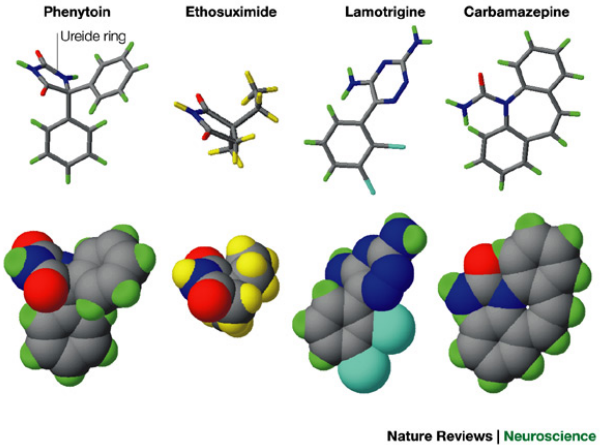


Antiepileptic Drugs (Anticonvulsants)

NEPHAR 305

Pharmaceutical Chemistry I

Assist.Prof.Dr. Banu Keşanlı

Anticonvulsants

✓ **Anticonvulsants**, sometimes also called **antiepileptics**, belong to a diverse group of pharmaceuticals used in prevention of the occurrence of epileptic seizures.

✓ The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure.

✓ Anticonvulsant drug decreases the frequency and/or severity of seizures in people with epilepsy.

✓ They treat the symptom of seizures, not the underlying epileptic condition

What are seizures?

✓ Seizures are episodes of neurologic dysfunction arising from abnormal synchronous activity of neurons.

Epilepsy is a disease characterized by spontaneous recurrent seizures. It is a group of disorders characterized by excessive excitability of neurons within the central nervous system (CNS) and is common, affecting about 1% of the population.

Classification of Anticonvulsants

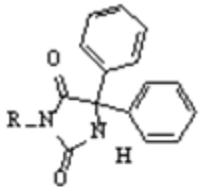
Classical

- **Phenytoin**
- **Phenobarbital**
- **Primidone**
- **Carbamazepine**
- **Ethosuximide**
- **Valproate** (valproic acid)
- **Trimethadione** (not currently in use)

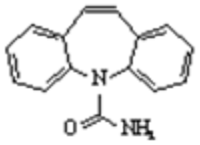
Newer

- **Lamotrigine**
- **Felbamate**
- **Topiramate**
- **Gabapentin/Pregabalin**
- **Tiagabine**
- **Vigabatrin**
- **Oxycarbazepine**
- **Levetiracetam**
- **Fosphenytoin**

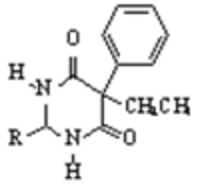
Antiepileptic Drugs



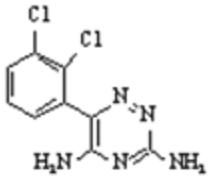
R = H, Phenytoin
R = $CH_2OPO_3^{2-}$, Fosphenytoin



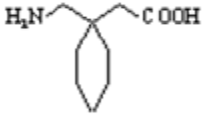
Carbamazepine



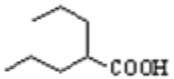
R = H, Primidone
R = =O, Phenobarbital



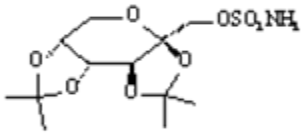
Lamotrigine



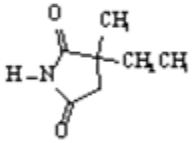
Gabapentin



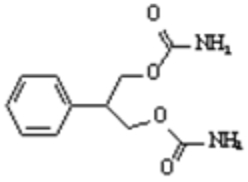
Valproic Acid



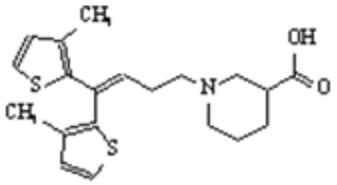
Topiramate



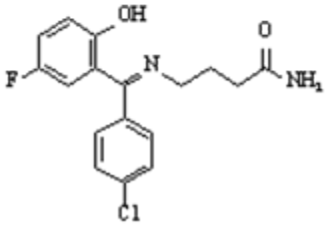
Ethosuximide



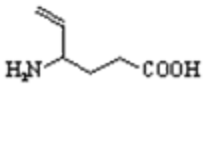
Felbamate



Tiagabine



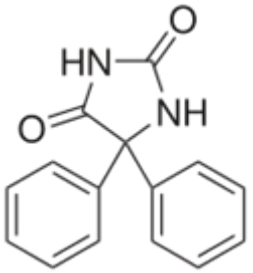
Progabide



Vigabatrin

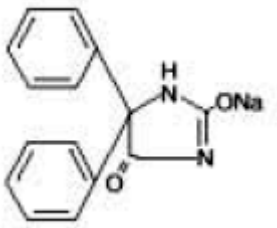
Anticonvulsants - Phenytoin

Phenytoin sodium (**Dilantin**) is one of the oldest and most widely used anticonvulsants. It is used to control certain type of seizures, and to treat and prevent seizures. It works by decreasing abnormal electrical activity in the brain. Mechanism uncertain, but probably related to effect on Na^+ channels.

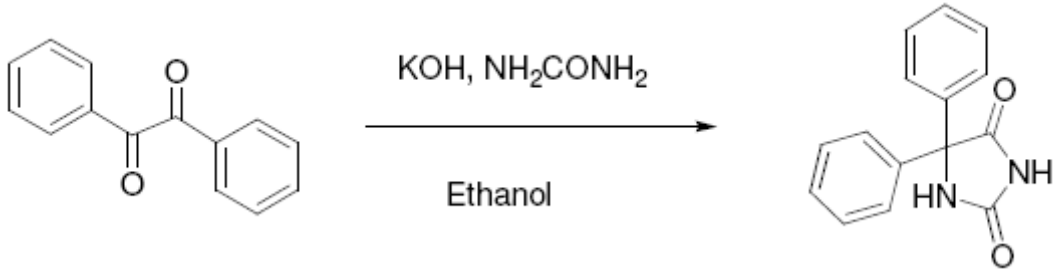


* has Hydantoin structure

5,5-diphenylimidazolidine-2,4-dione

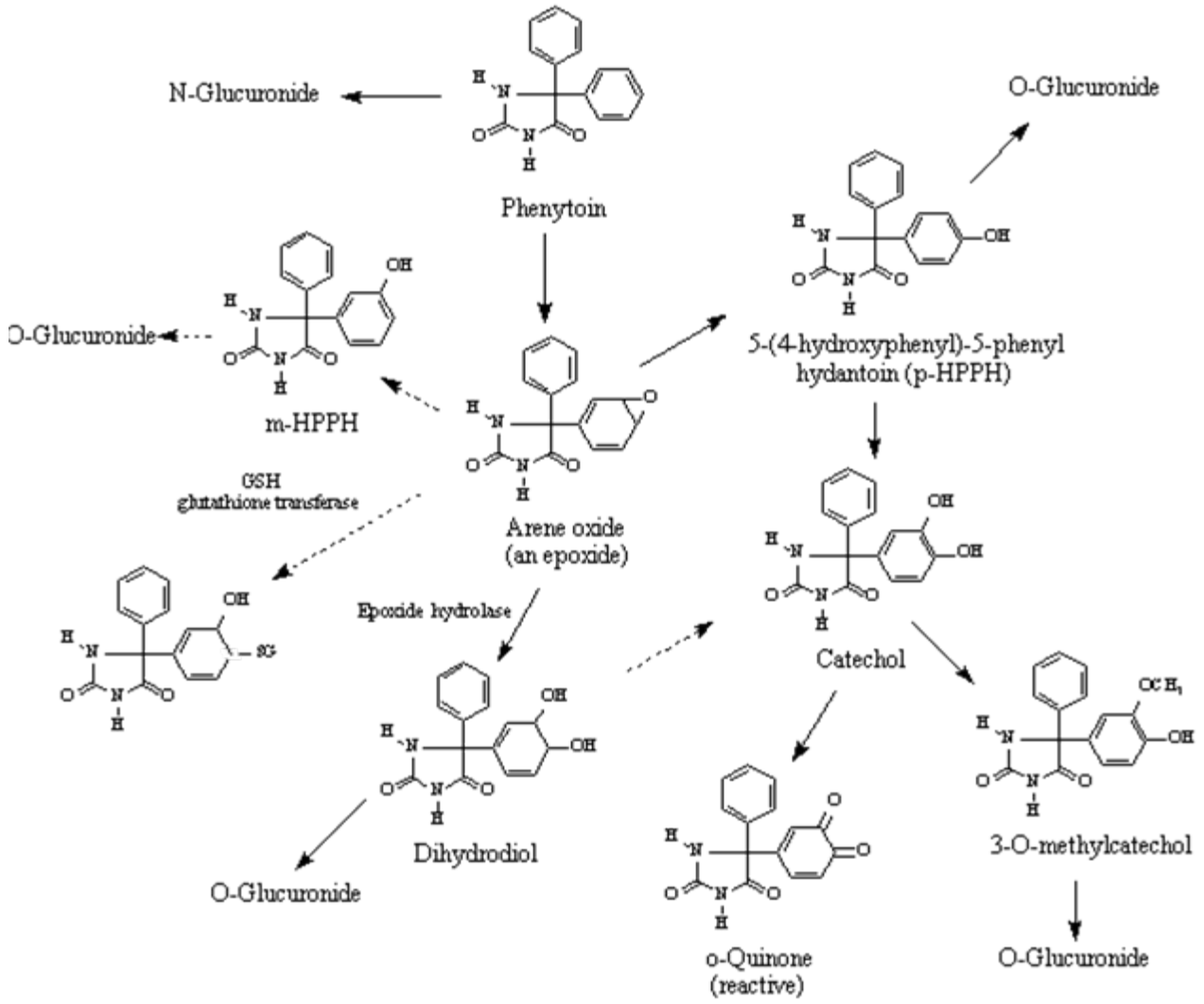


Synthesis: 5,5-diphenylimidazolidinedione is synthesized in two different ways. The first involves a base catalyzed addition of urea to benzil followed by a benzilic acid rearrangement (1,2 phenyl migration) to form the desired product.



Metabolism of Phenytoin

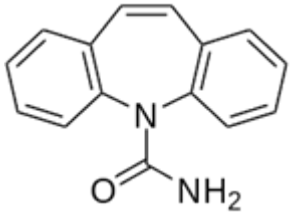
✓ The principal metabolic pathway of Phenytoin in human is aromatic hydroxylation



Anticonvulsants - Carbamazepine

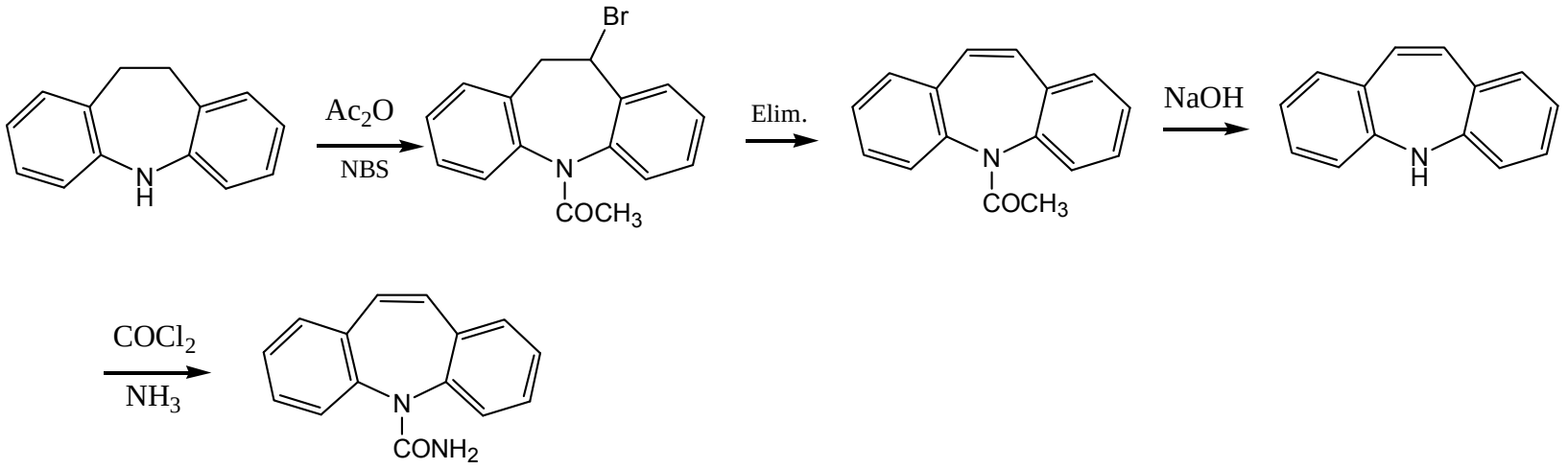
Carbamazepine (Tegretol, Equetro) is an anticonvulsant and mood-stabilizing drug used primarily in the treatment of epilepsy and bipolar disorder.

✓ Structural features similar to phenytoin; mechanism of action likely similar as well.



5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide

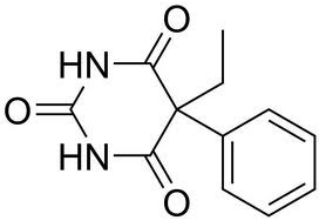
Synthesis of Carbamazepine



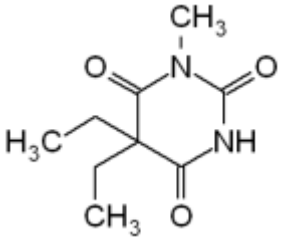
Anticonvulsants - Barbiturates

Barbiturates are sedative hypnotics with anticonvulsant activities but only a few of them are used as antiepileptic drug.

✓ Mechanism probably related to increased GABA-mediated chloride conductance



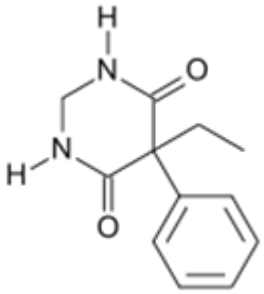
Phenobarbital



Metharbital

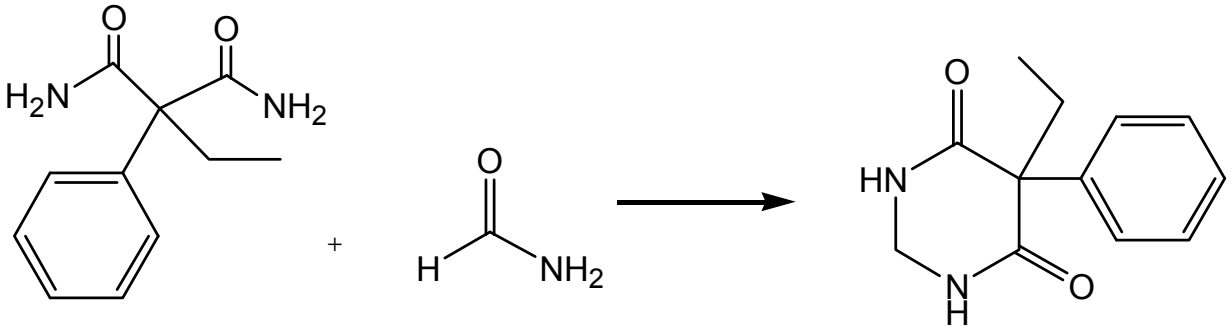
Anticonvulsants - Primidone

Primidone is an anticonvulsant of the pyrimidinedione class, but is metabolized rapidly by the liver to phenobarbital (major) and phenylethylmalonamide (PEMA) (minor), which are also anticonvulsants.



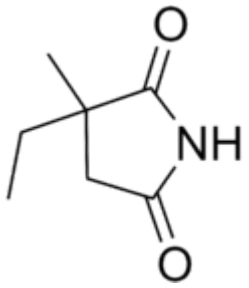
5-ethyl-5-phenyl-hexahydropyrimidine-4,6-dione

Synthesis of Primidone: By reacting ethylphenylmalonic acid diamide with formamide.



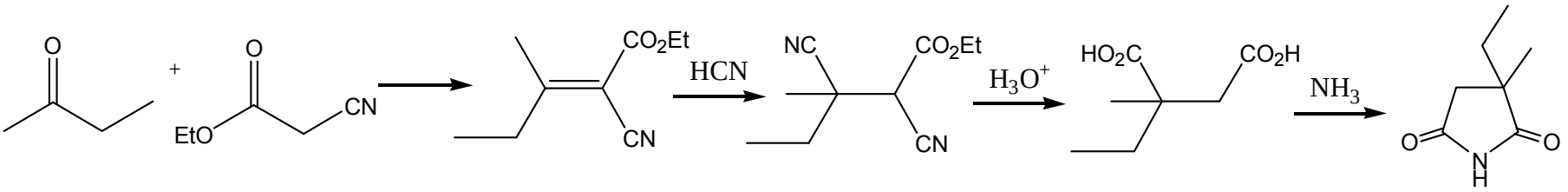
Anticonvulsants - Ethosuximide

Ethosuximide is a succinimide anticonvulsant



(*RS*)-3-ethyl-3-methyl-pyrrolidine-2,5-dione

Synthesis: methylethylketone and cyanoacetic ester, which undergo condensation. Then hydrogen cyanide is added. After acidic hydrolysis and decarboxylation of the synthesized dinitrile, 2-methyl-2-ethylsuccinic acid is formed. Reacting this product with ammonia gives the diammonium salt, and heterocyclization into ethosuximide takes place during subsequent heating.

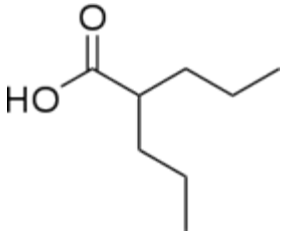


Anticonvulsants - Valproic acid

✓ **Valproic acid** (**Valproate**), is a carboxylic acid compound, structurally distinct from other current classes of anticonvulsants.

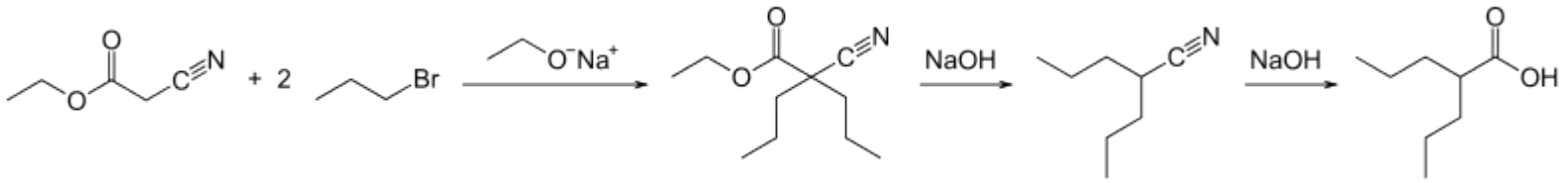
✓ Mechanism is uncertain; it is effective in the treatment of epilepsy, bipolar disorder, and less commonly, major depression.

✓ **Valproate** is a liquid at room temperature, but it can be reacted with a base such as sodium hydroxide to form the salt sodium valproate, which is a solid.



2-Propylpentanoic acid

Synthesis: by the alkylation of cyanoacetic ester with two moles of propylbromide, to give dipropylcyanoacetic ester. Hydrolysis and decarboxylation of the carboethoxy group gives dipropylacetonitrile, which is hydrolyzed into valproic acid

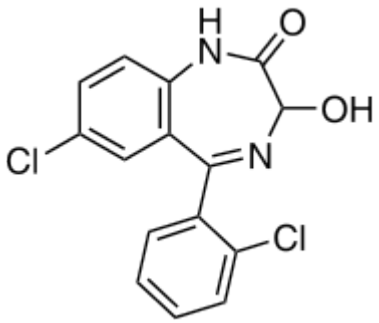


Anticonvulsants - Benzodiazepines

✓ **Benzodiazepines** can be used as anticonvulsants to decrease seizures.

✓ Two agents are frequently used, **diazepam** and **lorazepam**. These are particularly suitable because of rapid action after intravenous injection.

diazepam



lorazepam

New Anticonvulsants

✓ Because they are new, the clinical indications for these agents are not yet completely defined, and none are currently used as the first treatment for epilepsy.
✓ Many of them are used as an “add-on” medication
✓ These newer anticonvulsants have good efficacy, fewer toxic effects, better tolerability, and no need for blood level monitoring were developed.

Examples are:

Felbamate

Lamotrigine

Gabapentin

Topiramate

Tiagabin

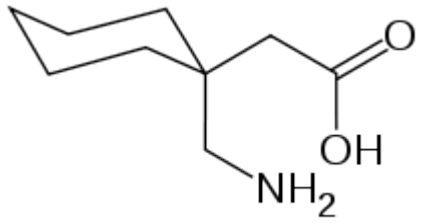
Levetiracetam

Vigabatrin

Zonisamide

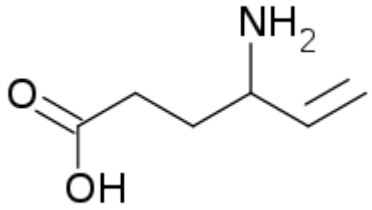
New Anticonvulsants

Gabapentin (**Neurontin**) is a pharmaceutical drug, specifically a GABA analog. It was originally developed to treat epilepsy, and currently is also used to relieve neuropathic pain.



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

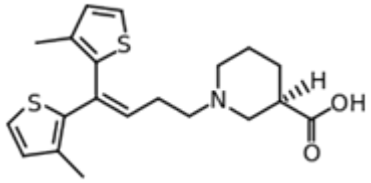
Vigabatrin (**Sabril**) is an antiepileptic drug that inhibits the catabolism of *gamma*-aminobutyric acid (GABA) by irreversibly inhibiting GABA transaminase. It is an analog of GABA.



(*RS*)-4-aminohex-5-enoic acid

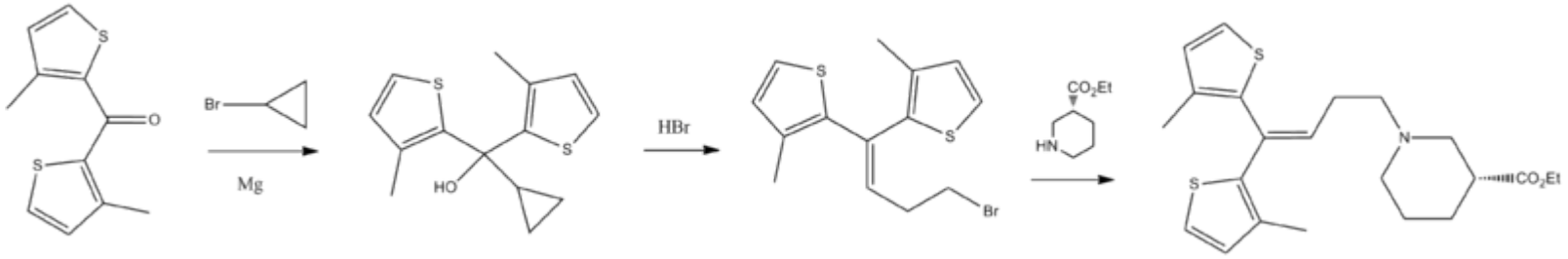
New Anticonvulsants

Tiagabine (**Gabitril**) is an anti-convulsive medication

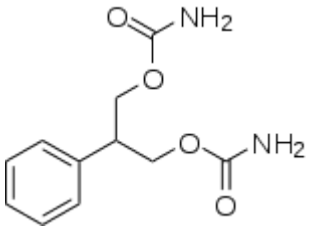


(*R*)-1-[4,4-bis(3-methylthiophen-2-yl)but-3-enyl] piperidine-3-carboxylic acid

Synthesis of Tiagabine



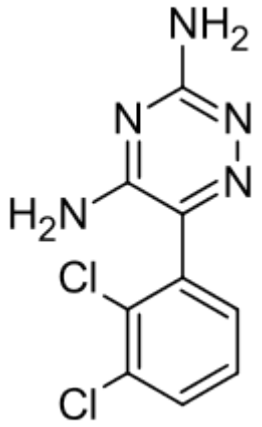
Felbamate (**Felbatol**) is an anti-epileptic drug used in the treatment of epilepsy.



(3-carbamoyloxy-2-phenylpropyl) carbamate

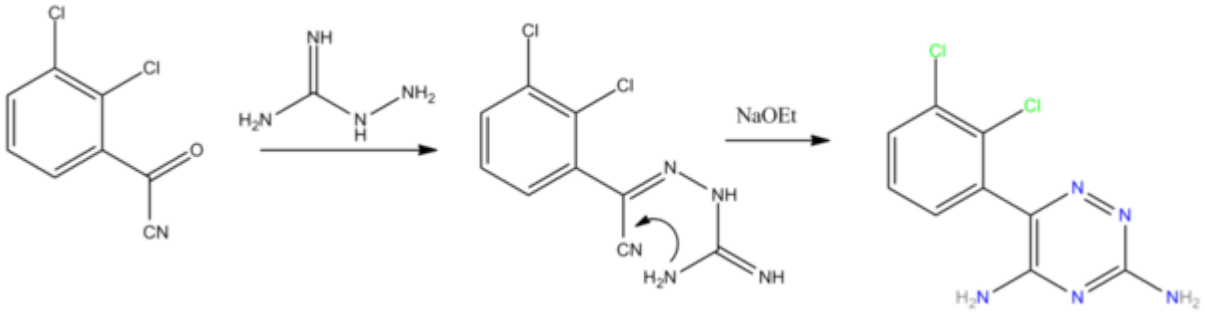
New Anticonvulsants

Lamotrigine (**Lamictal**) is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder.



6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine

Synthesis: Lamotrigine can be prepared from 2,3-dichlorobenzoyl cyanide



Anticonvulsants