

Drug Acting On The Central Nervous System

Abdu Tuha(B. Pharm., MSc.)

Drugs affecting the CNS provide:

- Anesthesia,
- Treats psychiatric disorders,
- Relieve anxiety,
- Provide sleep or sedation,
- Prevent epileptic seizure, and suppress movement
 - Lipid soluble non-ionized molecules pass readily into the CNS (BBB)

1. Sedative and hypnotics

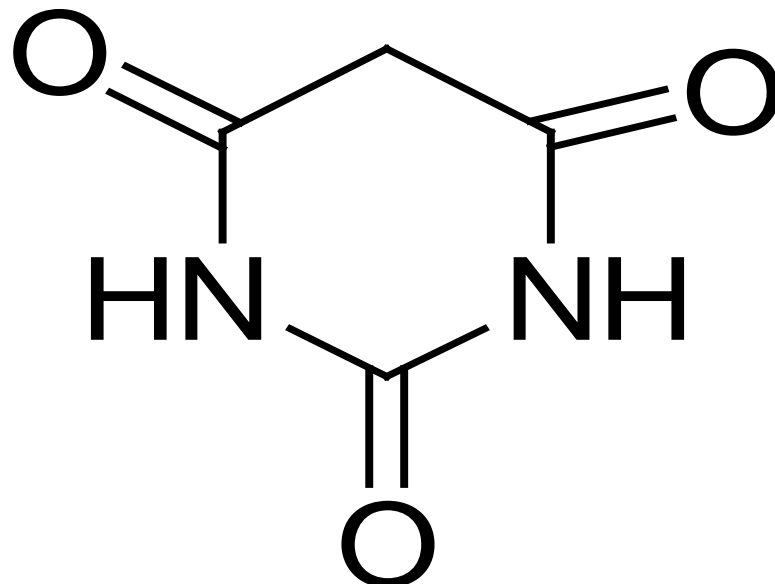
- Sedative drugs provide a **calming** effect accompanied by **relaxation** and rest but not necessarily sleep
 - No sharp distinction between the two types
- Also employed as anticonvulsant, muscle relaxant and anti-anxiety

Classification of Sedative-Hypnotics

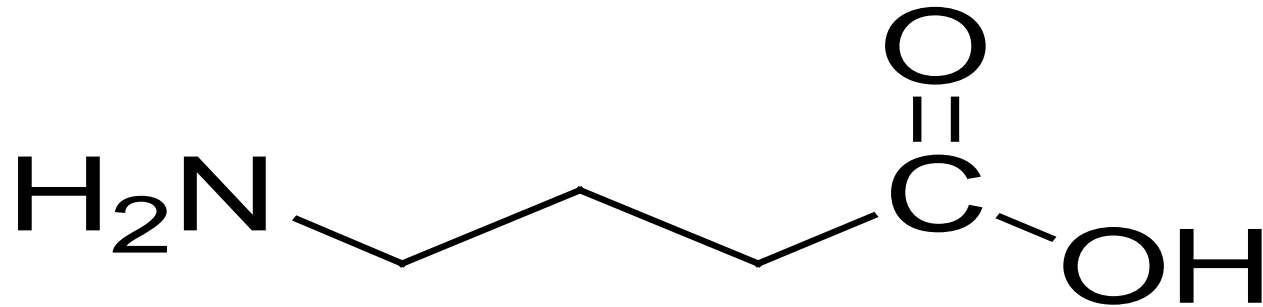
- Arbitrarily the sedative-hypnotics may be classified as follows:
 - Barbiturates
 - Benzodiazepines
 - Halogenated compounds (chloral hydrate, ethchlorvynol, carbromal)
 - Heterocyclic compounds (piperidinediones, thiazoles, pyrrolopyrazinones, imidazopyridines, pyrazolopyrimidines)
 - Other sedative-hypnotics (valnoctamide, propofol, plant extracts, endogenous sleep factors, melatonin)

i. Barbiturate

- A major event in the field was the launching of barbital (5,5-diethylbarbituric acid) in 1903 and phenobarbital (5-ethyl-5-phenylbarbituric acid) in 1912.
- Are 5, 5 disubstituted derivatives of barbituric acid



- Produce generalized CNS depression
- MOA- prolong the inhibitory action of GABA



GABA- γ amino butyric acid

- Barbiturates bind to GABA receptors on the **allosteric site**.

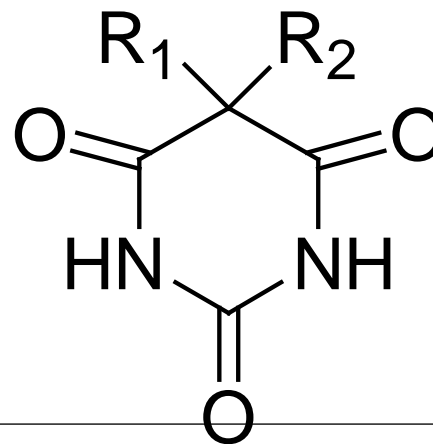
❖ The pharmacologic effects of barbiturates:

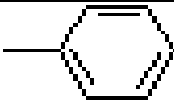
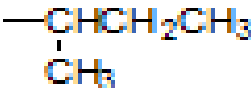
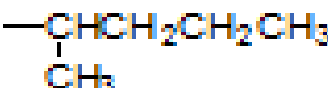
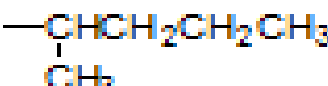
- Barbiturates are general CNS depressants. They depress the CNS at all levels in a dose dependent fashion.
- Barbiturates decrease the amount of time spent in REM sleep.
- In sufficient doses, barbiturates are anticonvulsant and suppress convulsant activity.
- In sedative doses, barbiturates have little effect on the cardiovascular system. Toxic doses can cause circulatory collapse.

- Barbiturates depress respiration at any dose level.
- Barbiturates induce hepatic microsomal drug-metabolizing enzymes resulting in an increased degradation of barbiturates,
 - ultimately leading to barbiturate tolerance.
- Because of their enzyme-inducing effects, barbiturates can cause increased inactivation of other compounds (anticoagulants, phenytoin, theophylline, digoxin, glucocorticoids, etc.).
 - This may lead to serious problems with drug interactions.

SAR

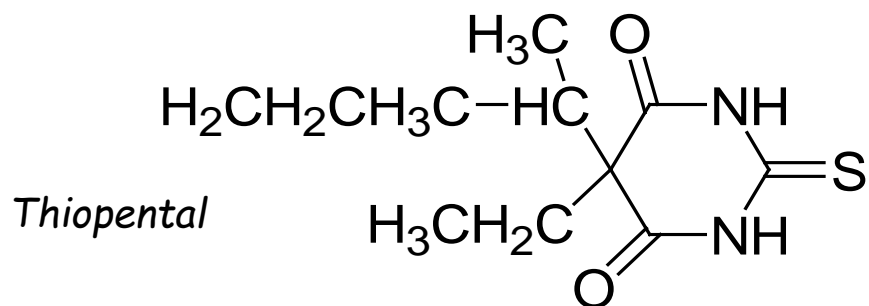
- Hypnotic activity increases with lipid solubility until the total number of carbon atoms at both C-5 substituents is between 6 and 10.
- Further increase in the sum of the number of carbon atoms decreases hypnotic activity despite increased lipophilicity, indicating that lipophilicity must remain within certain limits.
- Within the same series, the branched chain isomer generally has greater lipid solubility, hypnotic activity, and shorter duration of action than the straight chain isomer.



Drugs	R ₁ substituent	R ₂ substituent	Duration
Phenobarbital	—CH ₂ CH ₃	— 	Long
Amobarbital	—CH ₂ CH ₃	—CH ₂ CH ₂ CH(CH ₃) ₂	Intermediate
Butabarbital	—CH ₂ CH ₃	— 	Intermediate
Pentobarbital	—CH ₂ CH ₃	— 	Short
Secobarbital	—CH ₂ CH=CH ₂	— 	Short

- Within the same series, the unsaturated **allyl**, **alkenyl**, and **alkynyl** derivatives are more hypnotic than the saturated analogs with the same number of carbon atoms.
- Compounds bearing **alicyclic** or **aromatic substituents** are more potent than those having aliphatic substituents with the same number of carbons.
- Conversion of a 5, 5-disubstituted barbituric acid to a 1, 5, 5-trisubstituted analog does not result in a significant change in hypnotic activity.

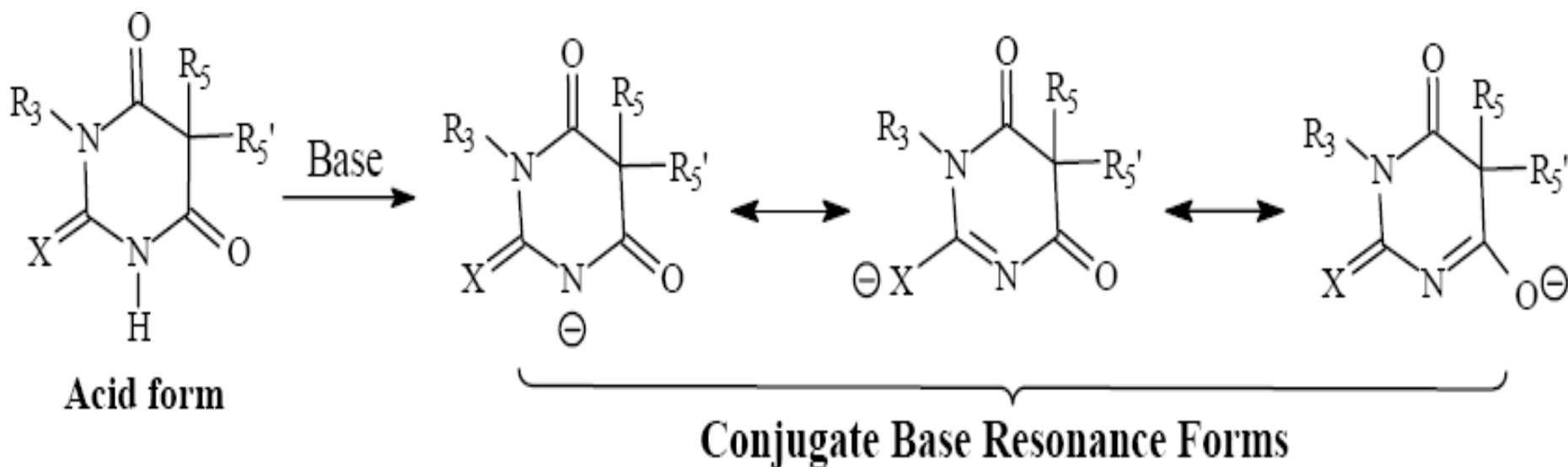
- Introduction of polar substituents (OH, NH, COOH, CO, RNH, etc) into an aromatic moiety at the 5-position decreases lipid solubility and potency.
- Replacement of the oxygen at C-2 by a sulfur atom results in faster onset but **shorter duration** of hypnotic activity.



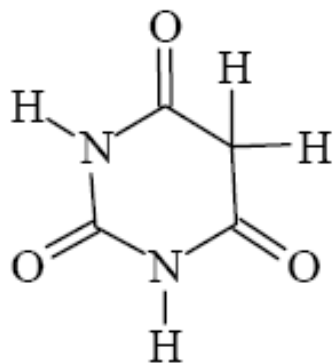
- Replacement of more than one carbonyl oxygen by sulfur causes a loss of activity, again indicating an upper limit to lipophilicity.

Barbiturate Ionization, Acidity and Salt Formation

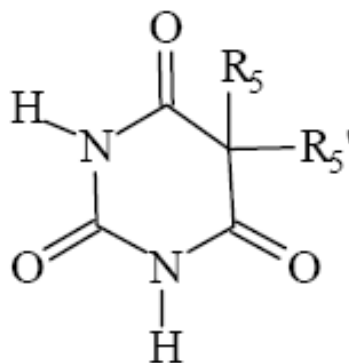
- Barbiturates containing at least one **N-H** hydrogen atom are acidic.
- Acidity results from the ability of the N to lose hydrogen and the stabilization of the resulting anionic charge of the conjugate base by resonance delocalization as shown below:



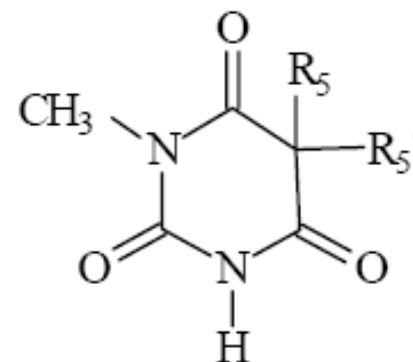
- The relative acidity of different barbiturates is a function of the degree of N substitution and C-5-substitution as shown below (electron donors decrease acidity!):



barbituric acid: pKa 4.12



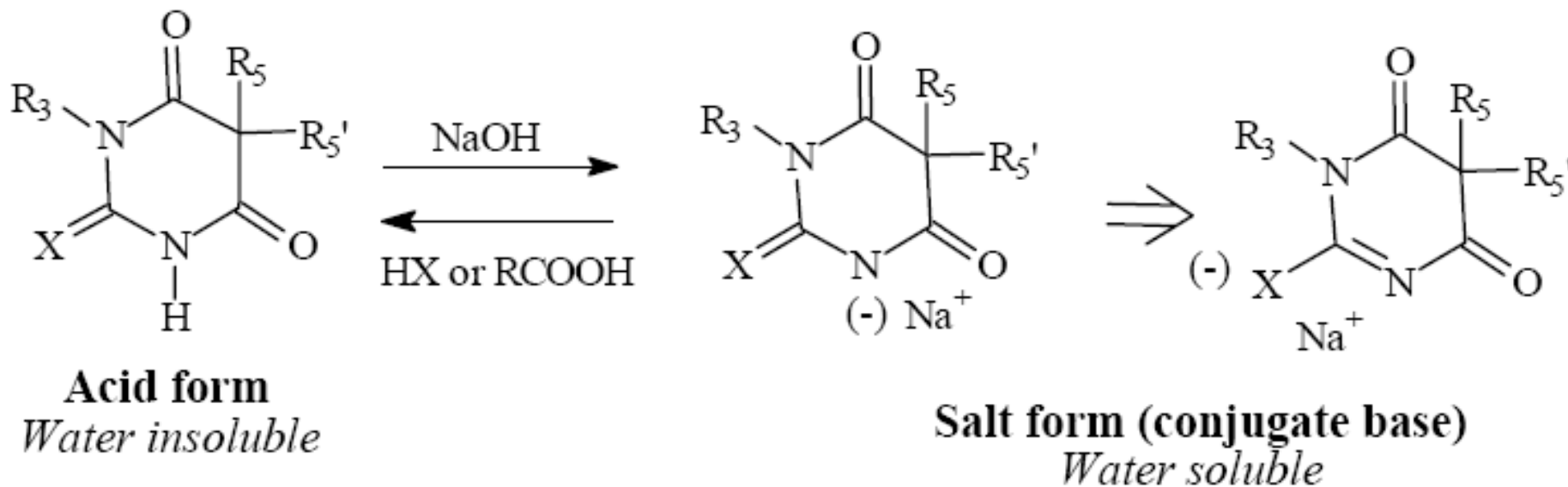
**5,5'-Disubstituted
barbituric acid: pKa 6.5-8**



**3,5,5'-Trisubstituted
barbituric acid: pKa > 8**

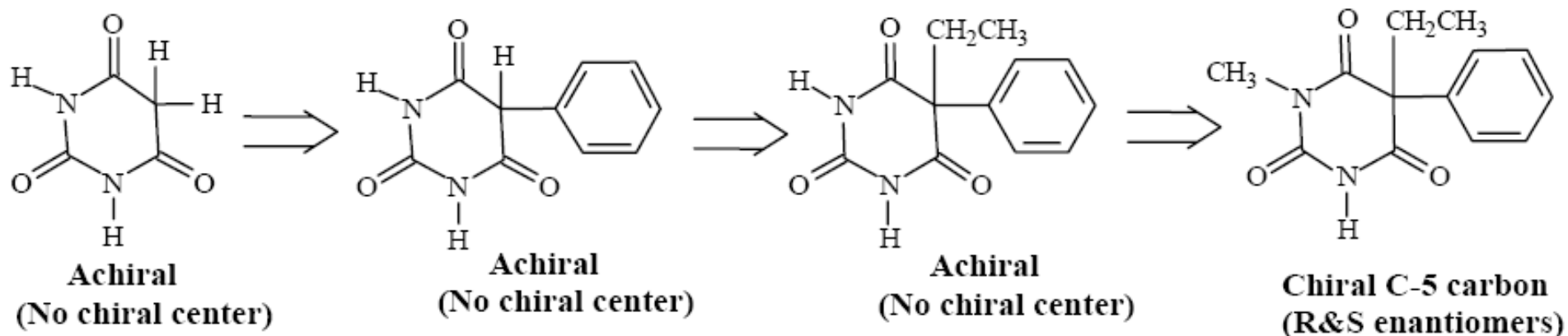
- Barbituric acid (N- and C-5-unsubstituted) is the highly acidic (but not active as a CNS depressant):
- Addition of substituents at the 5-position decrease acidity (raise pKa) due to the **electron donating** effects (+I) of the 5-alkyl groups:
- Substitution at one ring nitrogen atom reduces acidity (raise pKa) due to the electron donating effects (+I) of the N-alkyl group:
- Substitution at BOTH ring nitrogen atoms eliminates both acidic protons (nonacidic)
- It was shown that the ionized form of barbiturates can permeate liposomal bilayers provided that 5-substituents impart sufficient

- Due to the presence of one (or more) acidic protons, barbiturates can be converted to water soluble salt forms by treatment with an appropriate base as shown below.
- Note that the charge resides primarily on the more electronegative oxygen atom:

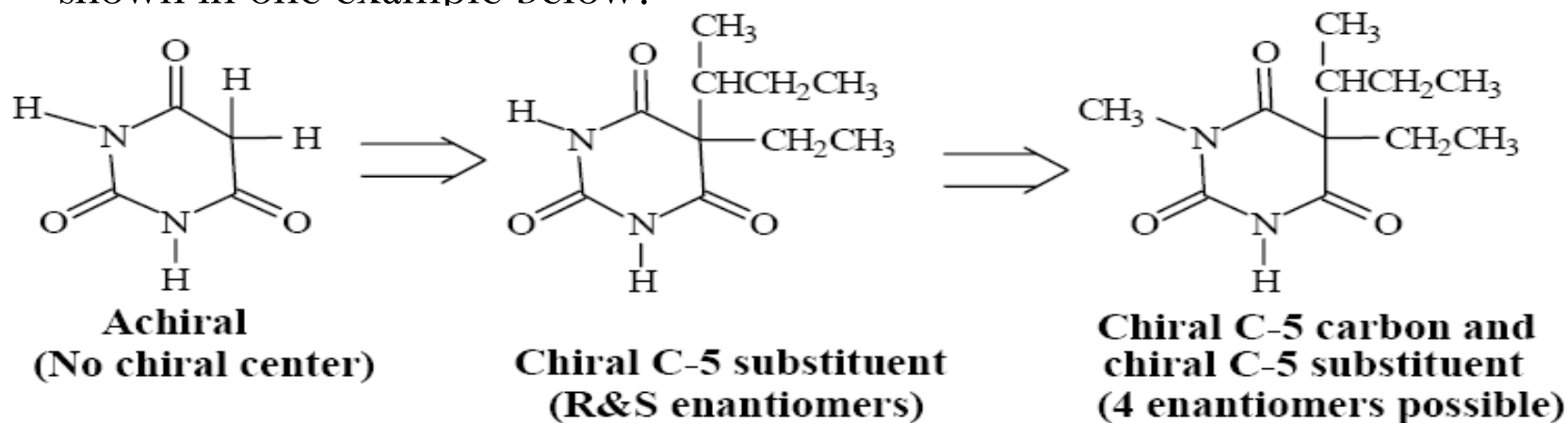


Barbiturate Chirality and Stereochemistry

- The barbiturate ring system is not chiral unless there are two different C-5 substituents and one substituent at one of the nitrogens.



- The C-5 substituents may contain chiral carbon atom(s)) and in such cases the barbiturate is chiral.
- Some barbiturates have BOTH a chiral C-5 atom AND a chiral side chain as shown in one example below:



- Enantiomers display comparable physicochemical properties, passive membrane permeability, intrinsic pharmacologic activities but may display differential metabolism.

Metabolism of barbiturates

There are four primary metabolic pathways for barbiturates

1. Oxidation of substituents attached to C₅

- It is the **most** important pathway of metabolism for the barbiturates.
- The oxidative processes may yield alcohols, ketones, and carboxylic acids.

2. N-Dealkylation (N-demethylation)

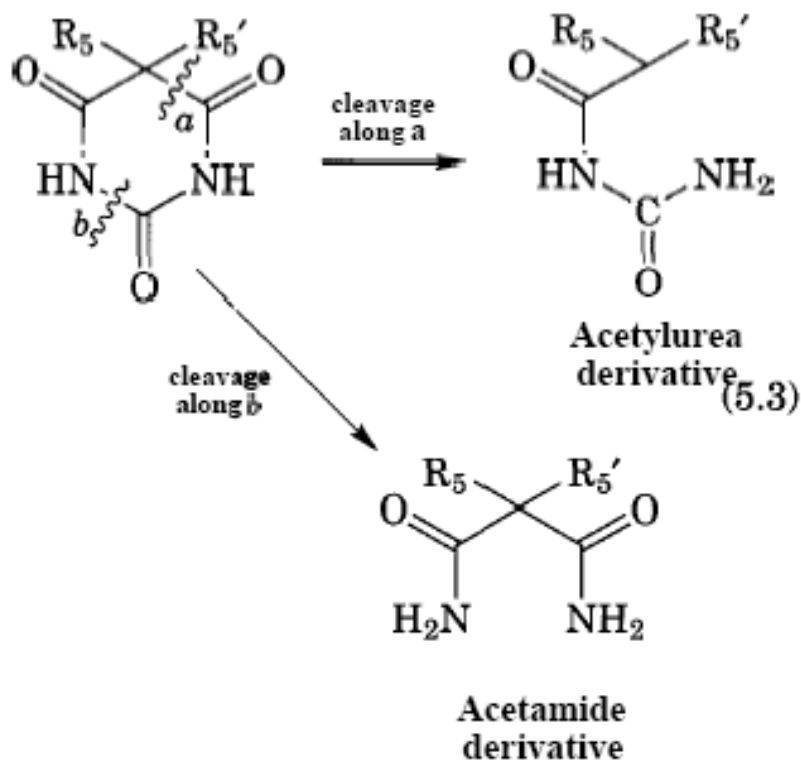
- It is an important metabolic pathway for N-substituted barbiturates.
 - Example mephobarbital (1-methyl-5-ethyl-5-phenylbarbituric acid) is metabolized to phenobarbital (5-ethyl-5-phenylbarbituric acid), which is subject to further metabolic processes.

3. Desulfurization of 2-thiobarbiturates

- Is a common metabolic process.
- Example, pentobarbital [5-ethyl-5-(1-methylbutyl) barbituric acid] is one of the metabolic products of **thiopental** [5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid].

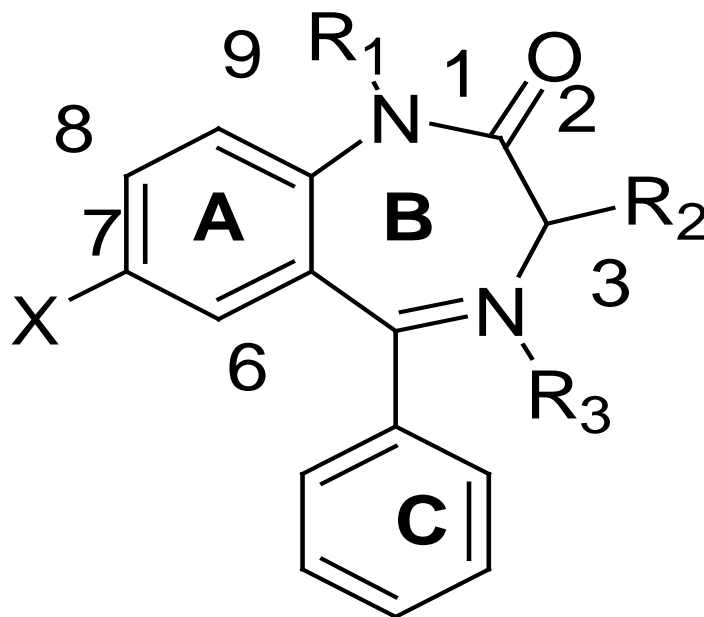
4. Ring scission of the barbituric ring

- Leads to the formation of acetamides or acetyl urea derivatives.



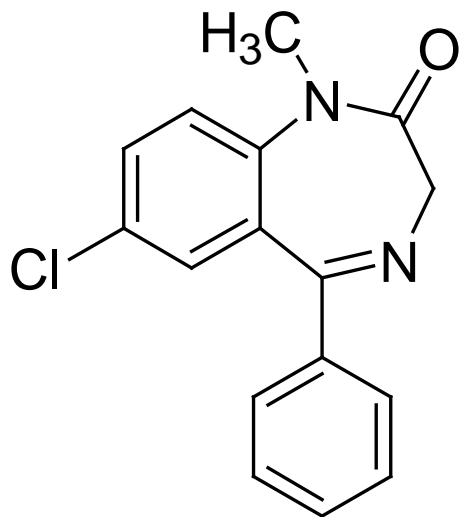
ii. Benzodiazepines

- Benzodiazepine refers to portion of the structure of benzene fused to seven membered diazepine ring

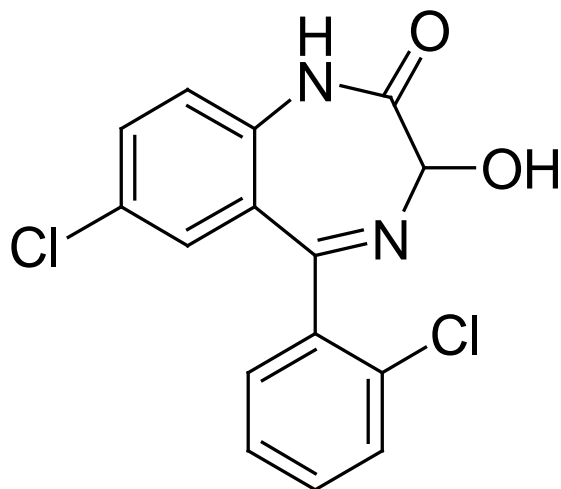


- Substituents at position marked R_1 , R_2 , R_3 and **X** result in different drugs

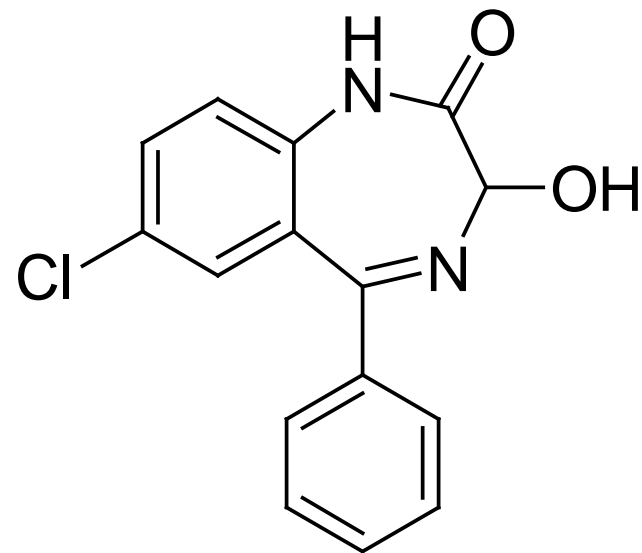
- The benzodiazepines are widely used sedative-hypnotics.
- Structurally they are 1,4-benzodiazepines, and most contain a carboxamide group in the 7-membered heterocyclic ring structure.
- A substituent in the 7 position, such as a halogen or a nitro group, is required for sedative-hypnotic activity.
- The structures of triazolam and alprazolam include the addition of a triazole ring at the 1,2-position



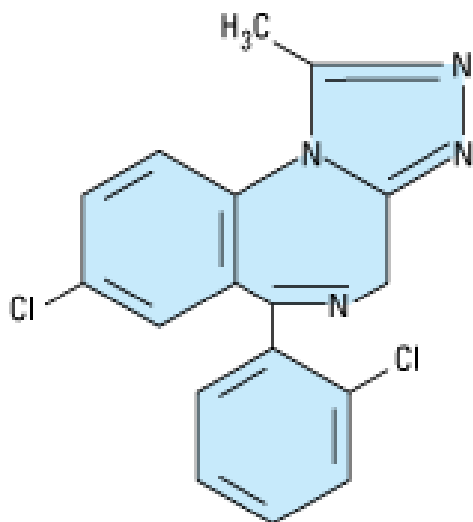
Diazepam



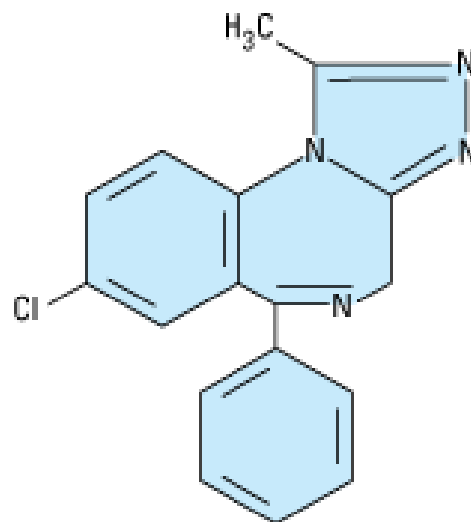
Lorazepam



Oxazepam



Triazolam



Alprazolam

The pharmacological effects of benzodiazepines

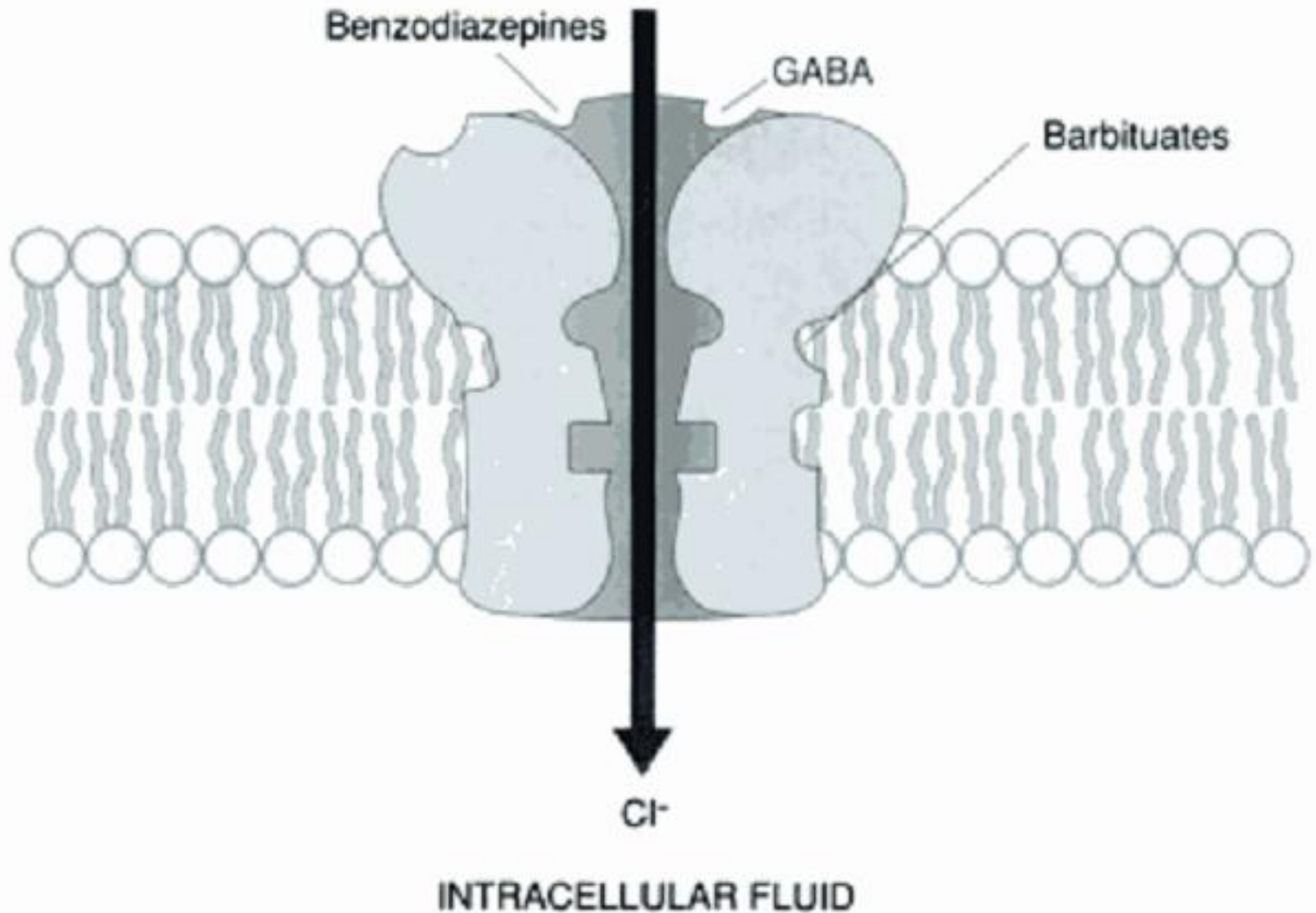
- They produce sedation, hypnosis, decreased anxiety, muscle relaxation, and anticonvulsant activity.
- Benzodiazepines have similar pharmacologic profiles, but the drugs differ in selectivity.
 - The clinical usefulness of benzodiazepine drugs varies accordingly.
- Benzodiazepines enhance GABAergic transmission in all CNS structures.
- All the effects of benzodiazepines that are mediated by receptors can be prevented or reversed by drugs that act as selective benzodiazepine antagonists.

- Benzodiazepines show **fewer** tendencies to tolerance and dependency than other older sedative-hypnotic drugs, especially barbiturates.
 - Also, benzodiazepines produce **less abuse** potential.
- Benzodiazepines are safer in overdose especially compared with barbiturates.
- Benzodiazepines produce **fewer drug interactions** because they do not induce hepatic microsomal enzymes

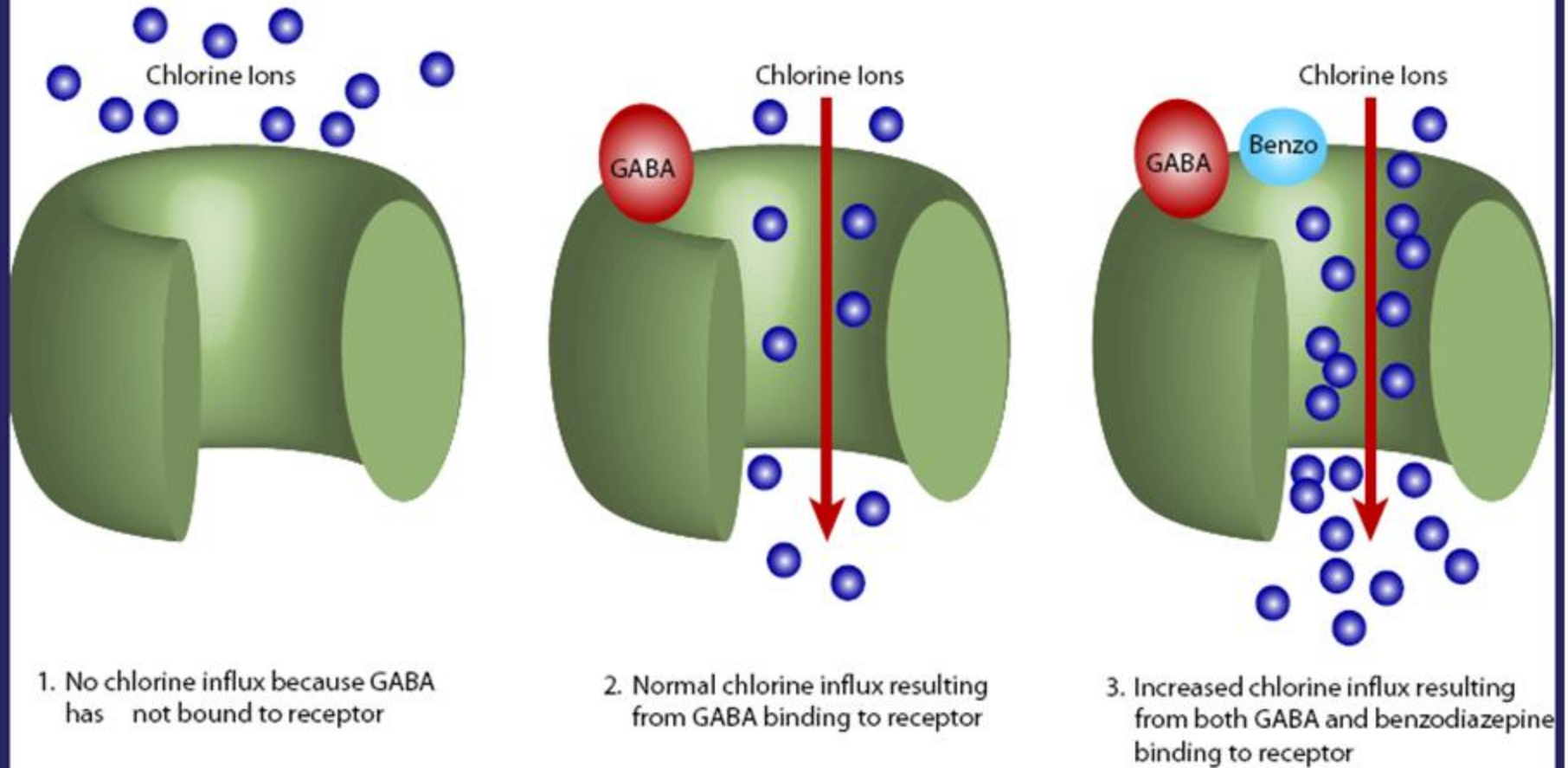
MOA

- Increase binding of GABA to GABA_A receptor and promote Cl⁻ influx
- The benzodiazepines and the barbiturates bind to molecular components of the GABA_A receptor in neuronal membranes in the central nervous system.
- This receptor, which functions as a chloride ion channel, is activated by the inhibitory neurotransmitter GABA

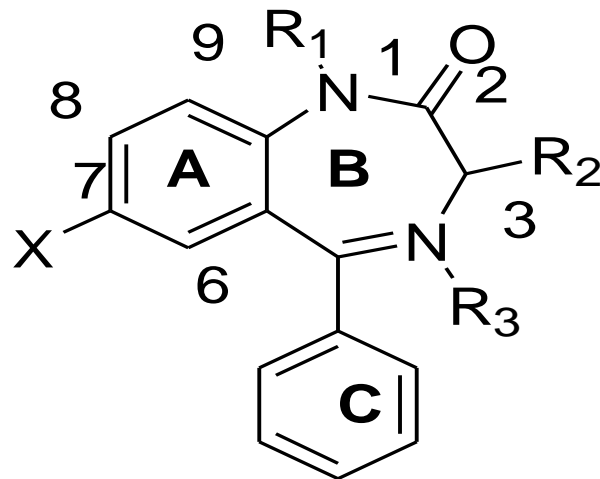
EXTRACELLULAR FLUID



Extracellular Side of GABA_A Receptor

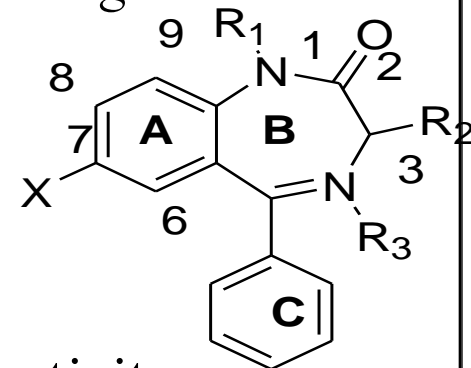


Intracellular Side of GABA_A Receptor



- Saturation of the 4, 5 double bond or shift to 3, 4-position decreases activity
- Position 6, 8, and 9 should not be substituted
- The N substitution should be small

- A phenyl group at the C₅ promotes activity
 - Ortho or di-ortho substitution with electron attracting Substituents increases activity.
 - Para substituents decrease activity
- Electron attracting Substituents at C₇ is required for activity
 - The more electrons attracting, the higher the activity
- Hydroxyl group at C₃ is important pharmacokinetically
 - Compounds without the hydroxyl group are non-polar and have longer half-life
 - Those with hydroxyl group are polar and readily excreted

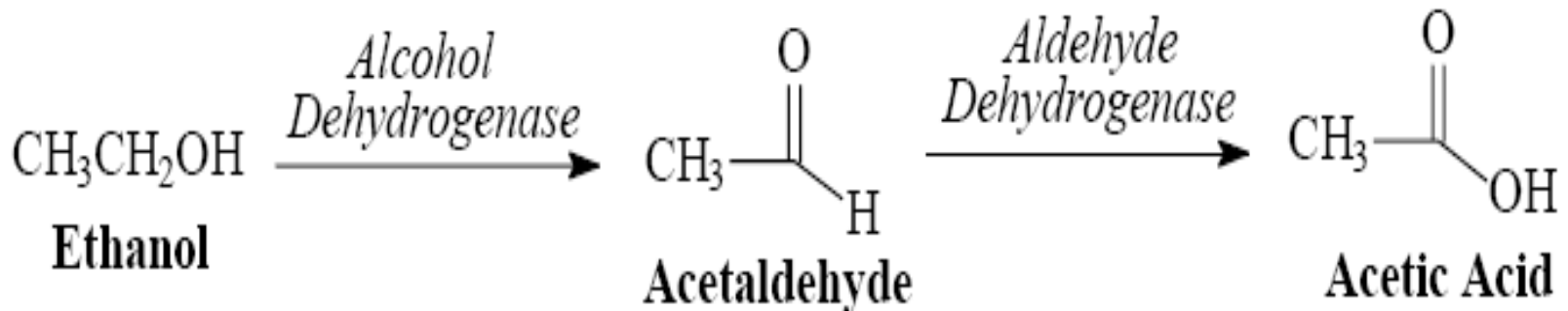


iii. Other sedative hypnotics

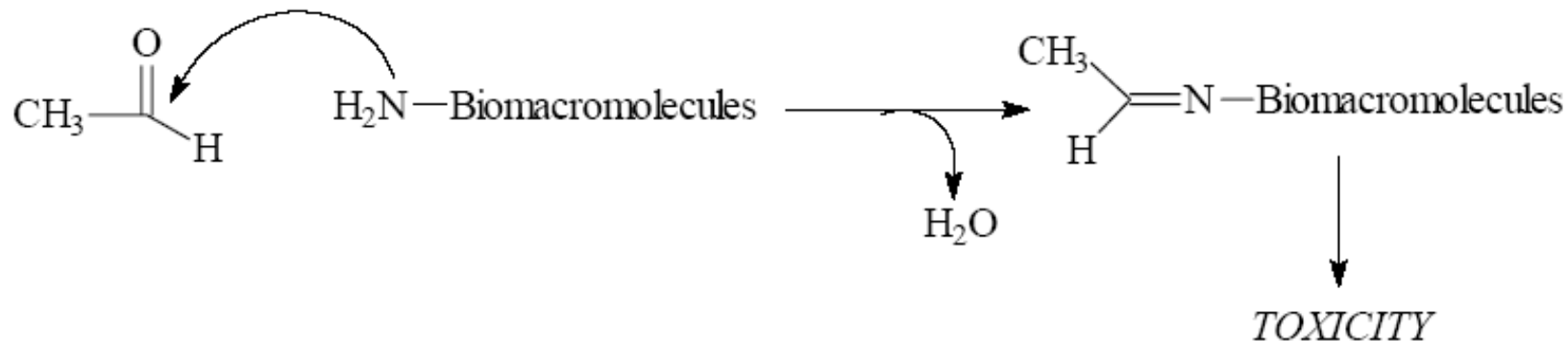
A. ALCOHOLS

- Actions: Acts at the GABA_A receptor to potentiate the action of GABA.
- Also inhibits NMDA glutamate receptors.
- These actions result in an array of actions including **CNS depression**.
- Ethanol has played a sedative –hypnotic role for centuries

- Because of problems associated with ethanol other alcoholic drugs are favored
- Rapidly and complete oxidized by alcohol dehydrogenase to **acetaldehyde**.
- The acetaldehyde formed is oxidized to acetic acid by aldehyde dehydrogenases/oxidases



- The metabolic intermediate acetaldehyde has been implicated in a number of ethanol-associated toxicities.
- This intermediate contains an electrophilic carbonyl which can react with nucleophilic groups (such as amines) on biomacromolecules as shown below.
- These complexes may compromise cellular structure and viability and result in toxicity:



SAR for hypnotic activity of alcohols

- Activity increases as the chain length increase with maximum at C_8
- Branching the chain increases activity
 - Tertiary > Secondary > Primary
- Replacing hydrogen with a halogen increases activity
 - E.g. Ethchlorvynol and chlorobutanol

Reading assignment

- Carbamates
- Aldehydes
- Amides
- Imides

Anticonvulsants (Anti- epileptics)

- Drugs that are used to prevent and control epileptic seizures

Epilepsy:

- CNS disorder characterized by recurrent abnormal discharge of CNS neurons
- Characterized by abnormal and excessive EEG and discharge
- May be limited to a focus or encompass wide area
- Causes disturbance of consciousness and hyperactivity of autonomic nerves system

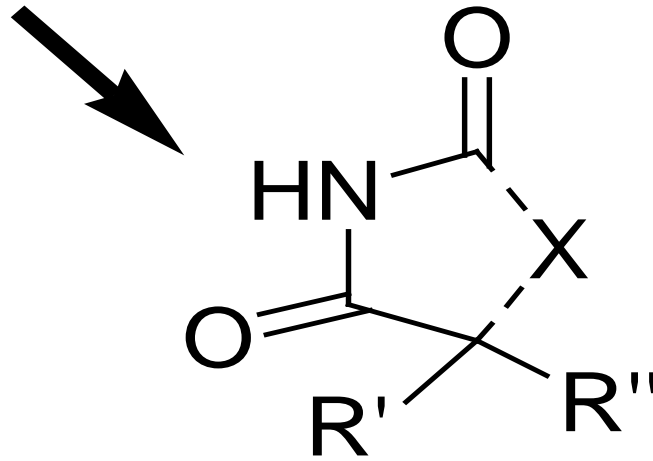
Major types

- Grandmal
 - Loss of consciousness
 - General muscle spasm lasting for 2 to 5 minutes
 - The individual may stop breathing
- Petitmal,
 - Non convulsive seizure
 - **Brief** loss of consciousness with no motor activity

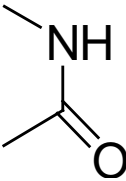
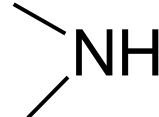
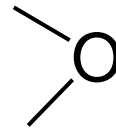
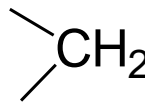
- The only effective way to control epilepsy is the use of drugs
- Anticonvulsant act selectively as depressant of convulsant activity in the brain
- Most of them have common structural features

- **Classification**

- Cyclic ureides and imides
- Urea and
- Miscellaneous

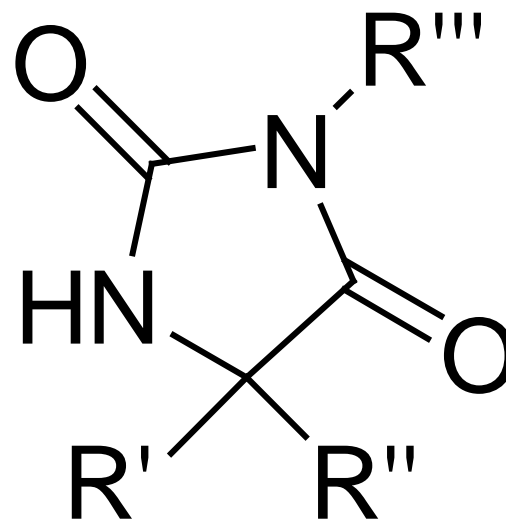


Class

- Barbiturate..... 
- Hydantoin..... 
- Oxazolidindions..... 
- Succinimides..... 

- If both R' and R'' are lower alkyl, the tendency is to be active against petit mal
- If one is an aryl group, activity tends to be directed to grand mal epilepsy
- It is believed the imide Hydrogen atom is involved in a strong hydrogen bond at the receptor
- The strength of activity depends on the Substituents

Hydantoins



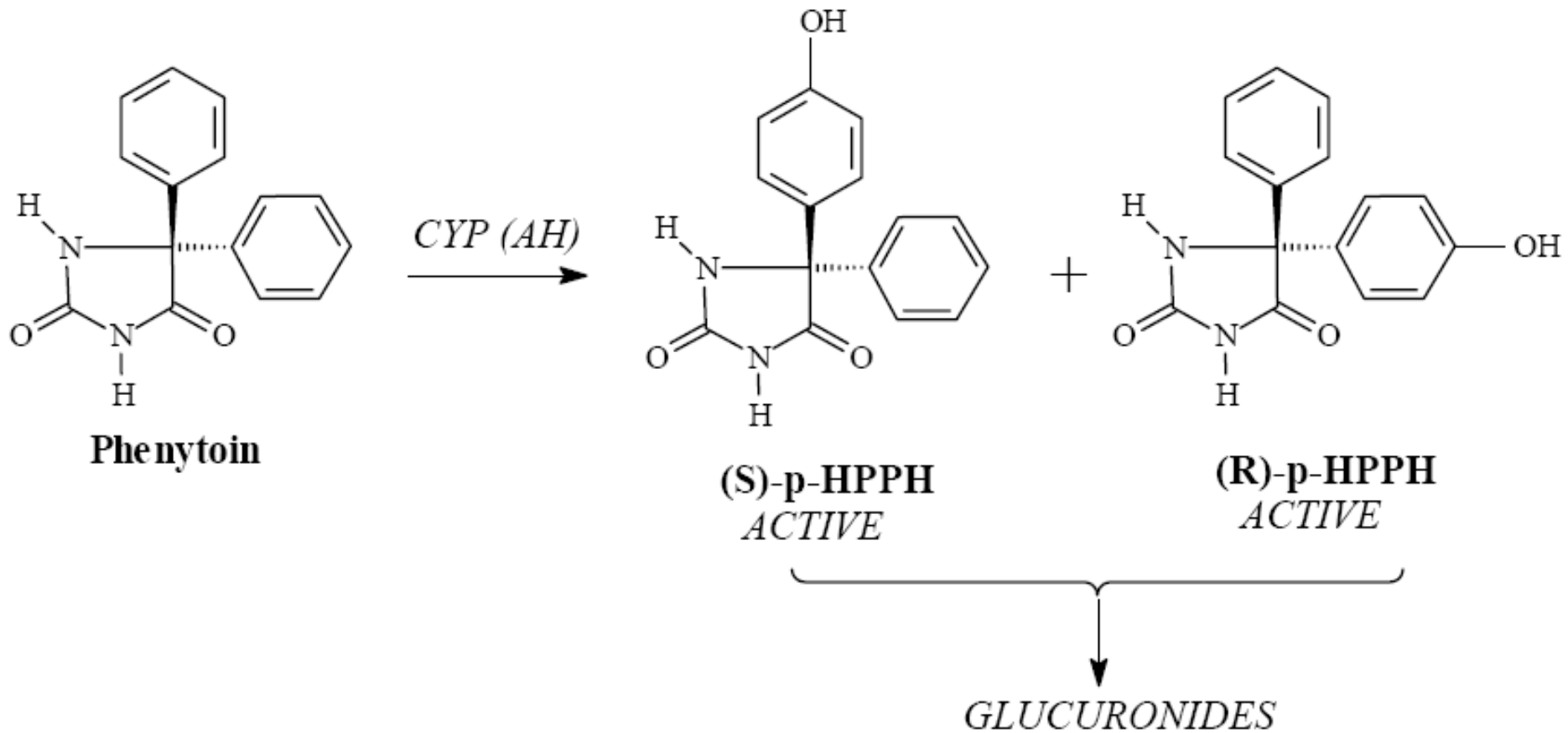
Name	R'	R''	R'''
Phenytoin	C ₆ H ₅	C ₆ H ₅	H
Ethotoin	C ₂ H ₅	C ₆ H ₅	H
Mephentyoin	C ₂ H ₅	C ₆ H ₅	CH ₃

- Phenytoin and the other hydantoins are “ringcontracted” analogues of the barbiturates (one carbonyl removed).
- These compounds have physicochemical properties similar to the barbiturates, including **acidity** when $R = H$ as in phenytoin (an acidic imide with pK_a 8.3).

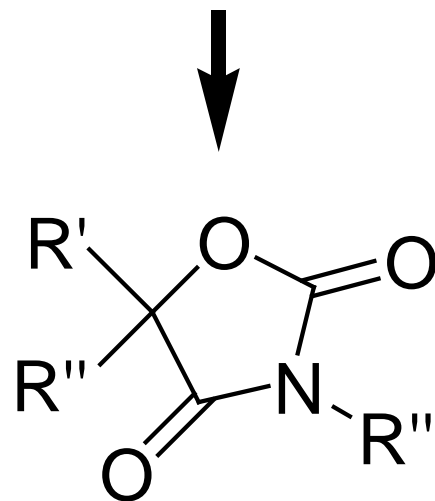
MOA

- The hydantoins appear to produce their anti-epileptic effects by depression of the **sodium action potential**.
- This may be related to a voltage dependent blockade of membrane sodium channels responsible for the action potential.
- Phenytoin is also a **weak antiarrhythmic** and these actions are also mediated through effects on sodium channels, in this case, in **Purkinje fibers**.

- At least **one phenyl** group is important for activity
- Phenytoin (a prochiral compound) is metabolized in the liver mainly to inactive enantiomeric phenols similar to aromatic barbiturates.
- These metabolites may be conjugated as **glucuronides** and excreted in the urine by tubular secretion.



Oxazolidinediones



Name

R'

R''

R'''

Trimethadione

CH₃

CH₃

CH₃

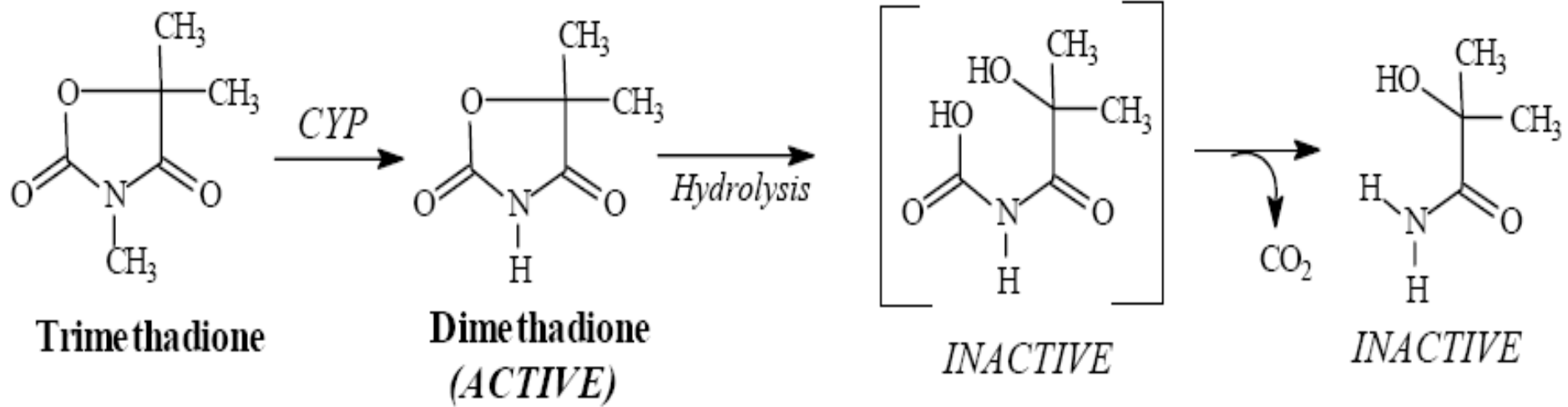
Paramethadione

C₂H₅

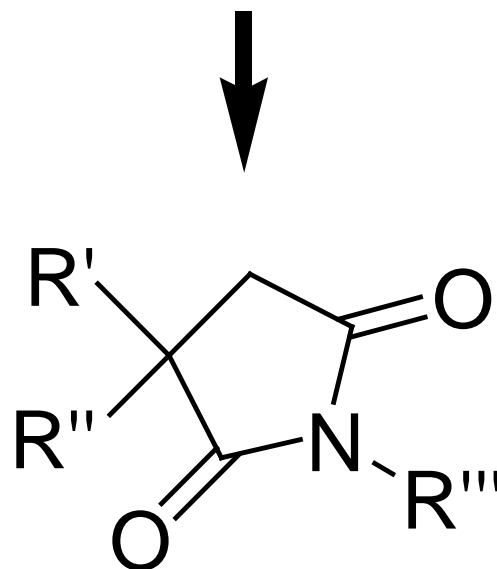
CH₃

CH₃

- Trimethadione and the other oxazolidinediones are “ring-contracted” analogues of the barbiturates (one carbonyl removed) or can be viewed as **isosteres** of the hydantoins (one ring N replaced with O).
- These compounds have physicochemical properties similar to the barbiturates, except they are not acidic (no imide).
- Unlike hydantoins and anticonvulsant barbiturates, the oxazolidinediones modifies maximal seizure pattern in humans receiving **electroconvulsive therapy**.

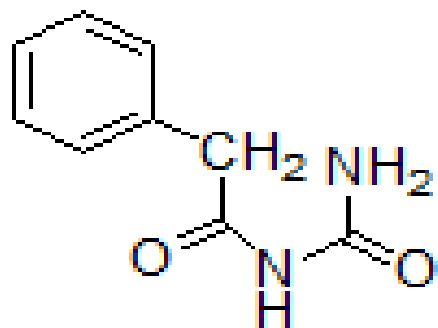


Succinimides

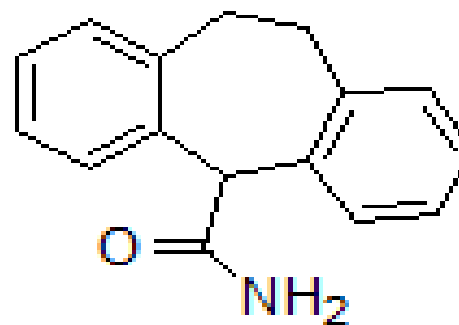


Name	R'	R''	R'''
Ethiosuccinimide	C ₂ H ₅	CH ₃	H
Methosuccinimide	C ₆ H ₅	CH ₃	CH ₃
Phensuccinimide	C ₆ H ₅	H	CH ₃

- Ethosuximide and the other succinimides are “ringcontracted” analogues of the barbiturates (one carbonyl removed) or can be viewed as isosteres of the hydantoins (one ring N replaced with CH_2).
- These compounds have physicochemical properties similar to the barbiturates, except only ethosuximide has an imide N-H and is acidic.
- The antiepileptic (petit mal) actions of the succinimides may be related to synaptic inhibition brought about by the **GABA mediated chloride** conductants

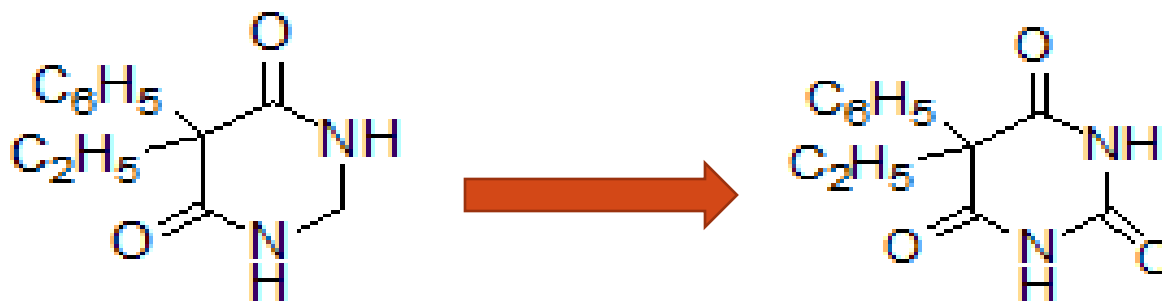


Phenacemide

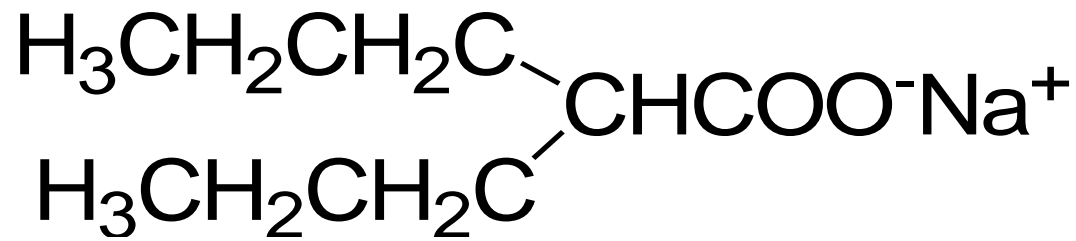


Carbamazepine

c) Miscellaneous



Primidone



- Sodium Valproic acid
- Primidone :
 - Is metabolized to phenobarbitone and it acts through its metabolite
- Valproic acid blocks GABA transaminase elevating GABA level and thus alleviating seizure
 - **GABA transaminase** is responsible for the destruction of GABA

Major Tranquilizers

Tranquilizers

- Give strong sedation without producing sleep and produce a state of **indifference** and **disinterest**.
- Effective in reducing excitation, agitation, aggressiveness and impulsiveness (major tranquilizers)
- They may be classified into
 - **Major tranquilizers:** used mainly for treatment of psychosis (schizophrenia and mania)
 - **Minor tranquilizers:** used to reduce pathological anxiety, agitation and tension

Tranquilizers...

- Dopamine hypothesis of Schizophrenia (and mania) suggests that schizophrenia results from increased **dopaminergic** neurotransmission
- Hence the strategy is to block these dopaminergic receptors (specifically D2 and D3 receptors)

Dopaminergic...

Three dopaminergic pathways

The mesolimbic pathway

- The mesolimbic pathway is important for **memory** and for **motivating behaviours**.
- By blocking this pathway, antipsychotic drugs reduce the **intense emotions** caused by conditions such as schizophrenia.

Dopaminergic pathways

The mesocortical pathway

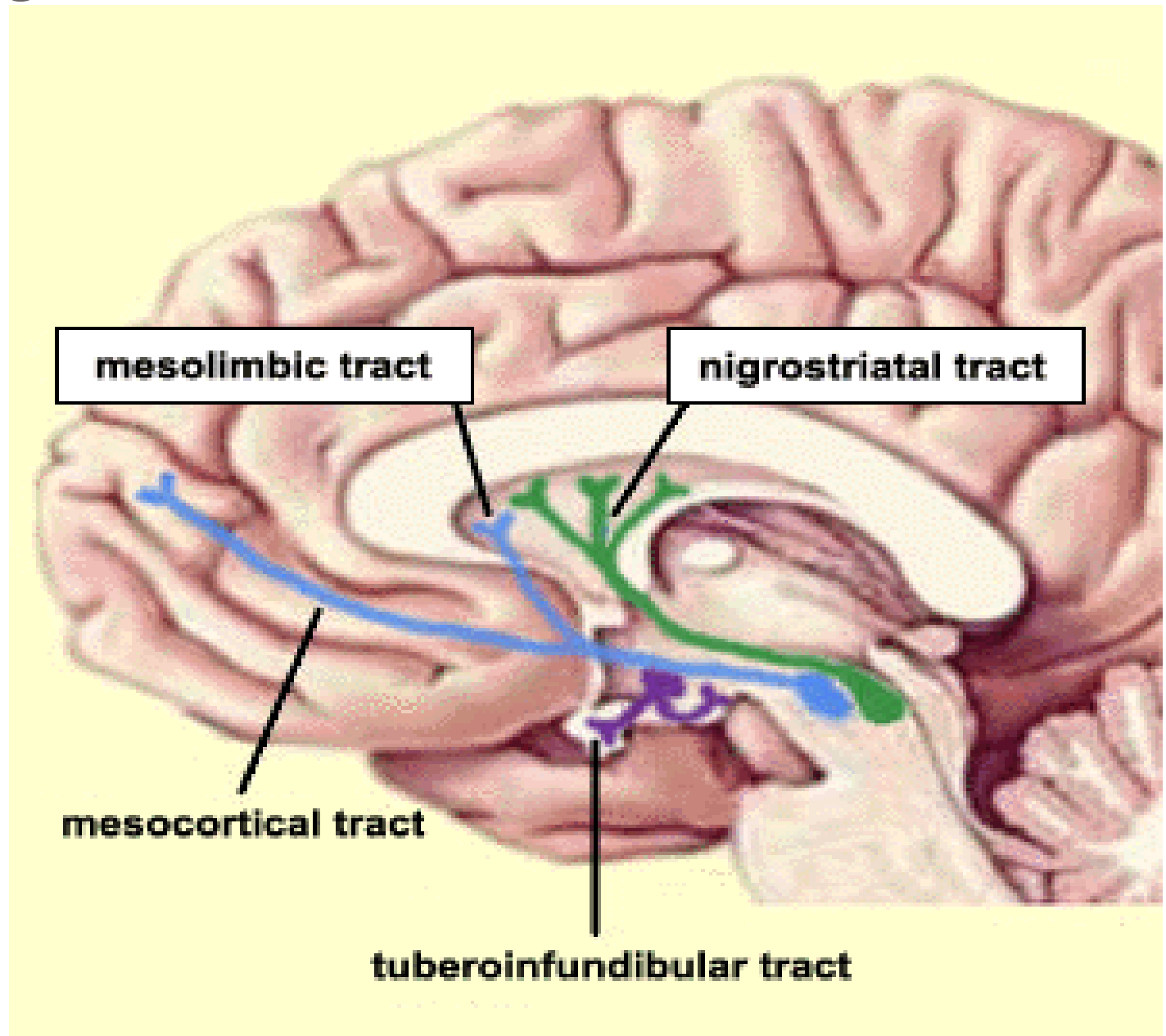
- Some evidence indicates that a malfunction in this pathway might be the cause of some of the symptoms of schizophrenia, such as hallucinations and disordered thinking.
- Medications that block this pathway reduce psychotic delirium, but also reduce the overall activity of the frontal lobes.

Dopaminergic...

The nigrostriatal pathway

- Involved in motor control
- Degeneration of the neurons in this pathway is associated with the trembling and muscular rigidity symptomatic of Parkinson's disease.

Dopaminergic...



Major neuroleptics

- **Major neuroleptics:**
 1. Tricyclic neuroleptics
 2. The fluorobutyrophenone derivatives

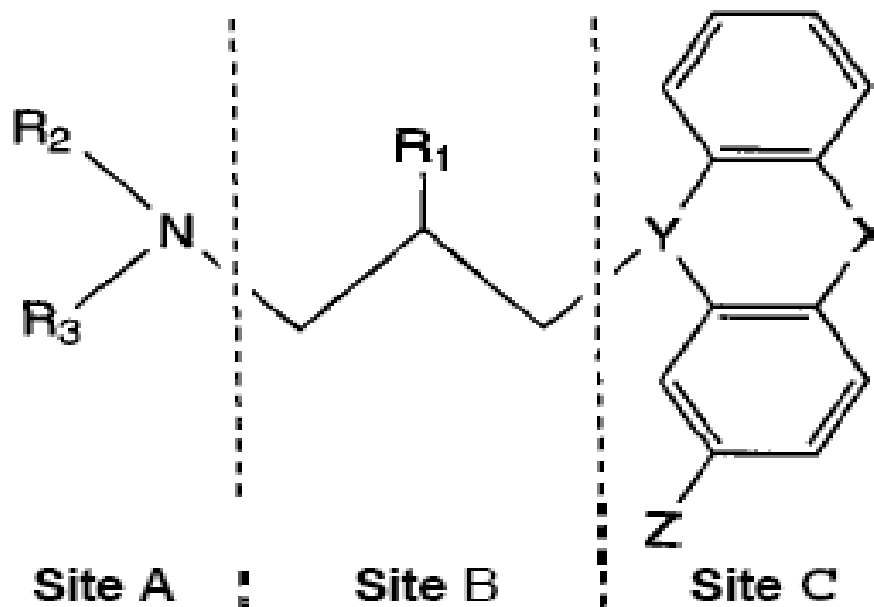
Major neuroleptics...

1. Tricyclic Neuroleptics

- After the introduction of chlorpromazine (CPZ) as a treatment for schizophrenia, thousands of new agents based on its tricyclic topology were prepared and examined pharmacologically.
- The neuroleptic potential of these agents was determined by measuring its "chlorpromazine index".

Major neuroleptics...

- The tricyclic antipsychotics may be dissected into three substructures as shown below,
 - Amine functionality (Site A),
 - The diaryl heterotricyclic (Site C), and
 - The intervening alkyl chain (Site B)

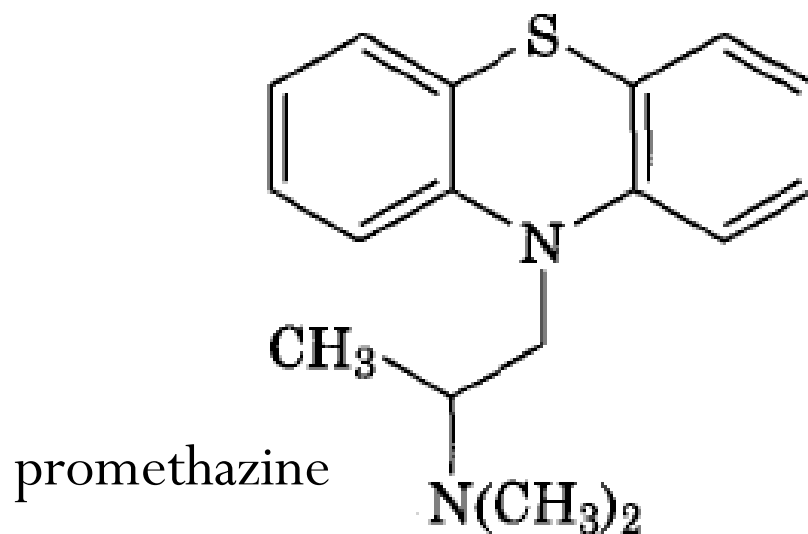
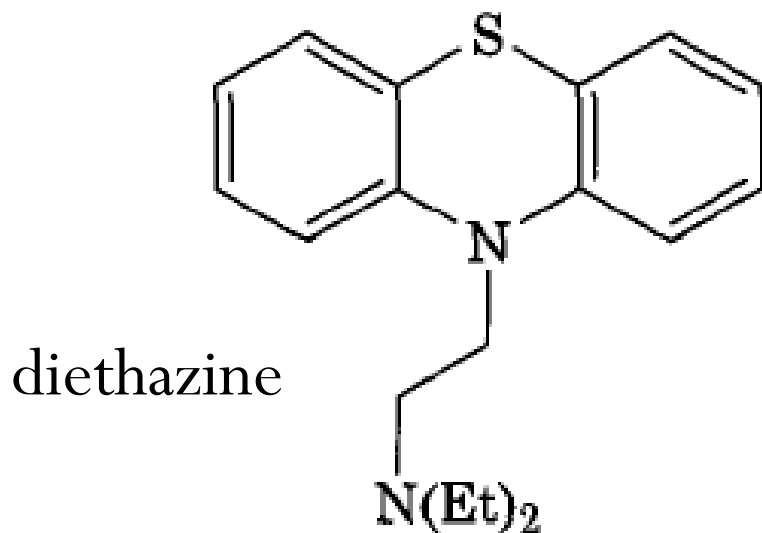


Major neuroleptics...

SAR

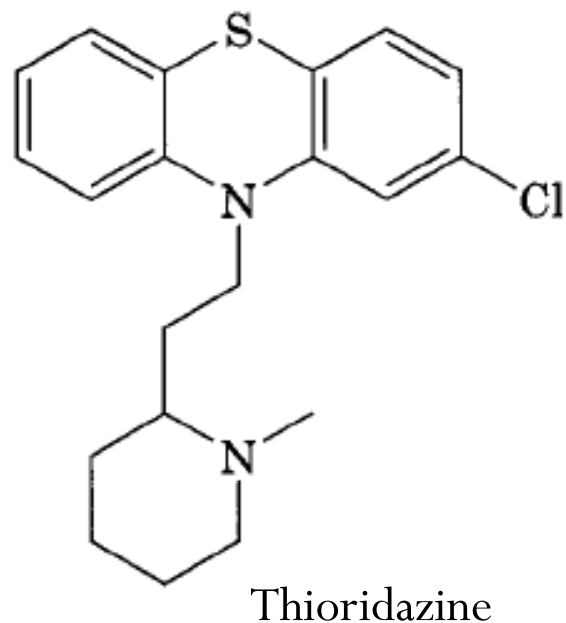
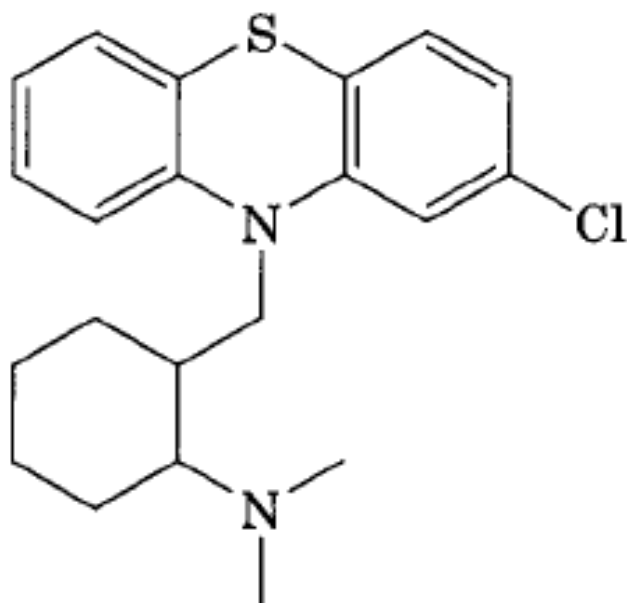
1. Modification at site B

- The distance between Sites A and C is critical for neuroleptic activity, with a **three** carbon chain being optimal.
- Shortening the chain to two carbons has the effect of amplifying the **anticholinergic** and **antihistaminic** properties.



Major neuroleptics...

- Small alkyl substituents such as methyl are tolerated at the C₂ carbon, larger substituents (i.e., R = phenyl) that restrict the free rotation decrease neuroleptic potency.
- Additionally, if rotation is restricted through ring formation, the chlorpromazine index is greatly reduced

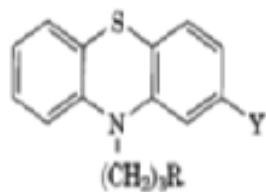


Major neuroleptics...

- **Effect of Aromatic Substitution within the Tricyclic System**
 - Substitution at position 2 provides compounds of enhanced potency in blocking conditioned response in rats
 - The electronic nature of the substituent also plays a role in determining the efficacy in this model.
 - **Electron withdrawing** groups such as chloro and trifluoromethyl show superior conditioned response blocking activity relative to the corresponding alkyl or alkoxy derivatives

Major neuroleptics...

- **Nature of the Amino Group**
 - The size and nature of the basic amino group has considerable influence on the behavioral profile of the phenothiazine neuroleptics
 - The effect is shown below

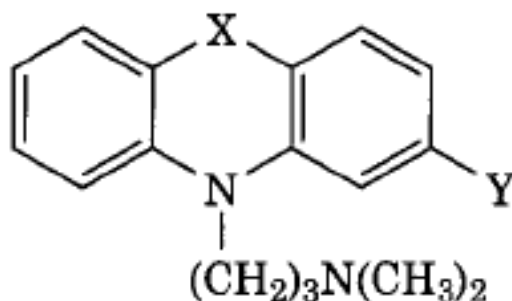


R	X	CPZ Index Blockade of Conditioned Response in Rats
$\text{N}(\text{Et})_2$	Cl	0.8
	Cl	0.7
	Cl	0.2
	Cl	0.05
	Cl	2.7
	CF_3	9.0
	CF_3	3.0
	Cl	9.0

Major neuroleptics...

• Variations within the Tricyclic Topology

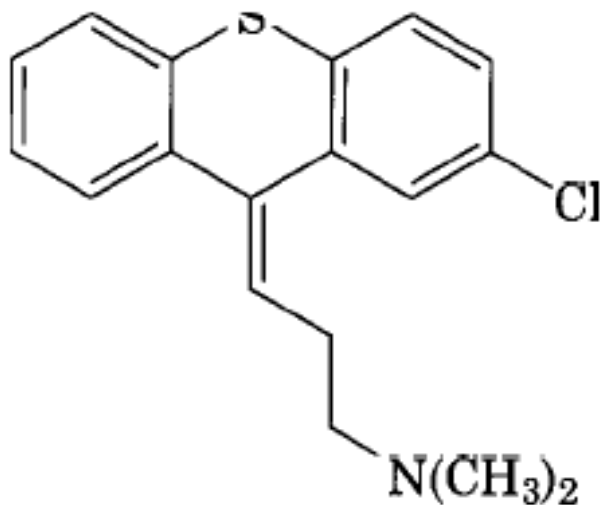
- Introduction of other group VI elements in place of the sulfur in the phenothiazines produced the corresponding **phenoxazine** and **phenoselenazine** derivatives



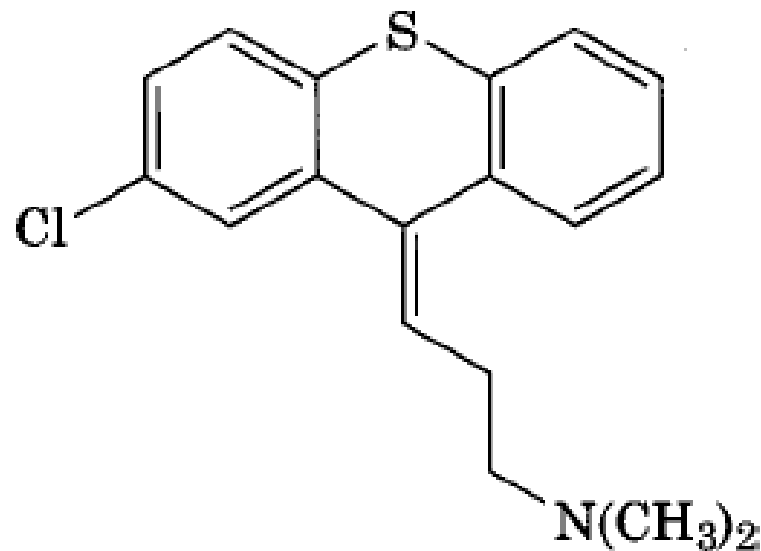
X	Y	Chlorpromazine Index Blockade of Conditioned Response in Rats
S	Cl	1
S	CF_3	1.7
O	Cl	0.38
O	CF_3	0.29
Se	Cl	0.1
Se	CF_3	1.1
CH_2	Cl	~ 0.1
$\text{C}(\text{CH}_3)_2$	Cl	> 0.1

Major neuroleptics...

- A unique series of neuroleptics results from the replacement of the nitrogen within the phenothiazine ring system with a methane carbon. These analogues are known as **thioxanthenes**
- The introduction of the double bond within the propylamino chain provides for geometric isomers (*cis* and *trans*)



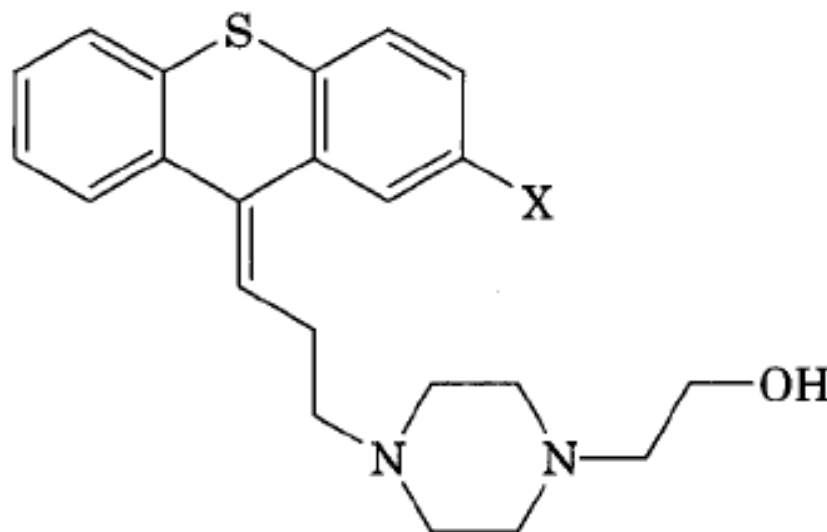
Cis chlorprothixine



trans chlorprothixine

Major neuroleptics...

- Generally the cis isomer display more neuroleptic potency than the corresponding trans isomer.
- The structure-activity relationships of the thioxanthenes mimic that of the phenothiazines
- Examples of thioxanthene derivatives that are potent



X= Cl, clopenthixol

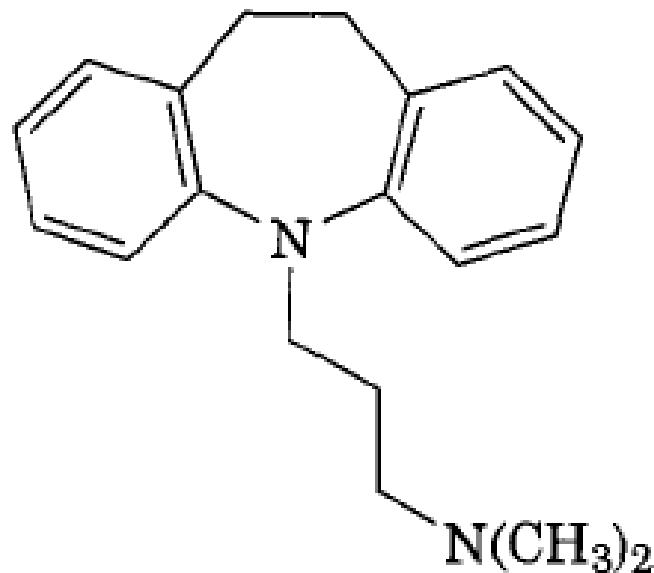
X= CF₃, flupenthixol

Major neuroleptics...

- The phenothiazines and thioxanthenes have the characteristic of two phenyl groups fused to a central six-member ring giving a so-called 6-6-6 system.
- An ethylene is a commonly used bioisostere for a thio linkage in medicinal chemistry
- Continued research in the area of the tricyclics led to the use of this and other two-atom linkages to provide the 6:7:6 ring system called **dibenzazepine** derivatives.

Major neuroleptics...

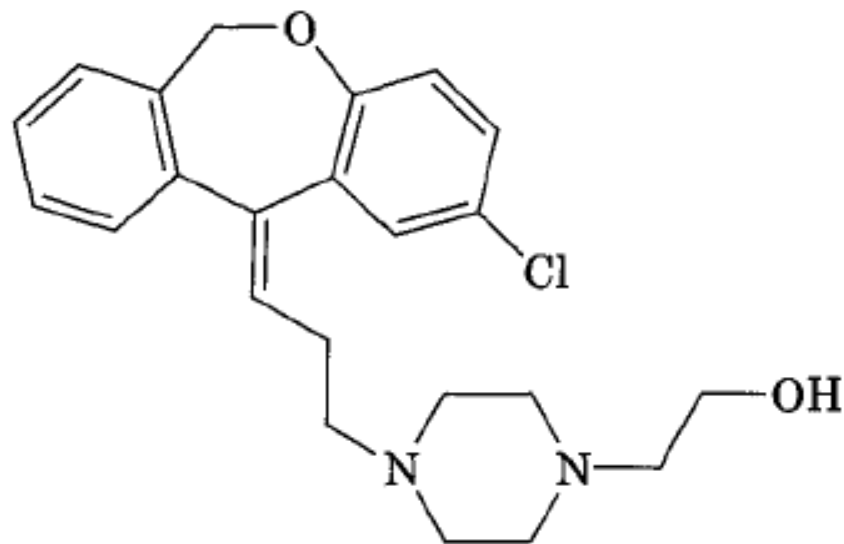
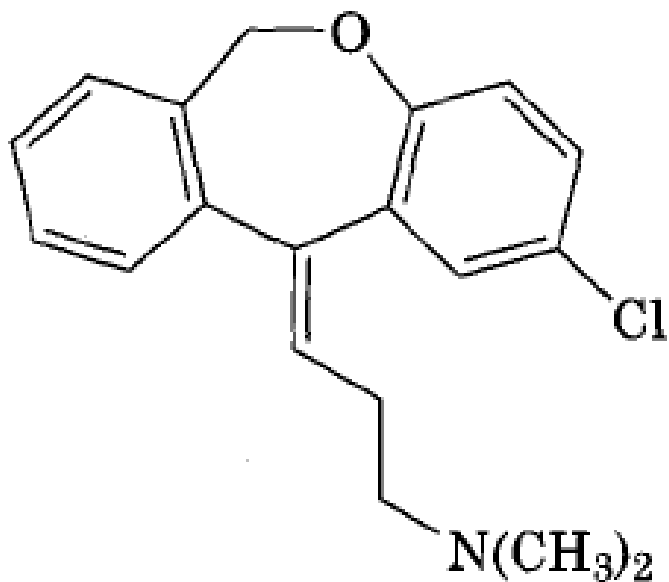
- During clinical studies of dibenzazepine derivatives, it was observed that **imipramine**, unlike the thioxanthenes, was a relatively ineffective antipsychotic agent but seemed to have efficacy in the treatment of **depression**.



Imipramine

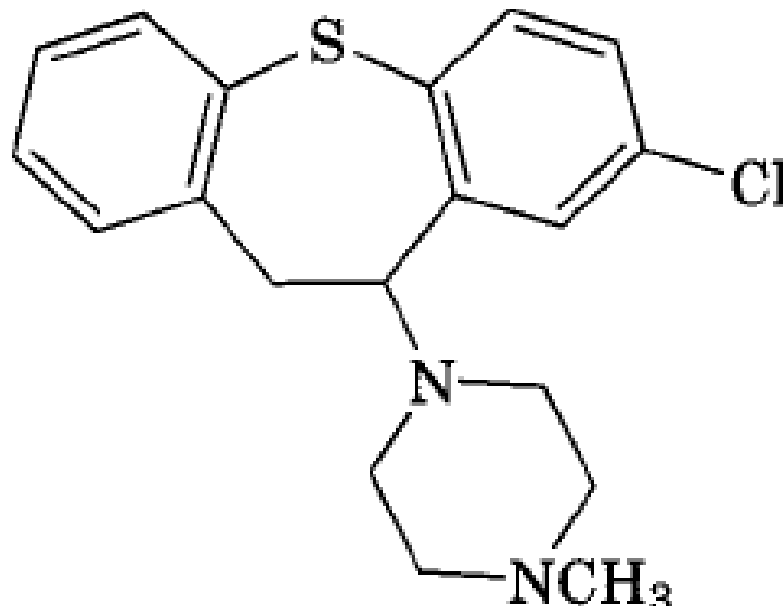
Major neuroleptics...

- Among the various dibenzazepine derivatives, two-substituted derivatives had observable neuroleptic actions
 - a) The **dibenzoxepin** derivatives showed chlorpromazine indices of 1 and 6, respectively



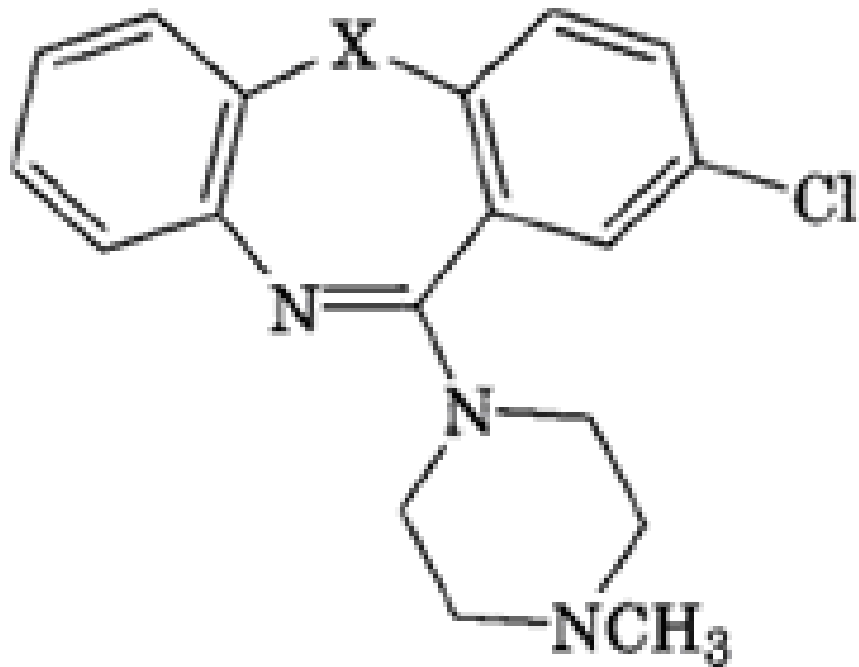
Major neuroleptics...

- b) **Dibenzothiepins**- representative of this class is **octoclothiepine** which is approximately six times more potent than chlorpromazine



Major neuroleptics...

- Another important class of neuroleptics is the dibenzazepines, which are represented in Fig. below.



X = **O** oxyclozapine

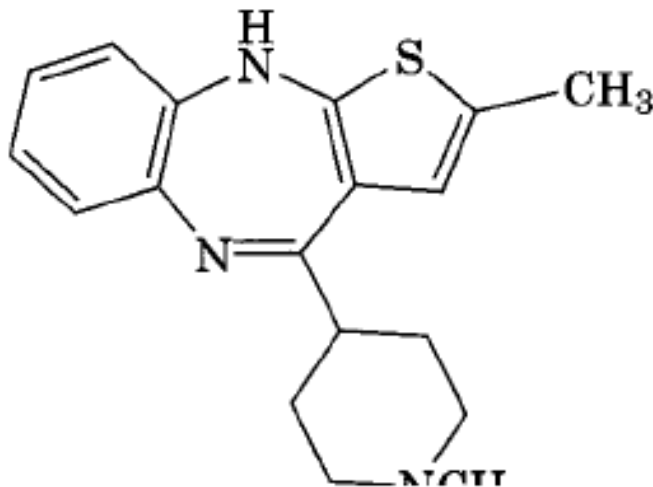
X = S clotiapine

X = NH clozapine

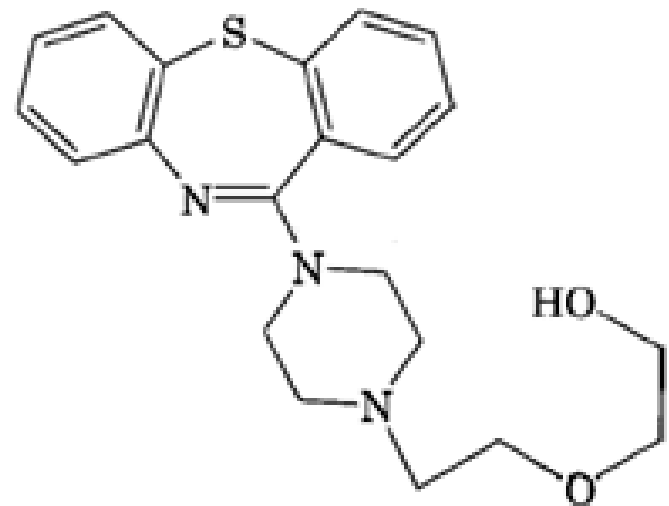
X = CH₂ perlapine

Major neuroleptics...

- From these agents, **clozapine** does not produce extrapyramidal side effects.
- Two drugs related to clozapine include the almost identical compound, **olanzapine**, and **quetiapine**.
- Both confer similar antipsychotic profiles and a minimal propensity to elicit extrapyramidal side effects



Olanzapine



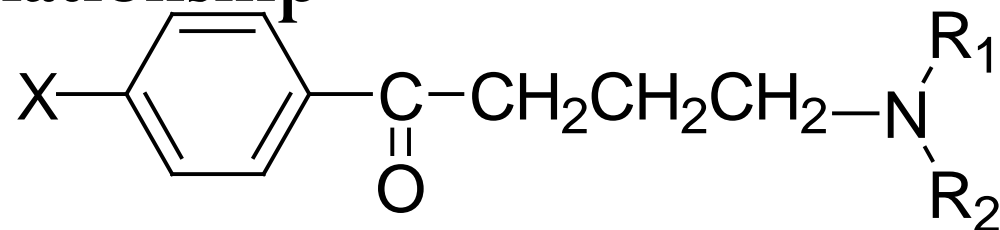
Quetiapine

Major neuroleptics...

2. Butyrophenones

- Are chemically unrelated to phenothiazines but have similar activity
- Display high neuroleptic potency

- **Structure activity relationship**

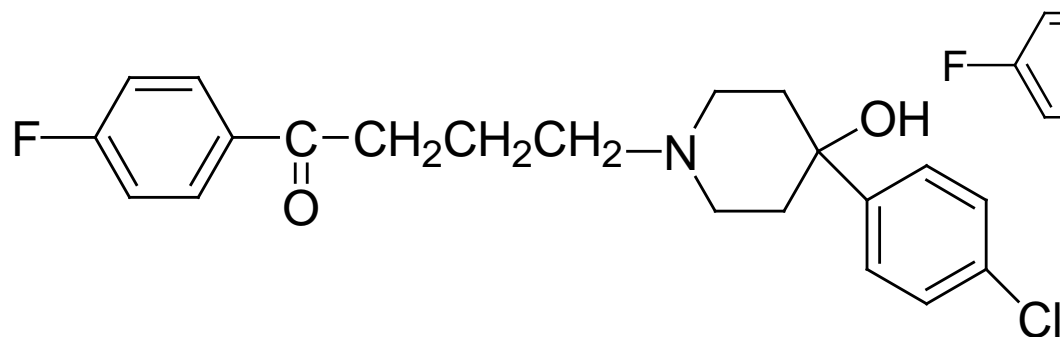


- Fluorine is usually found in the para position (at X) in most potent drugs.
- All butyrophenones possess a tertiary amine at C4 of butyl chain
- Lengthening, shortening or branching of propyl chain decreases neuroleptic potency

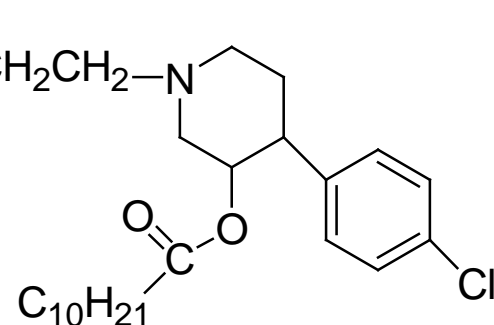
Major neuroleptics...

- The ketone group is important for activity
 - ❖ Replacement with thioketone, phenoxy, olefinic or hydroxyl decreases potency
- The tertiary amine may be incorporated into a variety of six membered ring without losing potency
 - ❖ Could be piperidine, tetrahydropyridine or piperazine

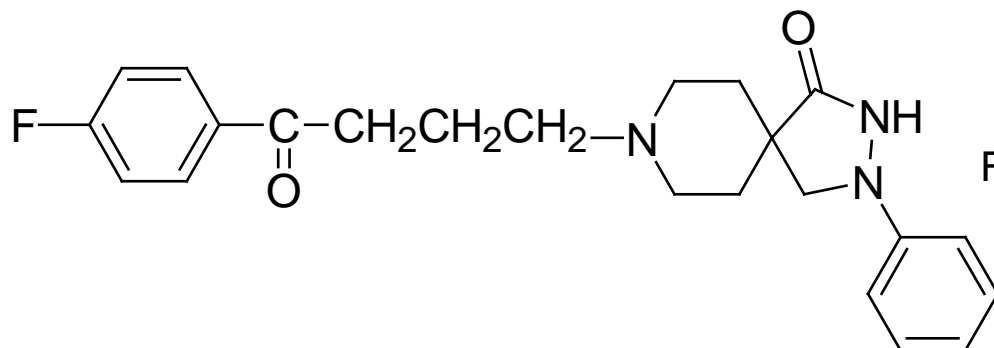
Currently available butyrophenones



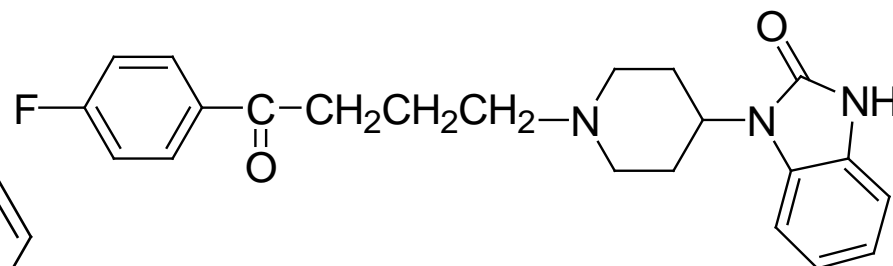
Haloperidol



Haloperidol decanoate



Spirperone



Droperidol

Major neuroleptics...

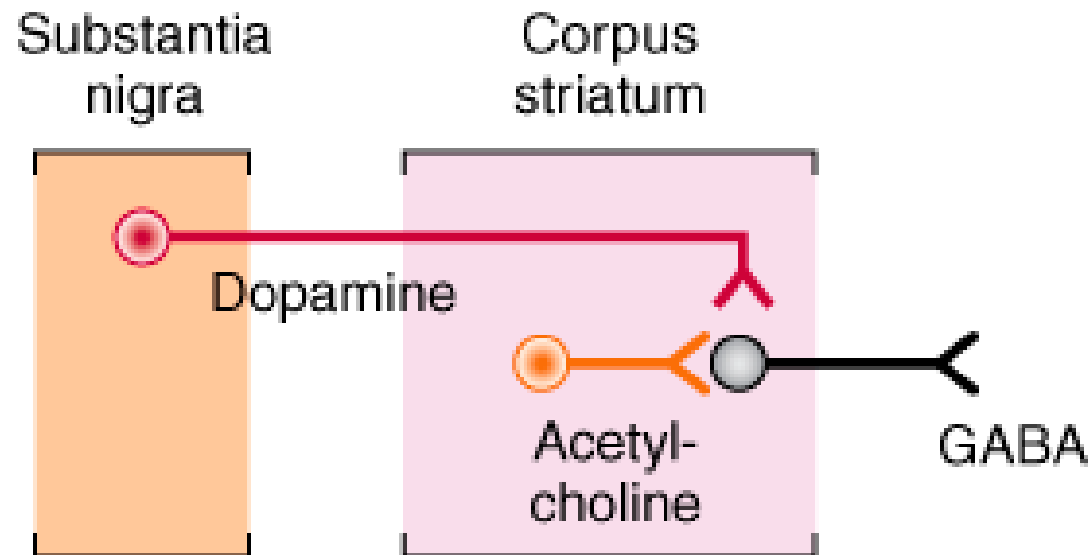
- **For long term treatment**
 - The hydroxyl group of haloperidol provides opportunity to attach alkyl ester group
 - Haloperidol decanoate serves as a prodrug releasing haloperidol into the blood stream over a period of time (i.m.)

Anti-parkinsonian Agents

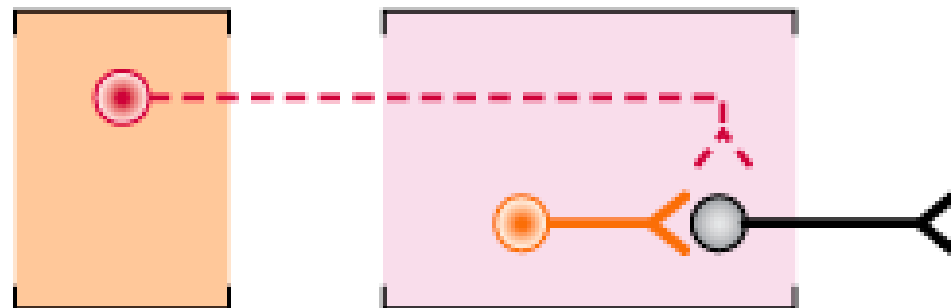
Anti-parkinsonian agents

- Parkinson disease is a slowly progressive degenerative neurologic disease
 - Tremor, rigidity, sluggish neuromuscular response and postural instability (dystonia).
- In Parkinsonism dopaminergic input is deficient and cholinergic output remain unchanged
- Antiparkinsonian agents are either **anticholinergic** or **dopaminergic**

Normal



Parkinsonism

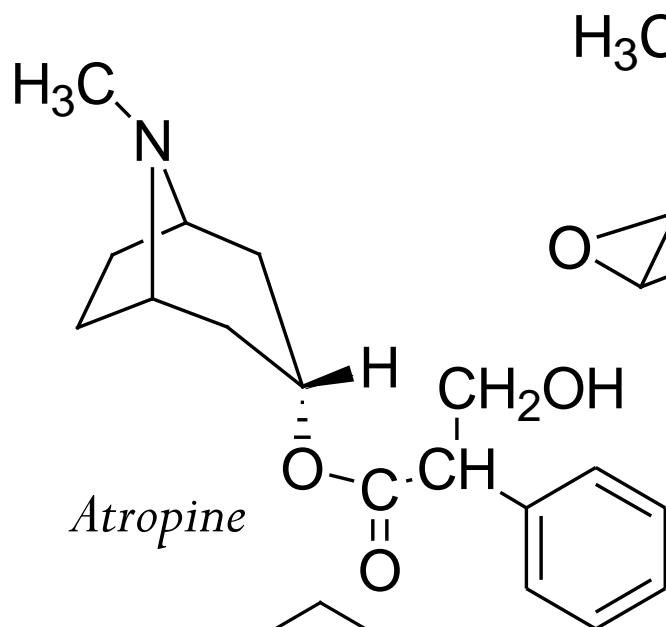


Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition: <http://www.accessmedicine.com>

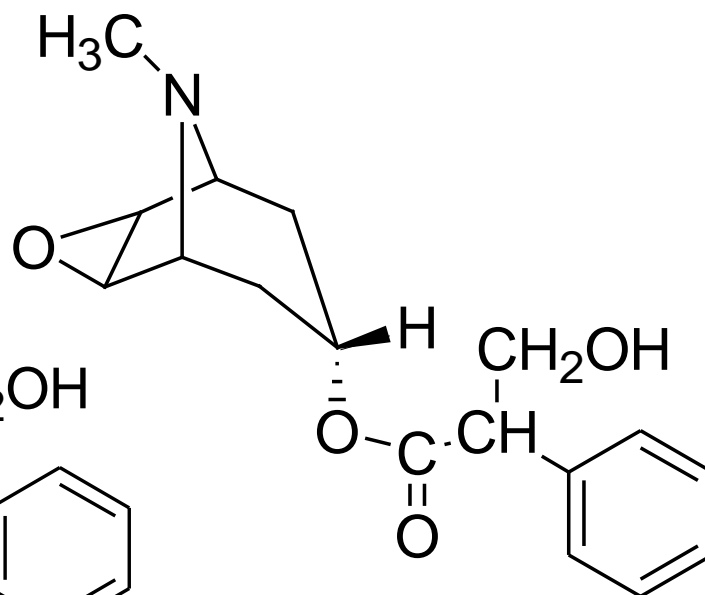
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Anticholinergics....

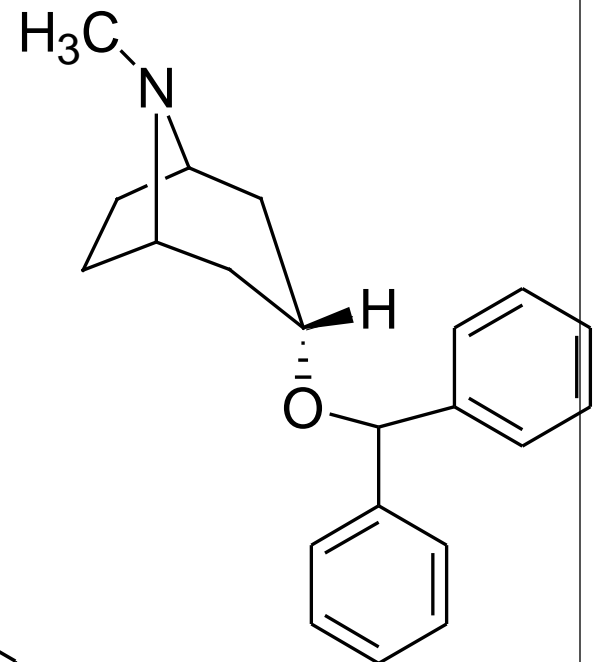
- Anticholinergics used



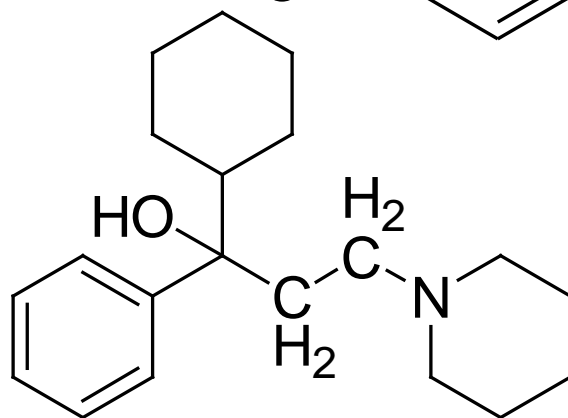
Atropine



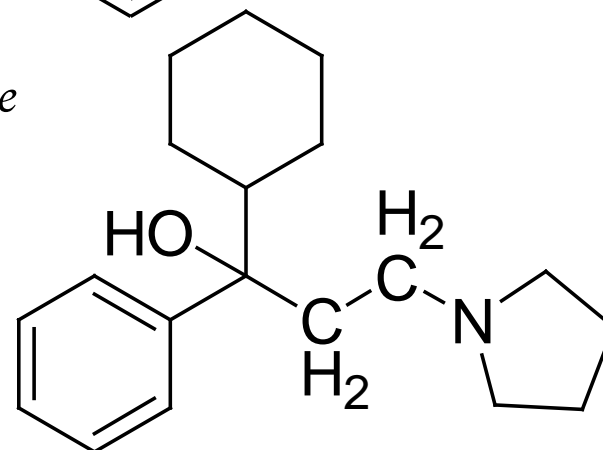
Scopolamine



benzotropine



trihexyphenidyl



procyclidin

Dopaminergic therapy

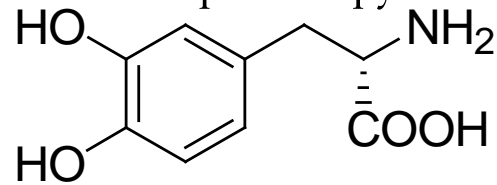
Dopaminergic therapy

- Several approaches are used to eliminate dopamine deficiency in striatum
 - Augmentation of brain synthesis of dopamine
 - Presynaptic dopamine release stimulation
 - Direct stimulation of dopamine receptor

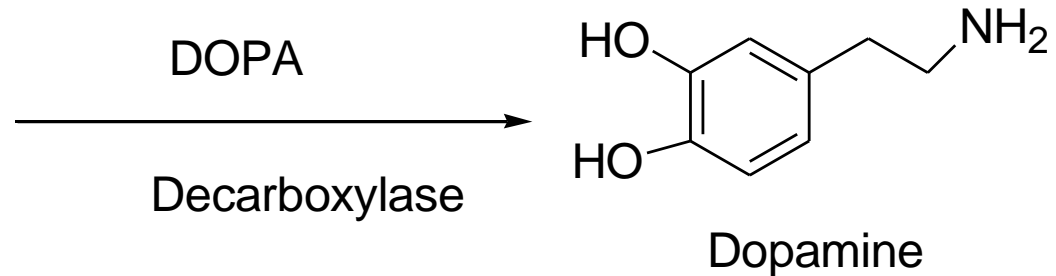
Dopaminergic ...

1. Augmentation of dopamine synthesis

- Levodopa therapy

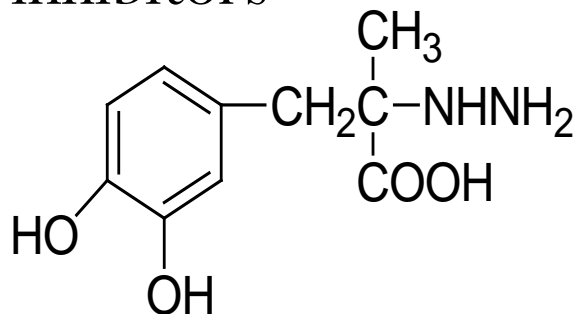


Levodopa

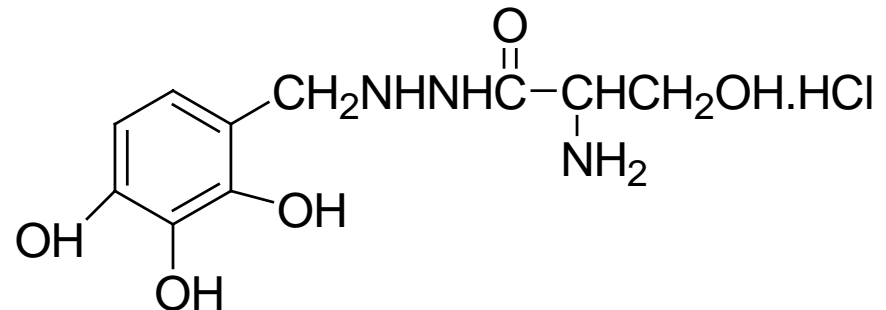


Dopamine

- Levodopa is co-administered with dopadecarboxylase inhibitors



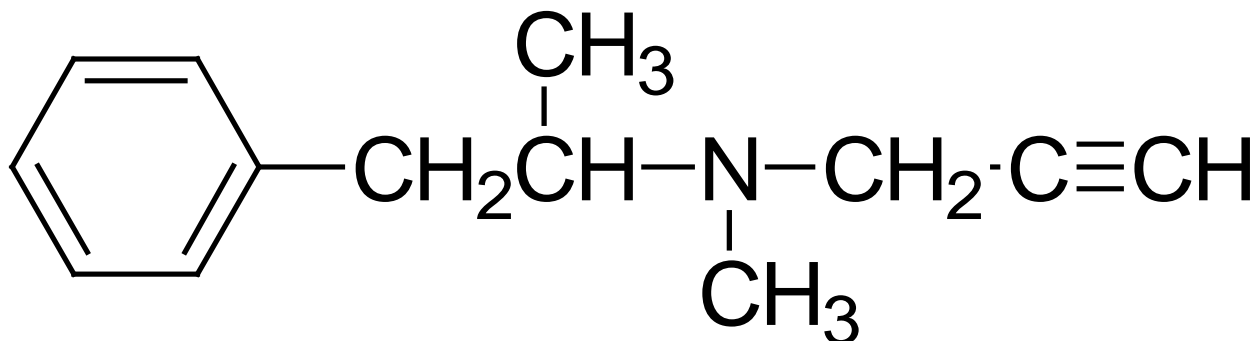
Carbidopa



Benserazide hydrochloride

Dopaminergic ...

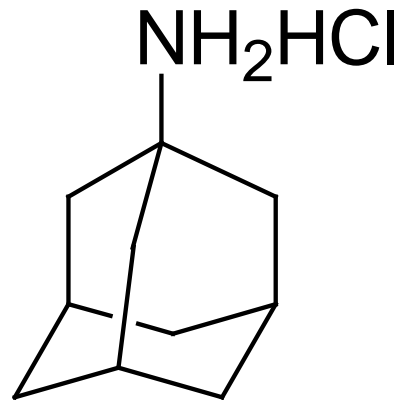
- Another means of increasing dopamine level is inhibition of MAO-B
- **Selegiline** is selective inhibitor of MAO type B and prevents breakdown of dopamine selectively



Dopaminergic ...

2. Stimulation of dopamine release

- Agents that release dopamine from neuronal storage can be used
- Amantidine is an example of such drug

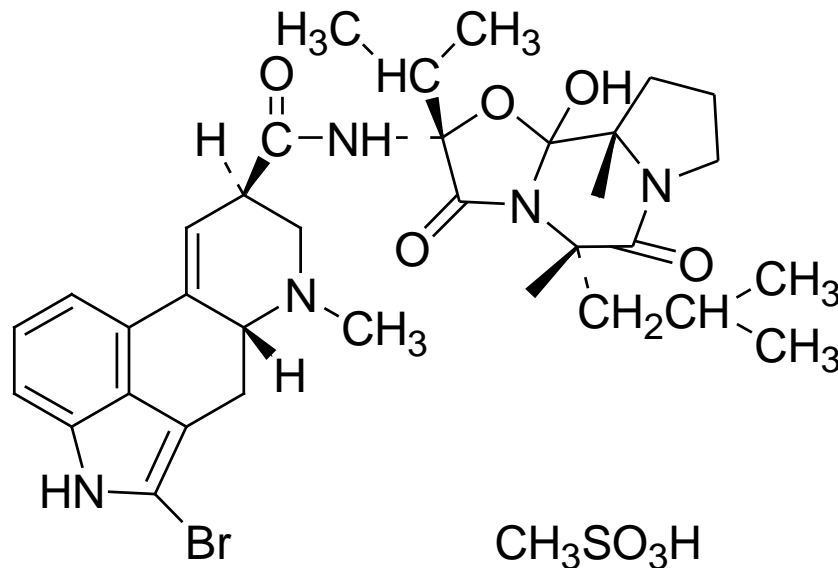


- Amantidine increase dopamine levels at postsynaptic receptor by decreasing presynaptic re-uptake and enhancing dopamine synthesis and release

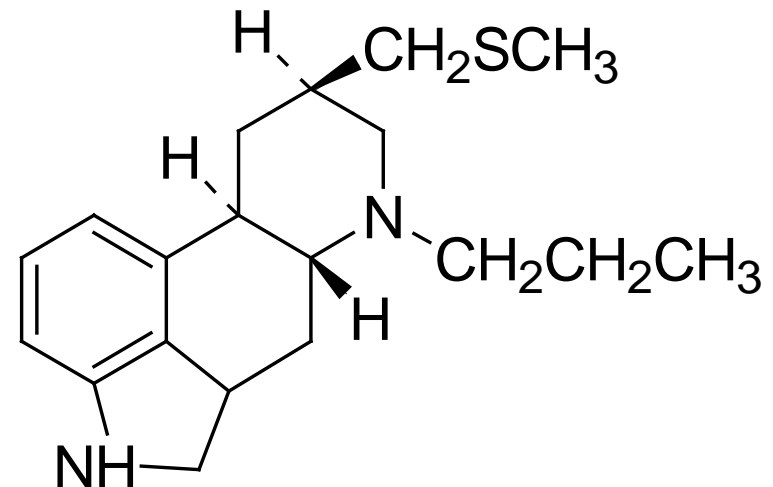
Dopaminergic ...

3. Direct Dopamine agonist

- Includes the ergot alkaloid derivatives **Bromocriptine** and **Pergolide**
- Dopamine agonists have the advantage in that their effect is independent of striato nigral degeneration



Bromocriptine



Pergolide

CNS Stimulants: Analeptics and Antidepressant agents

Analeptics

Analeptic - A CNS stimulant that causes muscle contraction and perhaps also convulsions. Particularly a term used to describe compounds that cause contraction and rigidity of the muscles of respiration. Strychnine is the most commonly recognized analeptic although it has relatively low potency.

Mechanisms of Action for CNS Stimulants:

1. Block neurotransmitter reuptake (Most reuptake inhibitors affect either NE or 5HT)
 - Tricyclic antidepressants
 - Cocaine
 - Selective Serotonin reuptake inhibitors
2. Promote Neurotransmitter Release
 - Phenylethylamines and related compounds. Amphetamine, Methylphenidate.
3. Block Metabolism - MAO inhibitors

Non-Therapeutic CNS stimulants (all seizure inducers)

Strychnine - Inhibits glycine receptors

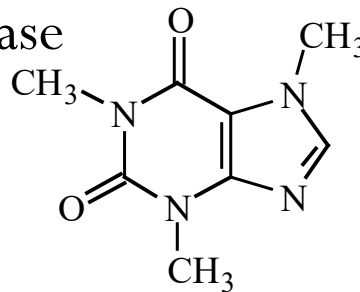
Picrotoxin - Acts on the chloride ion channel associated with GABA receptors.

Bemigrade - Barbiturate Antagonist

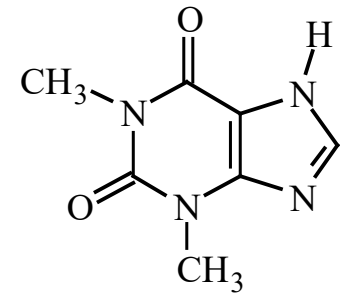
Xanthines (Caffeine, Theophylline, Theobromine)

Mechanism(s) of action:

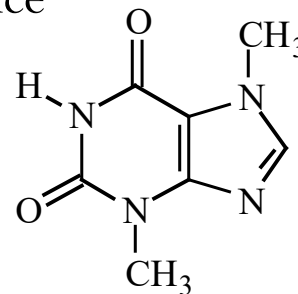
- Inhibition of cAMP phosphodiesterase
- Promote NE release
- Promote intracellular Ca^{+2} release



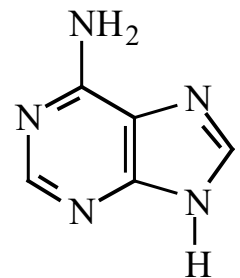
Caffeine



Theophylline



Theobromine



Adenine

The order of potency for CNS activity is
Caffeine > Theophylline > Theobromine

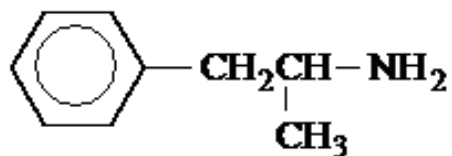
Theophylline is an important drug for maintenance
treatment of asthma,
but has some side effects as you might expect.

Phenylethylamines

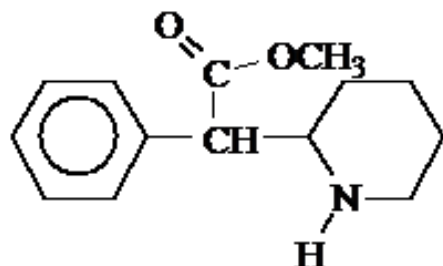
- Enhance neurotransmitter release
 - Block NT reuptake
 - Have direct agonist effects
 - MAO inhibition
-
- Phenylethylamines are used as anorectics, for narcolepsy, and ADHD but not legitimate antidepressants.
 - The phenyl ring and the distance between the amine and the phenyl is fairly strict

- For the phenidates, the SAR of methyl phenidate is optimal.
- Changes that affect the rate of methyl ester hydrolysis affect duration and potency.
- With the exception of **anorexia**, many of the CNS effect of phenylethylamines are thought to involve effects on **dopamine** release and reuptake.
- **“Amphetamine induces dopamine efflux through a dopamine transporter channel”**

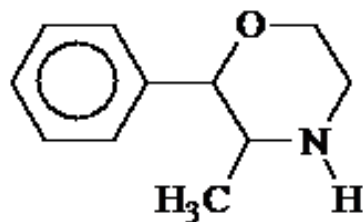
Amphetamine Structures



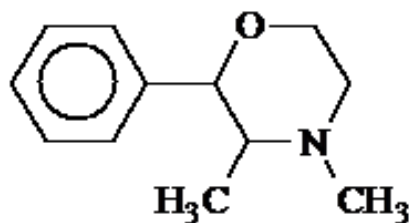
Amphetamine
Prototype phenylethylamine.



Methylphenidate
(Ritalin)
Used for attention-deficit-hyperactive disorder
Usually in children

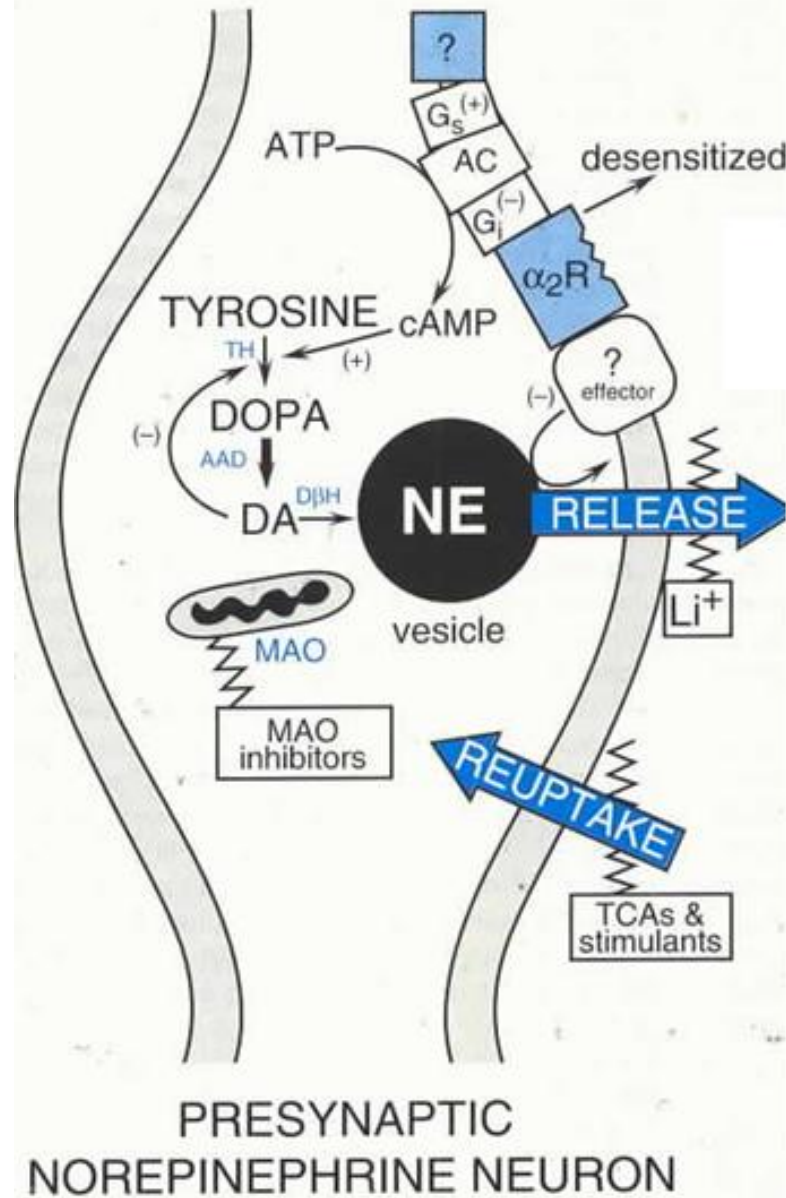


Phenmetrazine
(Preludin)
Anorectic

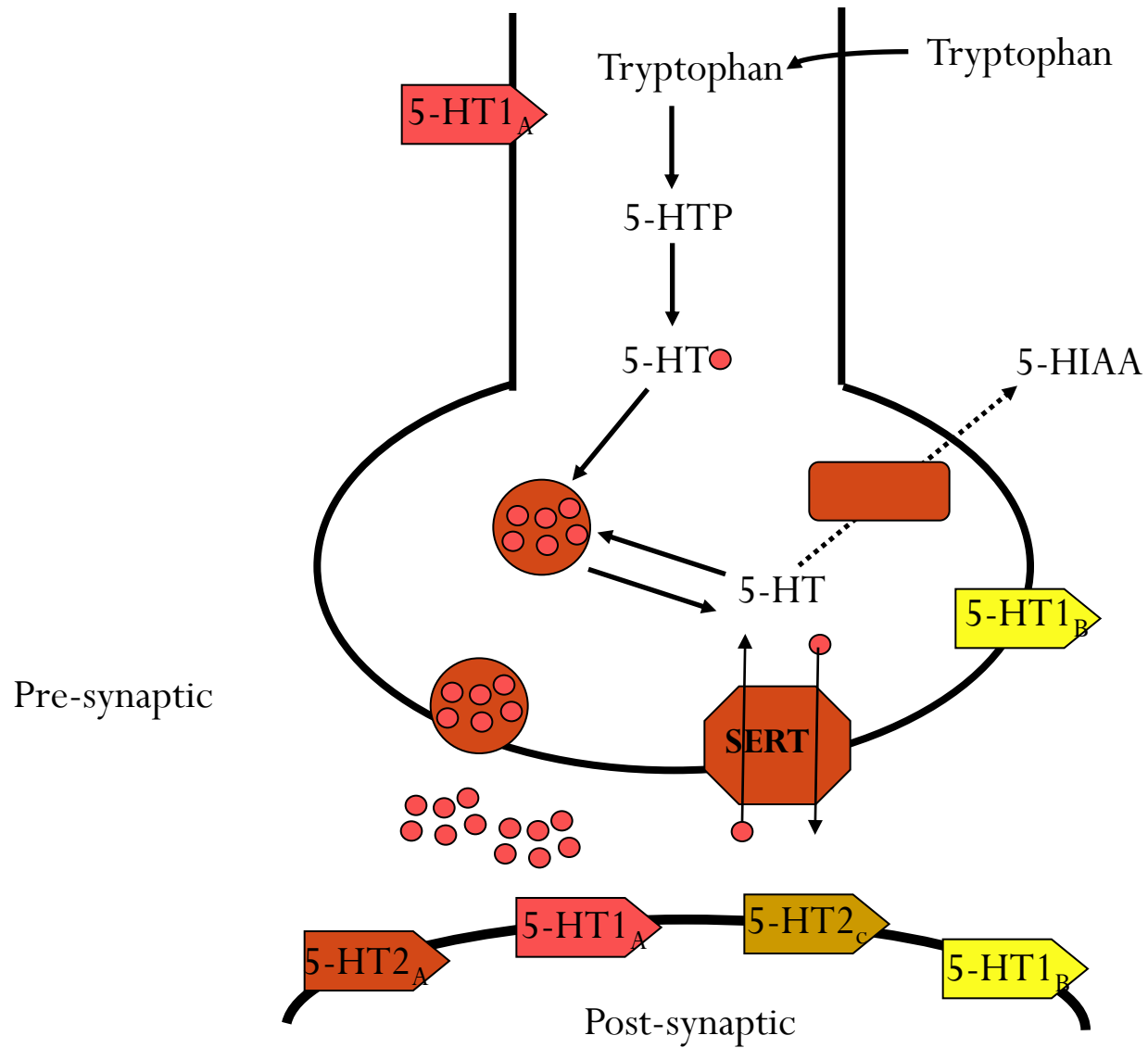


Phendimetrazine (Plegine)
Anorectic

Neuronal Synapse - NE Mechanism

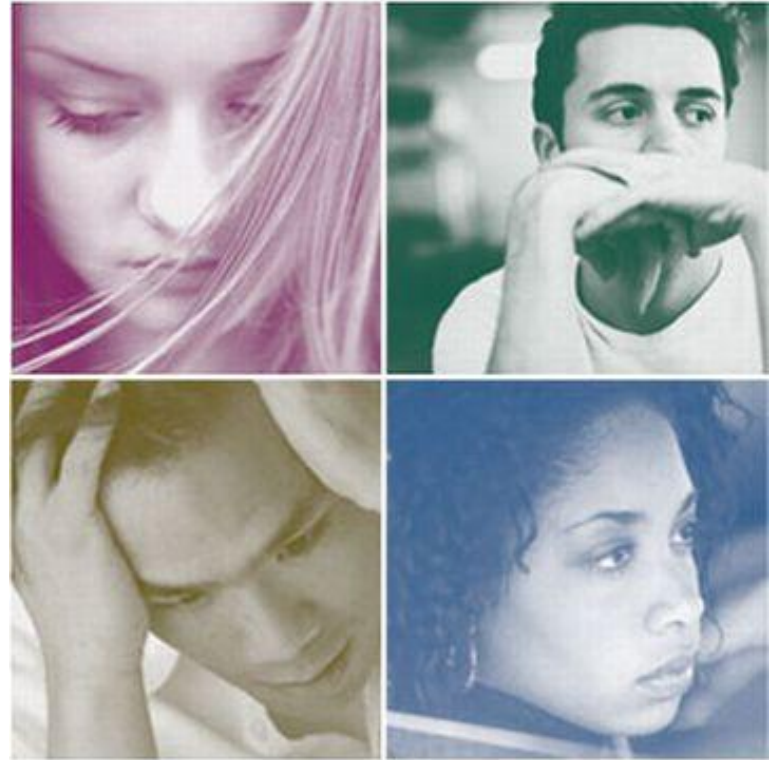


Neuronal Synapse - 5HT



Anti-depressants

- What is depression?
 - Types
 - Symptoms and Diagnosis
 - Biological Mechanism
- Antidepressants
 - History
 - Types (TCAs, MAOIs, SSRIs)
 - Mechanism of action
 - Side effects
 - Brain chemistry in the long-term



What is depression?



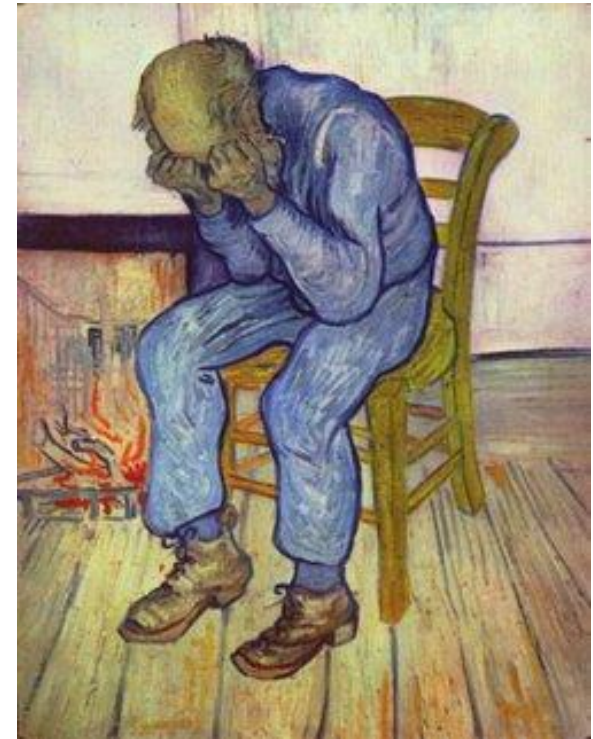
- Neurological disorder
- Prolonged depression of mood and impairment of function
- Causes include genetic predisposition, grief following the death of a loved one, abuse, major life changes, serious illness, personal disputes, and substance abuse
- Complex illness with many contributing factors
- Exact biological causes are not yet fully understood

Types

- Major
 - Symptoms interfere with ability to function normally
 - 10% of people in the US suffer at any one time
 - 2x more women are diagnosed than men
- Chronic (Dysthymia)
 - Less severe, but symptoms linger for longer
- Seasonal Affective Disorder (SAD)
- Psychotic
- Postpartum

Diagnosis and Symptoms

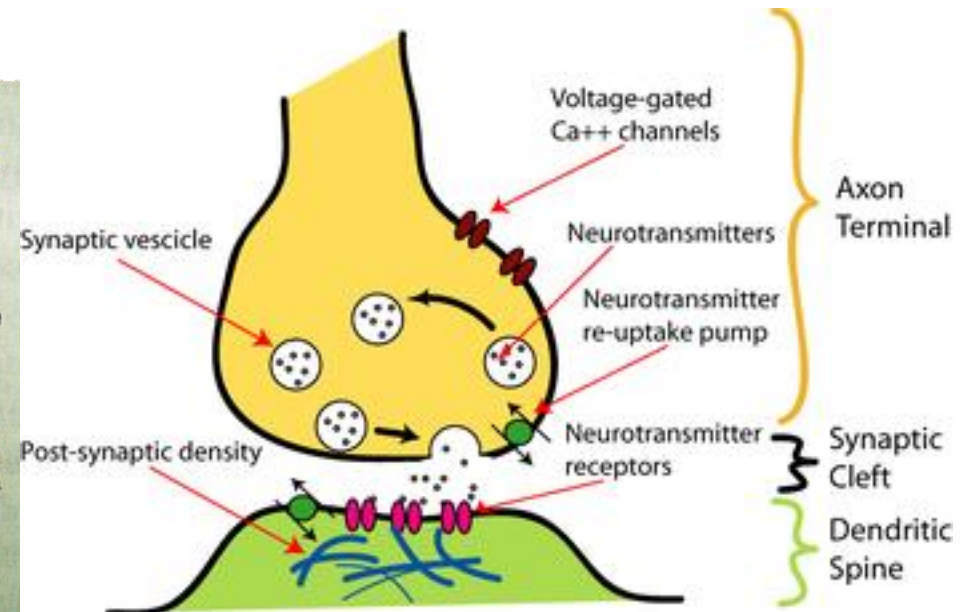
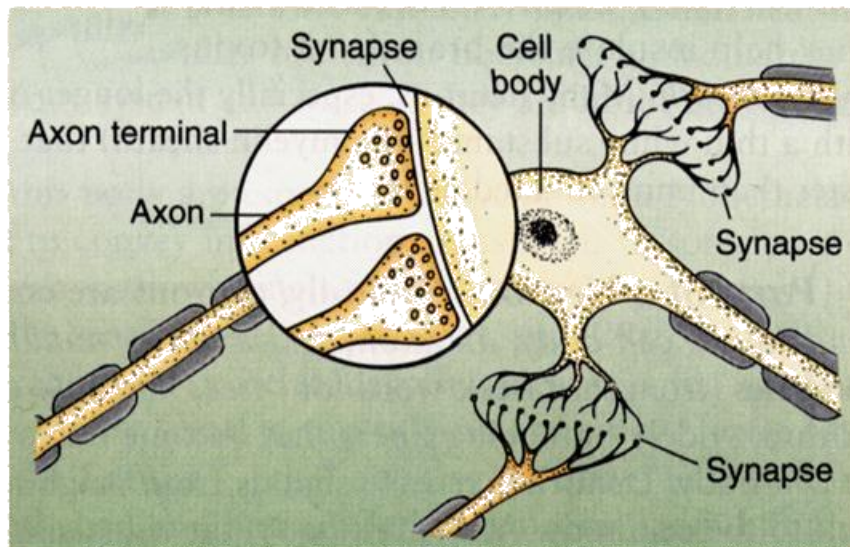
- Symptoms include:
 - Intense sadness or despair
 - Loss of concentration
 - Worry
 - Lack of pleasure
 - Self-deprecation
 - Agitation or hostility
 - Disruption in sleep patterns
 - Altered eating patterns
 - Lack of energy
 - Thoughts of suicide
 - Anxiety
 - Digestive problems



The neurochemistry of depression

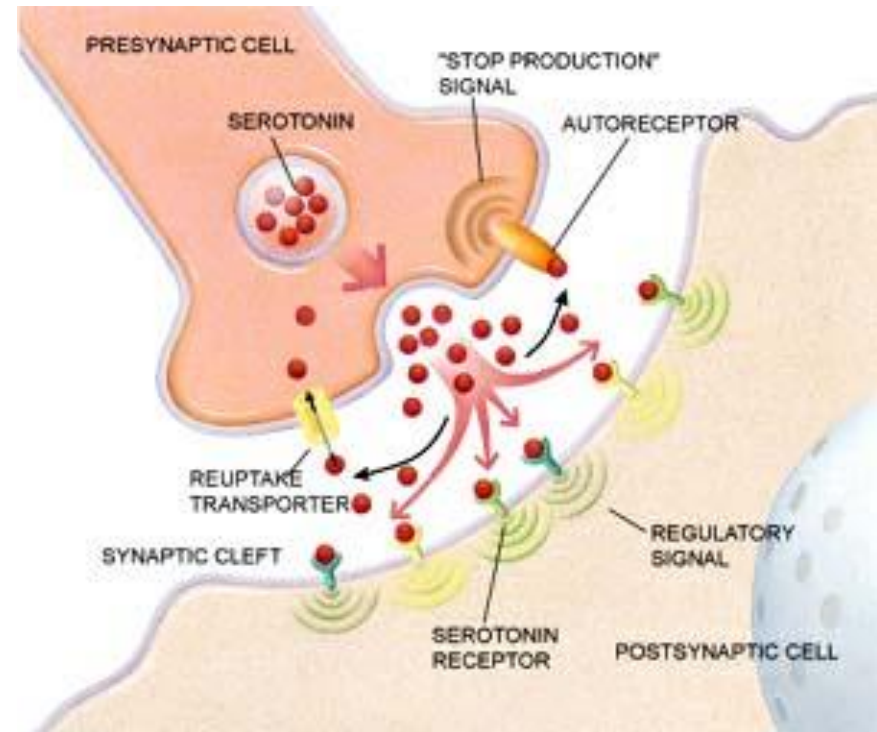
- Attributed to a deficiency in neurotransmitter transmission in the CNS
- Successful antidepressants affect a combo of NE, 5-HT, and histamine reuptake, but do only weakly act on DA

The Synapse



The serotonin transporter (SERT)

- Positioned periplanar to the pre-synaptic axon terminal
- Role- move serotonin back into the pre-synaptic cell for future use
- Opposite activity of the serotonin receptors that are positioned post-synaptically
- Fundamental in a biochemical understanding of depression



<http://www.psycheducation.org/mechanism/4WhyShortsLongs.htm>

The Antidepressants

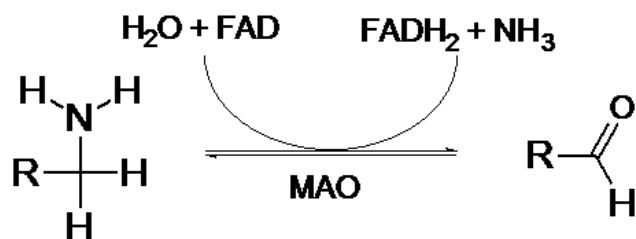
- MAOIs
 - Oldest antidepressant class that was discovered in 1952 with the use of iproniazid
- TCAs
- SSRIs (1970s)
 - Clinical benefits are delayed for 2-3 weeks

Alternative therapies

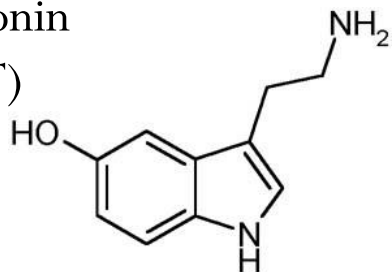
- Electroconvulsive Therapy (ECT)
 - Seizure induced using an electric current passed through the brain
- Exercise
- Counseling
- Lithium- commonly coupled with other treatments
- Natural Supplements
 - St. John's Wort

Monoamine Oxidase Inhibitors (MAOI)

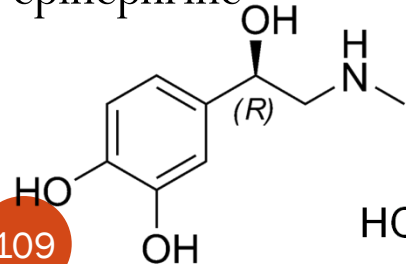
- MAO's degrade amines in the nervous system
 - MAO-A deaminates serotonin, norepinephrine, and epinephrine
 - MAO-B degrades phenethylamine
- A and B types both degrade dopamine and tyramine



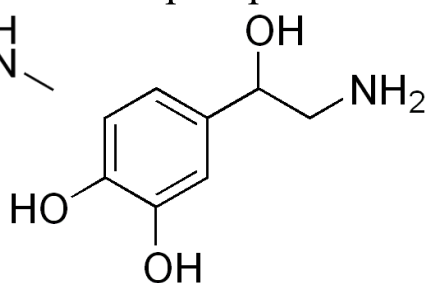
Serotonin
(5-HT)



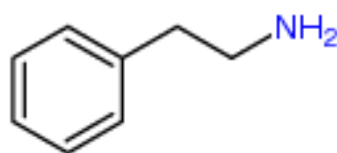
epinephrine



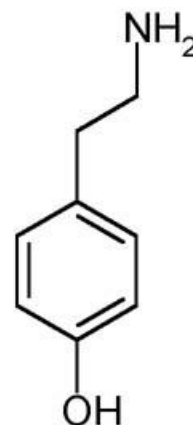
norepinephrine



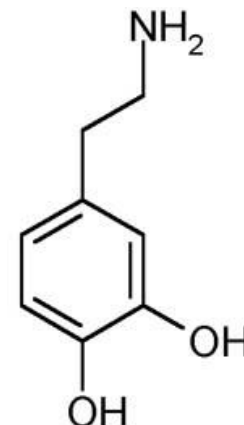
phenethylamine



tyramine



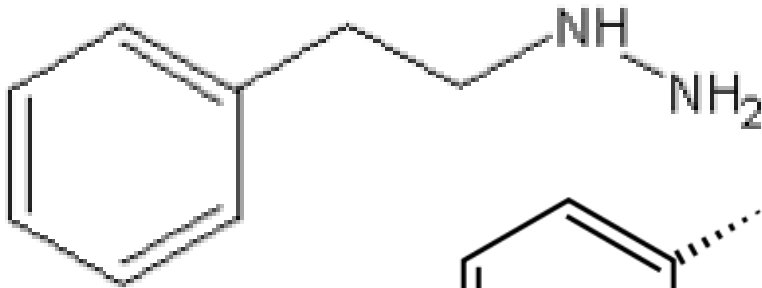
dopamine



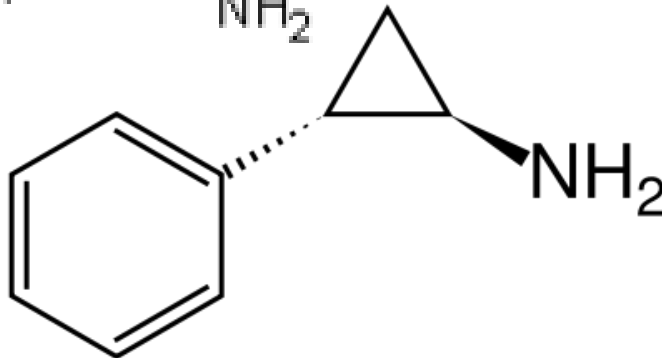
MAOI's continued...

- Thus, MAOI's cause an increase in the biogenic amine concentration
 - MAOI-A = clorgyline
 - MAOI-B = selegiline (approved for treatment of Parkinson's)
 - Nonselective MAOI = phenelzine, tranylcypromine, isocarboxazid
 - MAOI-A's are thought to be more effective in treating major depression

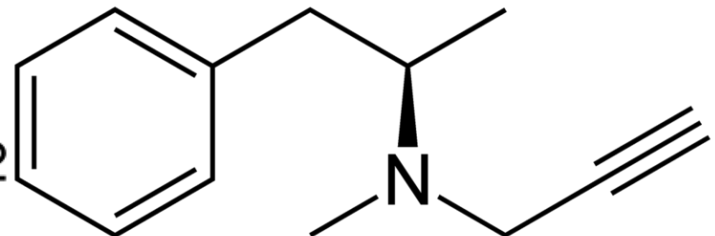
Phenelzine
(NARDIL)



Tranylcypromine
(PARNATE)

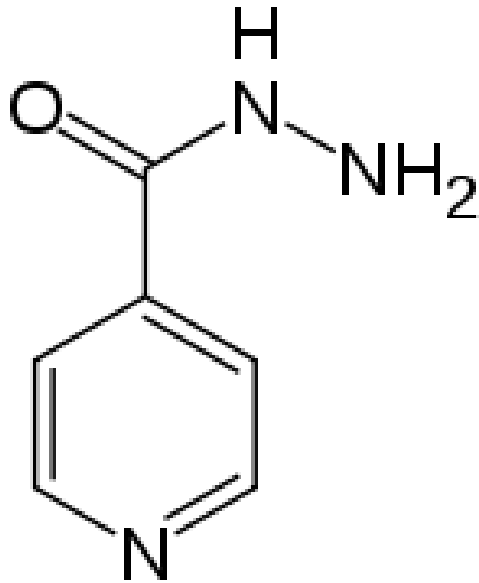


Selegiline
(ELDEPRYL)

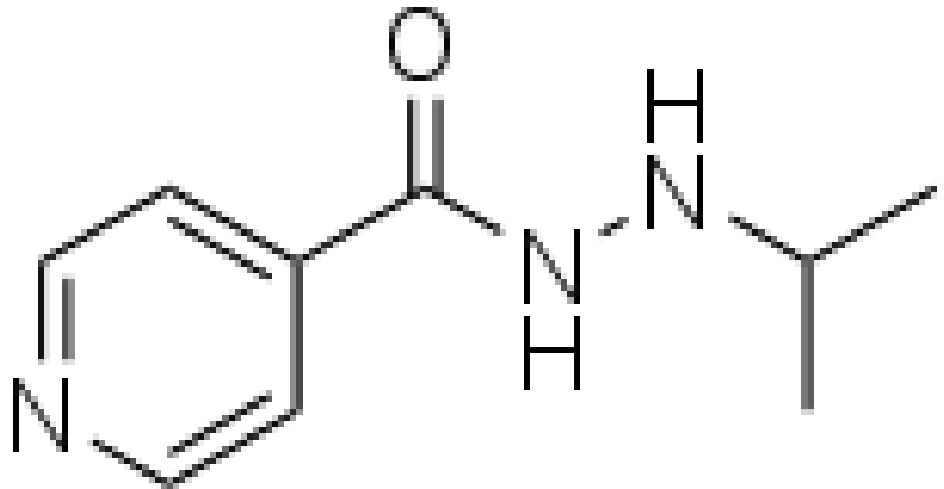


MONOAMINE OXIDASE INHIBITORS (MAOIS)

- Iproniazid was resulted by isopropyl substitution of Isoniazid
 - Iproniazid inhibits MAO



Isoniazid



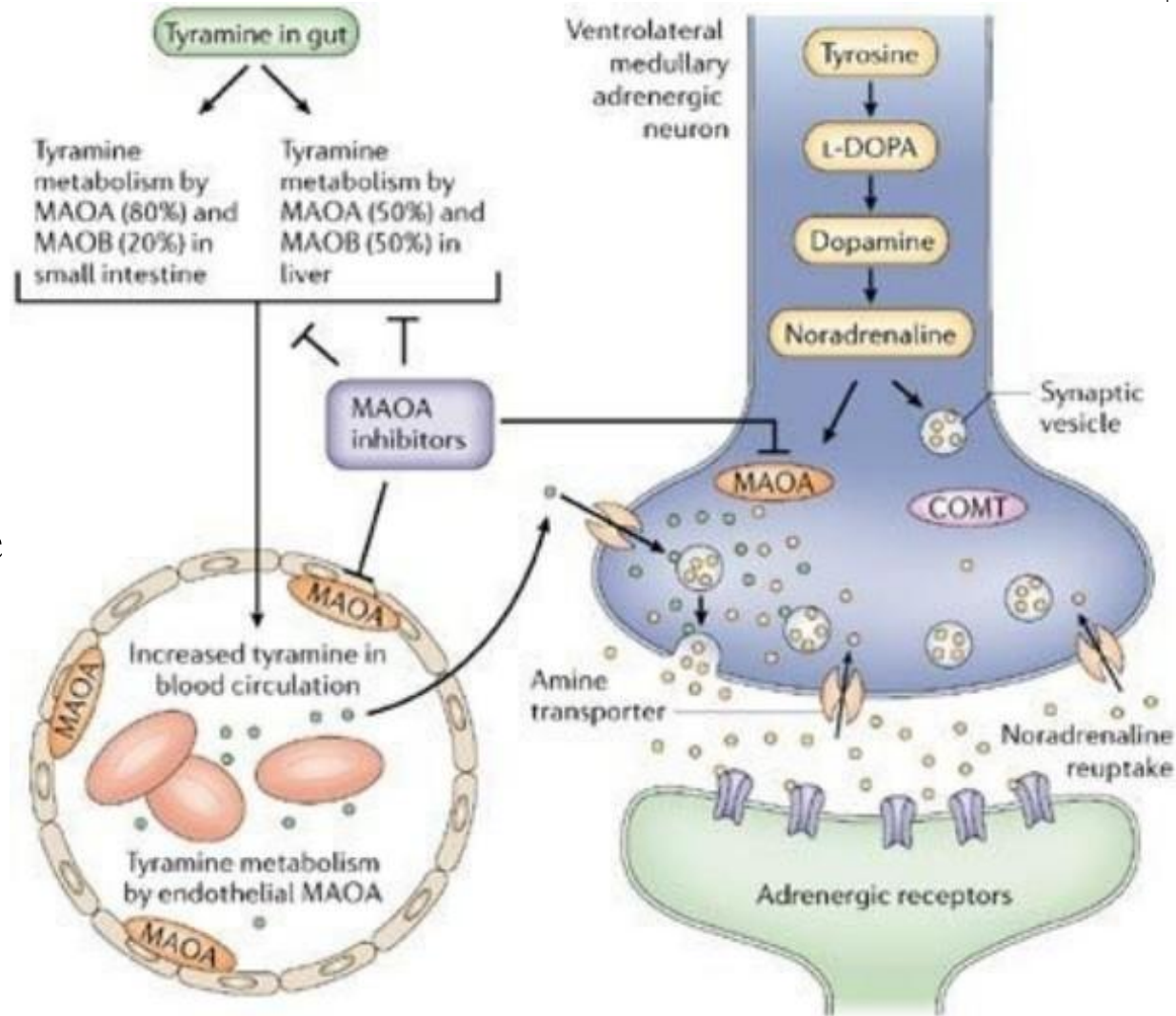
Iproniazid

MAOI ON THE MARKET

- MAO Inhibitors (nonselective)
 - Phenelzine (Nardil)
 - Tranylcypromine (Parnate)
 - Isocarboxazid (Marplan)
- MAO-B Inhibitors (selective for MAO-B)
 - Selegiline (Emsam)

MAOI MOA

- MAO contains a cysteinyl-linked flavin
- MAOIs covalently bind to N-5 of the flavin residue of the enzyme



MAOI SIDE EFFECTS

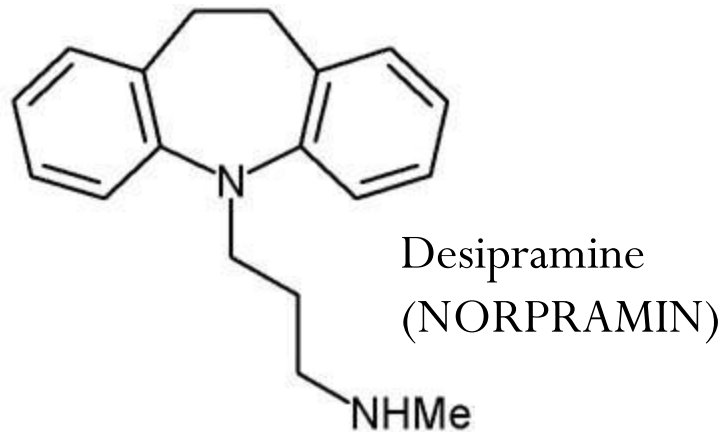
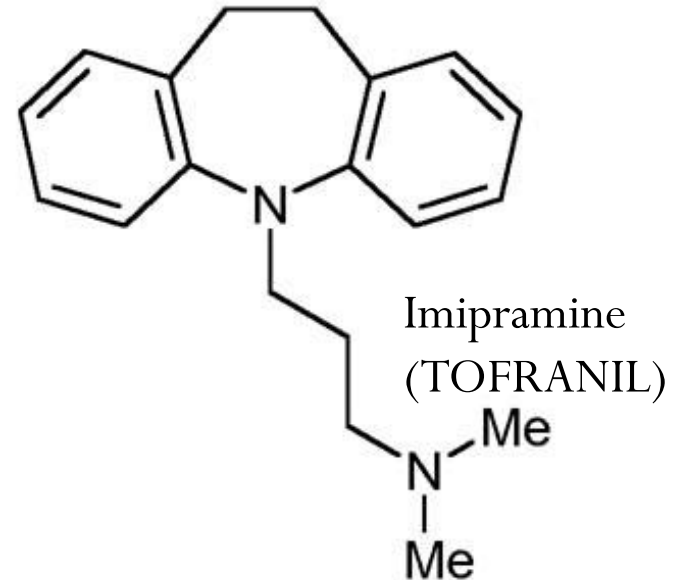
- **Drowsiness/Fatigue**
- Constipation
- Nausea
- Diarrhea
- Dizziness
- **Low blood pressure**
- Lightheadedness,
- Decreased urine output
- **Decreased sexual function**
- Sleep disturbances
- Muscle twitching
- **Weight gain**
- Blurred vision
- Headache
- Increased appetite
- Restlessness
- Shakiness
- Weakness
- Increased sweating

MAOI SIDE EFFECTS

- Side effects have put MAOIs in the second or third line of defense despite superior efficacy
- MAO-A inhibitors interfere with breakdown of tyramine
 - High tyramine levels cause hypertensive crisis (the “cheese effect”)
 - Can be controlled with restricted diet
- MAOIs interact with certain drugs
 - Serotonin syndrome (muscle rigidity, fever, seizures)
 - Pain medications (like tramadol and meperidine) and SSRIs must be avoided

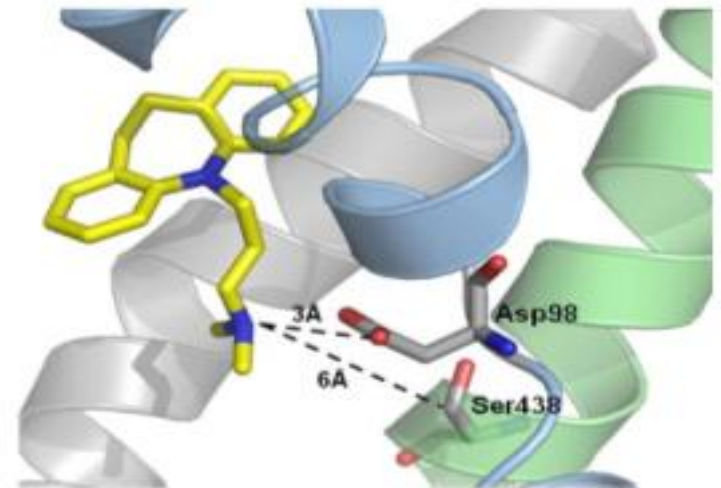
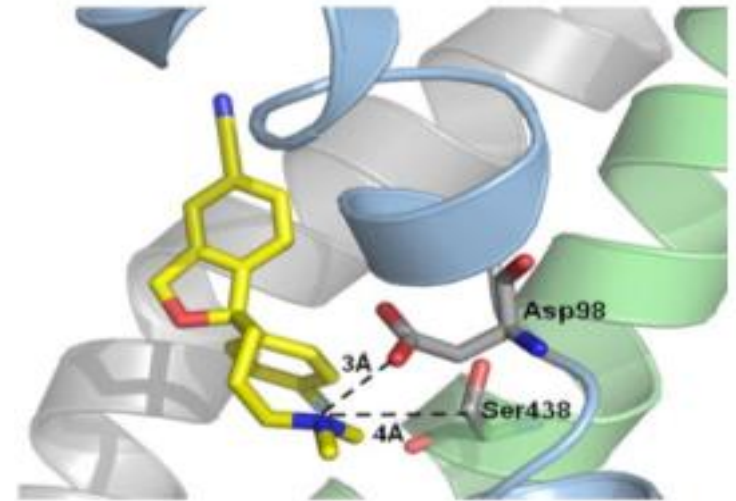
Tricyclic Antidepressants (TCA's)

- Imipramine discovered in 1958
 - Other TCA's are simply modifications of imipramine
- Work by inhibiting NE transport and variably inhibiting 5-HT transport



TCA MECHANISM OF ACTION

- TCAs inhibit serotonin, norepinephrine, and dopamine transporters, slowing reuptake
- All TCAs and SSRIs contain an essential amino group that appears to interact with Asp-98 in hSERT

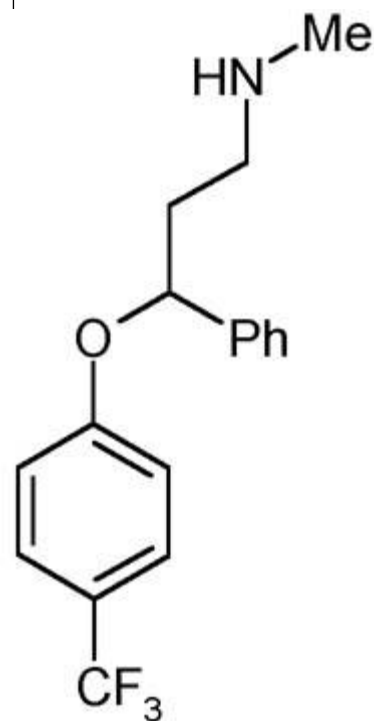


TCA SIDE EFFECTS

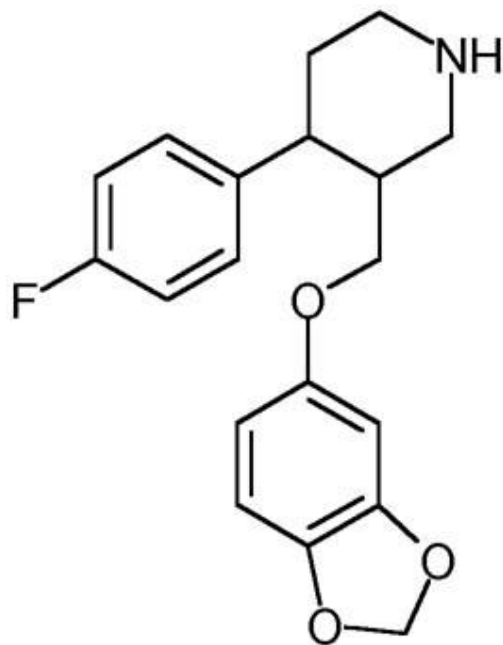
- Muscarinic M1 receptor antagonism - anticholinergic effects including dry mouth, blurred vision, constipation, urinary retention and impotence
- Histamine H1 receptor antagonism - sedation and weight gain
- Adrenergic α receptor antagonism - **postural hypotension**
- Direct membrane effects - reduced seizure threshold, arrhythmia
- Serotonin 5-HT₂ receptor antagonism - weight gain (and reduced anxiety)
- High potency can lead to mania
 - Contraindicated with persons with bipolar disorder or manic depression

Selective Serotonin Reuptake Inhibitors

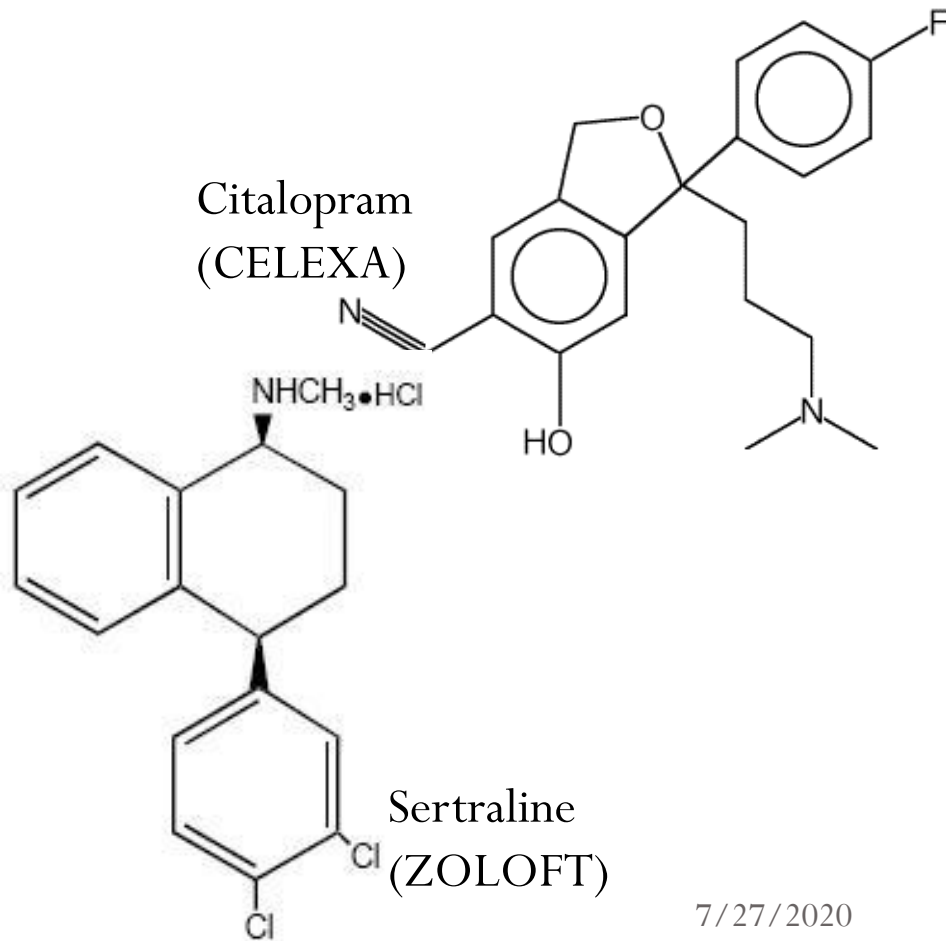
- Most prescribed type due to ↓ toxicity
- Treatment of choice for OCD



Fluoxetine
(PROZAC)



Paroxetine
(PAXIL)

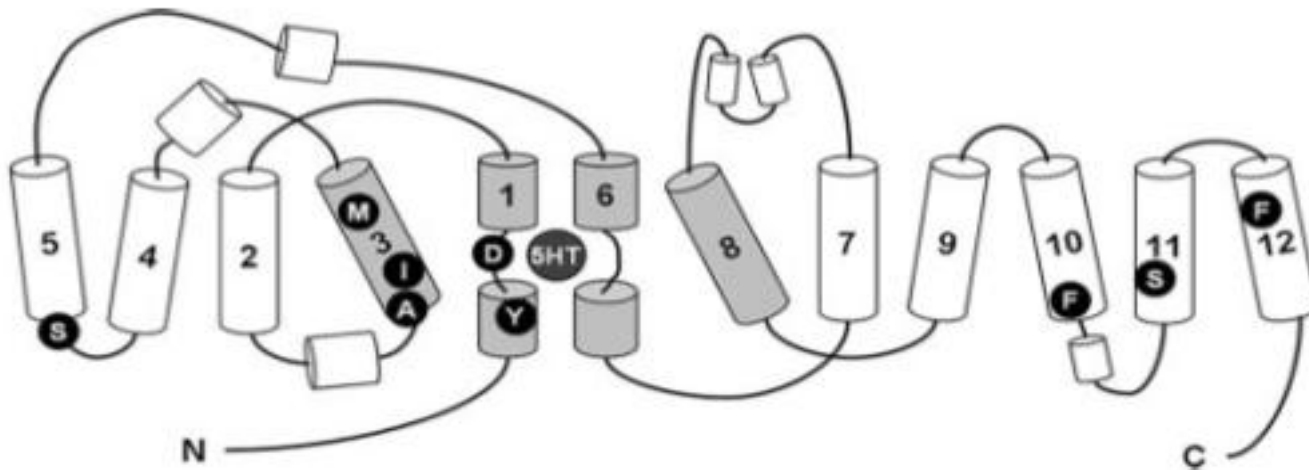


Citalopram
(CELEXA)

Sertraline
(ZOLOFT)

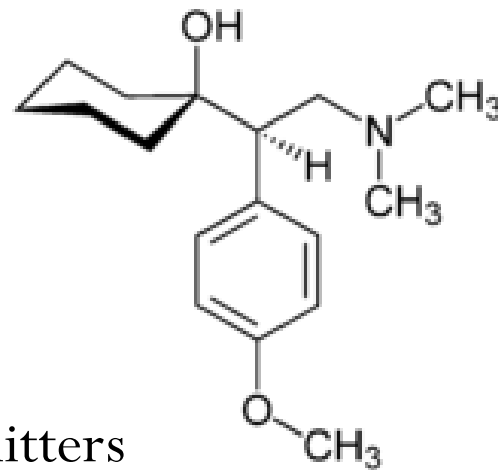
SSRIS MECHANISM OF ACTION

- Exact mechanism remains uncertain
- Ser-438 residue in the human serotonin transporter (hSERT) appears to be a determining factor in SSRI potency
- Antidepressants interact directly with **hSERT**

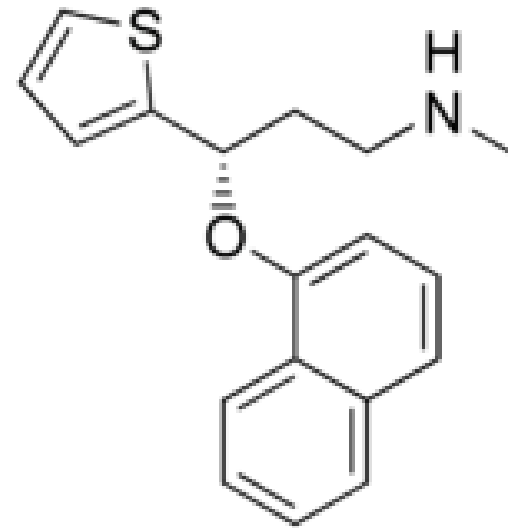


SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)

- Slightly greater efficacy than SSRIs
- Slightly fewer adverse effects than SSRIs
- Current drugs
 - Venlafaxine (Effexor)
 - Duloxetine (Cymbalta)
- Mechanism of Action
 - Very similar to SSRIs
 - Works on both neurotransmitters
- Side effects
 - Similar to SSRIs
 - Suicide



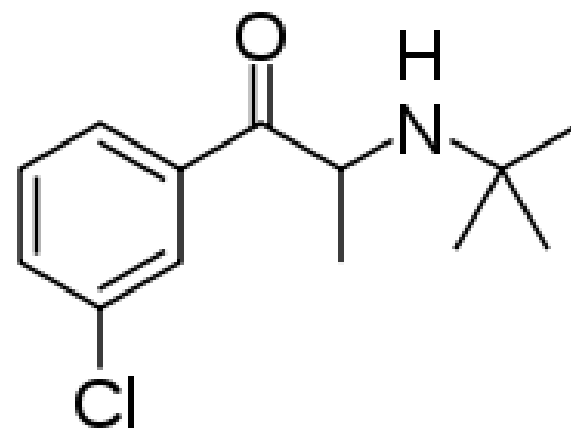
Venlafaxine



Duloxetine

NOREPINEPHRINE-DOPAMINE REUPTAKE INHIBITORS (NDRIS)

- Current drugs
 - Bupropion (Wellbutrin)
- Mechanisms of Action
 - Similar to SSRIs and SNRIs
 - More potent in inhibiting dopamine
- Adverse effects
 - Lowers seizure threshold
 - Suicide
 - Does not cause weight gain or sexual dysfunction (even used to treat the two)



Bupropion

Side effects

TCA's and MAOI's

- Generally, not prescribed unless patient does not respond to newer drugs
- Cardiotoxic at high doses
 - Lipophilic, strongly bind to tissues, affinity for cardiac
 - Many cardiac side effects!
- Dry mouth
- Constipation
- Dizziness
- Blurred vision
- Urinary retention

SSRI's and newer antidepressants

- Fewer side effects, less toxic
- Nausea/vomiting
- Headache
- Sexual dysfunction

Narcotic Analgesics

Introduction

- The term 'opium alkaloids' has been used to cover all narcotic analgesics, whether they are synthetic compounds, partially synthetic, or extracted from plant material.
- Extracted from opium—the sticky exudate obtained from the poppy (*Papaver somniferum*)

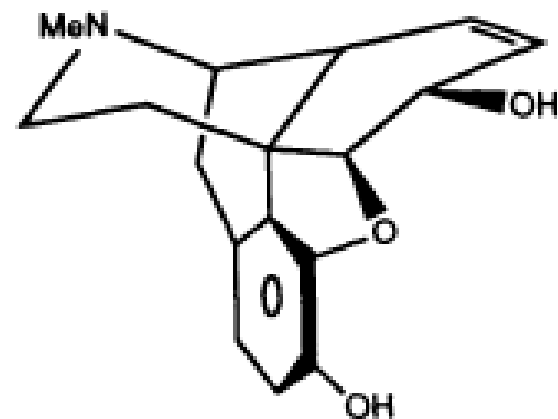
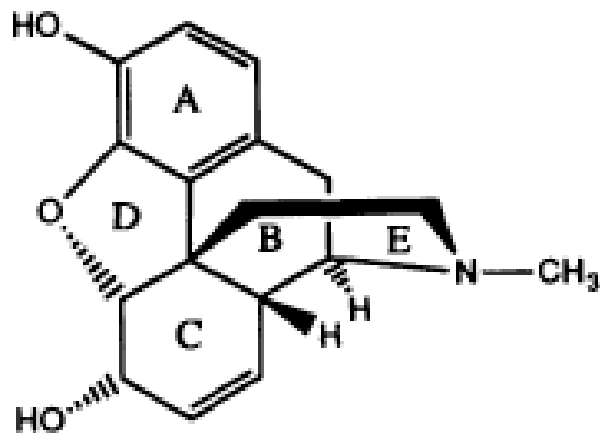
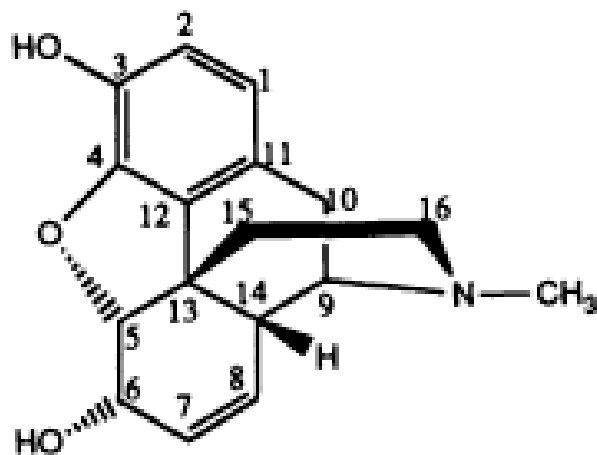


Introduction...

- The opiates are perhaps the oldest drugs known to man.
 - The use of opium was recorded in China over two thousand years ago and was known in Mesopotamia before that.
- Opium contains a complex mixture of almost **twenty-five** alkaloids.
 - The principal alkaloid in the mixture, and the one responsible for analgesic activity, is **morphine**, named after the Roman god of sleep—Morpheus.
 - Morphine was isolated commercially in 1833 and its structure was elucidated in 1925
 - It was fully synthesized in 1952

Morphine

- Structure and properties



- Morphine is still one of the most effective painkillers available to medicine.
- It is especially good for treating dull, constant pain rather than sharp, periodic pain.

Morphine...

- Unfortunately, it has a large number of side-effects which include the following:
 - **depression of the respiratory centre**
 - constipation
 - excitation
 - **euphoria**
 - nausea
 - pupil constriction
 - **tolerance**
 - **dependence**

Structure-activity relationships

- The molecule contains five rings labelled A-E and has a distinct **T shape**.
- It is basic because of the tertiary amino group, but it also contains a phenolic group, an alcohol group, an aromatic ring, an ether bridge, and a double bond.

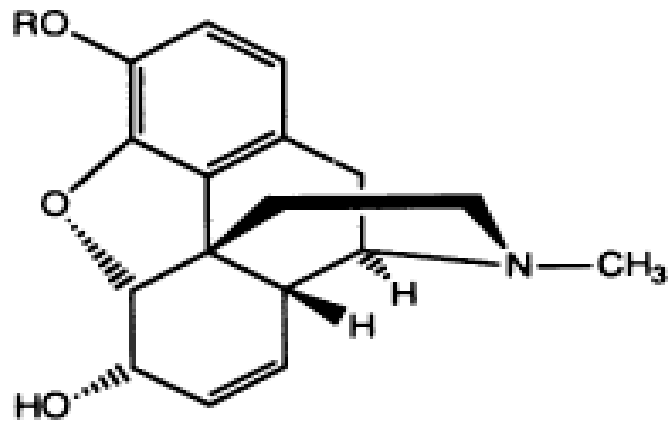
SAR...

i. Changes which do not affect the basic skeleton of the molecule

The phenolic OH

- By methylating the phenolic OH, the analgesic activity drops drastically and codeine is only 0.1 per cent as active as morphine.
- This drop in activity is observed in other analogues containing a masked phenolic group.
- Clearly, a free phenolic group is crucial for analgesic activity.

SAR...



R = Me
R = Et
R = Acetyl

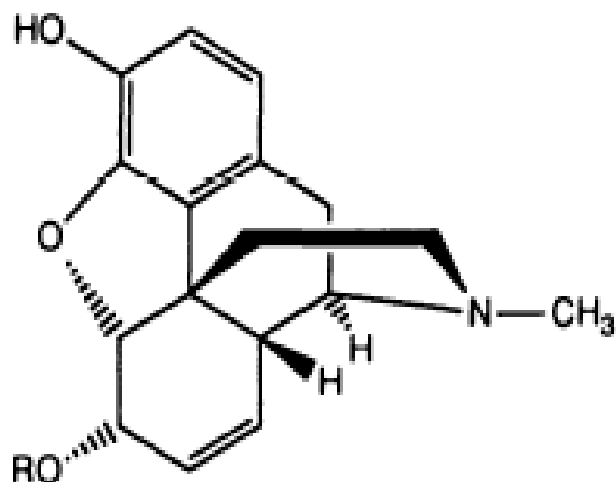
CODEINE
ETHYLMORPHINE
3-ACETYLMORPHINE

} Analgesic
Activity ↓

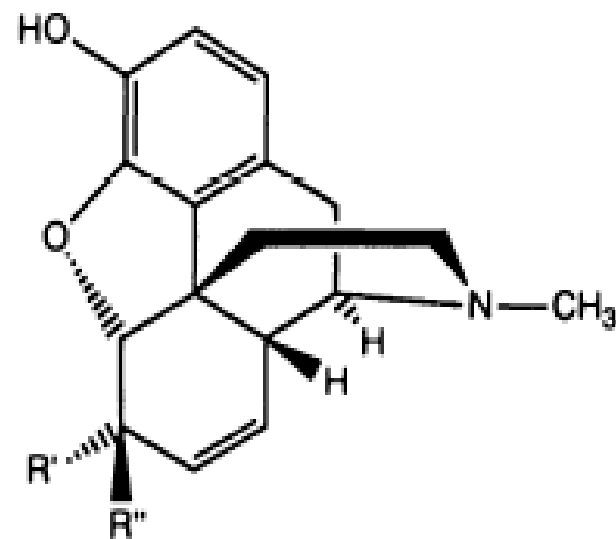
- Codeine a pro drug for morphine, it is metabolized *in-vivo* to morphine when it is given orally

SAR...

- The 6-alcohol



R		Analgesia wrt morphine
Me	Heterocodeine	5x
Et	6-Ethylmorphine	greater
Acetyl	6-Acetylmorphine	4x



R'	R''	Analgesia wrt morphine
H	OH	Increased or similar
H	H	
Ketone	Ketone	

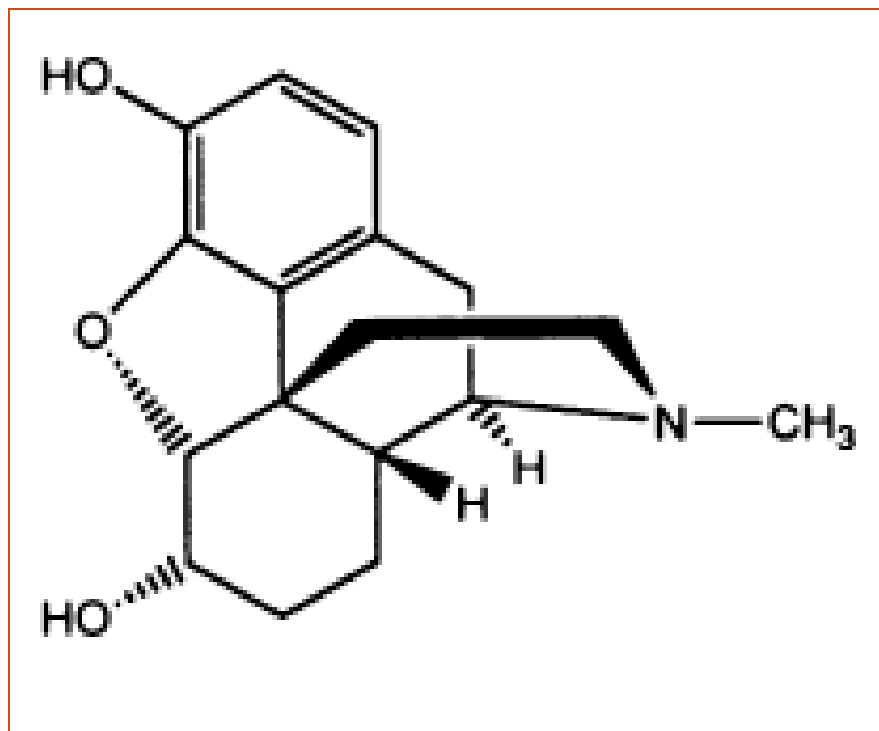
SAR...

- General observation;
 - Masking or the complete loss of the alcohol group does not decrease analgesic activity and, in fact, often has the opposite effect.
 - Improvement in activity is due to the pharmacokinetic properties of these drugs rather than their affinity for the analgesic receptor.
 - In other words it increase the amount of the drug that will reach to the CNS
 - Example compare the activities of morphine, heroine and 6 acetyl morphine.

SAR...

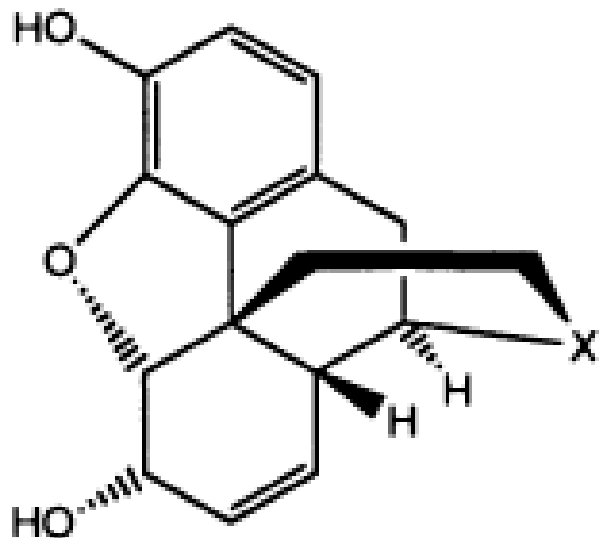
The double bond at 7-8

- Several analogues including **dihydromorphine** (below) have shown that the double bond is not necessary for analgesic activity.



SAR...

The N-methyl group



X		Analgesic Activity wrt morphine
NH	Normorphine	25%
	N-Oxide	0%
	Quaternary salt	0%

- The methyl group is not must but the nitrogen should be there and it must be un-ionized.

SAR...

The aromatic ring

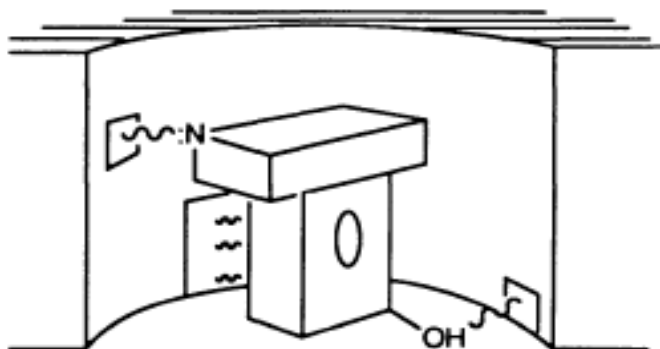
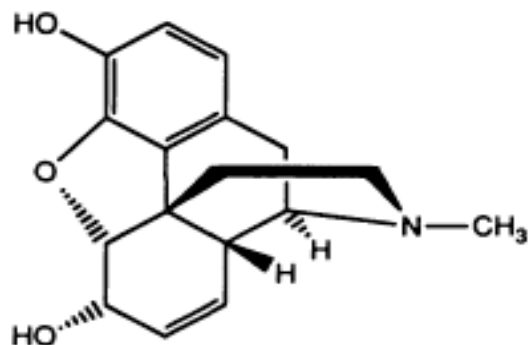
- The aromatic ring is essential. Compounds lacking it show no analgesic activity.

The ether bridge

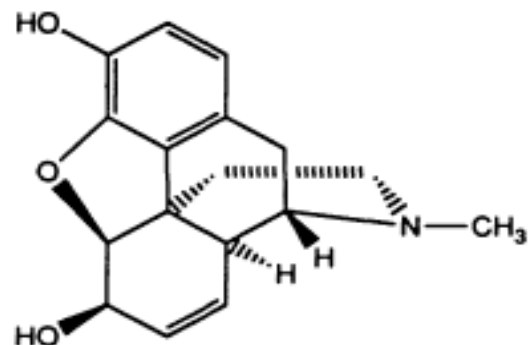
- The ether bridge is not required for analgesic activity.

SAR...

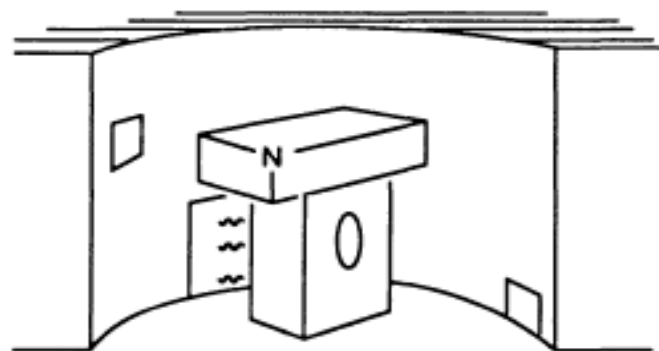
- Stereochemistry



3 receptor interactions



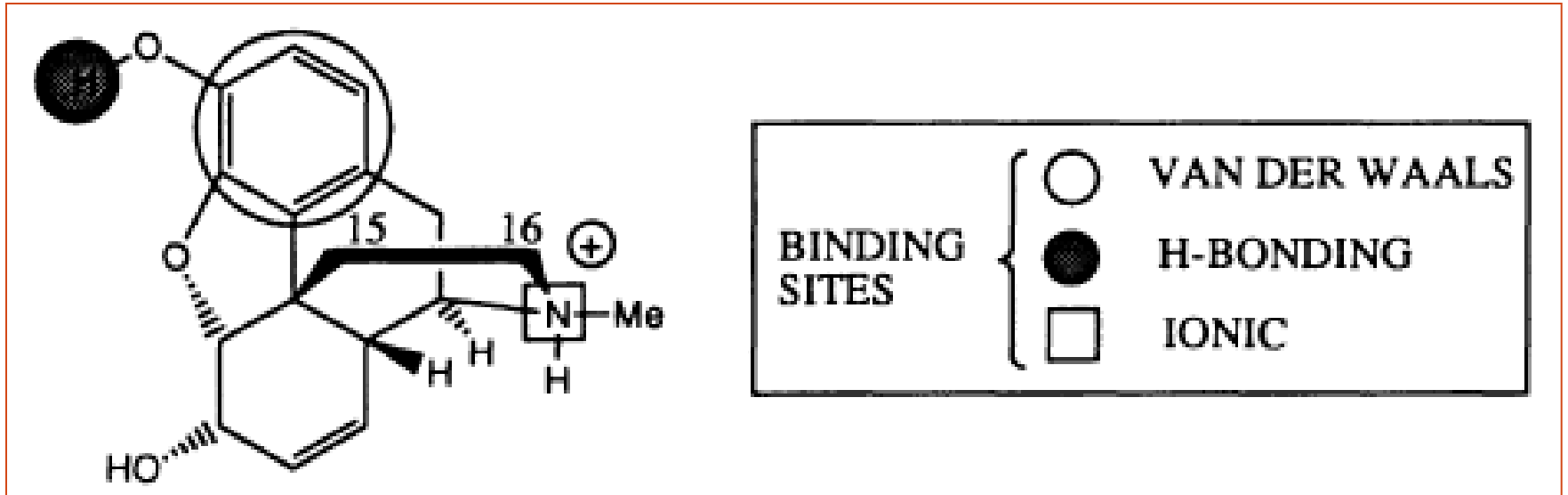
'Unnatural' Morphine (the mirror image)
No analgesic activity.



1 receptor interaction
(OH hidden in diagram) 7/27/2020

SAR...

- To sum up, the important functional groups for analgesic activity in morphine are shown below



Development of morphine analogues

- **Strategies in the development of morphine analogues**
 - Variation of substituents
 - Drug extension
 - Simplification
 - Rigidification

Development of...

A. Variation of substituents

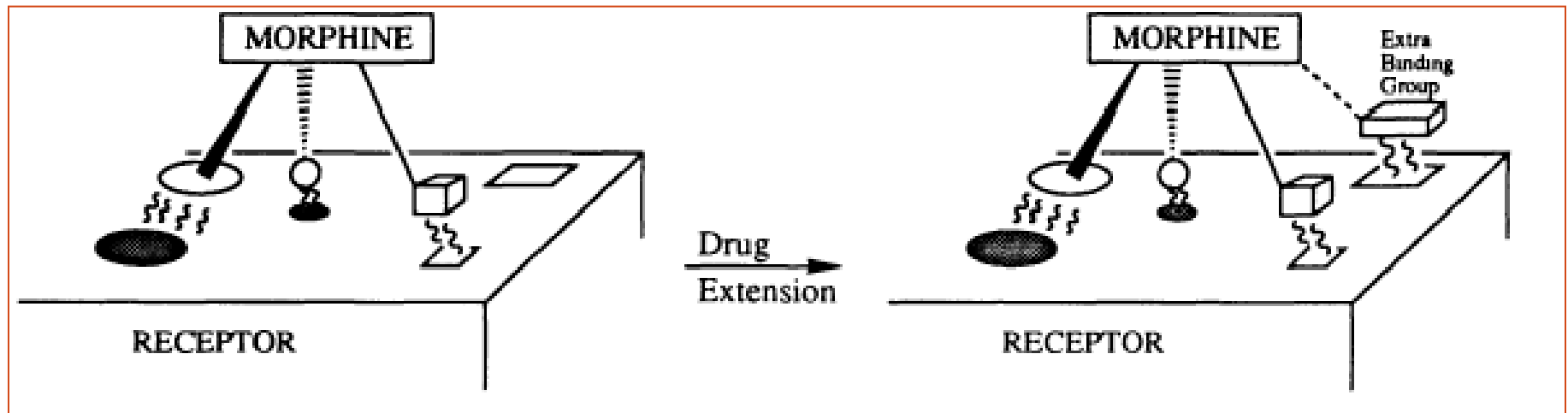
- A series of alkyl chains on the phenolic group give compounds which are inactive or poorly active.
- The removal of the N-methyl group to give **normorphine** allows a series of alkyl chains to be built on the basic centre.

Development of...

B. Drug extension

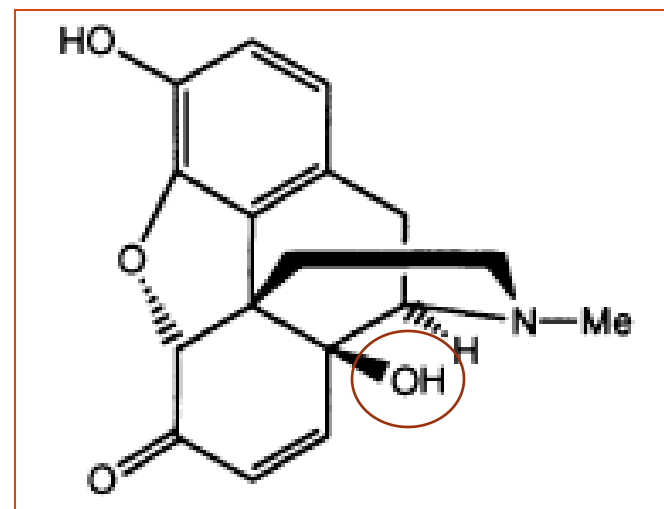
- Drug extension is a strategy by which the molecule is 'extended' by the addition of extra 'binding groups'.
- The reasoning behind such a tactic is **to probe for further binding sites**
- This is a reasonable assumption since it is highly unlikely that a compound such as morphine (which is produced in a plant) would be the perfect binding substrate for a receptor in the human brain

Development of...



Development of...

- Many analogues of morphine have been made with extra functional groups attached.
- These have rarely shown any improvement. However, there are two exceptions.
 - Introduction of hydroxyl group at 14-positions (fig. below) and
 - N-substitution (most successful approach)



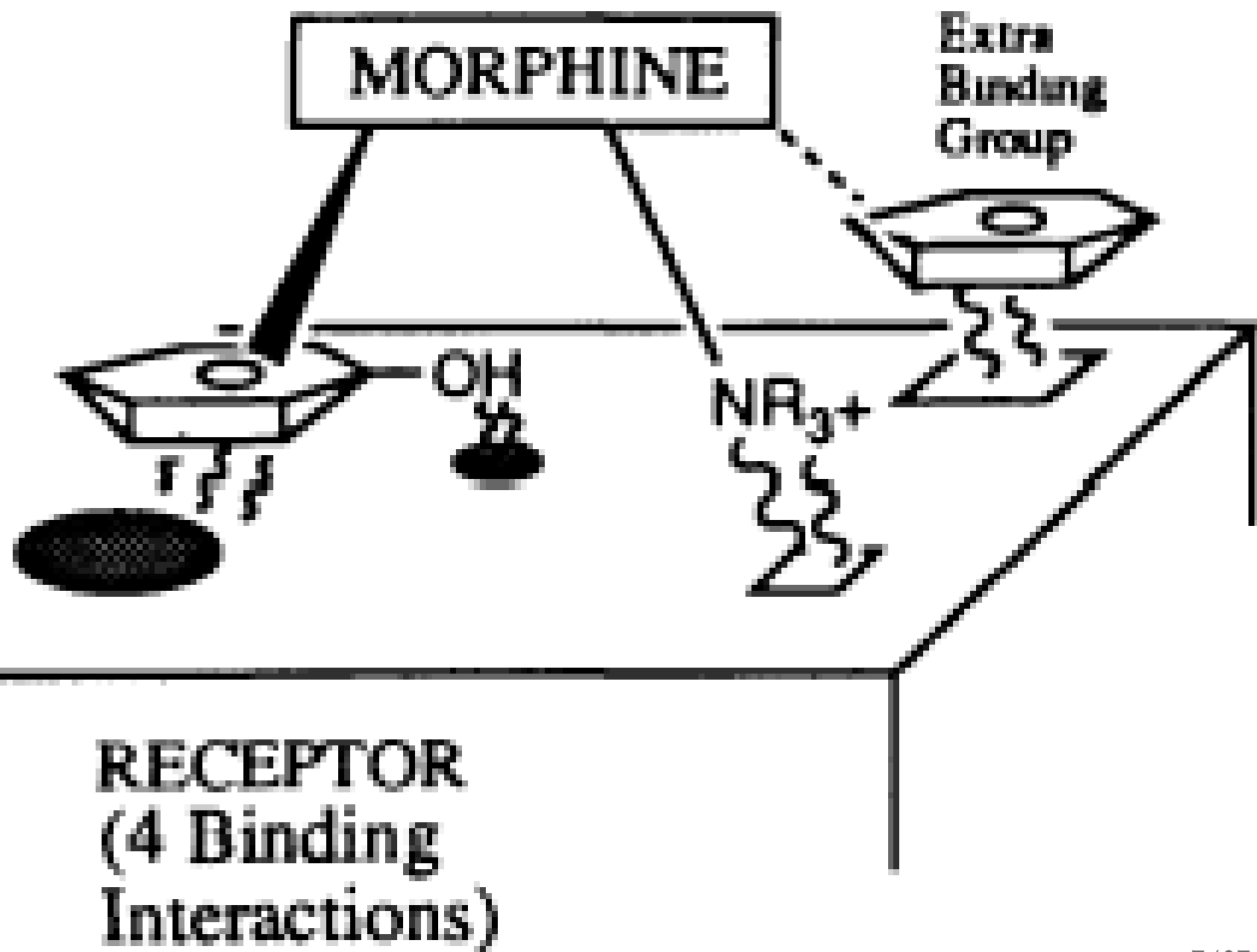
Development of...

Effect of N-substitution

R =	<div>Me Et Pr</div>	Bu	<div>Amyl, Hexyl</div>	CH ₂ CH ₂ Ph
	Agonism decreases Antagonism increases	Zero Activity	Agonists	14 x Activity wrt morphine

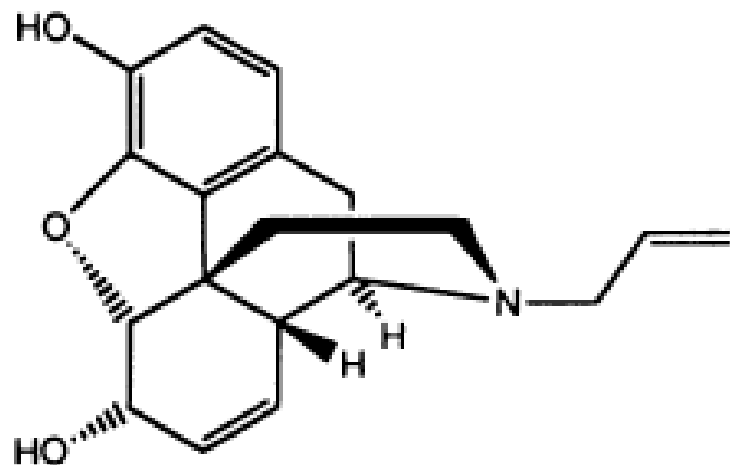
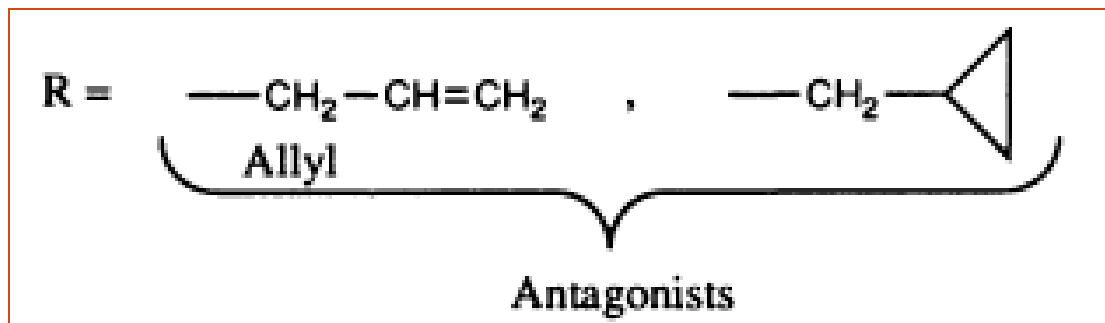
- As the alkyl group is increased in size from a methyl to a butyl group, the activity drops to zero
- However, with a larger group such as an amyl or a hexyl group, activity recovers slightly.
- when a **phenethyl** group is attached the activity increases 14 fold—a strong indication that a hydrophobic binding site has been located which interacts favourably with the new aromatic ring

Development of...

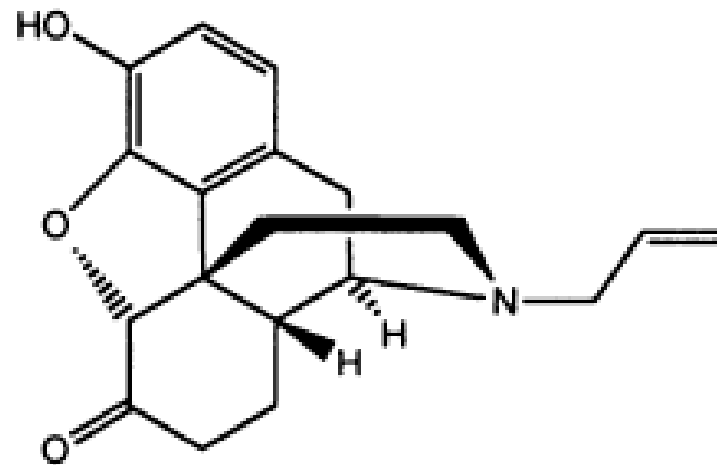


Development of...

- Another result by N-substitution



NALORPHINE



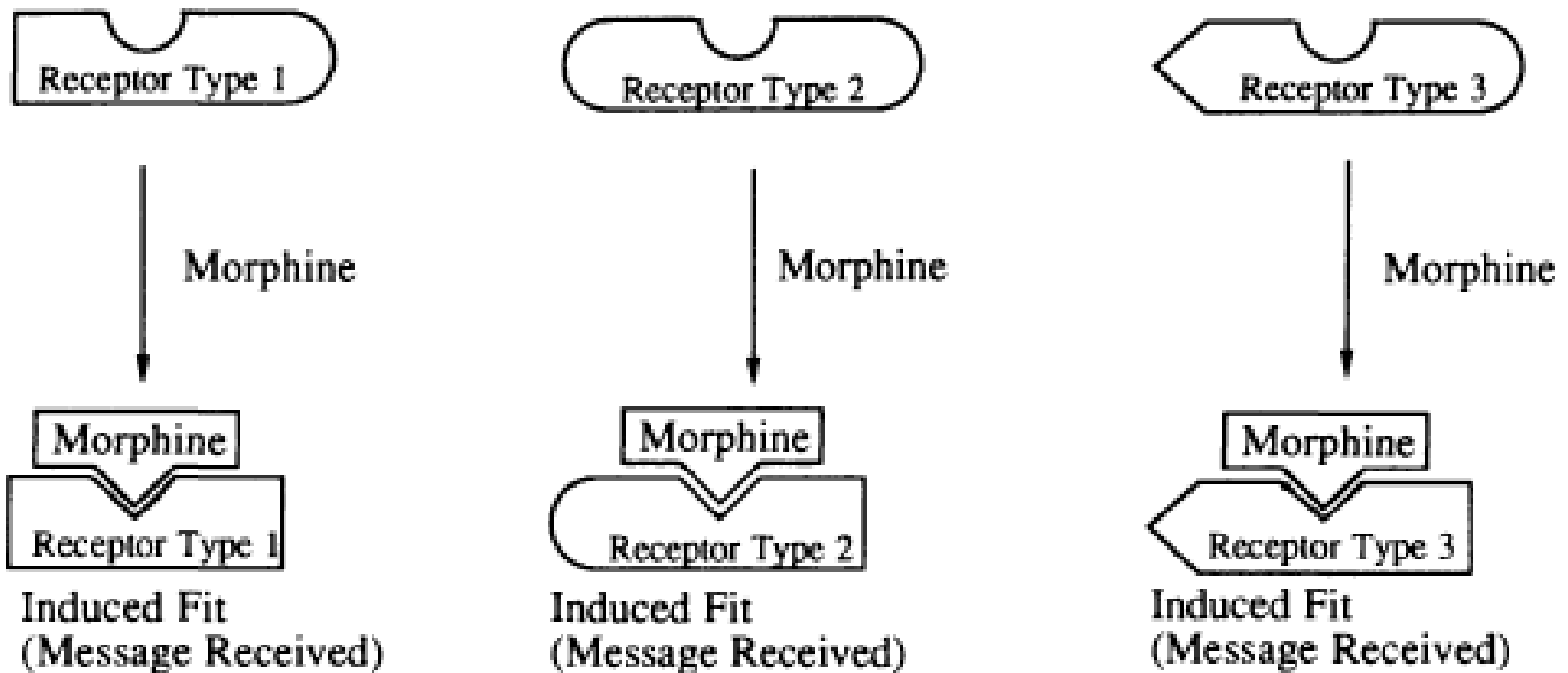
NALOXONE

Development of...

- Naloxone has no analgesic activity at all, whilst nalorphine retains only weak analgesic activity
- They are given whenever there is **morphine overdose**
- In addition the discovery of **nalorphine** helps for the synthesis of other morphine analogues with less addiction and CNS depressant activity

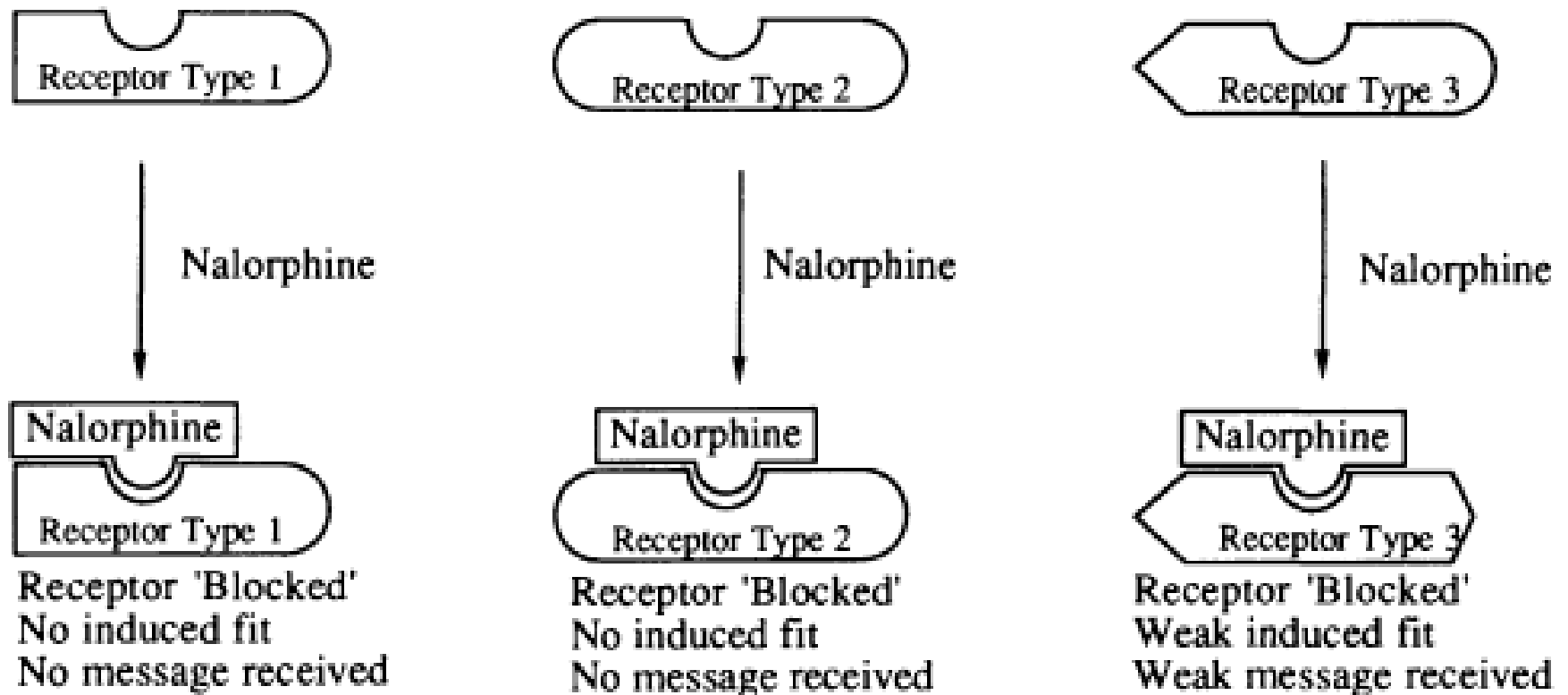
Development of...

(A) BINDING OF MORPHINE TO ANALGESIC RECEPTORS



Development of...

(B) BINDING OF NALORPHINE TO ANALGESIC RECEPTORS



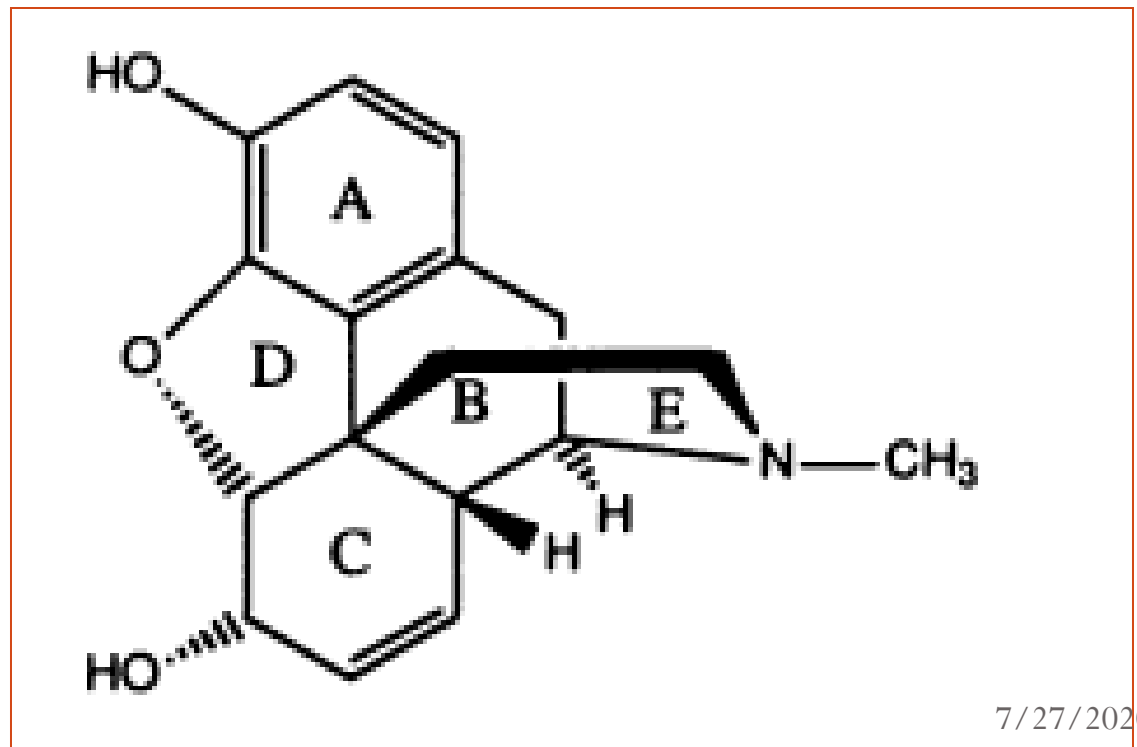
Development of...

C. Simplification or drug dissection

- **Objective**-to simplify the complex structure of morphine molecule, so that it would be easier to make it in the laboratory
- Allow the chemist to make analogues much more easily, and any useful compounds could be made more efficiently and cheaply.

Development of...

- From the five rings present in the structure of morphine, analogues were made to see which rings could be removed



Development of...

Removing ring E

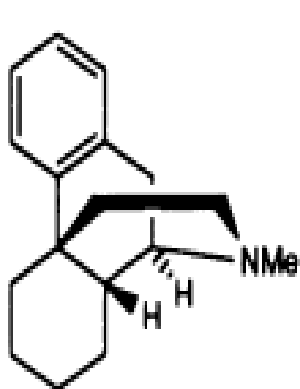
- Removing ring **E** leads to a complete loss of activity.

This result emphasizes the importance of the basic nitrogen to analgesic activity.

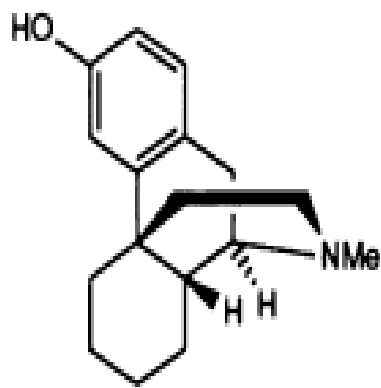
Development of...

Removing ring D

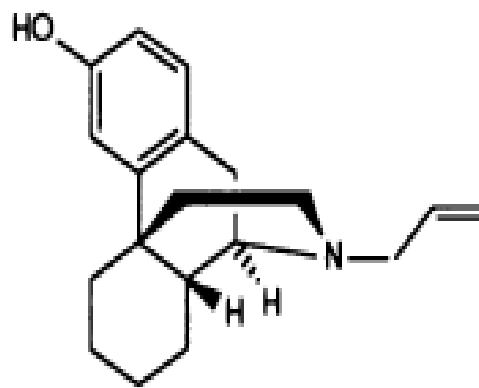
- Gives a series of compounds called the **morphinans** which have useful analgesic activity
- The oxygen bridge is not essential



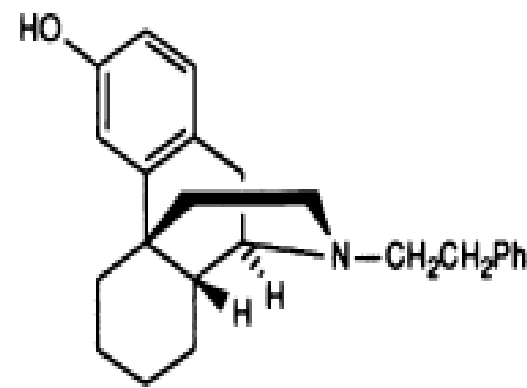
N-METHYL MORPHINAN
(20% activity of morphine)



LEVORPHANOL
(5x more potent than morphine)



LEVALLORPHAN
(Antagonist 5x more
potent than nalorphine)



(15x more potent than morphine)

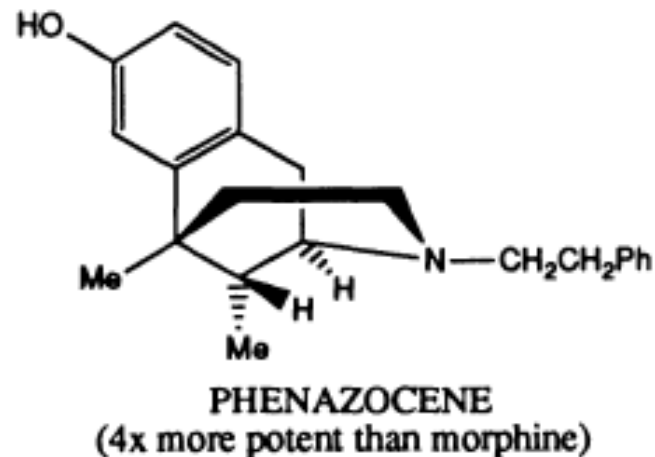
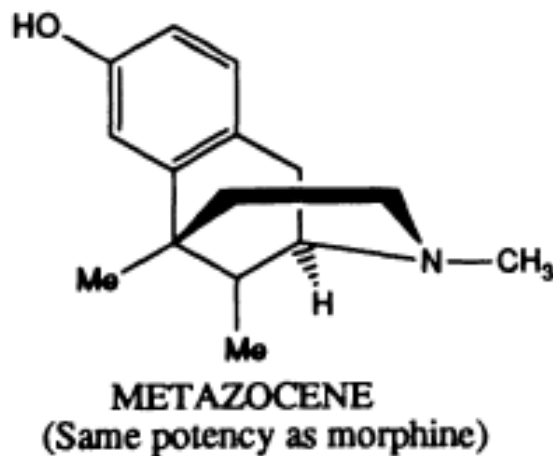
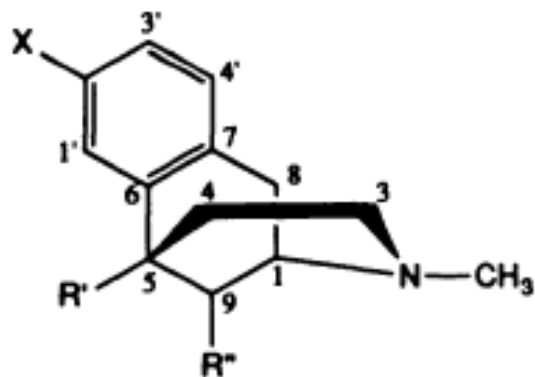
Development of...

- Morphinans are **more potent** and **longer acting** than their morphine counterparts, but they also have higher toxicity and comparable dependence characteristics
- The modifications carried out on morphine, when carried out on the morphinans, lead to the same biological results.
 - The same strategy of drug extension already described for the morphine structures was also tried on the morphinans with similar results. For example,
 - Adding an **allyl** substituent on the nitrogen gives antagonists.
 - Adding a **phenethyl** group to the nitrogen greatly increases potency.
 - Adding a 14-OH group also increases activity.
- The morphinans are easier to synthesize since they are simpler molecules

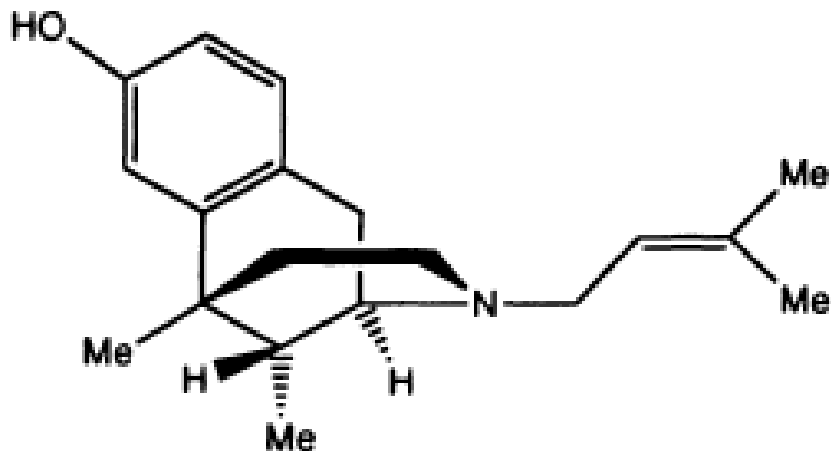
Development of...

Removing rings C and D

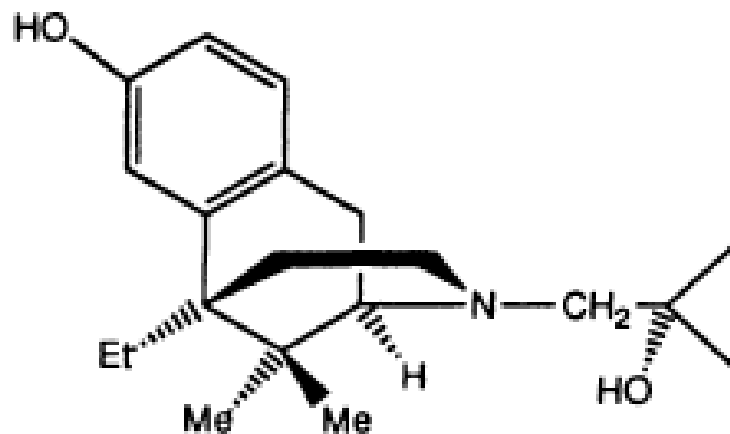
- Gives an interesting group of compounds called the **benzomorphans** which are found to retain analgesic activity.
- One of the simplest of these structures is metazocene which has the same analgesic activity as morphine



Development of...



PENTAZOCINE
(33% activity of morphine,
short duration, low
addiction liability)



BREMAZOCINE

A newer compound (bremazocine) has a **longer duration**, is 200 times the activity of morphine, appears to have no addictive properties, and does not depress breathing

Development of...

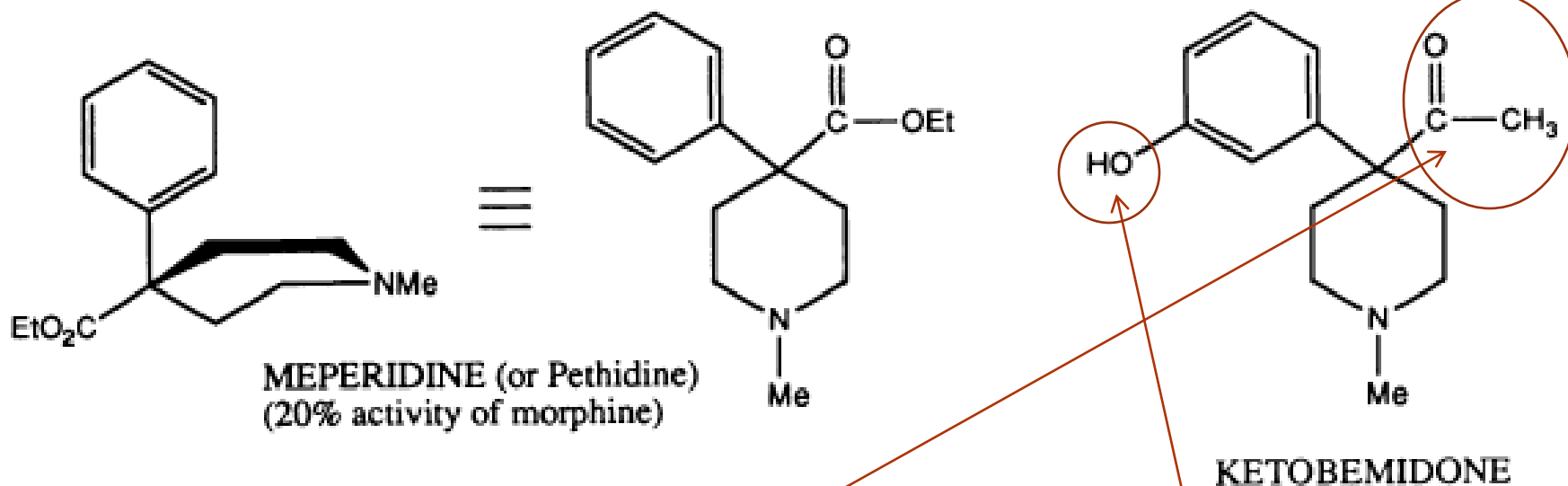
Conclusion about benzomorphans

- Rings C and D are not essential to analgesic activity.
- Analgesia and addiction are not necessarily coexistent.
- 6, 7-Benzomorphans are clinically useful compounds with reasonable analgesic activity, less addictive liability, and less tolerance.
- Benzomorphans are simpler to synthesize.

Development of...

Removing rings B, C and D

- Removing rings B, C and D give a series of compounds known as **4-phenylpiperidines**.
- The analgesic activity of these compounds was discovered by chance.



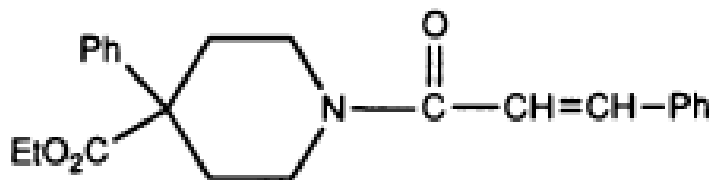
- Activity can be increased six fold by introducing the phenolic group and altering the ester to a ketone to give **ketobemidone**.

Development of...

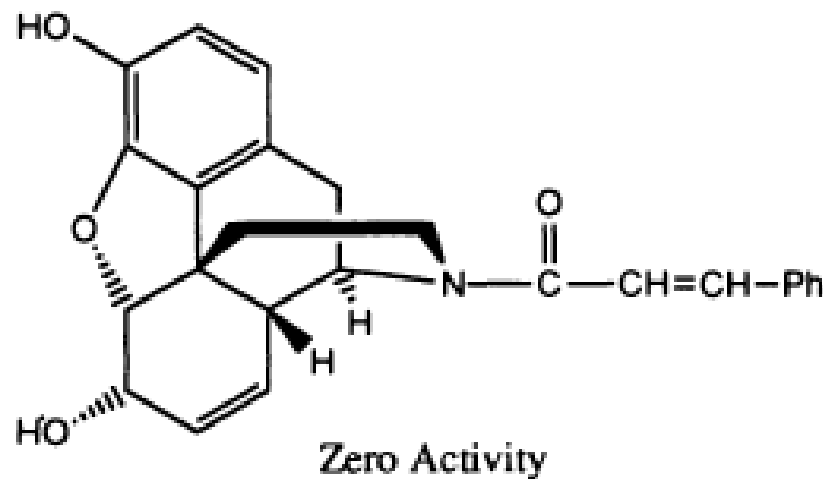
- Meperidine (pethidine) is not as strong an analgesic as morphine and also shares the same undesirable side-effects.
- However, it has a **rapid onset** and a **shorter duration** and as a result has been used as an analgesic for difficult childbirths
- The piperidines are more easily synthesized than any of the above groups and a large number of analogues have been studied.
- Adding allyl or cyclopropyl groups to N does not give antagonists.

Development of...

- The replacement of the methyl group of meperidine with a **cinnamic acid** residue increases the activity by 30 times, whereas putting the same group on morphine eliminates activity



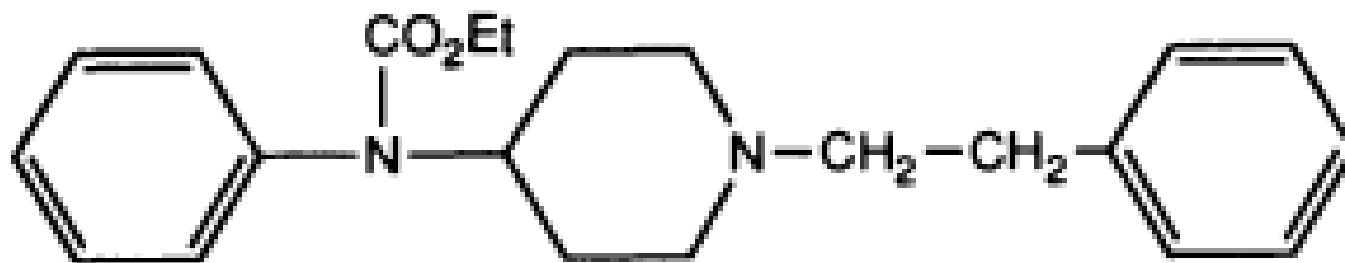
30x more potent than pethidine

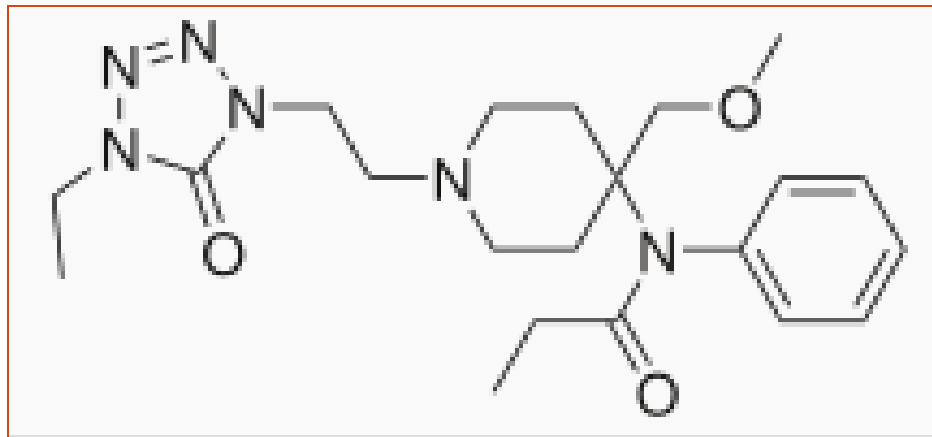


Zero Activity

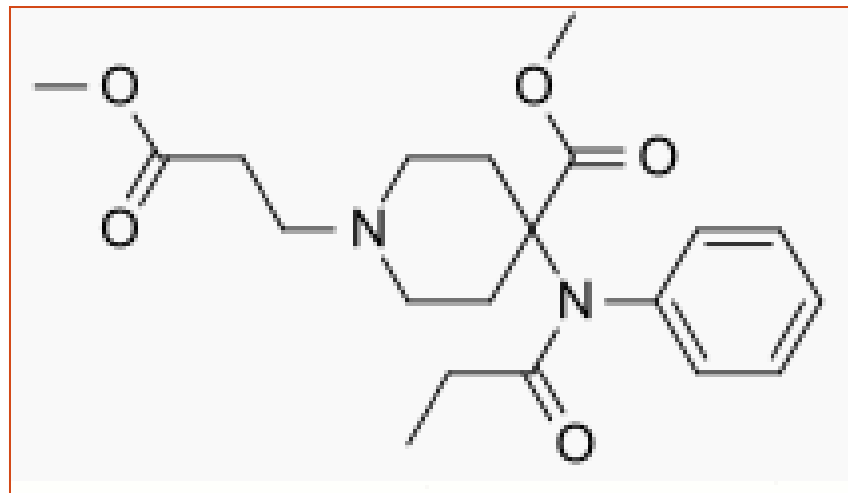
Development of...

- One of the most successful piperidine derivatives is **fentanyl** which is up to 100 times more active than morphine

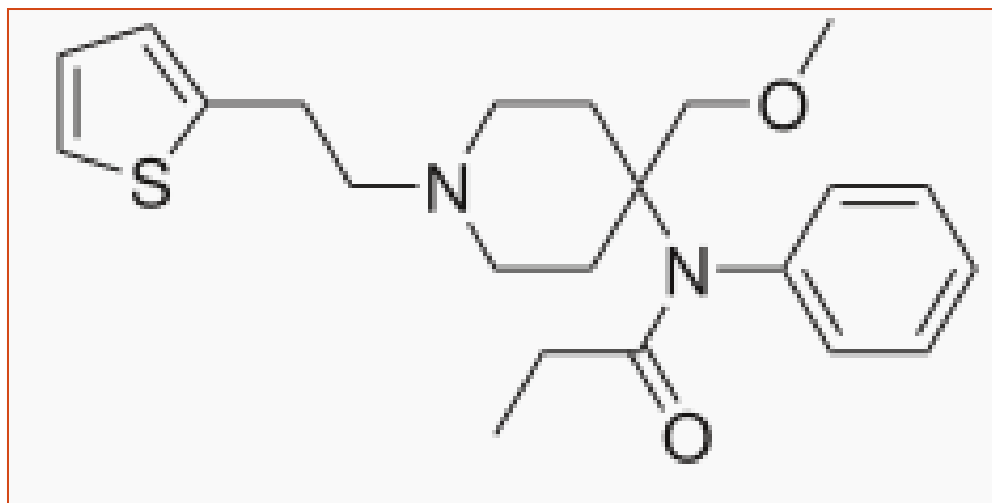




Alfentanil



Remifentanil



Sufentanil

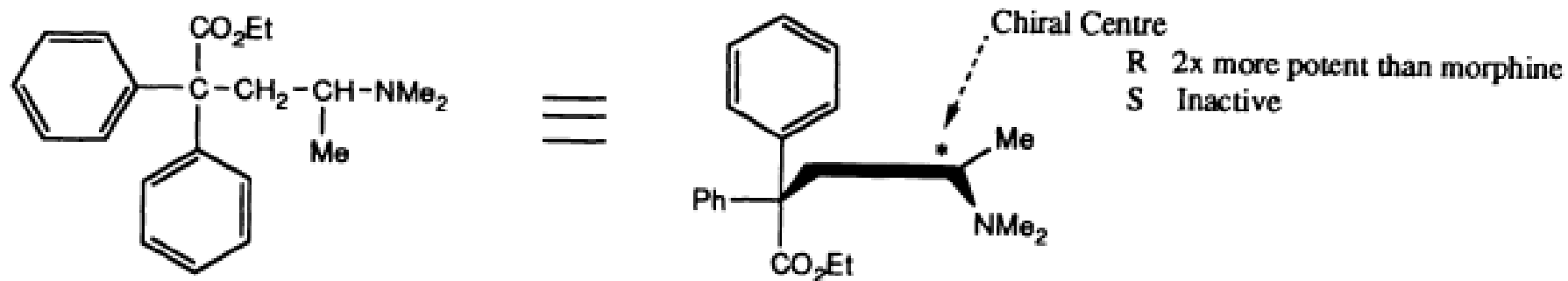
Development of...

Conclusions:

- Rings B, C, and D are not essential for analgesic activity.
- Piperidines retain side-effects such as **addiction** and **depression of the respiratory centre**.
- Piperidine analgesics are faster acting and have shorter duration.
- The quaternary centre present in piperidines is usually necessary (fentanyl is an exception).
- The aromatic ring and basic nitrogen are essential to activity, but the phenol group is not.
- Piperidine analgesics appear to interact with analgesic receptors in a different manner to previous groups.

Development of...

Removing rings B, C, D and E



- The analgesic **Methadone** was discovered in Germany during the Second World War
- The compound has been given to drug addicts as a substitute for morphine (or heroin) in order to wean them off these drugs.

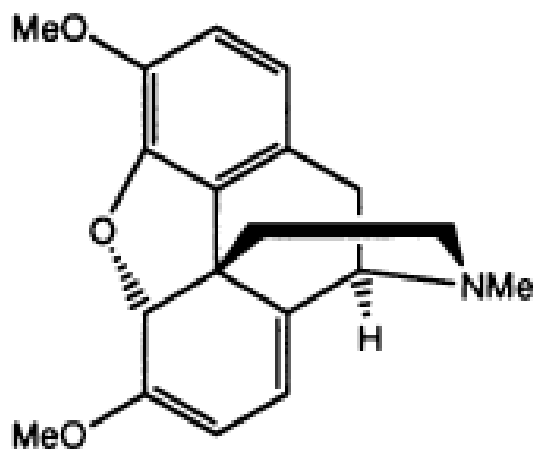
Development of...

D. Rigidification

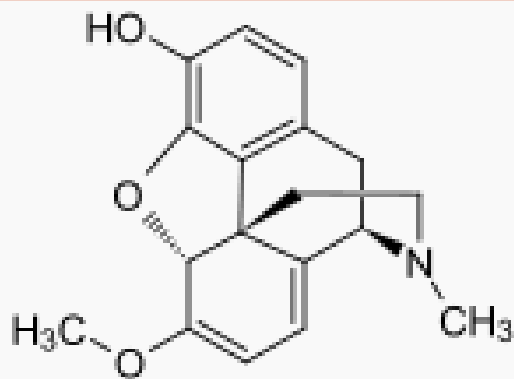
- This strategy is usually employed in an attempt to remove the side-effects of a drug or to increase activity.
- Rigidification restricts the molecule to the specific conformation which fits the desired receptor
- The best example of this tactic in the analgesic field is provided by a group of compounds known as the **oripavines**

Development of...

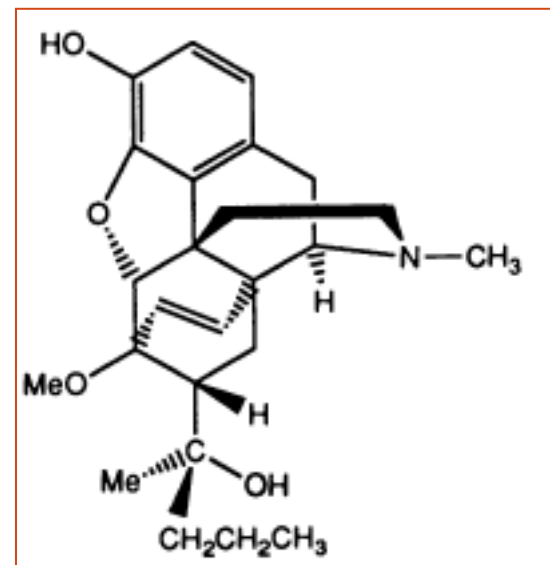
- The oripavines are made from an alkaloid Thebaine



Thebaine



oripavine

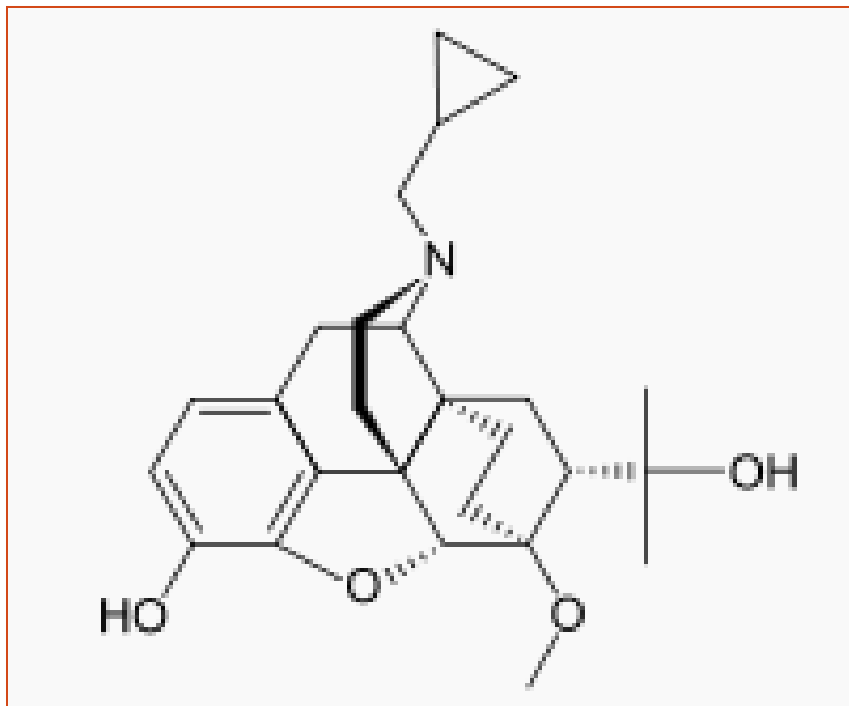


Etorphine

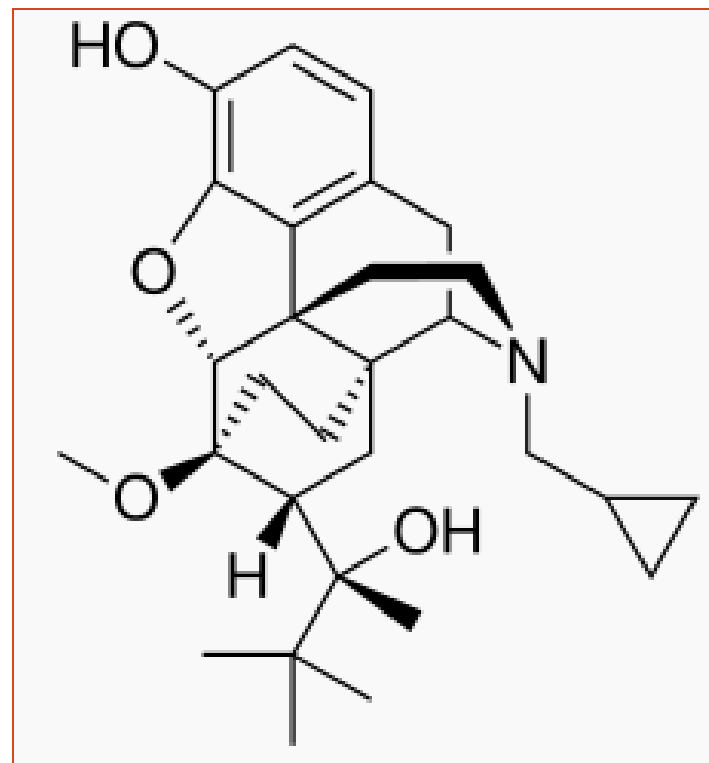
Development of...

- Because of their rigid structures, these compounds are highly selective agents for the analgesic receptors. Unfortunately, the increased analgesic activity is also accompanied by unacceptable side-effects.
- Putting on a **cyclopropyl** group gives a very powerful antagonist called **diprenorphine** which is 100 times more potent than nalorphine and can be used to reverse the immobilizing effects of etorphine.
 - Diprenorphine has no analgesic activity.
- Replacing the methyl group of etorphine with a **r-butyl** group gives **buprenorphine** which has similar properties to drugs like nalorphine and pentazocine, in that it has analgesic activity with a very **low risk of addiction**.

Development of...



Diprenorphine



Buprenorphine

Q?