

Drugs Acting on CNS

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Depressant Drugs

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Antiepileptic Drugs (AEDs)

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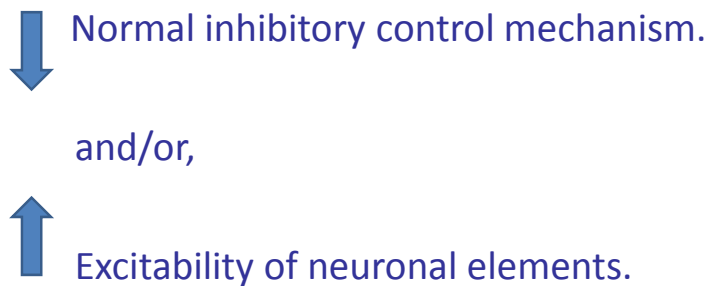
Epileptic Seizure

- Excessive neuronal activity in the brain.
- Disturbance of:
 - ✓ Physicochemical function.
 - ✓ Electrical activity.
- Manifested as:
 - ✓ Alteration in mental state.
 - ✓ Tonic or clonic movements.
 - ✓ Convulsions.
 - ✓ Other psychic symptoms.

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• **Causes:**



• **Seizure Classification:**

Antiseizure drugs			
Seizure type	Conventional	Recently developed	
Simple Seizures	Simple partial	Carbamazepine, phenytoin, phenobarbital, primidone, valproate	Gabapentin, lamotrigine
	Complex partial	Carbamazepine, phenobarbital, phenytoin, primidone, valproate	Gabapentin, lamotrigine
	Partial with secondary generalized tonic-clonic seizure	Carbamazepine, phenobarbital, phenytoin, primidone, valproate	Gabapentin, lamotrigine
Generalized seizures	Absence seizure (Petit mal)	Clonazepam, ethosuximide, valproate	Lamotrigine
	Myoclonic seizure	Valproate	
	Tonic-clonic seizure (Grand mal)	Carbamazepine, phenobarbital, phenytoin, primidone, valproate	

Antiseizure Drugs

- Highly effective with broad activity.
- Control & prevention of recurrent seizures
- Well tolerated:
 - ✓ No CNS side effects.
 - ✓ Harmless to body functions.
- Reasonable duration of action (oral route).
- Rapid onset of action (status epilepticus).

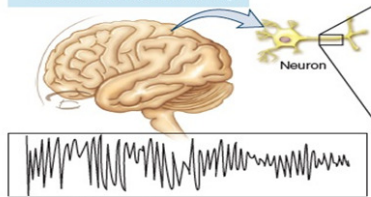
General Mechanisms of Action of Antiseizure Drugs

- Enhancement of GABA-mediated inhibition.
- Suppression of rapid repetitive firing through inactivation of Na⁺ channels.
- Reduction of current through T-type Ca⁺⁺ channels.
- Reduction of excitatory glutaminergic neurotransmission.

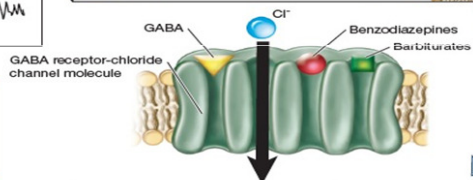
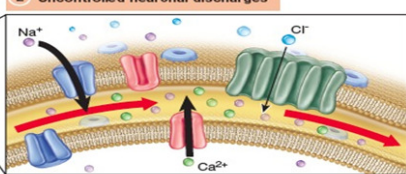
Model of the GABA Receptor–Chloride Channel Molecules in Relationship to Antiseizure Pharmacotherapy

1 Seizure activity: Epilepsy

Uncontrolled neuronal discharge



2 Uncontrolled neuronal discharges

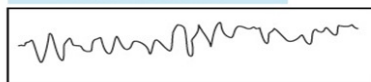


3 Administration of antiseizure drugs

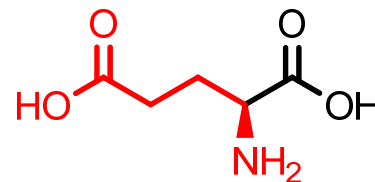
- Drugs that potentiate GABA actions: Benzodiazepines, Barbiturates
- Hydantoin and newer agents
- Succinimides

4 Management of seizure activity

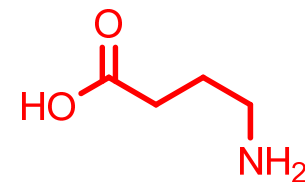
- Stimulating influx of Cl⁻
- Delaying influx of Na⁺ and Ca²⁺
- Antagonism of Glutamate



Normal EEG recording



L-glutamic acid

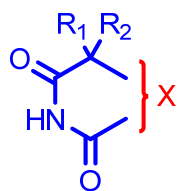


γ-aminobutyric acid
GABA

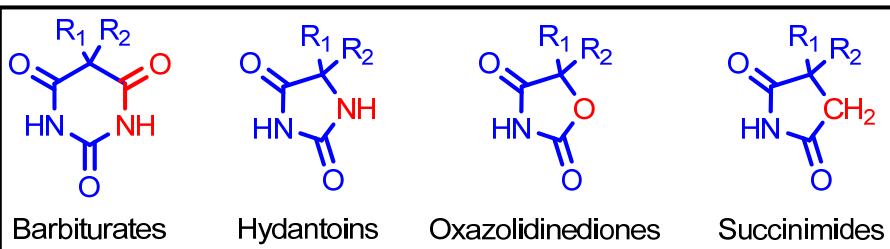
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Antiseizure Drugs Having Ureide Structure



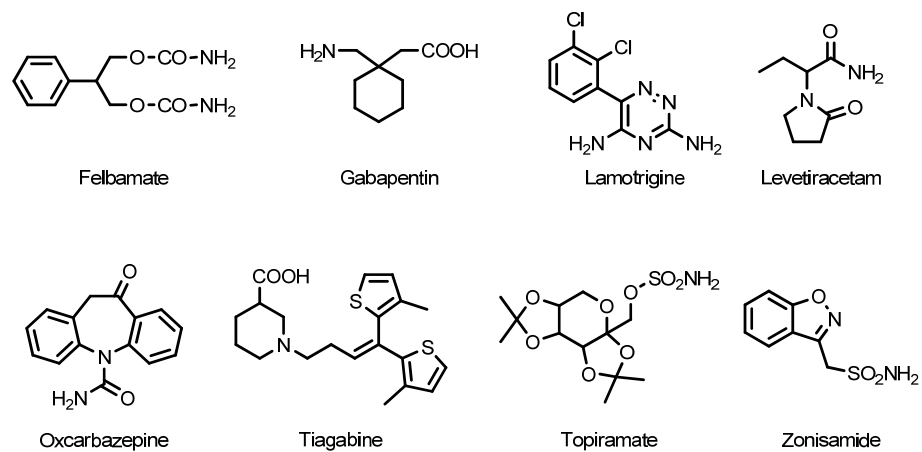
Ureide Structure



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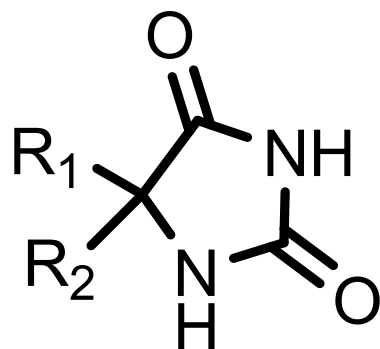
Non-Ureide Antiseizure Drugs



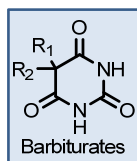
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Hydantoins

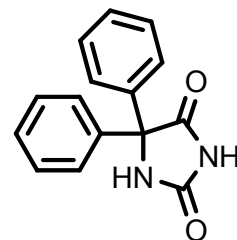


- Imidazo-2,4-dione structure.

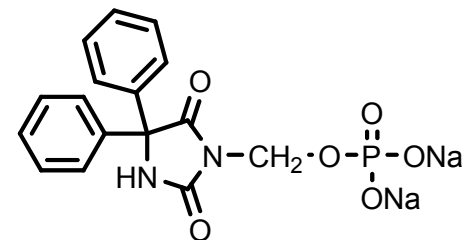


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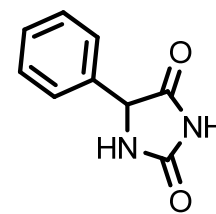
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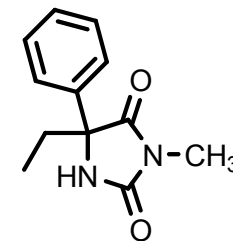
Phenytoin



Fosphenytoin



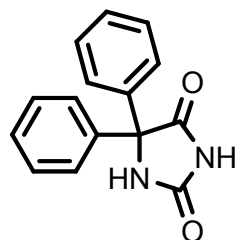
Ethotoin



Mephentyoin

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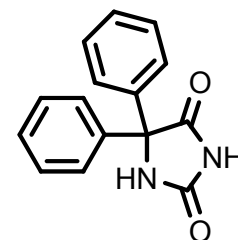


Phenytoin

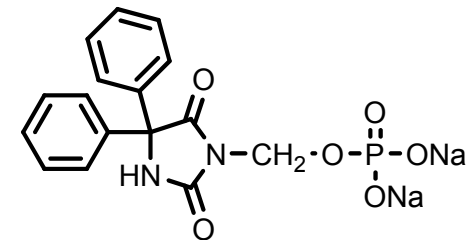
- Prototype.
- pK_a is in the range of 8.06 to 8.33.
- Water soluble sodium salt ($pH > 11$).
- CO_2 .
- Erratic absorption by IM route ($pH < 11$).

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Phenytoin

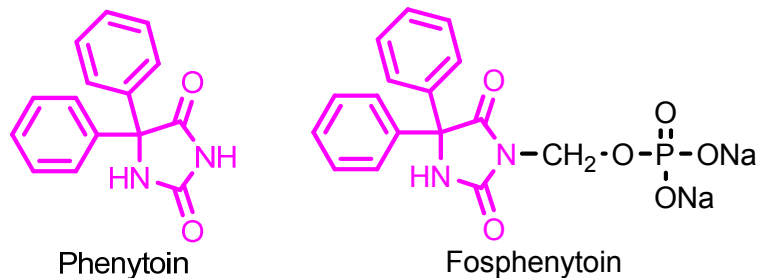


Fosphenytoin

- Prototype.
- pK_a is in the range of 8.06 to 8.33.
- Water soluble sodium salt ($pH > 11$).
- CO_2 .
- Erratic absorption by IM route ($pH < 11$).

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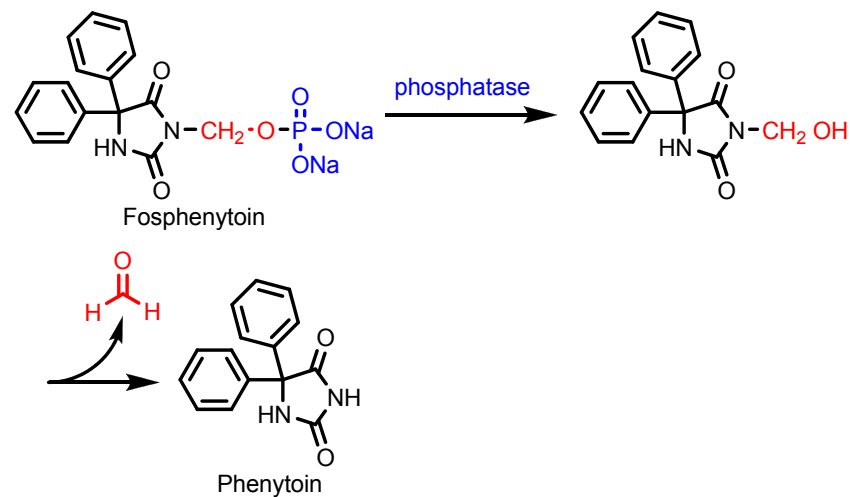


- Pro-drug ($t_{1/2} = 8-15$ minutes).
- Freely soluble in aqueous solutions.
- IV.
- IM (rapidly absorbed).

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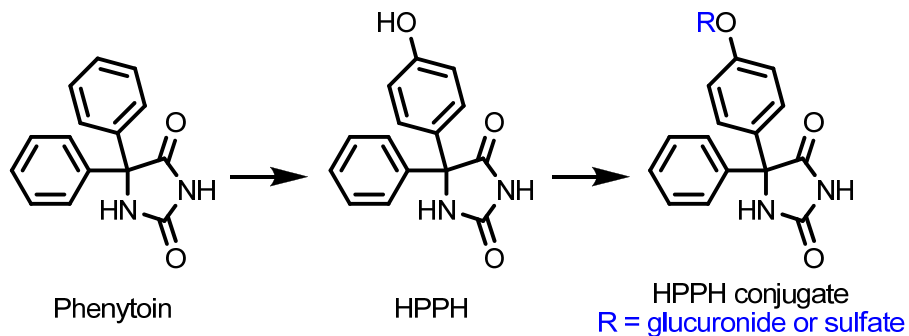
Bio-activation of Fosphenytoin



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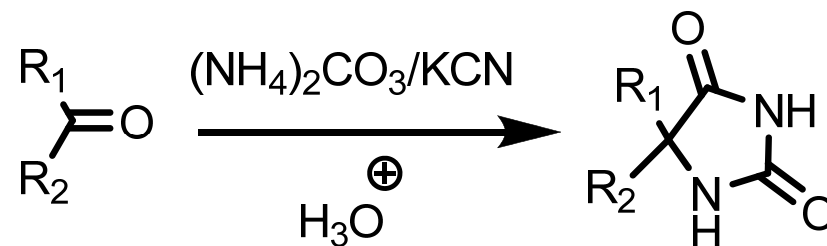
Metabolism of Phenytoin



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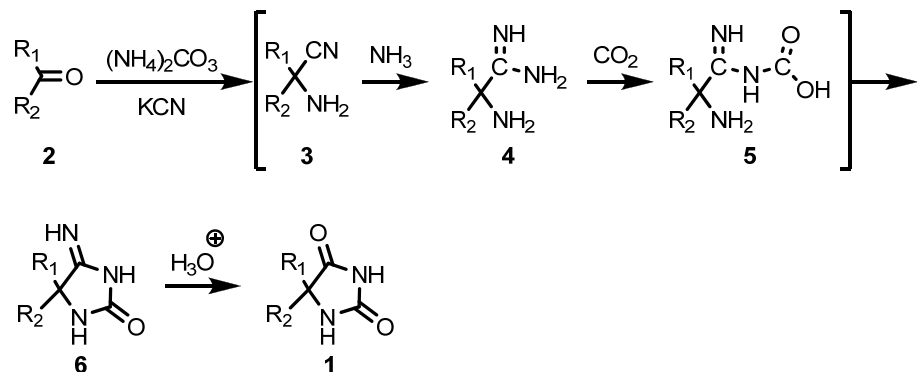
One Pot Synthesis of Hydantoins



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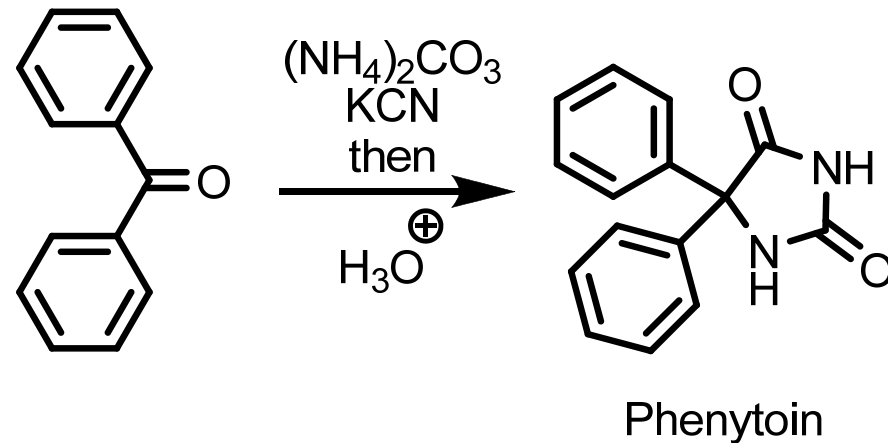
One Pot Synthesis of Hydantoins



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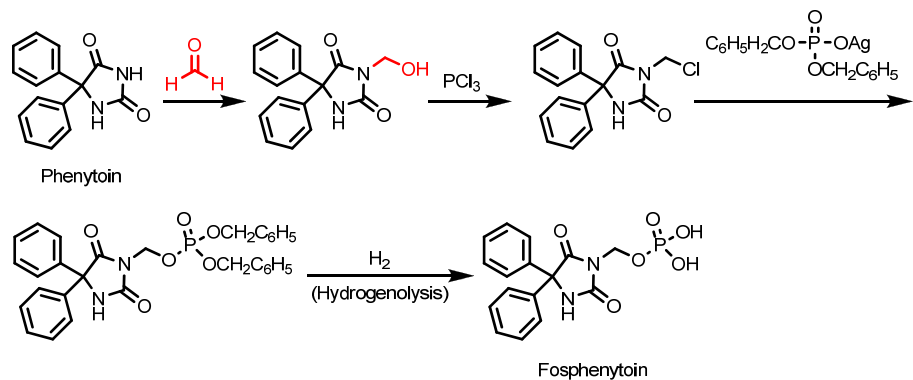
One Pot Synthesis of Phenytoin



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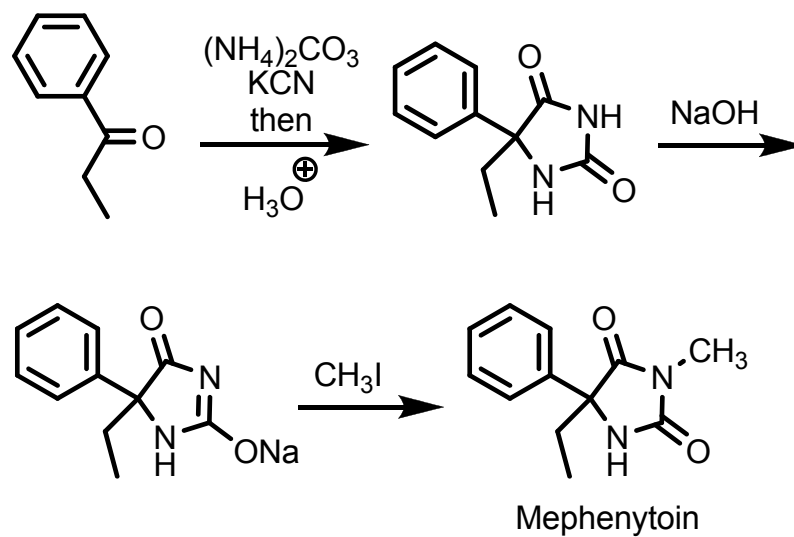
Synthesis of Fosphenytoin



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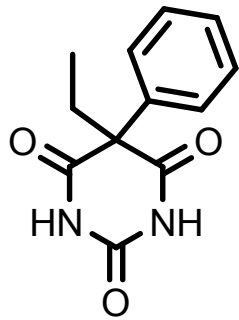
Synthesis of Mephenytoin



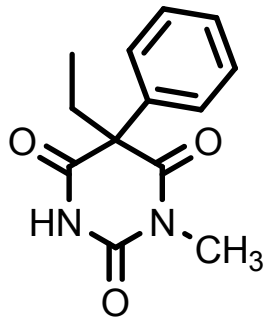
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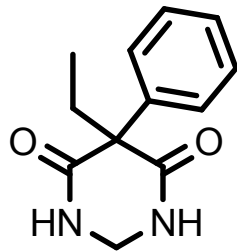
Barbiturates



Phenobarbital
 $pK_a = 7.4$



Mephobarbital
 $pK_a = 7.7$

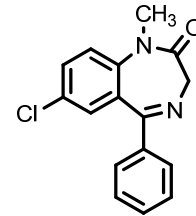


Primidone

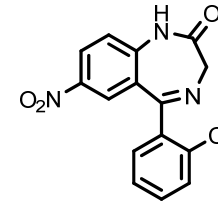
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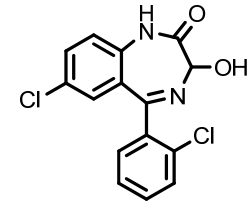
Benzodiazepines



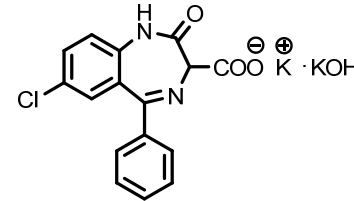
Diazepam



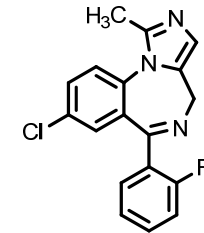
Clonazepam



Lorazepam



Clorazepate dipotassium

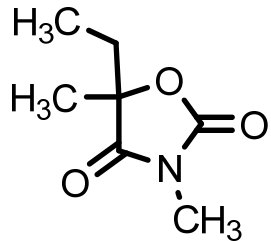


Midazolam

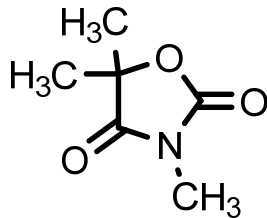
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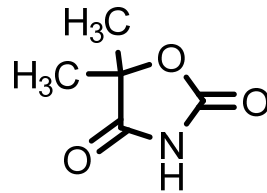
Oxazolidinediones



Paramethadione



trimethadione



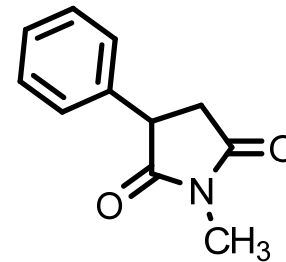
Dimethadione

- Potential side effects!

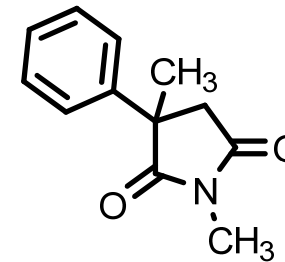
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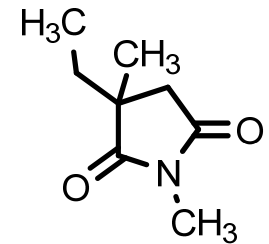
Succinimides



Phensuximide



Methsuximide



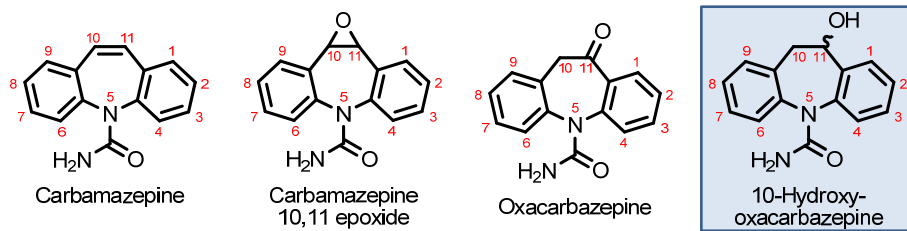
Ethosuximide

- Less toxic than oxazolidinediones!

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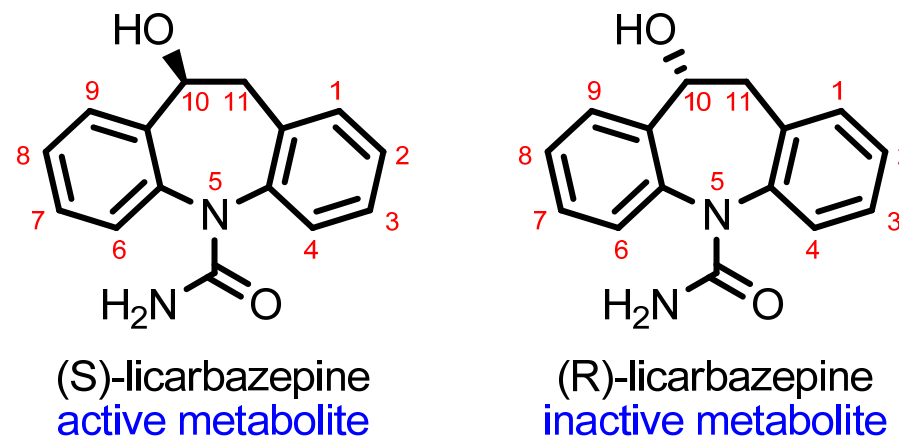
Iminostilbenes



- CBZ is highly effective & relatively less toxic.
- Epoxide is an active metabolite.
- *trans*-Dihydroxy metabolite is inactive.
- Oxacarbazepine is a prodrug!

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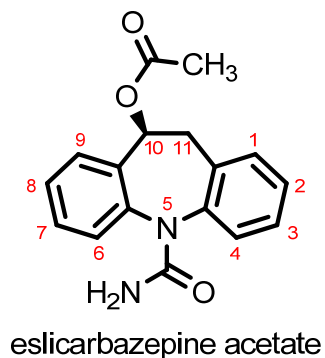
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Eslicarbazepine Acetate

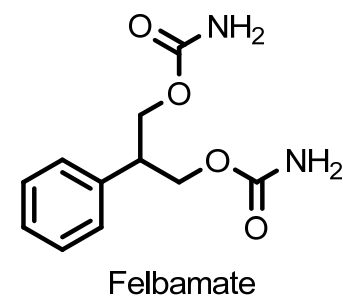


- Improved efficacy and safety.
- Prodrug for (S)-licarbazepine.
- For partial-onset seizures (FDA, 2009).

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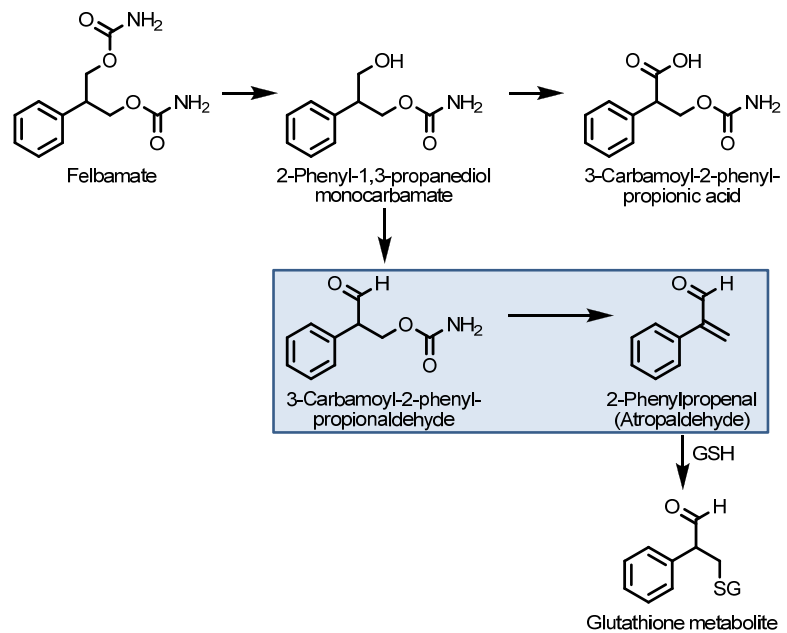
Bis-Carbamates: Felbamate



- Approved by the U.S. FDA in 1993.
- Aplastic anemia and severe hepatotoxicity.

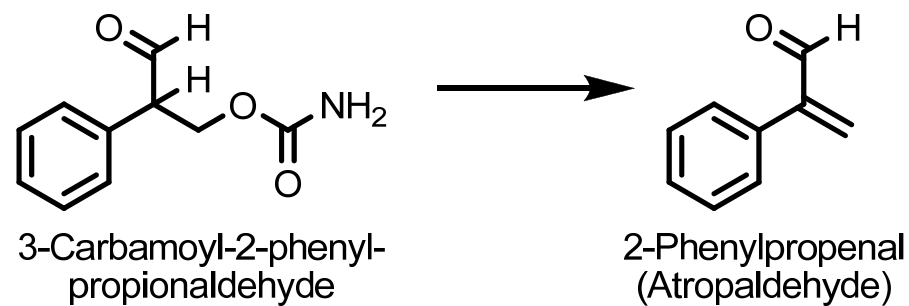
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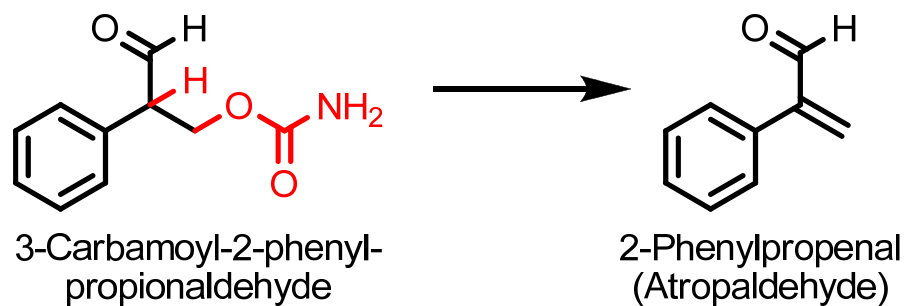
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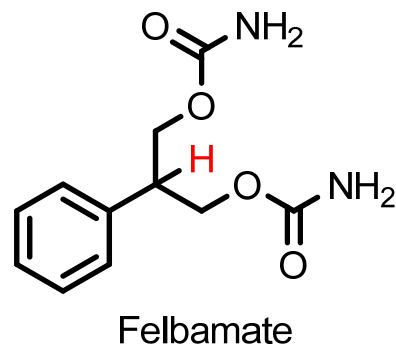
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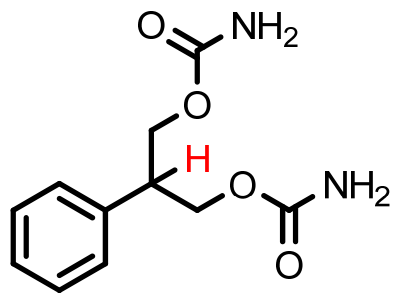
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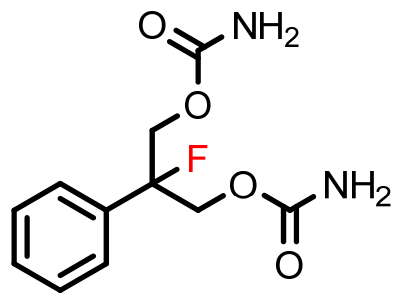


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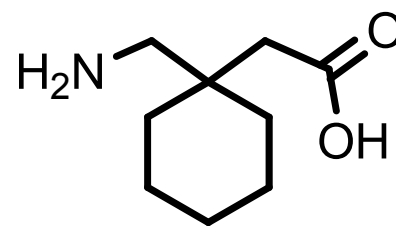


Felbamate

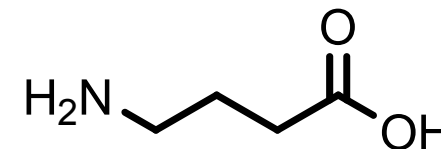


2-Fluorofelbamate

Gabapentin



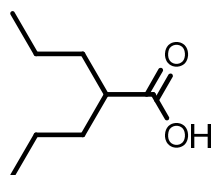
Gabapentin



GABA

- No direct GABA-mimetic activity.
- It raises brain GABA levels in patients with epilepsy.

Valproic Acid



Valproic acid
(dipropylacetic acid)

- pK_a of valproic acid is 4.7, the drug is completely ionized at physiologic pH.
- Discovered serendipitously.