PHARMACY INDIA

B.PHARMA

IVTH SEMESTER

MEDICINAL CHEMISTRY - I

BP 402 T

MODEL PAPER

PHYSICAL PHARMACEUTICS-II (BP-403T) MODEL PAPER

SECTION A

VERY SHORT ANSWERS TYPE QUESTIONS (10 × 2 = 20)

1. **Define metabolism.**

Answer

- Chemical alteration of the drug in a living organism is called biotransformation. The metabolism of a drug usually converts lipid-soluble and unionized compounds into water-soluble and ionized compounds. They are not reabsorbed in the renal tubules and are excreted.

2. **Point out the role of the partition coefficient in relation to the biological activity of the drug.**

Answer

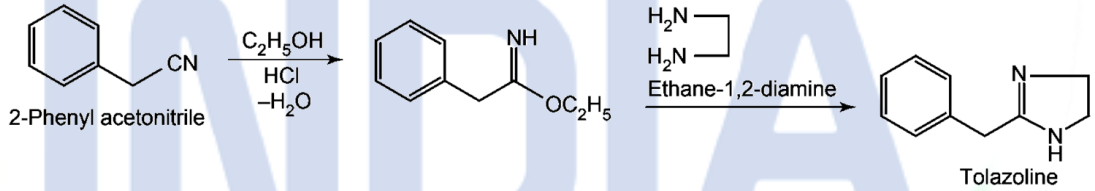
- The hydrophobic character of a drug can be measured experimentally by testing the drug's relative distribution in an octanol/water mixture.
- Hydrophobic molecules dissolve in n-octanol (CH_3 (CH_2)$_7$ OH).
- Hydrophilic molecules dissolve in the aqueous layer.

$$P = \frac{\text{Concentration of drug in octanol}}{\text{Concentration of drug in aqeous solution}}$$

- Hydrophobic drugs with high partition coefficients are preferentially distributed to hydrophobic compartments such as lipid bilayers of cells.
- Hydrophilic drugs (low partition coefficients) preferentially are found in hydrophilic compartments such as blood serum

3. **Describe the synthesis of tolazoline.**

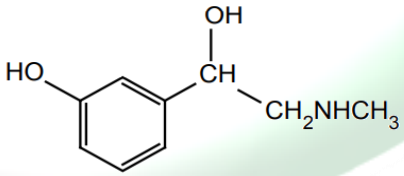
Answer



4. **Give structure and uses of Phenylephrine.**

Answer

Structure of Phenylephrine



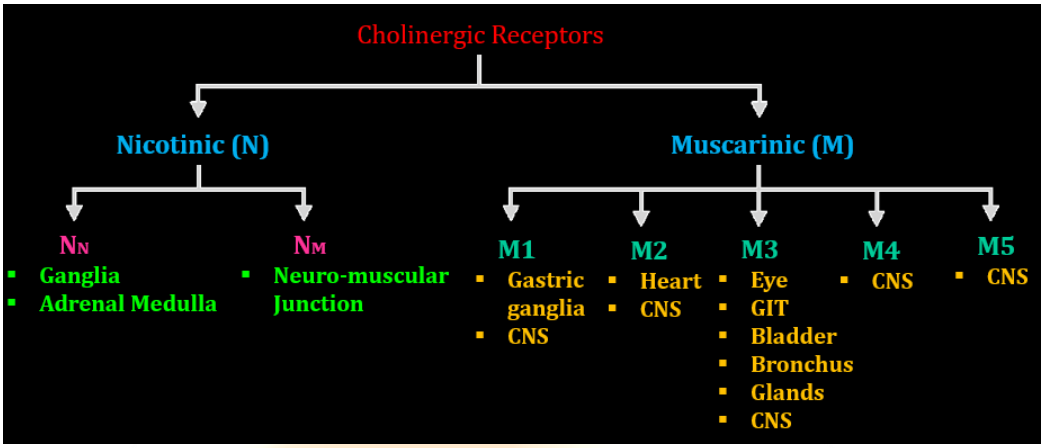
Uses

- Haemorrhoids
- Hypotension
- Priapism

5. **Discuss cholinergic receptors and their distribution.**

Answer

Types & Sites of Cholinoceptors



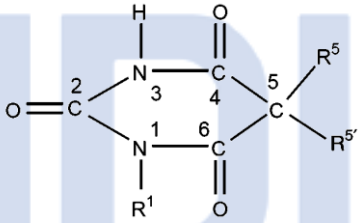
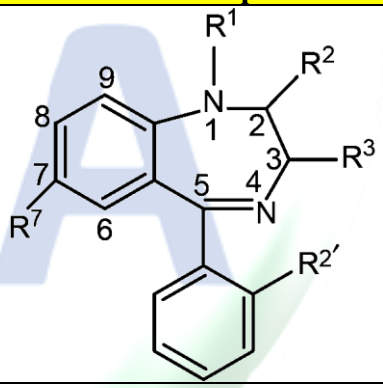
6. **Differentiate anticholinergics and anticholinesterase.**

Answer

- **Cholinesterase:** Immediately after release, Ach is hydrolyzed by the enzyme cholinesterase and choline is recycled.
- **Anticholinergics:** Anticholinergic drugs are agents which block the effects of acetylcholine on cholinergic receptors but conventionally antimuscarinic drugs are referred to as anticholinergic drugs.

7. **Compare the basic ring structure and mention the uses of barbiturates and benzodiazepines.**

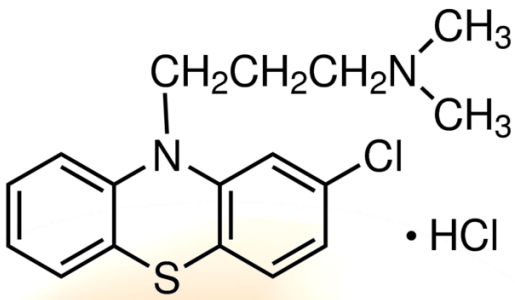
Answer

Drugs	Barbiturates	Benzodiazepines
Basic ring		
Uses	1. It is generally used in the treatment of epileptic seizures. 2. It is also used as a sedative and hypnotic in the treatment of insomnia.	1. It is used in the treatment of anxiety and insomnia. 2. It is also used to treat symptoms of alcohol withdrawal. 3. It is used as a premedication for the induction of sedation. 4. It is used to treat muscle spasms, seizures and restless legs syndrome.

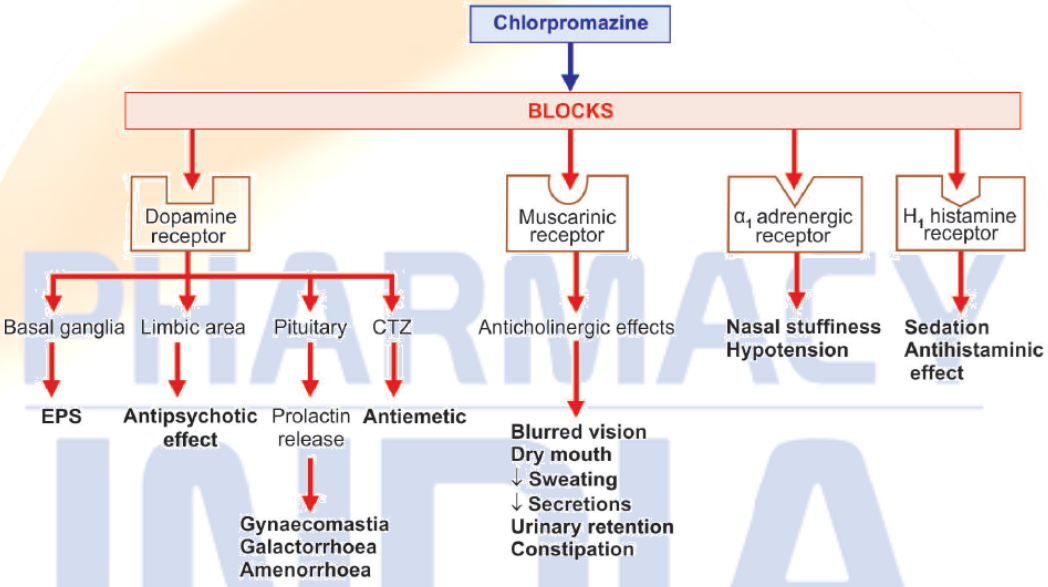
8. Give the MOA and structure of chlorpromazine.

Answer

Structure of Chlorpromazine



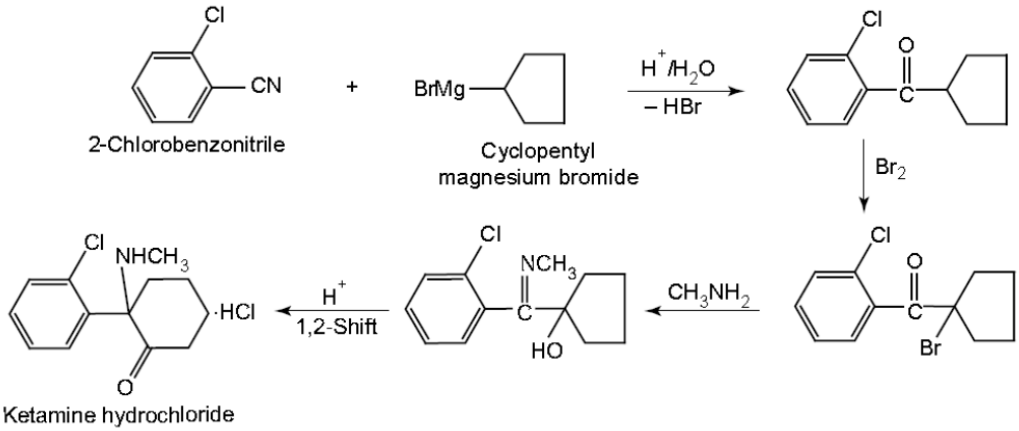
Mechanism of action



9. Discuss the synthesis of drug that causes dissociative anesthesia.

Answer

Synthesis of Ketamine HCl

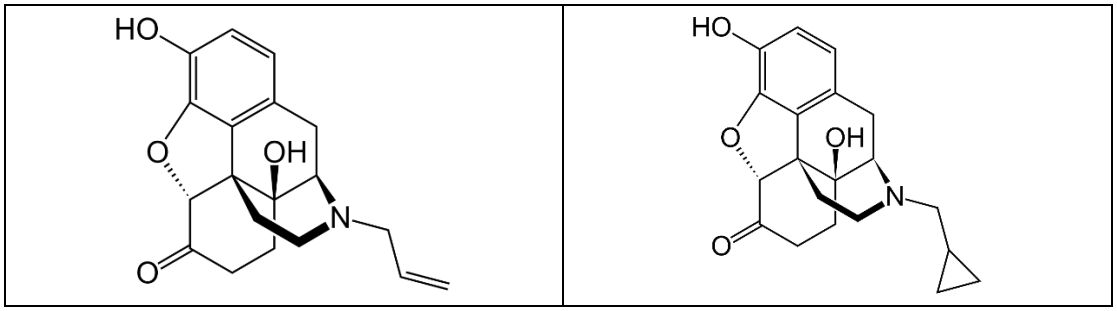


10. Name and give structure of any two narcotic antagonists.

Answer

Narcotic antagonist

Naloxone	Naltrexone



SECTION B

LONG ANSWERS TYPE QUESTIONS (2 × 10 = 20)

1. Summarize about various physiochemical parameters that affect the drugs action.

Answer

1. Ionization

- Ionized form imparts good water solubility to the drug which is essential for good binding interactions of drug with its receptor.
- While non-ionized form helps the drug to cross cell membranes. Hence, a good balance of ionized: non-ionized forms is essential for better pharmacokinetic and pharmacodynamic features.
- The unionised form is a function of both, the dissociation constant (pKa or negative logarithm of acidic dissociation constant) and the pH of the environment which is represented by Henderson-Hasselbach equation.

For Acid, $pKa - pH = \log (Cu/Ci)$

For Base, $pKa - pH = \log (Ci/Cu)$

where, Ci and Cu are the concentrations of the ionised and unionised drugs respectively.

2. Solubility

- About 30% of drug candidate molecules are rejected due to pharmacokinetic related failures.
- As the bioavailability of drugs from liquid orals mainly depends on their solubility in the given solvent system, it is considered as one of the important parameters for assessing the absorption of drugs into the systemic circulation.
- Lipinski et al. found that poor absorption or permeability is seen when
  (i) Compound has molecular weight above 500 amu (Atomic mass unit),
  (ii) Compound has log P > 5, and
  (iii) Compound has either five H-bond donars or ten H-bond acceptors.

3. Partition Coefficient

- The partition coefficient value (π) expresses the relative free energy change occurring when a drug molecule moves from one phase to another.
- It means, a positive value of π suggests that the drug favours organic (lipoidal) layer while a negative value implies that it prefers an aqueous phase.

- An excellent correlation between partition coefficients determined in CCl_4/ 0.1N HCl solvent system and gastric absorption rate for different barbiturates was established.
- The partition coefficient determined in the solvent system having pH nearly in the range of pH at the site of absorption gives a better understanding of drug absorption.

4. Hydrogen bonding

- Atoms which are capable of forming H-bonds are electronegative atoms; these include F, Cl, N, O and S.
- Though H-bonds are relatively weak bonds their presence may have a profound effect on the biological action of a drug.
- For Example: 1-phenyl-3-methyl-5-pyrazolone shows no analgesic properties while 1-phenyl-2,3- dimethyl-5-pyrazolone (antipyrine) is a well known analgesic agent. This effect appears to be best explained by the fact that the first compound through intermolecular H-bonding forms a linear polymer.

5. Protein Binding

- The reversible binding of drug with non-specific and non-functional sites on the body proteins without showing any biological effect is called as Protein Binding.
- Strong drug interactions with serum proteins can influence permeability
- A drug molecule, to less or more extent, has a capacity to enter into specific combination with plasma-proteins. These molecular interactions play an important role in deciding the intimate nature of drug action.

6. Complexation

- Since complexes of drug molecules cannot cross the natural membranous barriers, they render the drug biologically ineffective. The rate of absorption is therefore, proportional to the concentration of the free drug molecules i.e., the diffusible drug.
- Due to the reversibility of the complexation, there always exists an equilibrium between the free drug and the drug complex. Such equilibrium is represented below:

$$\text{Drug} + \text{Complexing Agent} \rightleftharpoons \text{Drug Complex}$$

2. Classify sedative and hypnotics. Outline the synthesis, mechanism of action and uses of diazepam.

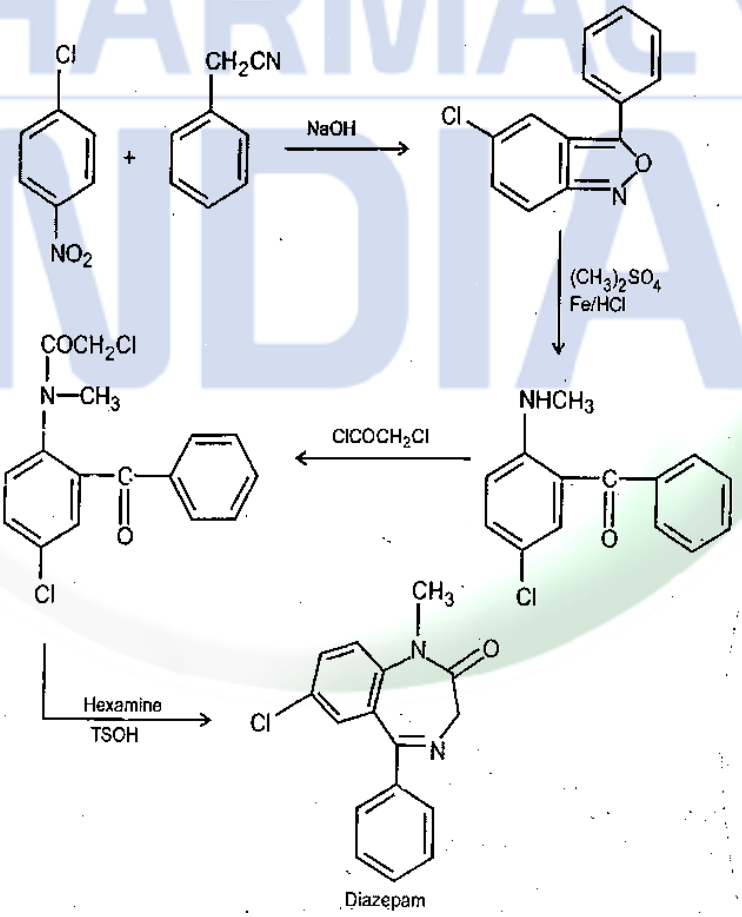
Answer

Classification of sedative & Hypnotics

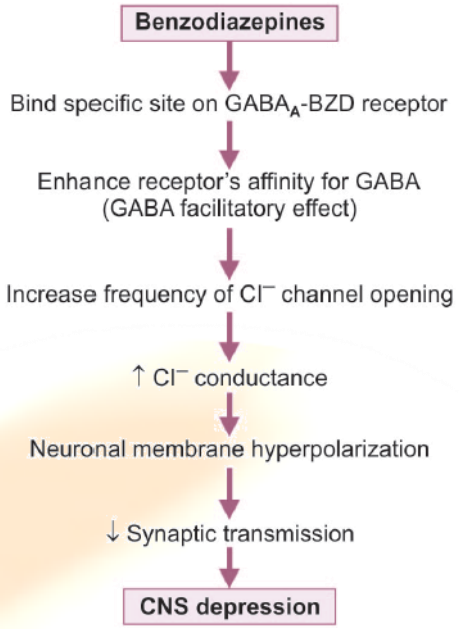
Class	Sub-class	Drugs
Barbiturates	Long acting	Phenobarbitone, Mephobarbitone
	Short acting	Butabarbitone, Pentobarbitone, Secobarbital

	Ultrashort acting	Thiopentone, Hexabarbitone
Benzodiazpines (BZDs)	Hypnotic	Diazepam, Flurazepam, Nitrazepam, Temazepam, Midazolam
	Antianxiety	Diazepam, Chlordiazepoxie, Oxazepam, Lorazepam
	Anticonvulsant	Diazepam, Clonazepam, Clobazam
	Centrally acting skeletal muscle relaxant	Diazepam, Clonazepam
Newer non-BZDs hypnotics	Zolpidem, Zopiclone	

Synthesis of Diazepam



Mechanism of action



Uses

- Insomnia
- In anxiety states
- Anticonvulsions
- Muscle relaxants
- Preanaesthetic medication
- General anaesthetia

3. Classify NSAIDs. Give the synthesis of ibuprofen.

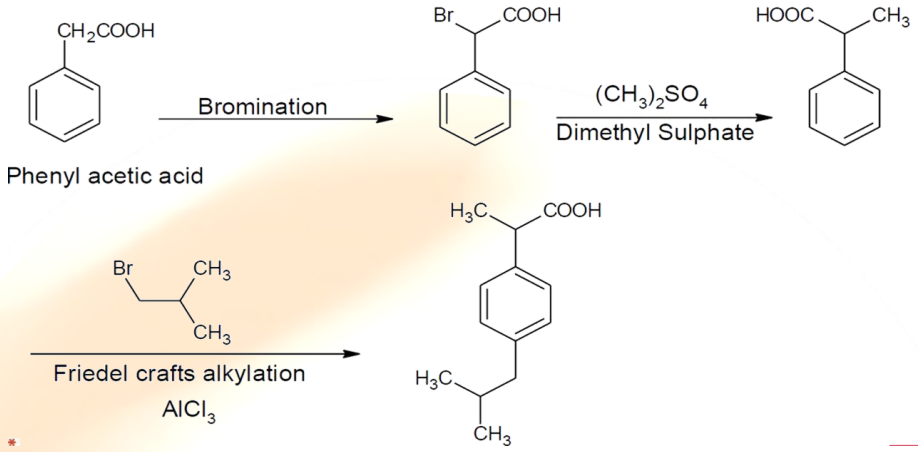
Answer

Classification of NSAIDs

Class	Examples
Nonselective COX inhibitors (traditional NSAIDs)	
• **Salicylates**	Aspirin
• **Propionic acid derivatives**	Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen
• **Fenamate**	Mephenamic acid
• **Enolic acid derivatives**	Piroxicam, Tenoxicam
• **Acetic acid derivatives**	Ketorolac, Indomethacin, Nabumetone.
• **Pyrazolone derivatives**	Phenylbutazone, Oxyphenbutazone
Preferential COX-2 inhibitors	Nimesulide, Diclofenac, Aceclofenac, Meloxicam, Etodolac
Selective COX-2 inhibitors	Celecoxib, Etoricoxib, Parecoxib
Analgesic-antipyretics with poor anti-inflammatory action	
• **Para-aminophenol derivative**	Paracetamol (Acetaminophen)

• **Pyrazolone derivatives**	Metamizol (Dipyrone), Propiphenazone
• **Benzoxazocine derivative**	Nefopam

Synthesis of Ibuprofen



SECTION C

SHORT ANSWERS TYPE QUESTIONS (7 × 5 = 35)

1. Compare Phase I and Phase II metabolism. Discuss the various factors affecting drug metabolism.

Answer

PHASE I METABOLISM: - NON-SYNTHETIC

Reaction	Definition	Examples
Oxidation	Addition of oxygen /removal of hydrogen	Phenytoin ,phenobarbitone, pentobarbitone ,propranolol
Reduction	Removal of oxygen/addition of hydrogen	Chloramphenicol ,methadone
Hydrolysis	Break down of compound by addition of water	Esters – procaine ,succinylcholine Amides – lignocaine, procainamide
Cyclization	Conversion of straight chain compound into ring structure.	Proguanil to cycloguanil
Decyclization	Breaking up of the ring structure of the drug.	Phenobarbitone & Phenytoin

PHASE II METABOLISM: - SYNTHETIC/ CONJUGATION

Conjugation	Endogenous substrate	Examples
Glucuronide	UDP glucuronosyl transferase	Chloramphenicol, Aspirin Phenacetin.
Acetylation	N-acetyl transferase	Sulfonamide, Isoniazid, PAS, hydralazine.
Methylation	Transmethylase	Adrenaline, Histamine, Nicotinic acid.
Sulphate	Sulphotransferase	Chloramphenicol, adrenal and sex steroids.
Glycine(rarely occur)	Acetyl CoA glycine transferase	Salicylate and other drugs having carboxylic acid group.
Glutathione	Glutathione transferase	Paracetamol

Factors affecting drug metabolism

- **Genetic variation** results in altered metabolism of drugs, e.g., succinylcholine is metabolized very slowly in people with defective pseudocholinesterase resulting in prolonged apnoea.
- **Environmental pollutants,** like cigarette smoke, cause enzyme induction.
- **Age:** At extremes of age, the activity of metabolic enzymes in the liver are low and hence there is increased risk of toxicity with drugs.
- **Diseases of the liver:** Markedly affect metabolism of drugs.

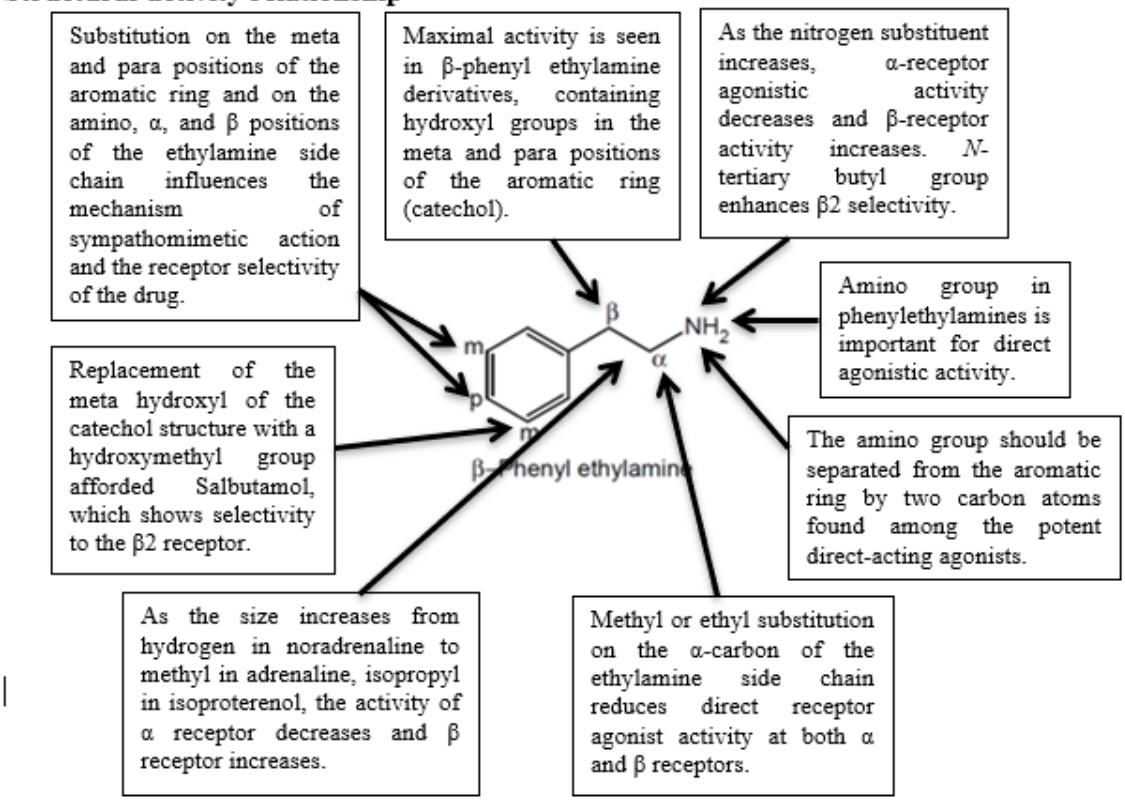
2. Outline the classification and SAR of sympathomimetics.

Answer

Classification of Sympathomimetics

Category	Drugs
On the basis of their mechanism of action	
Direct sympathomimetics	Adrenaline, Noradrenaline, isoprenaline (Iso), phenylephrine, methoxamine, xylometazoline, salbutamol
Indirect sympathomimetics	Tyramine, Mephetamine.
Mixed action sympathomimetics	Ephedrine, Dopamine, Mephentermine.
On the basis of their therapeutic use	
To raise pressure in shock (pressor agents)	Dopamine, Noradrenaline, ephedrine, phenylephrine, methoxamine, mephentermine.
Cardiac stimulant	Adrenaline, Dopamine, Dobutamine, Isoprenaline.
Bronchodilators	Salbutamol (Albuterol), Terbutaline
Nasal decongestants	Phenylephrine, Xylometazoline, Naphazoline, Pseudoephedrine, Oxymetazoline.
CNS stimulants	Modafinil, Amphetamine, Methamphetamine
Anorectics (reduces appetite)	Sibutramine, Mazindol, Phentermine.
Uterine relaxants	Ritodrine, Isoxsuprime, Salbutamol, Terbutaline.
Mydriatics	Ephedrine, Phenylephrine.

Structural-activity relationship



3. Illustrate the MOA, synthesis and uses of Dicyclomine HCl and Carbachol.

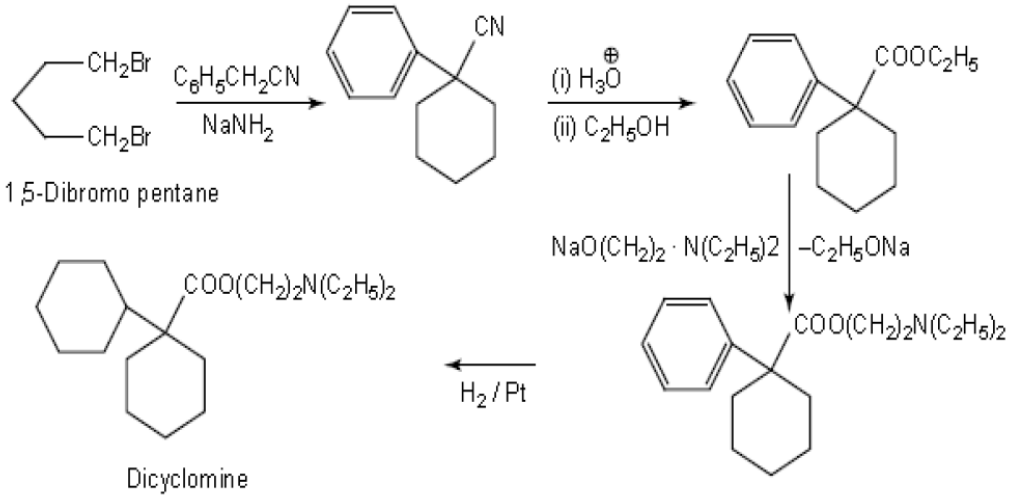
Answer

Dicyclomine HCL

Mechanism of action

- Dicyclomine hydrochloride antagonizes muscarinic receptors on smooth muscle in the gastrointestinal (GI) tract, thereby preventing the actions of acetylcholine and reducing GI smooth muscle spasms.

Synthesis



Uses

- Muscarinic antagonist used as an antispasmodic and in urinary incontinence.

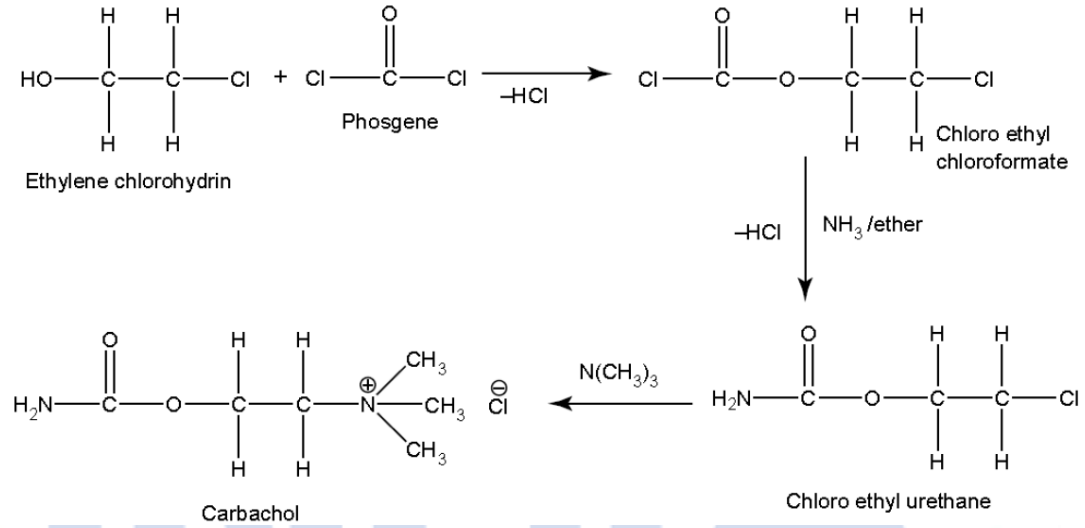
Carbachol

Mechanism of action

- These drugs mediate the actions through muscarinic and nicotinic receptor subtypes.
- Stimulation of M1 or M3 receptors causes hydrolysis of polyphosphoinositides and mobilization of intracellular Ca2+, as a consequence of interaction with a G-protein, and phospholipase C is activated, which phosphorylates the target protein.
- In contrast, M2 and M4 inhibit adenyl cyclase and regulate specification channels, that is, enhancement of K+ conductance in cardiac arterial tissue.
- Cholinergic stimulation affects cardiac function directly by inhibiting the effects of adrenergic activation.

Synthesis

Route I: From Ethylene chlorohydrin



Uses

- It possesses both muscarinic and nicotinic properties by cholinergic receptor stimulation.
- It is more slowly hydrolyzed by acetylcholinesterase
- It is used for its miotic actions in the treatment of glaucoma to reduce intra ocular pressure.

4. Classify anticonvulsants and give synthesis of phenytoin.

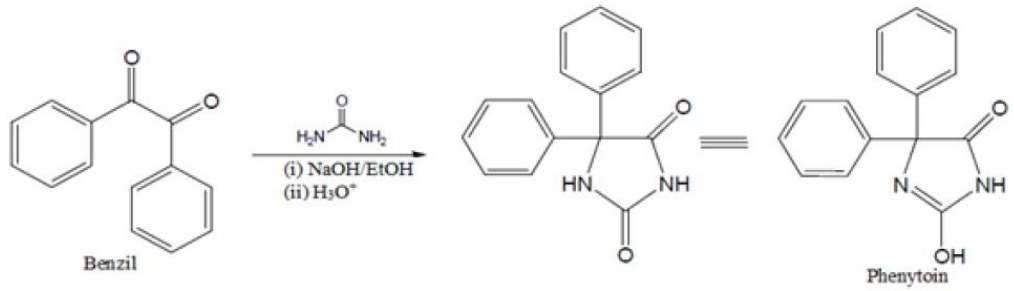
Answer

Classification of Anticonvulsants

Classes	Drugs
Hydantoins	Phenytoin, Fosphenytoin
Iminostilbenes	Carbamazepine, Oxcarbazepine
Phenyltraiziness	Lamotrigine
Aliphatic carboxylic acid	Valproate, Divalproex

Aliphatic carboxylic acid	Valproate, divalproex
Barbiturate	Diazepam, Lorazepam, Clobazam, Clonazepam
Benzodiazepines	Phenobarbitone, Pentobarbitone
Cyclic GABA analogue	Gabapentin, Pregabaline
Succinimides	Ethosuximide
Newer Drugs	Levetiractam
	Topiramide
	Zonisamide
	Lacosamide
	Vigabatrin
	Topiramate

Synthesis of Phenytoin



5. **Classify general anaesthetic. Give synthesis of halothane.**

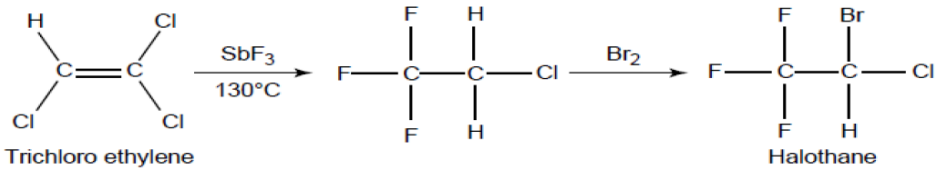
Answer

Classification of General anaesthetics

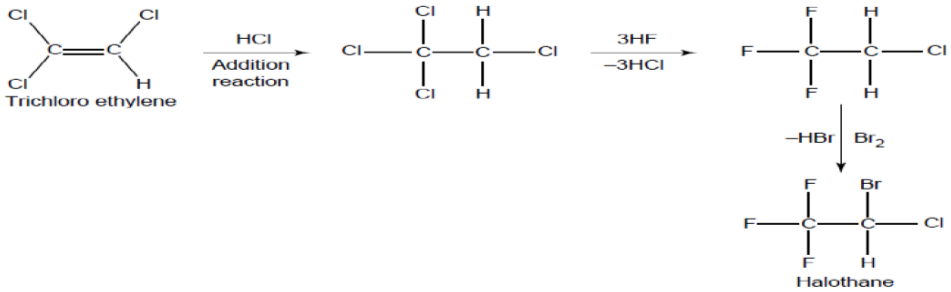
Inhalational	**Gas**	Nitrous oxide
	Volatile oil liquid	Ether, Halothane, Enflurane, isoflurane, Desflurane, Sevoflurane
Parenteral	**Inducing agent**	Thiopentone, methohexitone propofol, Etomidate
	Benzodiazepines	Diazepam, lorazepam, medazolam
	dissociative anesthesia	Ketamine
	Opioid analgesia	Fentanyl, Remifentanil

Synthesis of Halothane

- **Route 1**



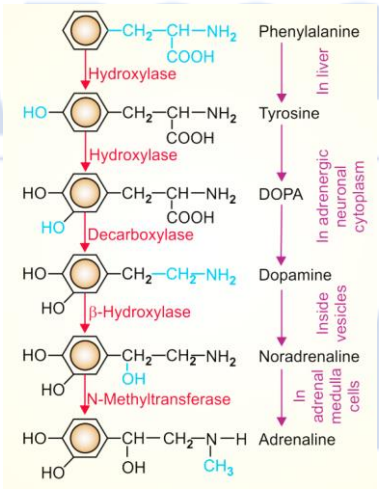
- **Route 2**



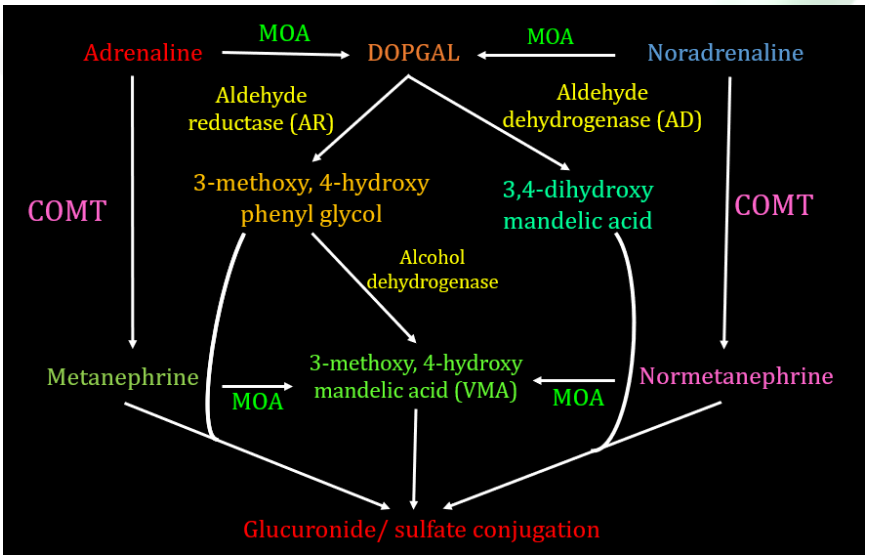
6. Explain the biosynthesis and catabolism of catecholamines.

Answer

Biosynthesis of catecholamine



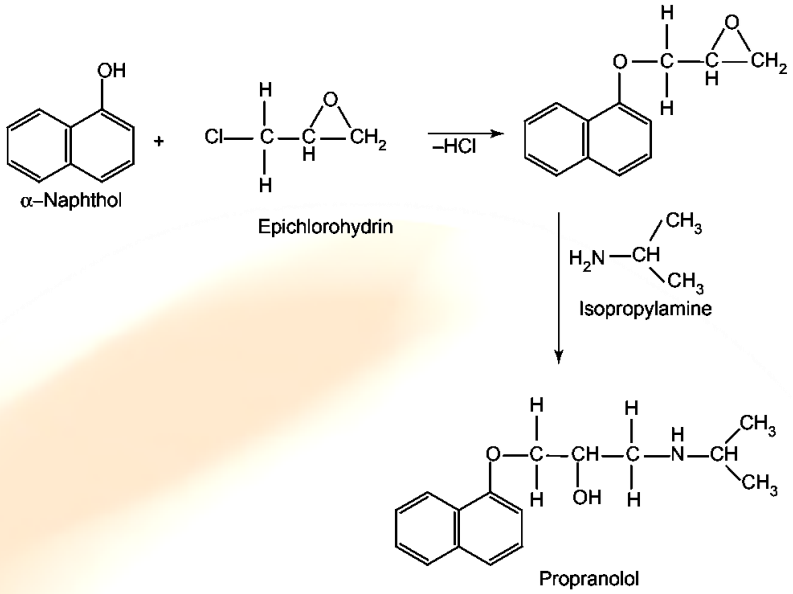
Catabolism of catecholamine



7. Give synthesis of propranolol and discuss SAR of β-blockers.

Answer

Synthesis of Propranolol



SAR of β-blockers

Ar-O-CH2-CH-CH2.NH.R
|
OH

- The O-CH2 group between aromatic ring and the ethylamino side chain is responsible for the antagonistic property.
- Replacement of catechol hydroxyl group with chlorine or phenyl ring retains the beta blocking activity.
- N,N- di substitution decrease beta blocking activity. Activity is maintained when phenylethyl, hydroxyl phenyl ethyl or methoxy phenyl ethyl groups are added to amine as a part of molecule.
- The two carbon side chain is essential for the activity.
- Nitrogen atom should be of secondary amine for optimum beta blocking activity.
- The carbon side chain having hydroxyl group must be S- configuration for optimum affinity to beta receptor.(Ex- Levobunolol, Timolol).
- The aryloxy propanolamines are more potent than aryl ethanolamines.
- Replacement of ethereal oxygen in aryloxy propanolamines with S, CH2 or N-CH3 is decreased the beta blocking activity.
- The most effective substituents at amino group is isopropyl and tertiary butyl group.
- The aromatic portion of the molecules could be varied with good activity.
- Converting the aromatic portion to phenanthrene or anthracene decrease the activity.

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