Al -Maaref University **College of Pharmacy**

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Organic Pharmaceutical Chemistry II
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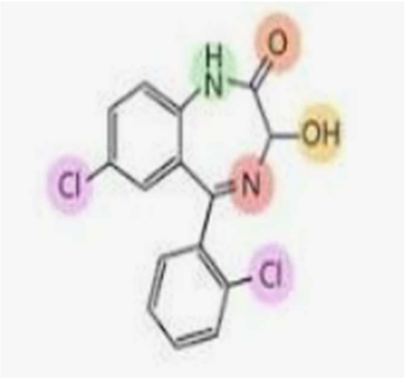
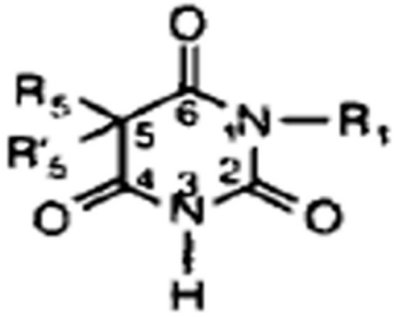
Central Nervous System (CNS) Depressants

G.A; S/H; Anxiolytic; C.M. Sk. M.R. &AC





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Assist. Prof Dr.Sameerah Fenjan Hasan

Central Nervous System (CNS) Depressants

Introduction

The common **activity o**f the **drug classes** considered in his chapter is **depression** of **neuronal** activity in the **central nervous system (CNS)**, that is. the **brain** and **spinal cord**.

In a **few cases act** as **skeletal muscle relaxants (C.M. Sk. M. R.).**

Classes of CNS Depressant drugs

The **classes** are the **followings:**

1. **General Anesthetics (G. A.)**.
2. **Sedative—hypnotics (S/H)**.
3. **Anxiolytics (Anxy.).**
4. **Anticonvulsants (AC** or **AE)**.
5. **Centrally Mediated Skeletal Muscle Relaxants (C.M. Sk. M. R.).**
6. **Antipsychotics (Antipsy.).**

Uses of CNS Depressant drugs

1. **General Anesthetic (GA) agents** are **used** to **produce controlled and reversible loss** of **consciousness** and **perception** in **painful surgical procedures**.

2. **Sedative—Hypnotic(S/H) drugs** are used in the **treatment** of some of the **insomnias**. which are **failures** to **get adequate sleep**.

3. **Anxiolytic (Anxy.) drugs** are used in **control** of the **anxiety disorders**, which are conditions **characterized**, by **excessive or inappropriate anxiety** such as **panic attacks**, **social phobia.** and **obsessive-compulsive disorder.**

4. **Centrally Mediated Skeletal Muscle Relaxants (C.M.Sk.M.R.)** are used in **skeletal muscle spasm.**

5. **Anticonvulsants (AC) or Anti-Epileptic (AE)** are used to **prevent** or **lessen sudden excessive electrical activity** in br**ain neurons** that is a **characteristic** of the **epileptics.**

6 Antipsychotics (Antipsy.). These drugs—**previously known** as **Neuroleptic** drugs, A**ntischizophrenic** drugs, or **Major Tranquilizers** which are **used** in the **symptomatic treatment** of t**hought disorders (psychoses),** most notably the **Schizophrenias** and **mania.**

n

The **first five classes** of drugs (**GA; S/H; Anxy; C.M.Sk.M.R.; &AE,),** are **non-selective** in their **CNS depressant effect**, there is **overlap between them because** of:

a. These classes often have a **number of structural features in common.**
b. These classes often **share at least one mode of action, positive modulation** of the **action** of **gamma amino butyric acid (GABA) at GABAA receptors.**
Many **anticonvulsants** are associated with **blockage of channels** of **sodium** and other **inorganic cations** such as **calcium**

The **Antipsychotics (Antipsy) class** is **the most selective** in its **CNS depressant** effect **because** these **agents** have a **hydrophobically substituted dopamine-like structure** and **act** as **competitive antagonist of dopamine (DA) at D2 and receptors.**

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1- GENERAL ANESTHETICS (GA)

General anesthetic (GA) agents are used to **produce revisable and controlled loss** of **consciousness and sensation** and therefore, **loss** of **perception to painful surgical procedures**

Mode of Action of GA

GA are **positive modulators** of **GABA on GABAA receptors** by **binding** to **allosteric binding sites (different sites exist** for **each drug group)**

Clinically, general anesthesia for **surgery uses multiple drug regimens.**
Some drugs may be **used** to **help the general anesthetic** agent **(e.g. neuroleptics** and **opioid analgesics)**, **other drugs** may **add an action (e.g. the skeletal muscle relaxants).**
Also, **drugs** such as **anticholinergics** may be used to **decrease adverse effects**.

Classes of G.A.

According to the **route** of **administration GA** can be broadly **categorized as:**

I. Inhalation
II. Intravenous (IV)

The **route** of **administration** of **GA** is **dependent** on the **physical state** of the **agents.**

I. Inhalation

The **inhalation anesthetics** in use **are either gases or volatile liquid** such as **Halothane, Enflurane, Isoflurane, Methoxyflurane, Sevoflurane, Desflurane,** and **Nitrous Oxide.**

Chemical classes of inhalation anesthetics

A. Halogenated hydrocarbons e.g. **Halothane.**
B. Halogenated ethers e.g. **Enflurane**.
C. Miscellaneous e.g. **Nitrous Oxide.**

A. Halogenated Hydrocarbons e.g. Halothane.

Halothane. 2-bromo-2-chloro- 1.1.1-trifluoroethane (Fluothane).

Volatile liquid (bp. 50°C), **halogenated hydrocarbon nonflammable.**
The drug has **high potency** and **induction** of and **recovery** from **anesthesia** are **relatively rapid (short onset &duration of action)**
Halothane has a **narrow margin** of **safety**.
Respiratory depression is **notable**, and **mechanical ventilation** and **increased oxygen concentrations** are often **required**

B. Halogenated Ethers.

Methoxyflurane 2,2-dichloro-1.1 -difluoro ethyl methyl ether. **$CHCl_2CF_2$-O-CH_3**

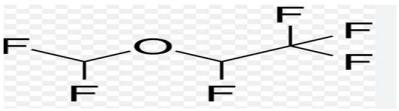
Volatile liquid (bp. 105°C), **halogenated ether.**
Has slow induction of **anesthesia** and **slow recovery.**
The agent **produces excellent analgesia** and **good muscle relaxation**.

Enflurane 2-chloro- I. I .2-trifluoroethyt difluoro methyl ether. **HF2COCF2CHFCI**

Volatile liquid
Induction is **relatively easy**
Have a **relatively low frequency** of **adverse cardiovascular** effects.
Respiration is **depressed,** so **mechanical ventilation** and **oxygen supplementation are used**.
Should not be **used** in **epileptic patients** (At **high** doses **causes tonic—clonic convulsion**).

Isoflurane I -chloro-,2.2.2-triflunrnethyl difluoro methyl ether.

Close structural relative of **enflurane** and **shares many properties** with **it**.
Tonic—Clonic activity is **not reported**.



Desflurane. 1,2,2,2-tetrafluoroethyl difluoro methyl ether
Close structural relative of **enflurane** and **shares many properties** with **it**.

C. Miscellaneous

Nitrous Oxide. Nitrogen monoxide. N_2O
Gas at room temperature and is **supplied** as l**iquid** under **pressure** in metal cylinders.
It is a **good anesthetic**
It is often **used** in **combination** with **other agents.**
It has **analgesic effects.**
It is a **positive modulator** of **GABA** on **$GABA_5$** receptors, which is the basis for its **general anesthetic action**.

II. Intravenous Anesthetics

Sold in **nature.**
Have an exceptionally high lipid/water partition.
Respiratory depression is **marked** with the **barbiturates at anesthetic doses**.

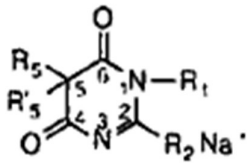
Chemical Classes

A. Ultra-short acting Barbiturate.
B. Benzodiazepines.
C. Miscellaneous.

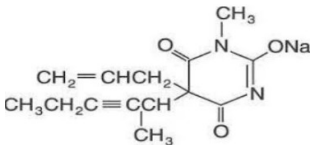
A. Ultra-short acting Barbiturate.

The **sodium salts** of the **ultra-short-acting barbiturates** may be **administered intravenously** in **aqueous** solutions to **induce anesthesia.**
Unconsciousness (onset) is **produced within seconds** of intravenous injection.
The **duration** of **action** is **about 30 minutes (rapid onset &very short duration).**
The **rapid onset** of **action is due to rapid partitioning** from the **blood, across the blood brain barrier (BBB), into the sites** of **action** in the **brain.**
The **very short duration** of **action is due** to **repartitioning** from the **brain** into **peripheral tissue**s **(body fat)**.
The **structures** of the **compounds** are **given** in **Table given below:**

General Structure



Generic Name / Proprietary Name	Substituents R_5	R'_5	R_1	R_2
Methohexital sodium *Brevital Sodium*	$CH_2=CH-CH_2-$	$CH_3CH_2C\equiv C-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-$	CH_3	O
Thiamylal sodium *Surital Sodium*	$CH_2=CH-CH_2-$	$CH_3CH_2CH_2\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-$	H	S
Thiopental sodium *Pentothal Sodium*	CH_3CH_2-	$CH_3CH_2CH_2\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-$	H	S



Methohexital Sodium.

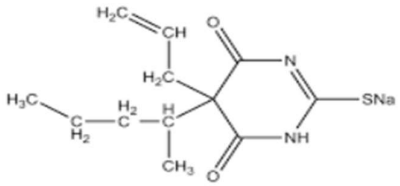
N-Methyl barbiturate with pK**a of 8.4.** versus about **pKa 7.6 for the non-N-methylated** compounds.

This **change** in **pKa increases** the **concentration** of the **lipid-soluble** form at **physiological pH.**

The **compound** also has **extensive hydrophobic character (total of nine hydrocarbons carbons). Therefor** the **lipid/ water partition coefficient** of the **free acid form is high**.

The **compound** has the **properties** to **rapidly penetrate** the **CNS** after **IV** injection and then **redistribute rapidly** to other **body sites.**

It also **undergoes rapid metabolic inactivation.**



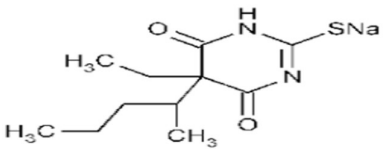
Thiamylal Sodium.

It is a **highly hydrophobic**.

Thiobarbiturate that has **structural features closely related** to those of **thiopental**.

It has **biological properties similar** to those of **Thiopental.**

Onset is **seconds** and **duration is 30 minutes.**

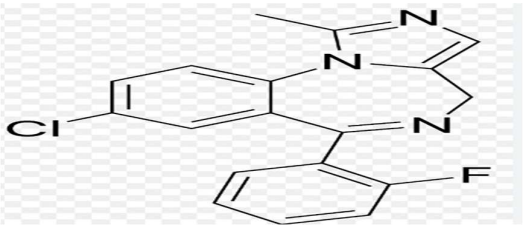


Thiopental Sodium.

The **most widely used ultra-short-acting anesthetic barbiturate**.
The **compound** is the **prototype** for the **SAR** studies of **ultra-short-acting barbiturates**.
The **compound's onset** is **very short** and the **duration** is **30 minutes**.

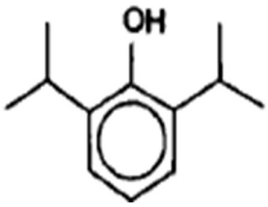
B. Benzodiazepines.

Benzodiazepines alone **cannot produce surgical anesthesia.**
Some of the **more potent CNS-depressant (more lipophilic) benzodiazepines** are **used IV** to **induce anesthesia.**
Example Midazolam



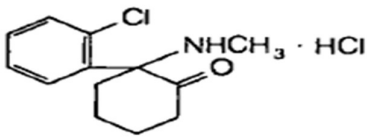
. **Midazolam**

C. Miscellaneous.



Propofol

phenols derivative.
2**,6-isopropyl groups** of **propofol favorably influence** the **biological properties** of the **hydroxyl group**.
Propofol is **useful** for **induction and maintenance** of **anesthesia.**
It is not water soluble, so an **emulsion** is given **intravenously**.
Penetration into the **brain is rapid**, and **redistribution** to other tissues is also **rapid**.
Have **high lipid/water partition coefficient.**
The drug **binds allosterically** to **GABAA receptors** at a **site different** from the **benzodiazepine site.**



Ketamine Hydrochloride

Has a **different mode of action** from the other **anesthetic** agents in this review.
The **drug** may be **used** mainly for minor surgical procedures in children.
It can be **used to induce anesthesia**.

(2-4)- ANXIOLYTICS, SEDATIVE/ HYPNOTICS & CENTRALLY MEDIATED SKELETAL MUSELE RELAXANTS (C.M.Sk.M.R.)

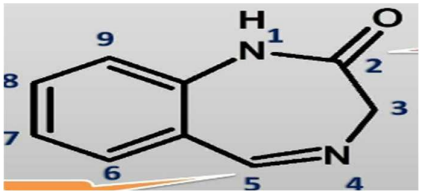
Chemical Classes

A. **Benzodiazepines.**
B. **Barbiturate**
C. **Miscellaneous.**

Number of **drugs belonging** to **other pharmacological** may **possess one or more** of the **anxiolytic, sedative,** and **hypnotic properties**. These **classes** include **H1 -antihistamines**, **antiadrenergic, antipsychotics,** and **anticonvulsants.**
Additionally. other **areas are being explored** for **sleep-promoting** agents.
a. Adenosine-2A receptor (A2A) agonists.
b. Melatonin-2 receptor (MT2) agonists.
These agents are **under study**.'
Both **adenosine** and **melatonin** are thought be **involved** in **natural mediation** of **sleep.**
Adenosine is considered a possible **endogenous sleep-producing** agent
Melatonin affects circadian rhythms and may be a **weak sedative—hypnotic.**

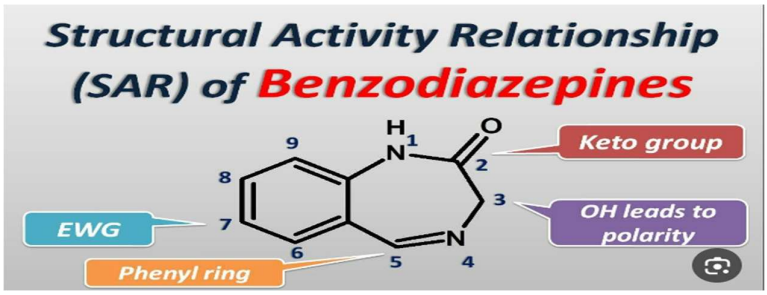
A. Benzodiazepines and Related Compounds

Benzodiazepines are a **psychoactive(anti-anxiety)** drug whose **core chemical structure** is the **fusion of** a **benzene ring** and a **diazepine ring** is **inactive.**



Benzodiazepine ring
Inactive

The **benzodiazepine ring should be suitably substituted to be active** as we will see in the **SAR studies. And as follows:**

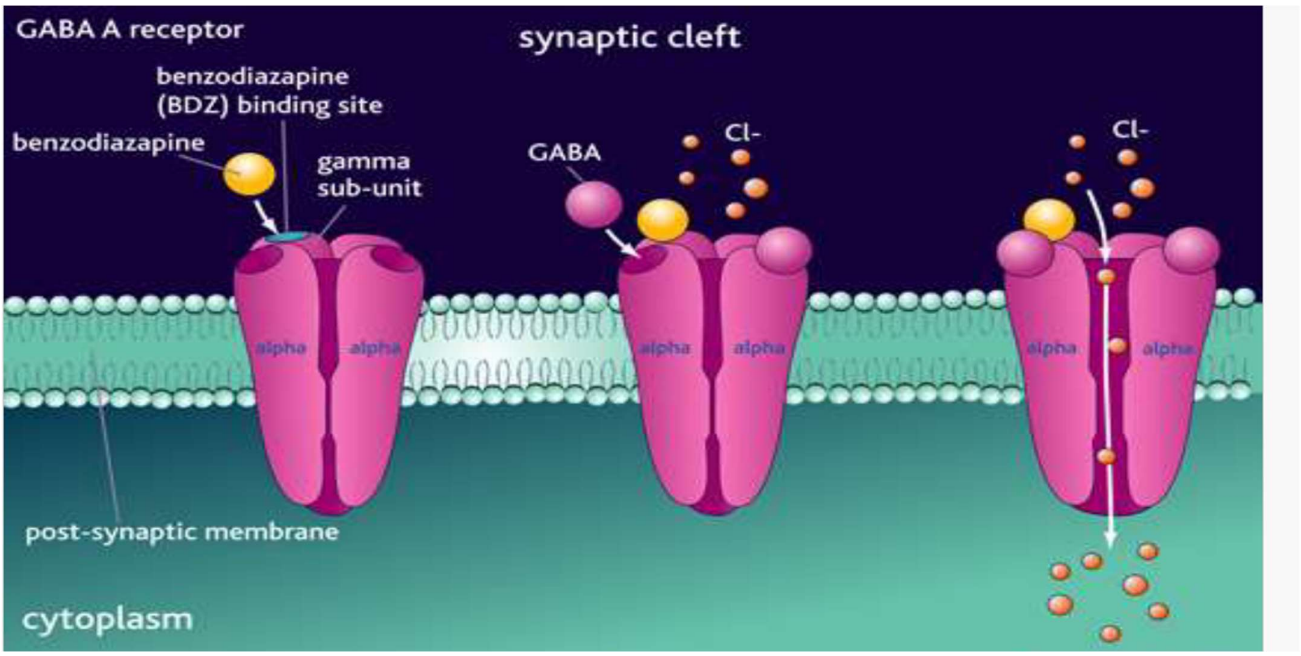


Benzodiazepines are the **most widely** used **anxiolytic** drugs, they **enhance** the effect of The **neurotransmitter gamma-aminobutyric acid**, which results **in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anti -convulsant, muscle relaxant and amnesic action.**

The **first Benzodiazepin**e is **Chlordiazepoxide (Librium),** was discovered accidentally 1955, and made available in 1960 by Hoffmann–La Roche, which has also marketed later **Diazepam (Valium)** since 1963.

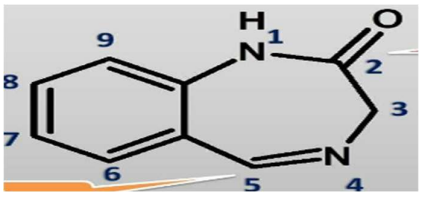
Mode of Action

Benzodiazepines and **benzodiazepines like drugs bind** to **benzodiazepine recognition site**, one of several **allosteric** sites of **GABAA** receptor subtypes as in the given **diagram.**
Most **classical benzodiazepines** arc **positive modulators of GABAA receptor subtypes**



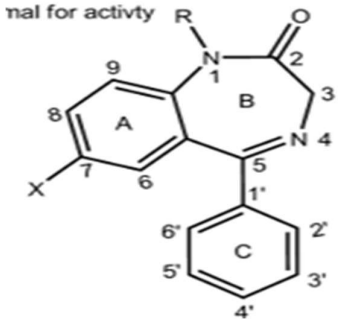
Structural—Activity Relationships (SAR) for Antianxiety Activity of Benzodiazepines

Unsubstituted Benzodiazepine ring (structure below) is **inactive.**



Benzodiazepine ring
Inactive

Therefore, it should be suitably as in the following **structure:**



General Structure Anxiolytic Benzodiazepines
Active

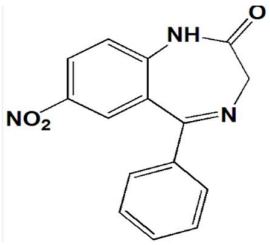
The **SAR** study carried on **Benzodiazepines involved** the following **sites:**

1- Ring A

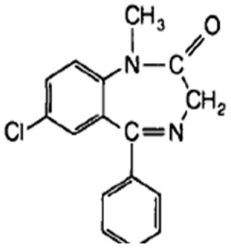
i) **Aromatic** or **heteroaromatic** ring for **ring A** is **required** for the **activity.**

ii) An **electronegative (electron withdrawal group (EWG)) substituen**t at **position 7** is **required** for **activity.**

iii) The **more electronegative substituent** at **position 7** is, the **highe**r the **activity, e.g. Nitrazepam** is **more potent** than **Diazepam.**



Nitrazepam



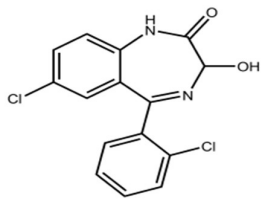
Diazepam

iv) **Positions 6, 8,** and **9** in **ring A should not be substituted**.

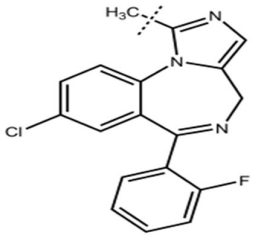
2- Ring C

i) **Ring C should be phenyl ring** at **position5** of the **benzodiazepine** ring to **promotes** the **activity.**

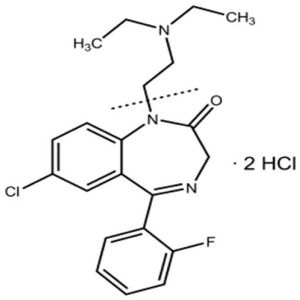
ii) **If** this **phenyl group** is **ortho (2_)** or **di-ortho (2_,6_) substituted** with **electron--withdrawing** groups, **activity is increased, as in Lorazepam, Midazolam (G.A.)** and **Flurazepam given below:**



Lorazepam



Midazolam



Flurazepam hydrochloride

iii) In **ring C, para substitution decreases activity greatly.**

3- Ring B

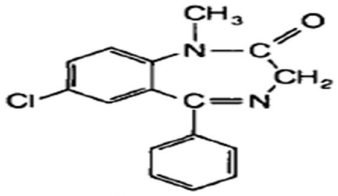
i) In **diazepine** ring **B**, **saturation** of the **4,5-double bond** or a **shift of it to** the **3,4-position decreases activity.**

ii) **Nature of substitution** at the **3-position (Hydroxyl; H;or Alkyl) affects pharmacokinetic parameters** and **onset& duration**.

iii) **Substitution** of **hydroxyl group (OH)** at **3 positions does not decrease activity.**

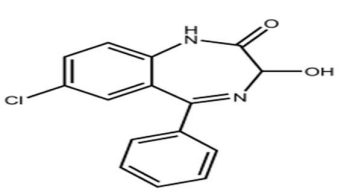
iv) The **presence** or **absence** of the **3-hydroxyl group** in ring **B** is **important Pharmacokinetically** as in the **following:**

a. **Compounds without** the **3-hydroxyl** group are **nonpolar**, **undergo3-hydroxylation** in **liver slowly** to **active 3-hydroxyl metabolites**, and **have long half-lives** as in **Diazepam.**



Diazepam

b. **Compounds** with the **3-hydroxyl** arc **much more polar** and are **readily converted** to the **excreted glucuronide,** therefore **shorter overall half-lives,** and **safer** to be **given** to **patients** with **hepatic disorder as in Oxazepam.**



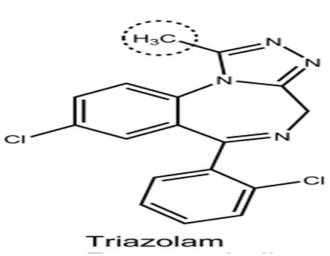
Oxazepam, Log P = 2.31

v) The **2-carbonyl function** is **optimal for activity**.

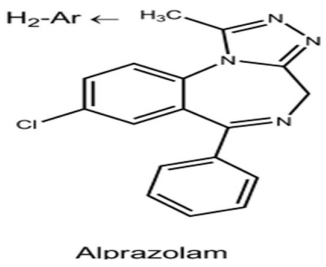
vi) The **nitrogen** atom at **position l** is **optimal for activity**, and the **N-substituent should be small.**

vii) Additional research yielded **compounds** with a **fused heterocyclic ring** on **benzodiazepine ring increases the activity** such as **triazolo** ring, as in **Triazolam** and **Alprazolam**, or **fused imidazolo** as in **Midazolam which (GA).**

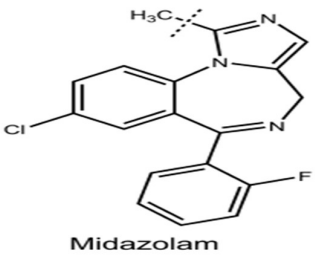
viii) An **electron attracting** group at **position 7**of **benzodiazepines** with a **fused heterocyclic ring** is **not required** for **activity** in **these compounds**.



Triazolam



Alprazolam



Midazolam

The overall summary of Benzodiazepines SAR is the following:

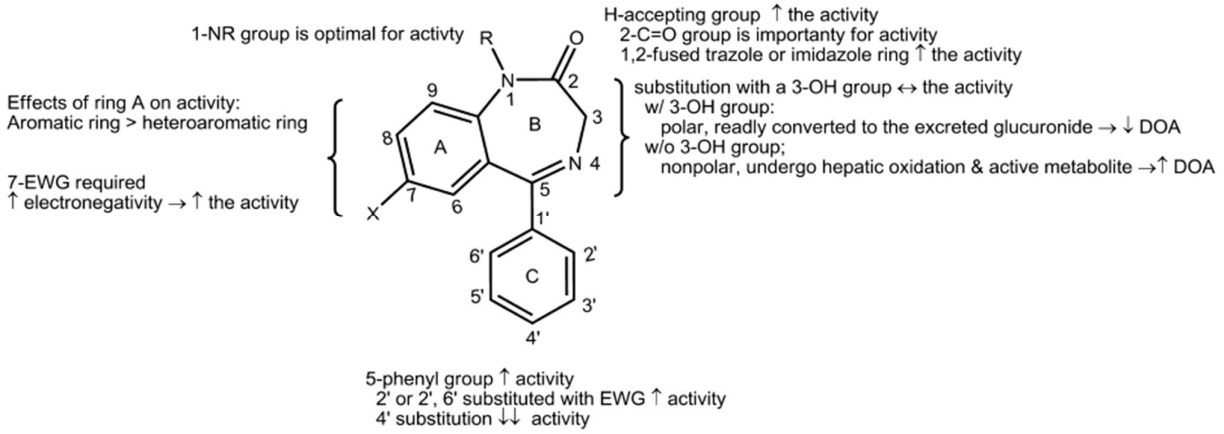


Figure 12.1 ● General structure and SAR of benzodiazepines.

General Structure

n

Therapeutics uses

Treatment of **anxiety associated** with **pain disorder**.

Insomnia.

Seizures.

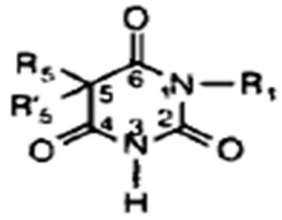
Alcohol withdrawal.

Pre medication for **medical** or **dental procedures; Muscle spasm.**

Contraindication

1- Pregnancy.
2- People with myasthenia gravis, sleep apnea, bronchitis and Chronic Obstructive Pulmonary Disease (COPD).
4- Elderly.

General Structure



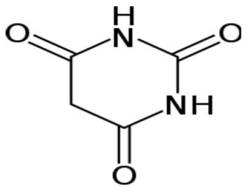
B. Barbiturates

Barbiturates are **derivatives of barbituric acid.** They are **cyclic diacylureas(cyclic diurades).**

.

The **Barbiturates** were **used extensively** as **sedative–hypnotic drugs ('sleeping pills').** As **Sedative–Hypnotic Barbiturates** have been **replaced** largely **by** the **much safer Benzodiazepines.**
Some members of **Barbiturates** are used as **Anticonvulsants** (**AE**).and **General Anesthetics** (**GA)**

The **different properties** of the **various barbiturates depend upon** the **side groups attached to the ring (barbituric acid).**



Barbituric acid (malonylurea) pharmacologically inactive

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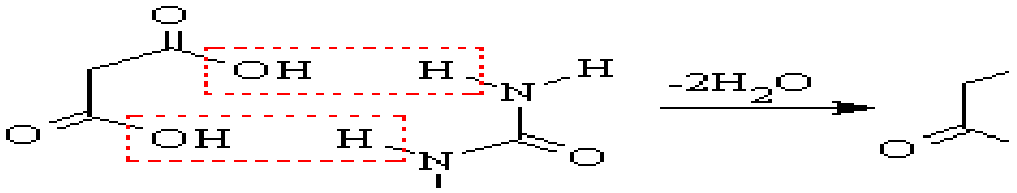
Barbituric acid was first discovered by the German chemist 1864 by combining **urea** (an animal waste product) with **malonic acid** (derived from the **acid of apples**), as follows:



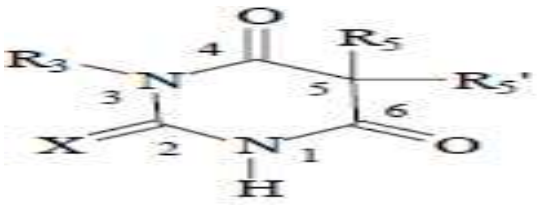
Barbituric acid is **made** by **combining malonic acid (left)** with **urea (right),** with the **elimination** of **two water molecules (shown in red).**

All **pharmacologically active barbiturates should be 5,5-disubstituted barbituric Acids derivatives.**

Mode of Action

Barbiturates exert most of their **characteristic CNS effects mainly** by **binding** to an **allosteric recognition site** on **GABAA receptors** that positively modulates the effect of the **GABAA receptor—G ABA binding**.
Unlike benzodiazepines, they **bind at different binding sites** and appear to **increase** the **duration** of the **GABA-gated chloride channel openings**.
In addition, by **binding** to the **barbiturate modulatory site**, **barbiturates can** also **increase chloride ion flux without GABA attaching** to its **receptor site** on **GABAA.** This has been **termed a GABA mimetic effect**, which is **related** to the **profound CNS depression effect of barbiturates.**

The basic structure of **barbiturates** is **a ring composed** of **4 carbon atoms** and **2 nitrogen atoms.**



Barbiturate

Certain side chains added to the **ring (at N-1or N-3; C-2; &C-5)** can **dramatically alter the potency, onset, and duration** of the **drug** -

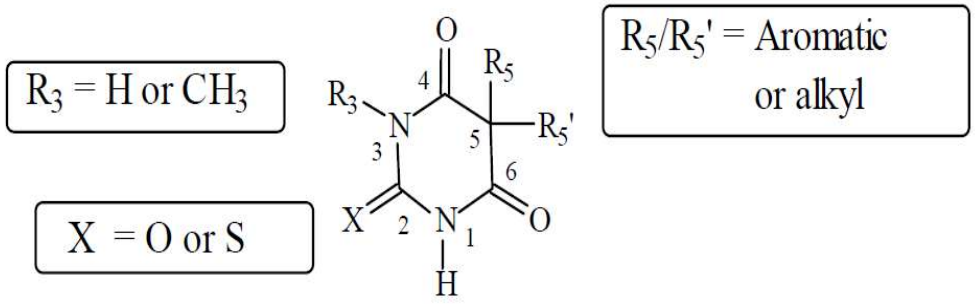
In **some cases,** the **addition** of a **single carbon atom** converts an **inactive form** of the **compound into an active**

All **pharmacologically active barbiturates should be 5,5-disubstituted barbituric Acids derivatives.**

Consideration of the **structure of 5,5-disubstituted** barbituric acids **reveals their acidic character**.
Those **without methyl substituents** on the **nitrogen atoms (N-1&N-3)** have **pKa's** of about **7.6**; while **those** with a **methyl substituent** at **N-1&N-3** have **pKa's** of about **8.4**.
The **free acids** have **poor water solubility** and **good lipid solubility (presences** of **two alkyl substituents** at **C-5).**
Some **barbiturates** have **sulfur atom** at **C-2 (2-Thiobarbiturates**) **increases lipid Solubility.**

Barbiturates contain a "balance" of hydrophilic (2,4,6-pyrimidinetrione ring structure) and lipophilic (5,5'-substituents) functionality. The overall hydrophilic (polar) or lipophilic (non-polar) character of the barbiturates is a function of:

- The hydrophilicity of the pyrimidinetrione ring which is a function of the number of N-substituents and the pKa of the acidic proton(s), and
- The overall size and structure of the two substituents at the 5-position

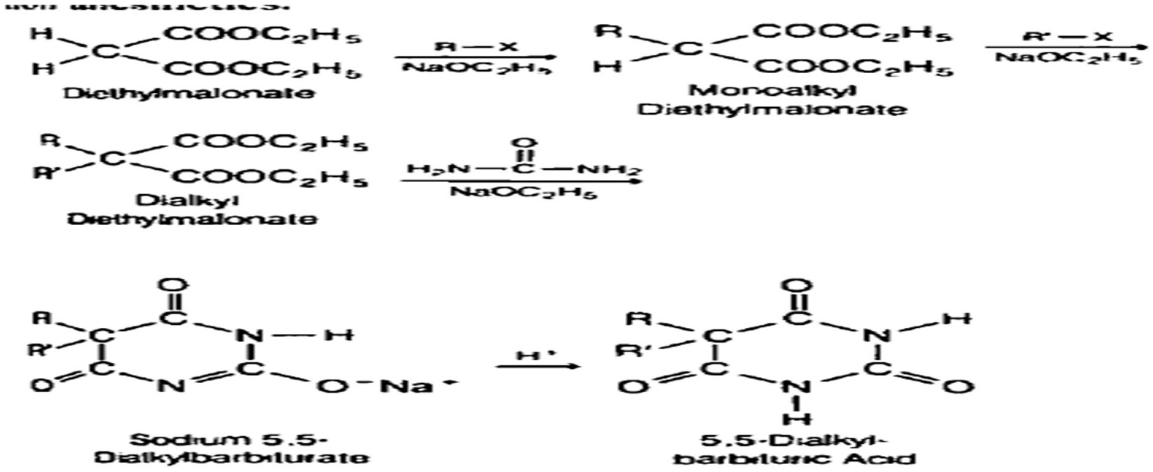


Barbiturate

The first historical **sedative—hypnotic barbiturate, 5,5-dialkylbarbituric acid,** was Introduced in 1903. With time many members were added, and the **barbiturates dominated** the **sedative—hypnotic** field until the discovery of the **benzodiazepines** which are **much safer** to **use** and **replaced** the **barbiturates** as the **most broadly useful agents in sedative/ hypnotic** applications.

Synthesis of Barbiturates

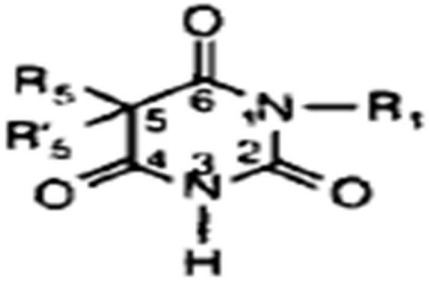
The **barbiturates** are **5,5-disubstituted barbituric acid derivatives**
The following scheme shows how the **5.5-dialkyl** compounds are **synthesized.**



Substitution of **thiourea** for **urea** in the above **reaction produces** the **2-thiobarbiturates**, useful as **induction anesthetics**.
Substitution of **N-methyl urea** for **urea** in the above **reaction produces** the **N-methylated B arbiturates.**

Structure–Activity Relationships (S.A.R)

General Structure



Three positions in above basic structure of barbiturates are important for SAR study; these are the followings:

I. Position 5

i) The **barbituric acid** which has **two H atoms** at **C-5 lacks CNS depressant activity, because** these **H** atoms are **highly acidic undergoes tautomerization**

(pKa4), and exists largely in the **anionic form** at **physiological pH,** with **little nonionic lipid-soluble compound available** to **cross the blood-brain barrier**.

ii) The **replacement** of **both hydrogens** at **position 5** with **alkyl or aryl groups confers** the **activity.**

iii) Therefore, **both hydrogen atoms** at the **5-position** of **barbituric acid must** be **replaced**.

iv) In general, **increasing lipophilicity increases hypnotic potency** and the **onset** of **action** and **decreases** the **duration** of **action**.

v) There is an **inverse correlation between** the **total number** of **carbon atoms substituted** on the **5-position** and the **duration** of **action**.

v) **The total number** of **carbon atoms** in **R groups substituted** at **C-5 determine** the **duration, therapeutic use** and **type** of **barbiturates.**

Classes of barbiturates.

According to the **duration barbiturates are classified** into:

1. **Long-Acting Barbiturate (LAB): Duration more** than **6 hr.** & **total number** of **carbon atoms** in **R groups** at **C-5 is 4 carbon atoms** e.g**.2 ethyl or ethyl &phenyl. Used** as **Sedative / Hypnotics** and **some anticonvulsants.**

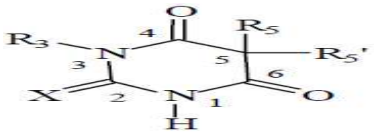
2. **Intermediate- Acting Barbiturate (IAB): Duration 3–6 hr.**& **total number** of **carbon atoms** in **R groups** at **C-5** is **5-6 carbon atoms** e.g. **ethyl &isobutyl. Used** as **Sedative / Hypnotics.**

3. **Short- Acting Barbiturate (SAB): Duration less than 3hr.**& **total number** of **carbon atoms** in **R groups** at **C-5 is 7-9 carbon atoms** e.g. **ethyl &isobutyl. Used** as **Sedative / Hypnotics.**

4. **Ultra-Short- Acting Barbiturate (USAB): Duration 30 min.** & **total number** of **carbon atoms** in **R groups** at **C-5** is **7-9 carbon atoms in addition** to **S** at **C-2 or methyl at N-1. Used** as **General Anesthetics**

II. Position 2

X = O or S



Barbiturate

In all **Sedative / Hypnotics Barbiturate there is oxygen at C-2(X=O)**

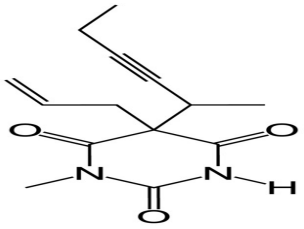
Sulfur instead of **oxygen** atom at **position 2 (X=S) increases** the **lipophilicity,** therefore, **increases potency** and have **more rapid onset** and **shorter duration of action**. **Used** as **General Anesthetics**

Example:
Thiamylal and **Thiopental** have **more rapid onset** and **shorter duration** of action than **Secobarbital** and **Pentobarbital**, respectively)
Thiamylal and **Thiopental** are **used** as **General Anesthetics**

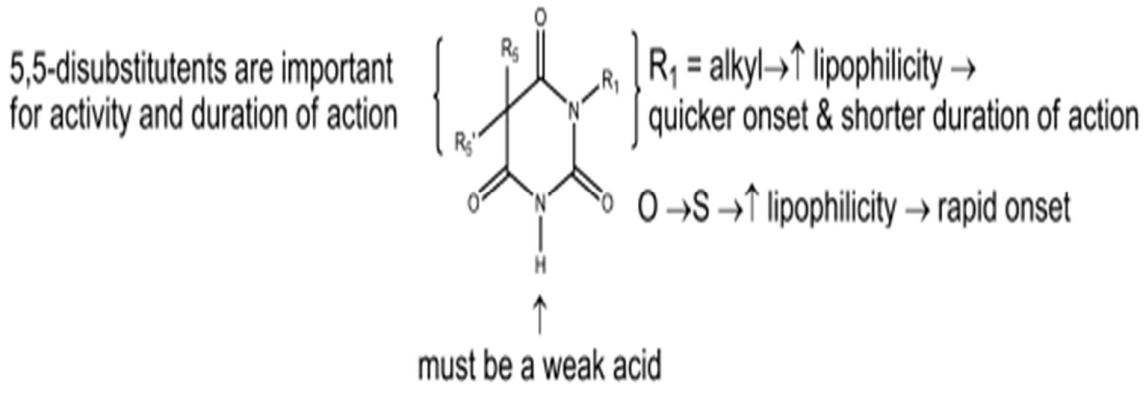
III. Positions 1or 3

Methylation at **position 1** or **N-1 decreases duration** of **action due** to **increase pKa (pKa=8.4) increase** the **amount** of the **unionized form** of the **drug** at **physiological pH** which is **more lipophilic (decrease ionization). Methylation** of these **positions** also **increases CNS depressants effect.**

e.g. Methohexital (GA)



The overall summary of Barbiturates S.A.R is the following:



Classes of Barbiturates

Barbiturate Products and Onset and Duration of Action

According to the **duration** of **action barbiturates are classified** into **four classes**:

1. **LAB**
2. **IAB**
3. **SAB**
4. **USAB**

1. Long-Acting Barbiturates (LAB)

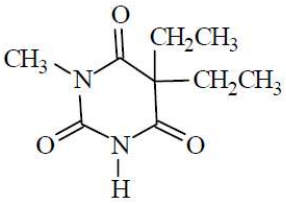
Sedative / Hypnotics and Anticonvulsants

Relatively **slow onset** and relatively **long duration (10-16 hrs.)**

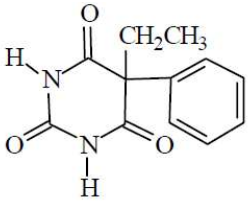
Structure: **N-H or N-Methyl** and **C-5 side chains consisting of two ethyl groups, or an ethyl and phenyl group (4 carbon atoms side chain at C-5).**

General Properties: Relatively **low lipophilicity**.

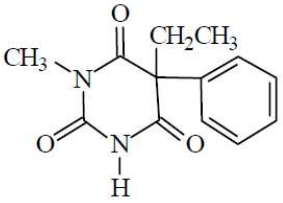
Examples



Metharbital



Phenobarbital



Mephobarbital

2. Intermediate-Acting Barbiturates (IAB)

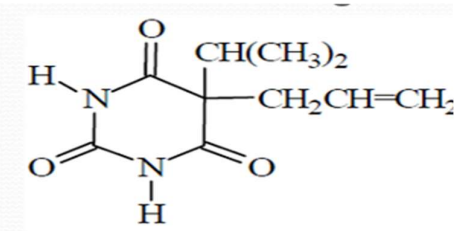
Sedative/Hypnotics

Relatively **slow onset** and **intermediate duration (3-6 hrs.)**

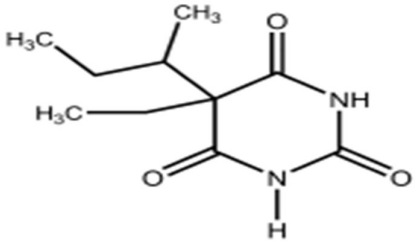
Structure: N-H and C-5 side substituents consisting of **ethyl or allyl &isobutyl carbon atom unit (5-6 carbon atoms side chain at C-5).**

General Properties: **Intermediate lipophilicity**.

Examples



Aprobarbital



Butabarbital

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3. Short-Acting Barbiturates (SAB)

Typically, **sedative/hypnotics**:

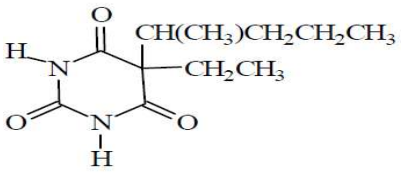
Relatively **rapid onset** and **relatively short duration (3 hrs.)**

Structure: N-H and **C-5 side chains consisting** of **ethyl or allyl** and **a 5-carbon unit (7-9 carbon atoms side chain at C-5).**

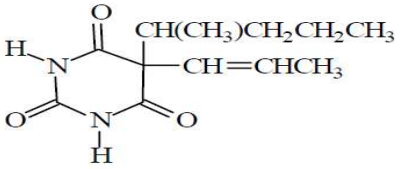
.

General Properties: **High lipophilicity** and **rapid distribution and redistribution.**

Examples



Pentobarbital
(Ethyl Substituted)



Secobarbital
(Allyl substituted)

4. Ulra-Short-Acting Barbiturates (USAB)

Induction of Anesthesia, Administered by **injection (as salts).**

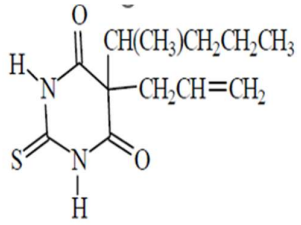
Immediate onset and **very short duration (30 min)**.

Structure: **N-H** with a **thiocarbonyl (C-2 has S)** and **C-5 side chains consisting** of **ethyl or allyl** with **5-carbon unit (7-9 carbon atoms side chain at C-5)**.

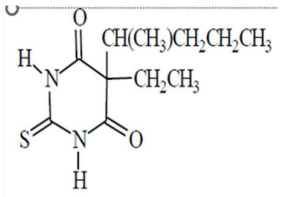
Some have **N-CH3** and **C-5 side chains** consisting of **ethyl or allyl** with **5-carbon unit (7-9 carbon atoms side chain at C-5) C-2 has O.**

General Properties: **Very high lipophilicity** and **rapid distribution** and **redistribution.**

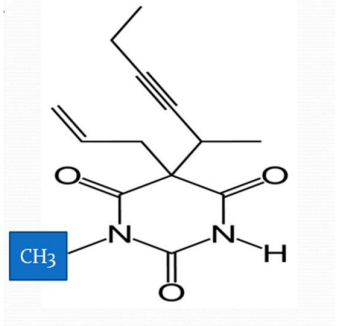
Examples



Thiamylal
(Allyl Substituted)



Thiopental
(Ethyl substituted)



Methohexital

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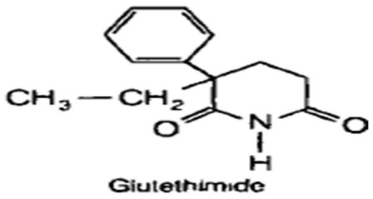
Miscellaneous Sedative-Hypnotics (Non-Barbiturates S/H) A& B 30/10

A wide **range** of **chemical structures** can produce s**edation** and **hypnosis resembling** those **produced** by the **barbiturates**.
These **compounds** have generally a **hydrophobic portion** and a **semipolar portion** that can **participate** in **H bonding.**

These **compounds chemically include:**

I. **Imides and Amides.**
II. **Alcohols and Their Carbamate Derivatives**
III. **Aldehydes and Their Derivatives.**

Modes of action similar to those proposed for **barbiturates**.



Glutethimide

I. Imides and Amides.

Glutethimide.
Has many **structural relationships** with the **barbiturates** and **resembles them** in **many respects biologically.**

II. Alcohols and Their Carbamate Derivatives

The very simple alcohol **Ethanol (CH_3CH_2OH)** has been used as a **sedative and hypnotic.**
The use of **Ethanol** has so **many hazards** it is **not as medical agent.**

Structure–Activity Relationships (S.A.R)

Basic Structure **R-OH**

SAR studies include the **followings:**

1. **Ethanol CH_3CH_2OH (**discussed above).

2. In **higher homologous series** of **ethanol,** the **CNS depressant potency increases** up to **eight carbon atoms**, then **activity decreased.**

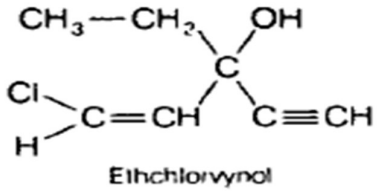
3. **Branching** of the alkyl chain **depressant activity increases** the **order** of **potency** is: **Tertiary > Secondary > Primary.** This may he **because tertiary** and **secondary alcohols** are not **metabolized** by **oxidation to** the **corresponding carboxylic acids.**

4. **Replacement** of a **hydrogen** atom in the **alkyl** group (R) by a **halogen increases** the **potency because lipophilicity increases.**

5. **Carbonylation** of **alcohols** generally **increases depressant potency** and **duration, Carbamate** groups are generally **more resistant** to **metabolic inactivation** than **hydroxyl** functions.

6. **Bifunctional** (**di hydroxy)** compounds **(e.g. diol carbamates)** have **depressant action** on the **spinal cord** in **addition** to the **brain** and therefore have skeletal **muscle relaxant properties.**

Examples

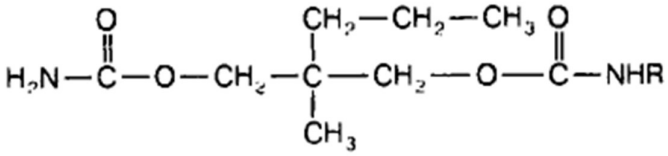


Ethchlorvynol

Ethchlorvynol.

Sedative—Hypnotic with a **rapid Onset** and **short duration.**

Meprobamate



Meprobamate R = H
Carisoprodol R = —CH(CH3)2

Indicated as an **antianxiety** agent, it is also a **sedative—hypnotic** agent.

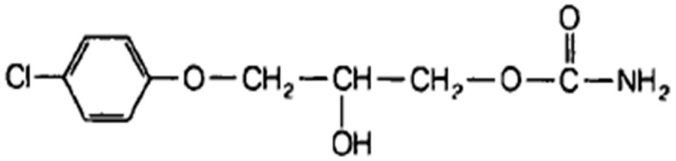
Meprobamate and other **dihydroxy alcohols** are also a **centrally acting skeletal muscle relaxant.**

These **agents are therapeutically** used in **acute muscle spasm** such as **strains** and **sprains**

.

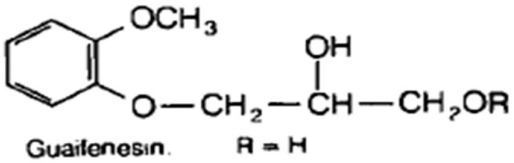
Carisoprodol.

Structure above, similar action to **Meprobamate.**



Chlorphenesin Carbamate

Chlorphenamine Carbamate.

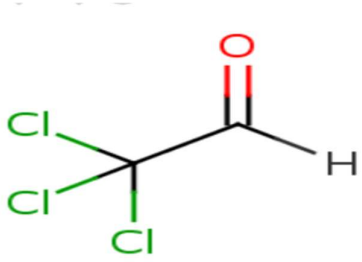


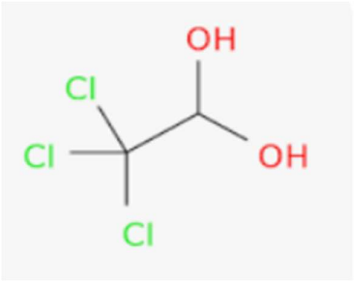
Guaifenesin. R = H

Methocarbamol. R = —C(=O)—NH2

Methocarbamol.

III. Aldehydes and Their Derivatives.





Chloral Hydrate

Trichioroacetaldehyde monohydrate.

Therapeutically used as **sedative—hypnotic** agent.

Acts principally through a metabolic **reduction** to **trichloroethanol** which is **potent sedative—hypnotic** agent.

Potentially lethal effect of the **combination of ethanol** and **chloral hydrate** because of **synergism b**etween **ethanol** and **chloral hydrate**.

5- ANTICONVULSANT OR ANTIEPILEPTIC DRUGS

The terms **anticonvulsant (AC)** and **antiepileptic drug (AED)** are used to describe a group of **medications used clinically** to **provide seizure control in patients** with **epilepsies.**

Most of these **newly diagnosed seizure disorders** can be **effectively controlled initially** with the **use** of **AEDs** to **prevent recurrence of seizure activity** such as:

a. Valproic acid (VPA). **b. Carbamazepine (CBZ).**

c. Ethosuximide. **d**. **Phenytoin.**

Mode of Action of Anticonvulsants (ACs)

At the **cellular level, three basic mechanisms** are believed to **contribute** to the **antiepileptic** action of the anticonvulsants, these are:

(a) Modulation of **voltage-gated ion channels (Na+, Ca ++, and K+).**

b) Enhancement of **γ-Aminobutyric acid (GABA)-mediated inhibitory**

Neurotransmission e.g. **benzodiazepines** and **barbiturates**.

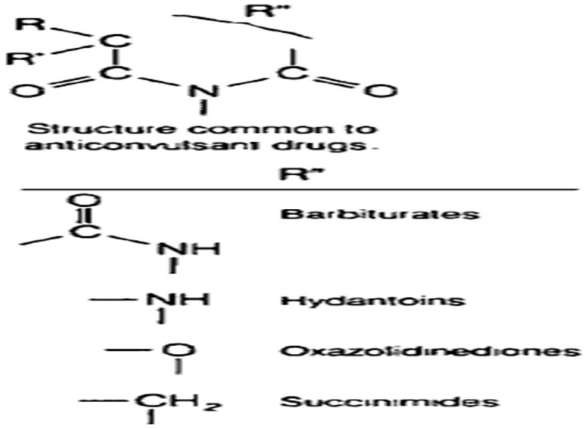
(c) Block the excitatory (particularly glutamate-mediated) neurotransmission in the **brain.**

Structural Activity Relationship Studies (SAR) of Anticonvulsants

Several **major groups** of **drugs** have the **common structure** shown below:

Classes of Anticonvulsants

I. Barbiturates.
II. Hydantoins.
III. Oxazolidinediones.
IV. Succinimides.
V. Ureas and monoacylureas
VI. Miscellaneous Agents



I. Barbiturates

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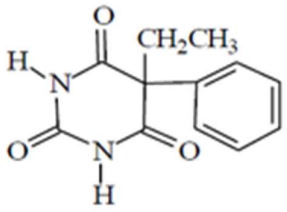
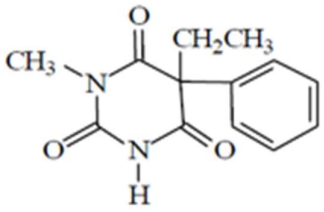
cyclic diacylureas (Cyclicdiurides).

Among **S/H barbiturates** only **Phenobarbital** and **Mephobarbital** display enough **anticonvulsant activity.** (For the structures of these agents see **S/H barbiturates** given earlier)



Phenobarbital

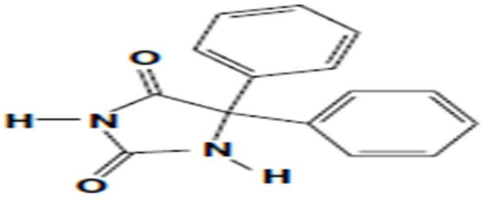


Mephobarbital

II. Hydantoins

The **hydantoins** are **close structural relatives** of the **barbiturates differing** in **lacking** the 6**-oxo group**.
They are cyclic **monoacylureas** rather than **cyclic diacylureas**.

Example:

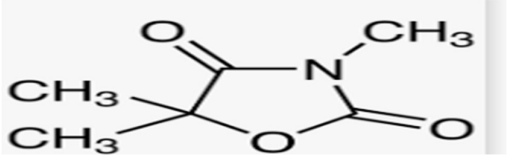


Phenytoin

III. Oxazolidinediones

Replacement of the **N-H** group at **position I** of the **hydantoin** system with an **oxygen atom** yields the **oxazolidine-2.4-dione** system.

Example:

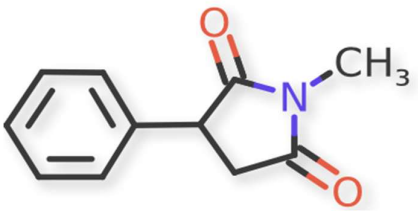


Trimethadione.

IV. Succinimides

In **oxazolidine-2,4-diones** the **replacement** of **O by CH_2** generates **succinimides.**
Example:

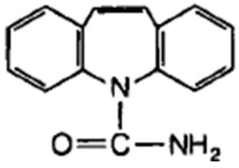
Phensuximide,



V. Ureas and monoacylureas

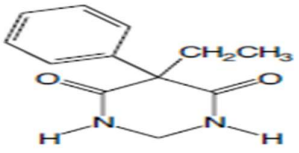
Example:

Carbamazepine.

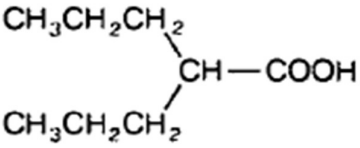


VI. Miscellaneous Agents

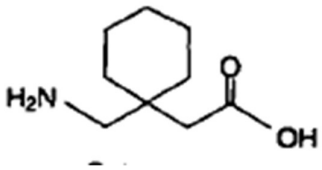
Primidone.



Valproic Acid.

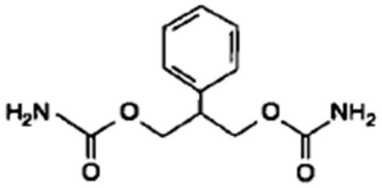


Gabapentin



Despite the **fact** that **gabapentin structure** is a **relative** of **GABA structure** with **increased hydrophobic character**, its **mechanism** of **action does** not appear **to involve** an **interaction with GABAA receptors**. The **mode of action** of the d**rug** is considered **unclear.**

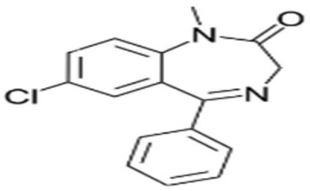
Felbamate



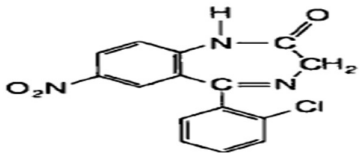
Benzodiazepines

Examples

Diazepam.



Clonazepam.



Clorazepates.