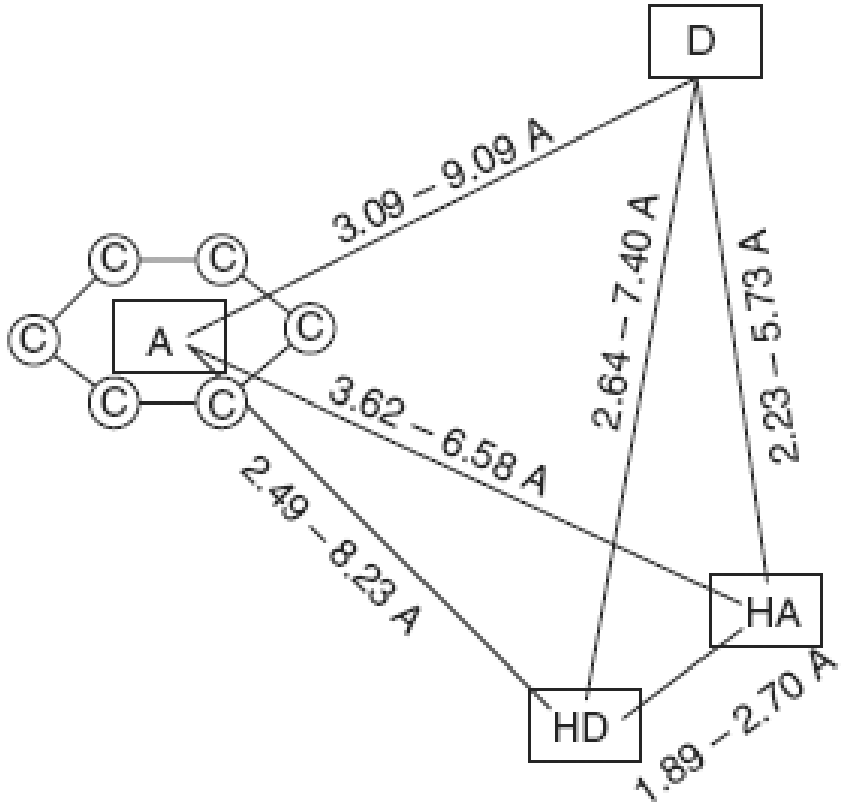


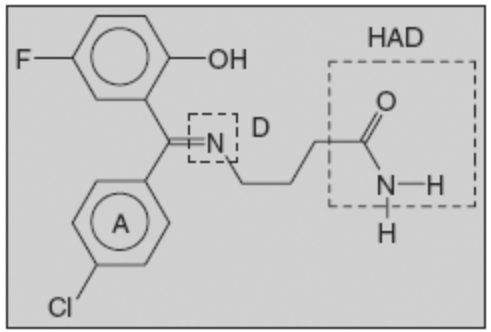
Ralitoline



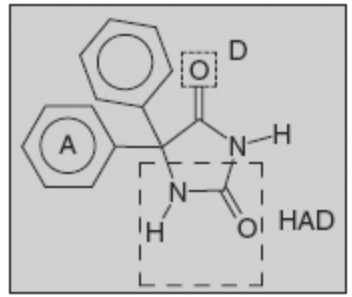
Zonisamide

The distances between these structural elements should be optimal in the ranges depicted in the following figure. These distances are calculated using various computational tools for the 3D structures of the drugs.

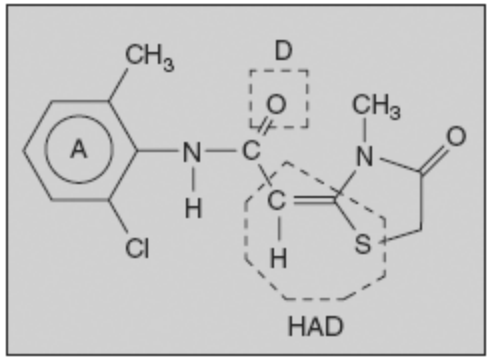




Progabide



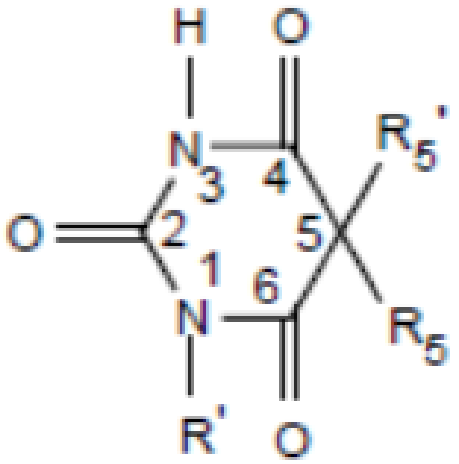
Phenytoin



Ralitoline

I. Barbiturates

- Most of the barbiturates are sedatives and hypnotics. Only a few of them show anticonvulsant characters. Three important barbiturates that show anticonvulsant properties and used for tonic-clonic seizures



- **MOA:** The mechanism is facilitated by GABA receptor mediated synaptic inhibition, opens the chloride channels, and inhibits the calcium dependent release of neurotransmitters. In addition, at very high concentrations, barbiturates depress sodium and potassium channels and reduce the abnormal discharge of electrical impulse.

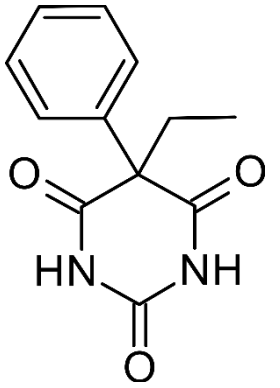
Name	R'	R_5	R_5'
Phenobarbitone	–H	–Ph	–Et
Mephobarbiton	$–CH_3$	–Ph	–Et
Metharbital	$–CH_3$	–Et	–Et

I. Barbiturates

SAR

1. Attachment of alkyl groups to both nitrogen produce an inactive compound.
2. Only one of the substituent groups at position 5 may be a cyclic group which make it Optimum in activity
3. SAR is discussed in Chapter 12 ‘Sedatives and Hypnotics.

I. Barbiturates – Phenobarbital

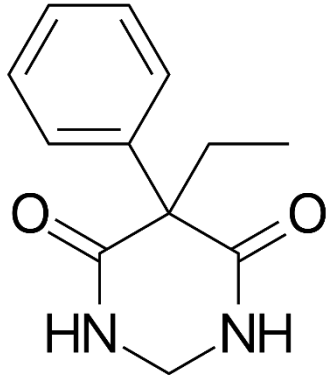


- Used for tonic-clonic seizures (partial and generalized).
- **Mechanism of action:**
  - Act by increasing the duration of Cl- ion channel opening by activating neuronal GABAa receptors.
  - Causing hyperpolarisation of the AP, making it less likely to fire again
  - Essentially, acts like GABA and can even potentiate the effects of GABA when present.

- **Pharmacokinetics:**
  - Almost complete absorption.
  - Elimination is by heptic and renal (25% excreted unchanged).
  - Biotransformed in the liver into 2 active metabolites.
  - Plasma concentrations relate poorly to seizure control, use only for monitoring of patient compliance.
- **Adverse effects:**
  - CNS effects (sedation and fatigue)
  - Restlessness/Hyperactivity
  - Folate deficiency
  - Tolerance
  - Dependence with physical withdrawal reactions.
  - Adverse drug-drug reactions (contraception and warfarin).
- **Contraindications:**
- Do not use with patients with respiratory depression, children or elderly.

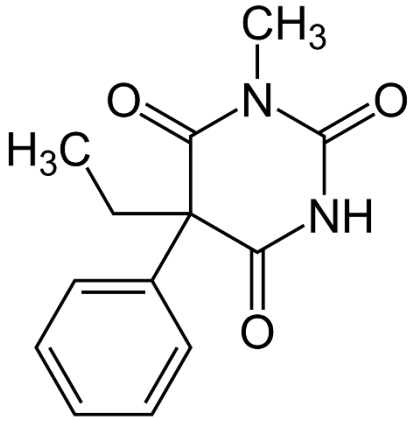
I. Barbiturates – Primidone

- Primidone is metabolized (by oxidation) to phenobarbital and phenylethylmalonamide (PEMA)-All these are active compounds.
  - In infants the drug is slowly metabolized.
- It is effective against partial and generalize seizures.
- Completely absorbed orally, Half-life 6-8 hours.
- Adverse effects are dose related and resemble phenobarbital's adverse effects.

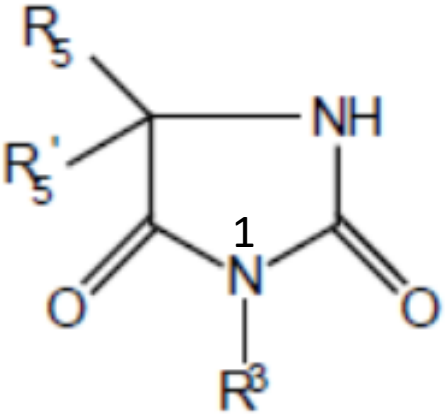


I. Barbiturates – Mephobarbital

- Mephobarbital is the *N*-dealkylated to phenobarbital,
- it effective against generalized tonic-clonic and partial seizures.
- The same MOA of phenobarbital



II. Hydantoins



- Hydantoin was first isolated in 1881 by Adolf von Baeyer in the course of his study of uric acid. He obtained it by hydrogenation of Allantoin hence the name

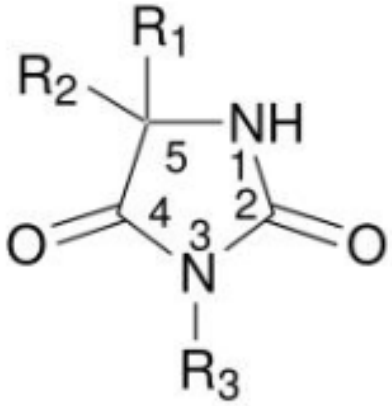
Name	R^3	R^5	R_5'
Phenytoin	–H	$-C_6H_5$	$-C_6H_5$
Phenyl ethyl hydantoin	–H	$-C_2H_5$	$-C_6H_5$
Mephenytoin	$-CH_3$	$-C_2H_5$	$-C_6H_5$
Ethotoin	$-C_2H_5$	–H	$-C_6H_5$

- **MOA:** its prevent repetitive detonation of normal brain cells during depolarization shift. This is achieved by prolonging the inactivated state of voltage gate sensitive sodium channels and governs the refractory period of specific neurons, moreover,

reduces the calcium influx and inhibits the glutamate activity. Intracellular storation of Na+ leads to the prevention of repetitive firing.

Pharmacophore

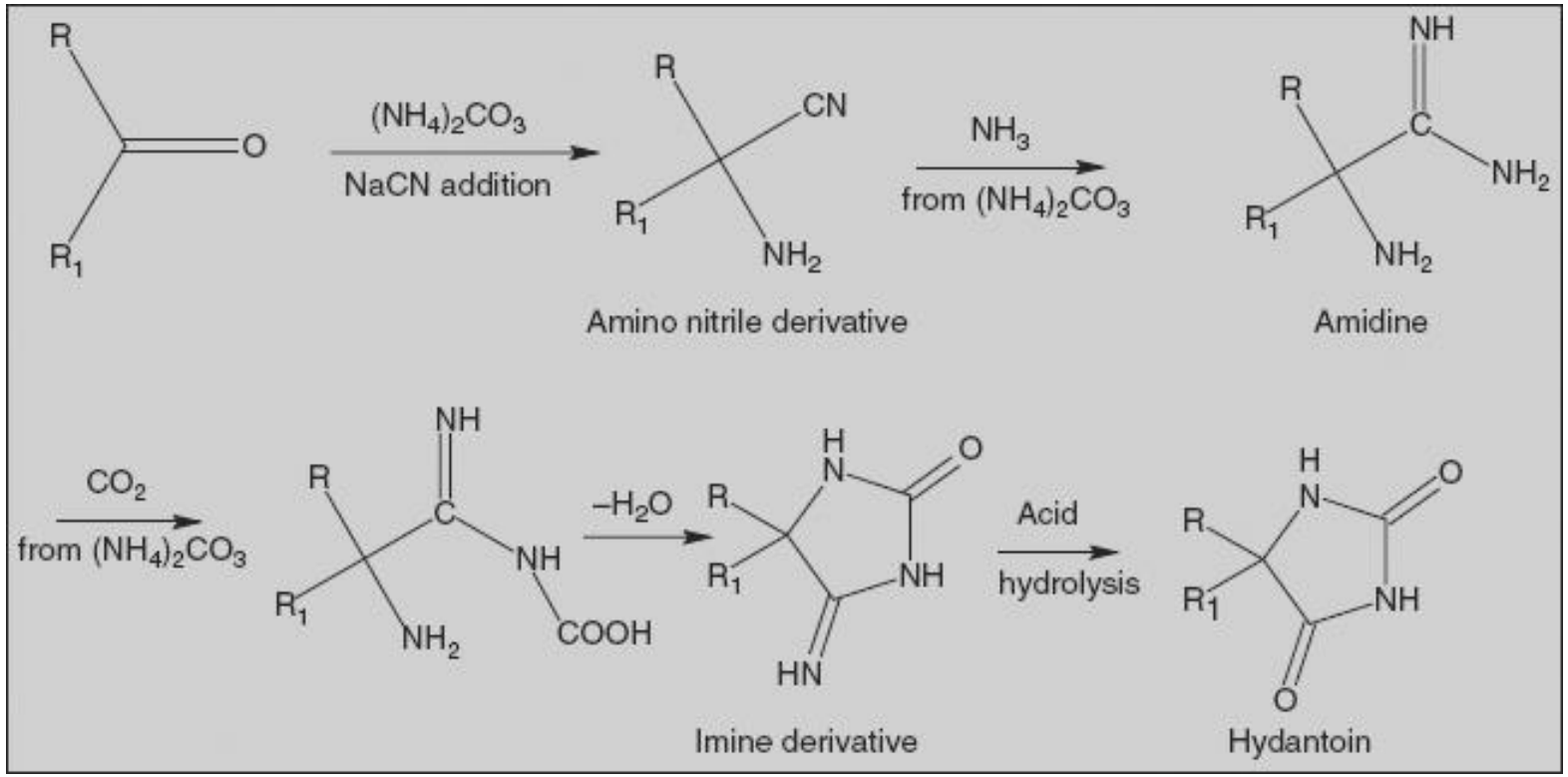
- Close structural relatives of barbiturates
- Only lacking the 6-oxo group and are cyclic monoacylureas rather than diacylureas
- As a consequence of losing a carbonyl group weaker organic acids than barbiturates and thus their sodium salt (e.g., phenytoin sodium) generates stronger alkaline solution



SAR of Hydantoins

- 5-phenyl or other aromatic substitution is essential for activity.
- Alkyl substituent at position 5 may contribute to sedation, a property absent in phenytoin.
- Among other hypnotics 1,3-disubstituted hydantoins, exhibit activity against chemically induced convulsion, while it remains ineffective against electric shock induced convulsion.

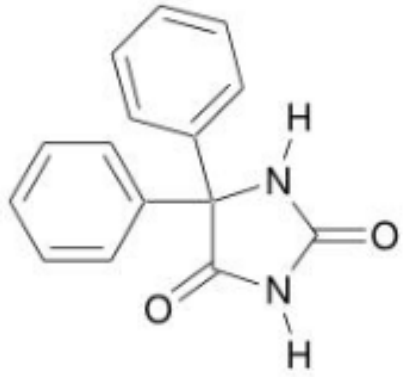
Hydantoins are synthesised by the treatment of appropriate carbonyl compound with sodium cyanide in the presence of excess ammonium carbonate. The first step in this complex sequence can be visualized as addition of the elements of ammonia and hydrogen cyanide to give an α-aminonitrile.



II. Hydantoins -Phenytoin

Clinical use

- Use for patients with Tonic-Clonic seizures (both partial and generalized seizure).



Phenytoin

Mechanism of action

- It blocks sustained-high frequency repetitive firing of action potential.
  - – Acts to promote intracellular removal of sodium duringthe refractory period
  - –Antagonism (blocking) of Na+ channels to reduce excitability
  - –Antagonism of Ca++ channels
    - This also reduce the calcium dependent release of neurotransmitters and hormones.
- Potentiation (activation) of GABA receptors to promote the inhibitory role of GABA.
- Inhibit the action of glutamate.

Pharmacokinetic

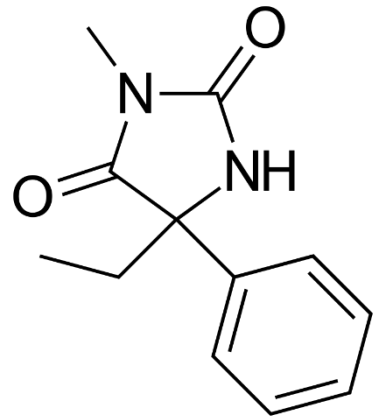
- Slowly absorbed from gut, use a slow IV if rapid action is required
    - Depends on formulation (particle size, additives) and dosage form
- Avoid IM – muscle damage
    - Phenytoin might precipitate in muscle tissues
- Highly bound to the plasma protein (90%)
    - Distribute well in to the brain, liver, muscle and fat
- Metabolized by hepatic biotransformation (to inactive metabolite)
    - Only small amount excreted unchanged
- Therefore half-life is dose dependent (lower to middle dose 12 to 36 hours & higher dose >2 days.

Synthesis: Using benzophenone as the starting material

II. Hydantoins -Methoin or mephenytoin

Properties and uses:

It is one of the first hydantoin introduced into therapy. It was introduced as a sedative-hypnotic and anticonvulsant under the name Nirvanol, but it was withdrawn because of toxicity, used to control various partial seizures.

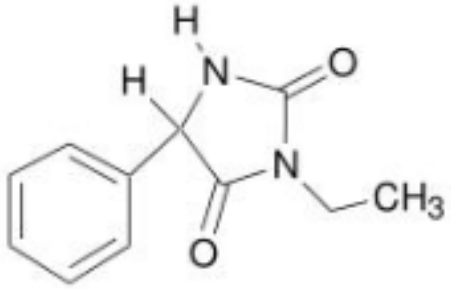


Synthesis: Using Propiophenone + hydrogen cyanide as the starting materials

Metabolism: It is converted into *N*-demethyl metabolite 5-phenyl-5-ethyl hydantoin.

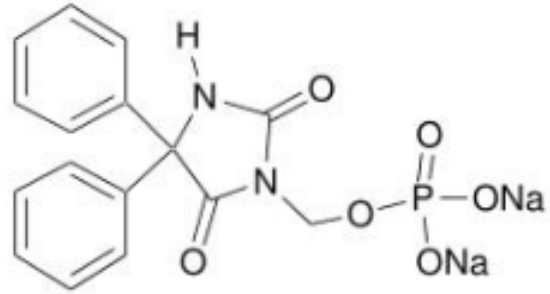
MOA: block frequency-, use- and voltage-dependent neuronal sodium channels, and therefore limit repetitive firing of action potentials.

Ethotoin is dealkylated to the active drug. In this case there is free hydrogen at C5, which explains its very low potency. Metabolism is also by p-hydroxylation and then glucuronidation



Ethotoin

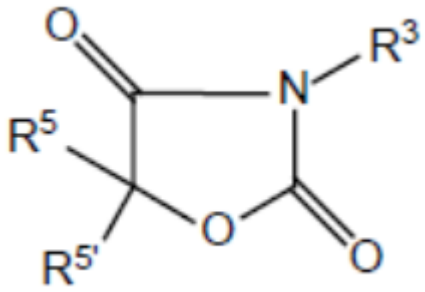
Fosphenytoin is Phosphate ester of phenytoin, rapidly hydrolyzed to phenytoin in vivo. Phenytoin sodium must be buffered to an alkaline pH to maintain solubility, thus is very irritating when injected. Fosphenytoin is neutral (pH~7) so is less irritating



Fosphenytoin

III. Oxazolidinediones

- These compounds are some of the oldest antiseizures in use, having been introduced into antiseizure therapy between 1946 and 1948. At that time, no effective drugs were available to control absence seizures (petit mal disorders).
- Oxazolidinediones is rapidly absorbed, is not protein bound, and has a half-life of 6 to 13 days for dimethadione. Because of its potentially fatal side effects, including aplastic anemia, nephrosis, idiosyncratic rashes, and exfoliative dermatitis, oxazolidinediones is rarely used today. It causes malformations or fetal death in up to 87% of pregnancies.



Name	R^3	R^5	$R^{5'}$
Trimethadione (or) Troxidone	$-CH_3$	$-CH_3$	$-CH_3$
Paramethadione	$-CH_3$	$-CH_3$	$-C_2H_5$
Malidione	$-CH_2-CH=CH_2$	$-CH_3$	$-H$
Dimidone	$-C_2H_5$	$-CH_3$	$-CH_3$

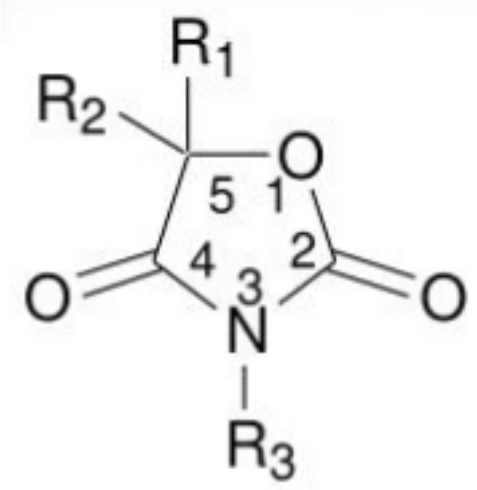
Pharmacophore

• Replacement of the -NH group at position 1 of the hydantoin system with an oxygen atom yields the oxazolidine-2,4-dione system.

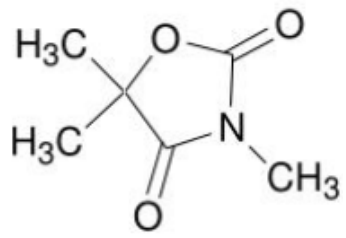
• 3,5,5-Trimethadione (tridione) was the first drug introduced specifically for treating absence seizures. It is also important as a prototype structure.

• The nature of the substituent on C-5 is important, example, lower alkyl substituents towards anti petit mal activity while acyl substituents towards anti grand mal activity.

• The *N*-alkyl substituent does not alter or afford the activity since all the clinically used agents from this class undergo *N*-dealkylation in metabolism.

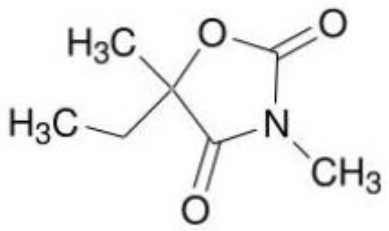


Trimethadione is useful for absence seizures. Note the absence of bulky substituents at the C5 position which are useful in absence seizures. It is metabolized to 5,5 dimethyl oxazolidine 2,4 dione (dimethadione) which is also active. Both trimethadione and dimethadione are excreted in the urine and are very toxic



Trimethadione

Paramethadione is also N dealkylated, half life is 12-24 hours. Some excreted by kidney. The metabolite is active and probably accounts for most activity the half life of which is 14 days and is excreted by the kidney. Also it is fairly toxic



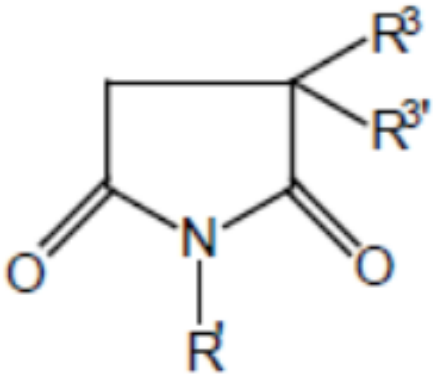
Paramethadione

Toxicity: Symptoms of overdose include clumsiness or unsteadiness, coma, dizziness (severe), drowsiness (severe), nausea (severe), and problems with vision.

MOA: reduce T-type calcium currents in thalamic neurons by inhibition of voltage dependent T-type calcium channels

IV. Succinimides

- Because oxazolidinediones are toxic, an extensive search was undertaken to replace them with less toxic drugs.
- Substituting the ring O in the oxazolidinediones with a methylene group gave the antiseizure succinimides. The clinically used succinimides include ethosuximide, methsuximide, and phensuximide, which were introduced between 1951 and 1958 and widely accepted for the treatment of absence seizures.
- **MOA:** Succinimides selectively acts on the transient current in calcium channels for the influx of calcium ions and inhibits the amplification of spikes.

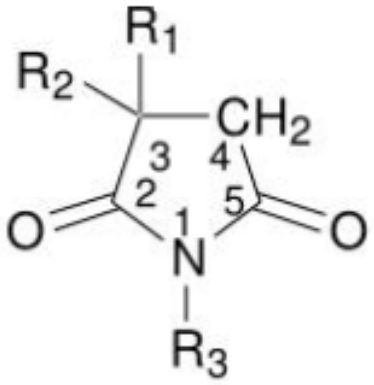


Name	R^1	R^3	$R^{3'}$
Phensuximide	$-CH_3$	$-H$	$-C_6H_5$
Methsuximide	$-CH_3$	$-CH_3$	$-C_6H_5$
Ethosuximide	$-H$	$-CH_3$	$-C_2H_5$

Pharmacophore

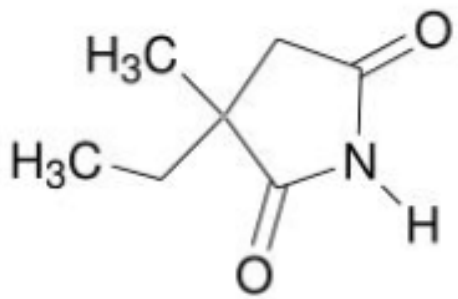
• The activity of antiepileptic agents, such as the oxazolidine 2,4-dione with substituted succinamides (CH2 replace O) was logical choice for synthesis and evaluation.

• *N*-demethylation occurs to yield the putative active metabolite. Both phensuximide and the *N*-demethyl metabolite are inactivated by *p*-hydroxylation and conjugation.

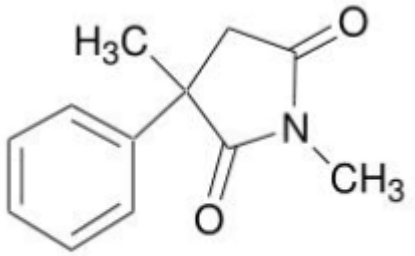


Succinimides

Ethosuximide is lacking bulky groups attached at C3 which corresponds to C5 in the other related structures and thus is good for absence seizures. Major metabolite is from oxidation of the ethyl group, hydroxyethyl and conjugated hydroxyethyl, both are inactive

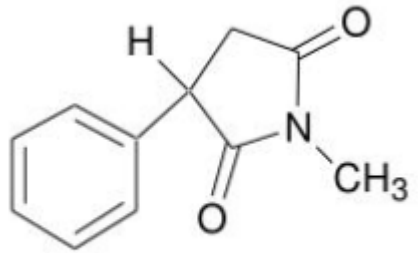


Methsuximide has a bulky group at C3 which is good for absence but also picks up some partial seizures activity. It is N-dealkylated to an active metabolite. Half life of methsuximide is 1.4 h, the N demethyl has a half life of 38 h. So most activity are due to metabolite, followed by p-hydroxylation and conjugation



Methsuccimide

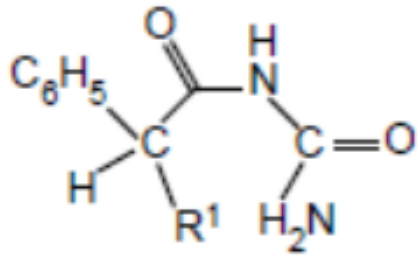
Phensuximide possesses the bulky group at C3 which is good for absence but also picks up some generalized tonic-clonic activity. Because of the free hydrogen at C3, it is much weaker than the disubstituted compounds. N-dealkylated to an active metabolite, but the half life is about the same as the parent (5-12 hr) and the activity is due to both species. Followed by p-hydroxylation and conjugation



Phensuccimide

V. Acetyl urea derivatives or phenyl acetyl ureas

- it is only used in cases of severe epilepsy when other, less-toxic drugs have failed.

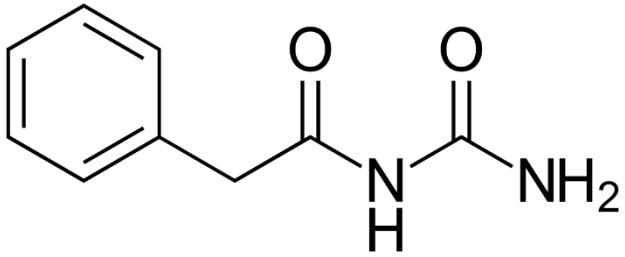


MOA:

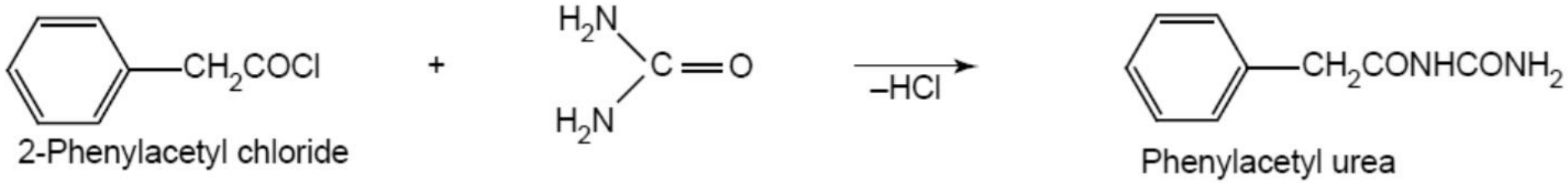
- blocking of Na+ & Ca++ channels to reduce excitability and reduce the calcium dependent release of neurotransmitters and hormones.
- Activation of GABA receptors to promote the inhibitory role of GABA
- Inhibit the action of glutamate.

Name	R^1
Phenacemide	–H
Phenyl ethyl acetyl urea	$-C_2H_5$

Phenacemide (Phenurone)



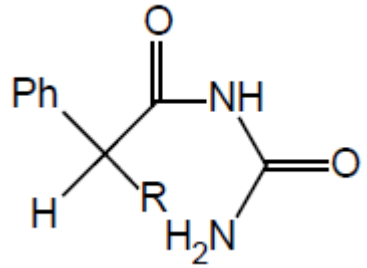
Synthesis



MOA: binds to and blocks neuronal sodium channels or voltage sensitive calcium channels. This blocks or suppresses neuronal depolarization and hypersynchronization. Hypersynchronization is what often causes seizures.

Met: Metabolized in the liver by hepatic microsomal enzymes, where it is inactivated by p-hydroxylation.

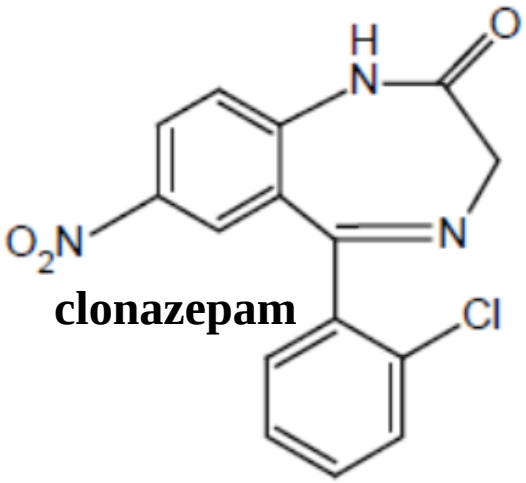
SAR of Phenacemide



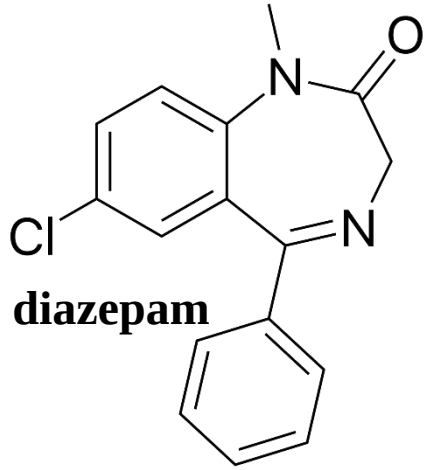
1. Among aliphatic acetyl ureas the highest anticonvulsant activity is found in those derived from the branched chain acids of about 7-carbon atoms.
2. With a further increase in molecular weight the anticonvulsant activity gradually terminates and hypnotic effect predominates.
3. Phenacemide is a most active agent among the aromatic acetyl urea.
4. Any substitution in nitrogen of phenacemide does not increase further the anticonvulsant activity.
5. The activity decreases with aromatic substituents of phenacemide with a gradual increase in hypnotic activity.

VI. Benzodiazepines

- Its widely used as sedative-hypnotics and antianxiety drugs. In laboratory animals, DZB's display outstanding antiseizure properties against seizures. Diazepam, lorazepam, clonazepam, clorazepate dipotassium, and midazolam are effective for seizure control.
- All DZB's enter cerebral tissue rapidly. Although the duration of action is short for diazepam (2 h), midazolam (3 to 4 h), longer for clonazepam (24 h).
- **MOA:** DZB acts by enhancing pre & postsynaptic inhibition through DZB's receptor, which is an integral part of $GABA_A$ receptor Cl^-channel. It opens the Cl^- channel through GABA facilitatory action. These drugs also induce hyper-polarization and decrease firing rate of neurons.



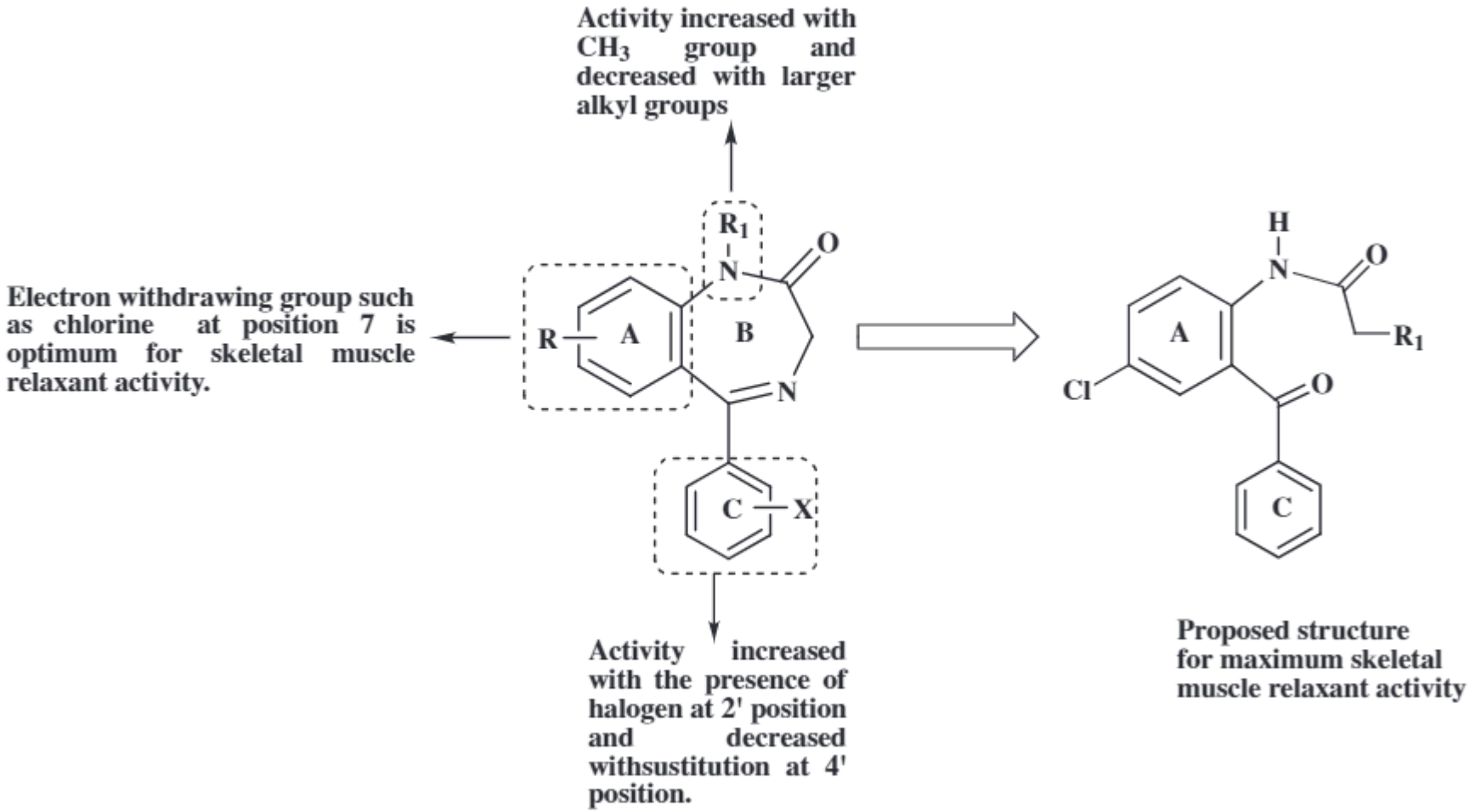
clonazepam



diazepam

- **Pharmacokinetics:**
  - Well absorbed from the gut, Lipid soluble to ensure ready penetration of the blood brain barrier, Slow elimination from body.
  - Metabolised in the liver to create active agents (prolonged therapeutic action).
- **Adverse effects:**
  - The most frequent side effect for diazepam is somnolence; dizziness, ataxia, headache, nervousness, euphoria, and rash occur less frequently.

Pharmacophore, SAR is discussed in Chapter 12 ‘Sedatives and Hypnotics.

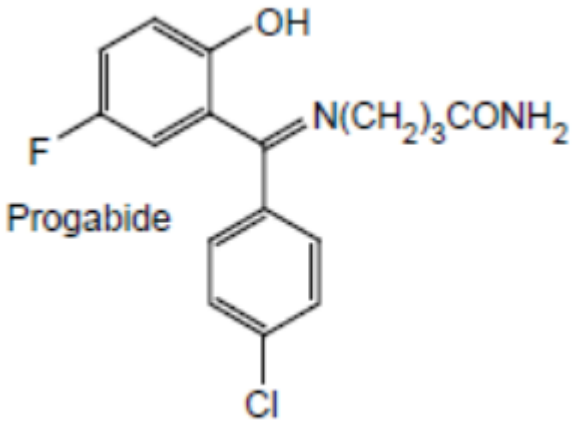


Diazepam (VALIUM): Diazepam is given orally for adjunctive control of convulsive disorders, as a rectal gel (Diastat) for refractory patients with epilepsy on a stable regimen of AEDs who require intermittent use of diazepam to control bouts of increased seizure activity, and parenterally as part of the regimen for the treatment of status epilepticus or other severe, recurrent seizures. Rectal diazepam gel is an effective and well-tolerated therapy for acute repetitive seizures.

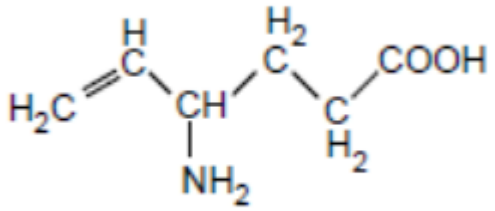
Clonazepam: was found to be effective in controlling absence seizures, but because of its high incidence of side effects, it is rated second to ethosuximide. It can be useful, however, in absence seizures when succinimide therapy has failed. It is considered to be a third-line drug after 1) ethosuximide or valproate and 2) lamotrigine or valproate for the treatment of absence seizures. It is ineffective for treatment of generalized clonic-tonic seizures.

VII. Gamma amino butyric acid (GABA) analogues

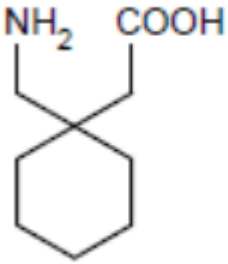
- Gamma-amino butyric acid (GABA) is an inhibitory neurotransmitter. It cannot cross the blood-brain barrier (BBB). This problem is overcome by enhancing the lipid solubility by the formation of Schiff ’s base of gabamide.
- **MOA:** GABA acts at inhibitory synapses in the brain by binding to specific transmembrane receptors in the plasma membrane of both pre- and post-synaptic neuronal processes. This binding causes the opening of ion channels to allow the flow of either negatively charged chloride ions into the cell or positively charged potassium ions out of the cell. This action results in a negative change in the transmembrane potential, usually causing hyper polarization.



Progabide

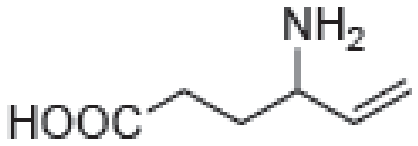


Vigabatrin



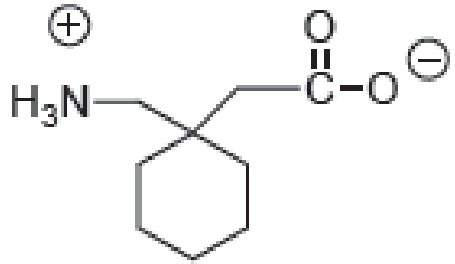
Gabapentin

Vigabatrin: Mechanism of action: Vigabatrin readily crosses the BBB and raises brain GABA levels by virtue of GABA-transaminase enzyme inhibition



Used in the treatment of infantile spasms in children of 1 month to 2 years of age and as adjunctive treatment of adults with refractory complex partial seizures who are not adequately controlled by other anticonvulsants.

Gabapentin: It does not bind with GABAA receptor, causes no inhibition on GABA reuptake, and is not a GABA-T inhibitor. Thus, the mechanism of action is unknown. " Recent studies have demonstrated gabapentin binding to calcium channels in a manner that can be allosterically modulated"



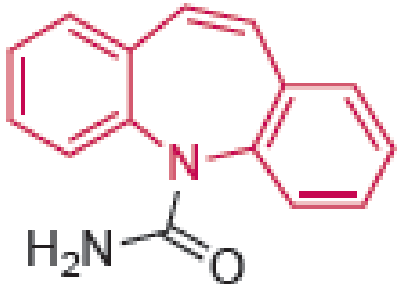
Gabapentin is indicated as an adjunct for use against partial seizures with or without secondary generalization, in patients older than 12 years

VIII. Iminostilbenes

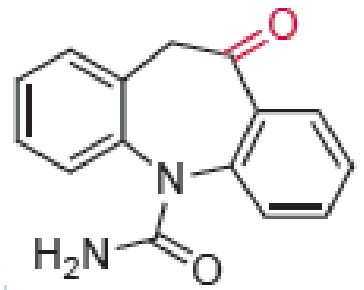
Its tricyclic structure resembles that of the psychoactive drugs imipramine, chlorpromazine, and maprotiline and also shares some structural features with the AEDs phenytoin, clonazepam, and phenobarbital

Mode of action: Similar to phenytoin, iminostilbenes limits the repetitive firing of action potential and appears to reduce the rate of recovery of voltage-gated sodium channel from inactivation.

Carbamazepine: Presently indicated as initial or adjunct therapy for complex partial, tonic-clonic, and mixed-type seizures. It is one of the two safest and most effective older AEDs for these seizure types (phenytoin is the other) and is chosen for monotherapy as a result of its high effectiveness and relatively low incidence of side effects



Oxcarbazepine (Trileptal) is the 10-keto analog of Carbamazepine. It is indicated as monotherapy or adjunctive therapy for partial seizures in adults with epilepsy, as monotherapy for the treatment of partial seizures in children 4 years of age or older, and as adjunct therapy in children 2 to 4 years of age.

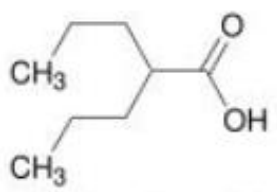


- Oxcarbazepine is completely absorbed, and food has no effect on its absorption.

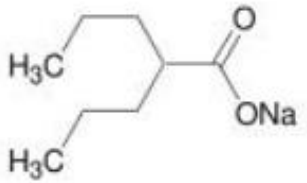
- It's produce a blockade of voltage-dependent sodium channels, thus decreasing repetitive firing and spread of electrical activity. An additional action on calcium and potassium channels can contribute to the therapeutic effect.

IX. Miscellaneous

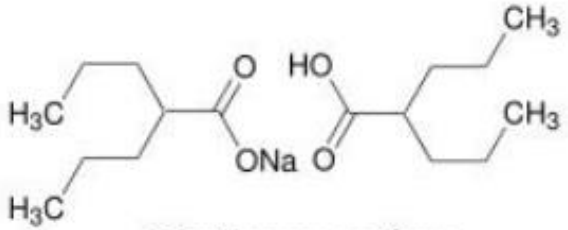
Valproic Acids



Valproic acid



Valproate sodium



Divalproex sodium

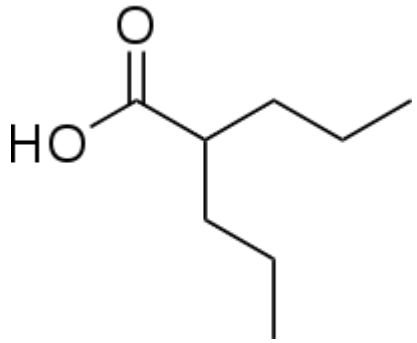
Mode of action: Valproate produces reduction in calcium channel influx and it also prolongs the transient activation time of inactivated sodium channels. Another potential mechanism contributed is to involve in the metabolism of GABA, which is an inhibitory neurotransmitter, by stimulating the GABA synthetic enzyme glutamic acid decarboxylase and inhibits the GABA degradative enzyme GABA transaminase.

Metabolism: It is metabolized by a conjugation of carboxylic acid group and oxidation on one of the hydrocarbon chains.

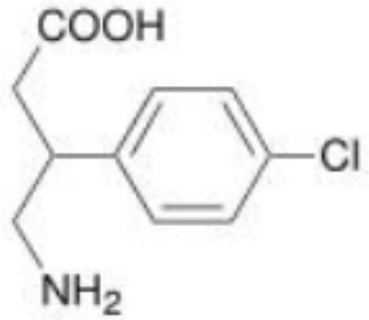
Uses: It has been effective in partial, generalized, and absence seizures.

SAR of Sodium Valproate

- The anticonvulsant activity increases with increased chain length.
- Introduction of a double bond decreases the activity.
- Introduction of a 2° or 3° alcohol group or replacement of carbonyl or hydroxyl have no effect.



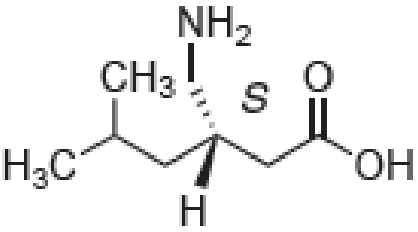
Baclofen modulates mammalian $GABA_B$ receptor. It is used for the treatment of spastic movement, especially in instances of spinal cord injury, spastic diplegia, multiple sclerosis, amyotrophic lateral sclerosis and trigeminal and glossopharyngeal neuralgias. Biotransformation is low and the drug is predominantly excreted in the unchanged form by the kidneys.



X. Newer—anticonvulsants

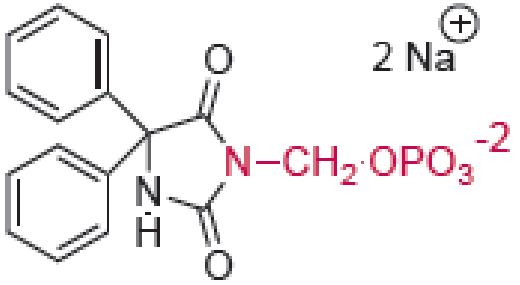
Pregabalin (LYRICA)

Pregabalin is a GABA analog with similarities in structure and effects to gabapentin; however, it is 3 to 10 times more potent as an AED than is gabapentin. It is the pharmacologically active *S*-enantiomer of 3-isobutyl GABA and is FDA approved for the adjunctive treatment of partial-onset seizures in adults.



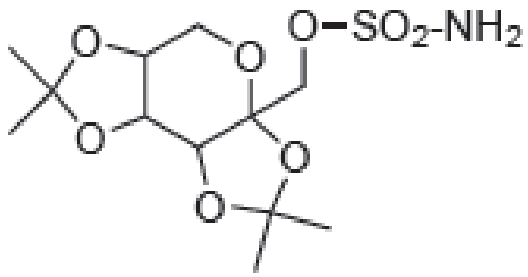
Fosphenytoin sodium

Is a soluble prodrug disodium phosphate ester of phenytoin that was developed as a replacement for parenteral phenytoin sodium, it is freely soluble in aqueous solutions and is rapidly absorbed by the IM route and rapidly metabolized to phenytoin by in vivo phosphatases.



Topiramate

Topiramate is a sulfamate-substituted monosaccharide derived from fructose with a broad spectrum of AED activity. It is FDA approved for monotherapy or as an adjunct drug for partial or primary generalized tonic-clonic seizures in patients older than 10 years, as adjunct therapy in children age 2 to 10 years with partial-onset seizures, topiramate also is approved for the prophylaxis of migraine headaches.



Mechanism of Action is unknown, but several actions are thought to contribute to its AED activity. It blocks repetitive firing by acting on sodium channels, can enhance GABAA- mediated chloride flux.

Agents used for treating epileptic disorders

Seizure type	First-line AEDs	Adjunctive AEDs
Generalised tonic-clonic	Carbamazepine, lamotrigine, oxcarbazepine, sodium valproate	Clobazam, lamotrigine, levetiracetam, sodium valproate, topiramate
Tonic or atonic	Sodium valproate	Lamotrigine
Absence	Ethosuximide, lamotrigine, sodium valproate	Ethosuximide, lamotrigine, sodium valproate

Seizure type	First-line AEDs	Adjunctive AEDs
Myoclonic	Levetiracetam, sodium valproate, topiramate	Levetiracetam, sodium valproate, topiramate
Focal	Carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate	Carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, topiramate
Prolonged or repeated seizures and convulsive status epilepticus in the community	Buccal midazolam Rectal diazepam Intravenous lorazepam	