Cholinergic Antagonists
(Anticholinergic drugs)
(Antimuscarinic agents)

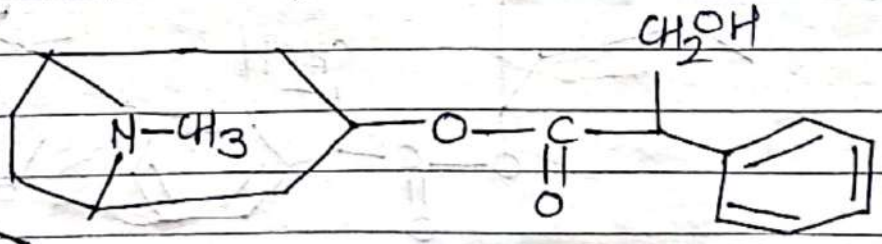
- Anticholinergic action by drugs and chemicals apparantly depends on their ability to reduce the number of free receptors that can interact with Acetylcholine

classification of Anticholinergic drugs :-

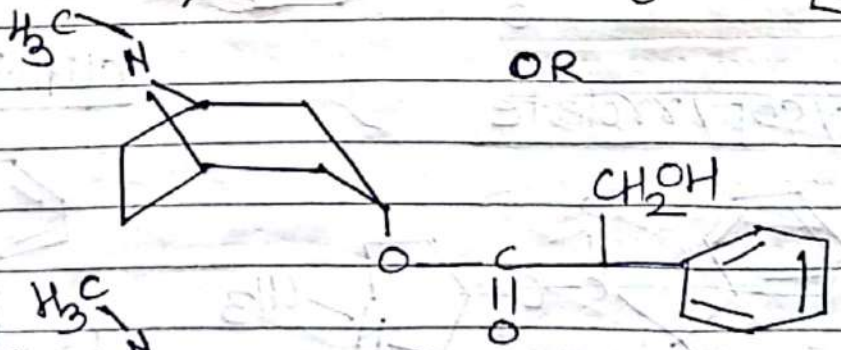
I. Solanaceous alkaloids & synthetic analogues.
II. Synthetic aminoalcohol esters.
III. Amino alcohol ethers.
IV. Amino alcohols.
V. Amino amides.
VI. Miscellaneous

- I Solanaceous alkaloids and synthetic analogues:-
(Amino alcohol esters)

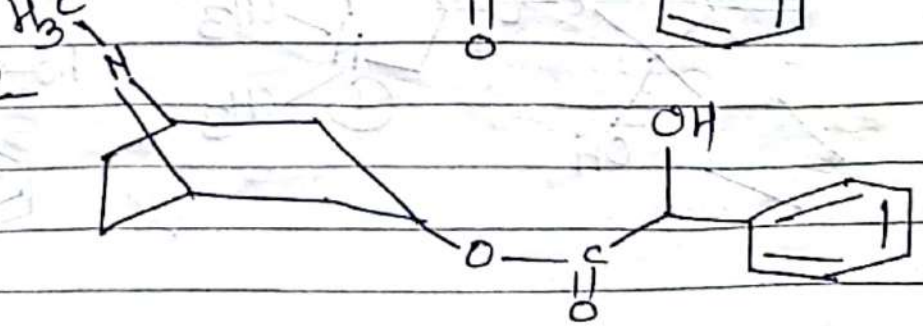
✓ Atropine



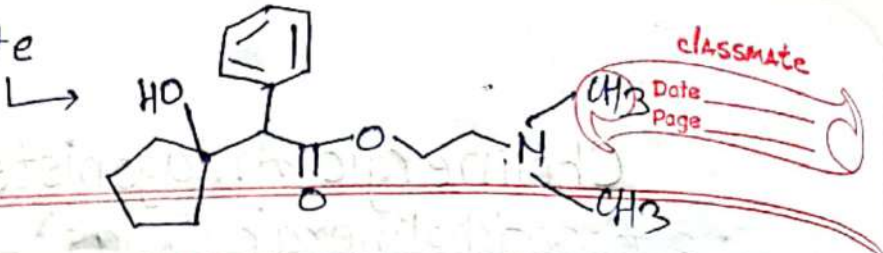
OR



Homatropine

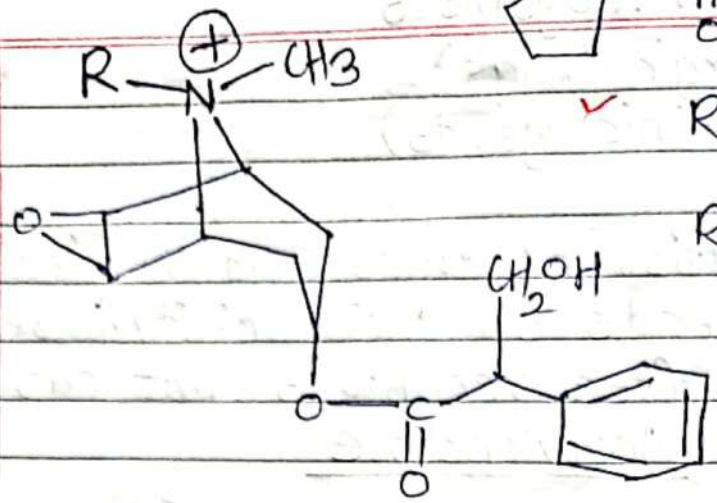


Cyclopentolate

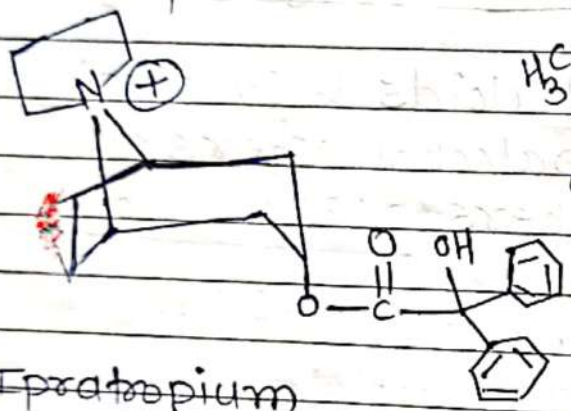


R=H, Scopolamine

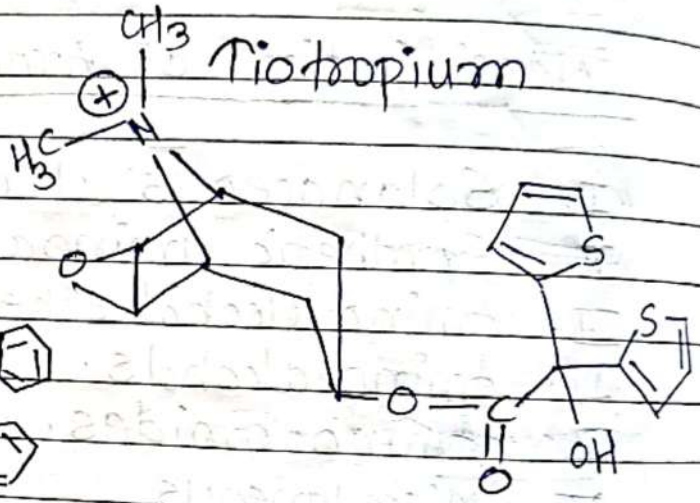
R=CH_3, Methscopolamine



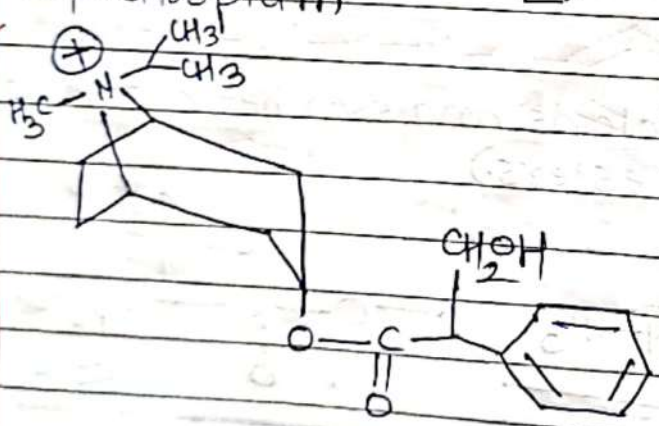
Trospium.



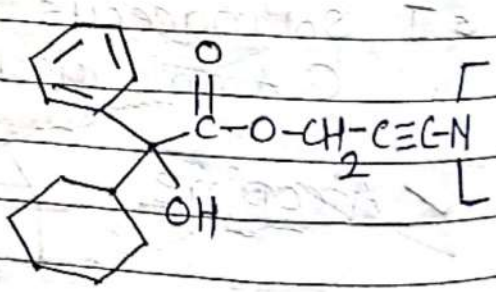
Tiotropium



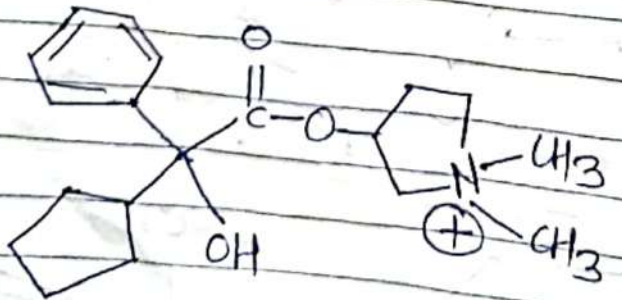
Ipratropium



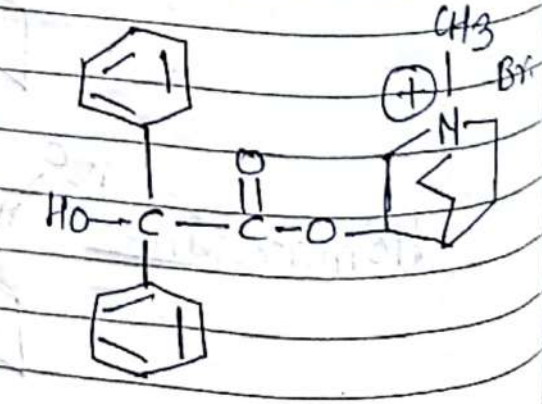
oxybutynin



Glycopyrrolate

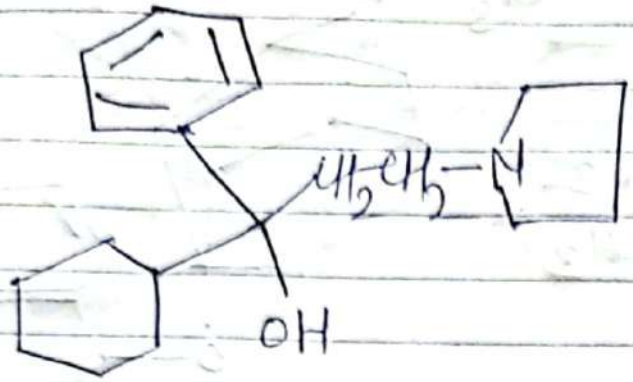


Clidinium bromide

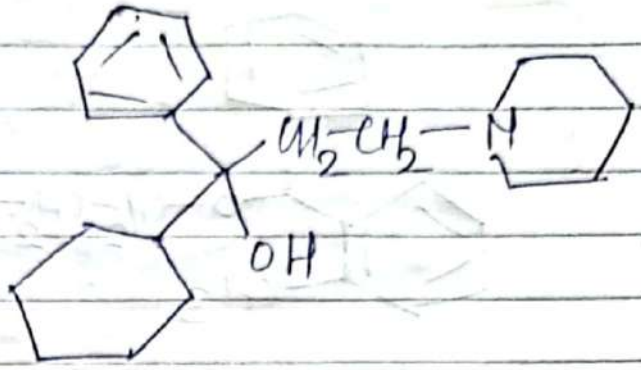


- Anticholinergic Amino Alcohols :-

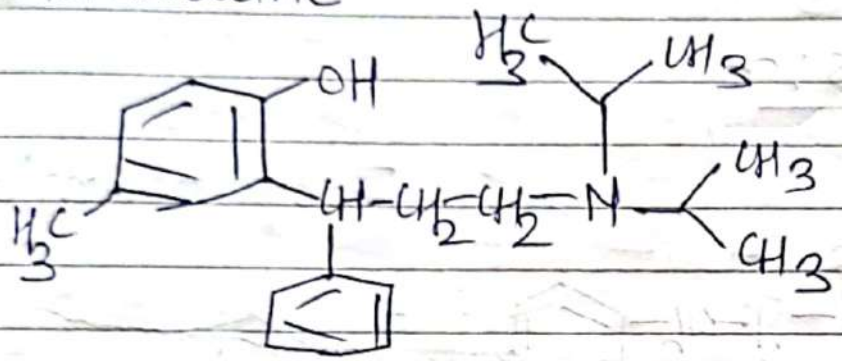
Procyclidine



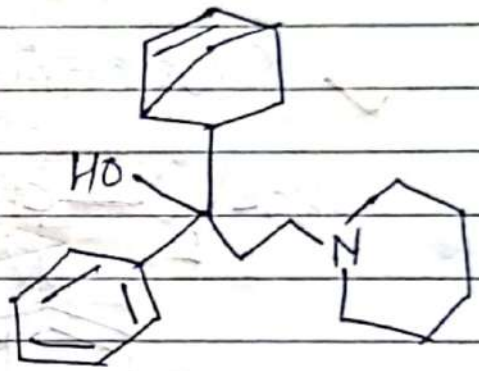
Trihexyphenidyl



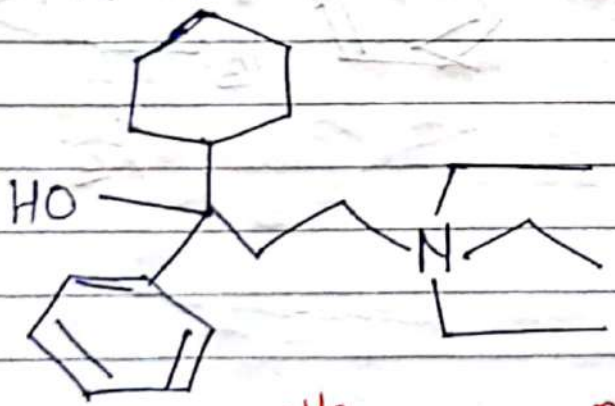
Tolterodine



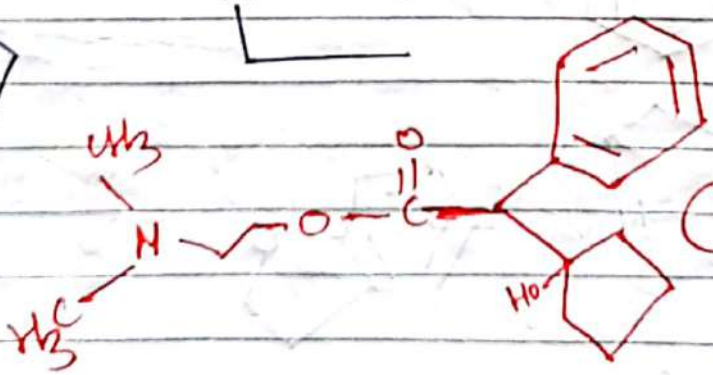
Biperiden



di
Trihexyethyl



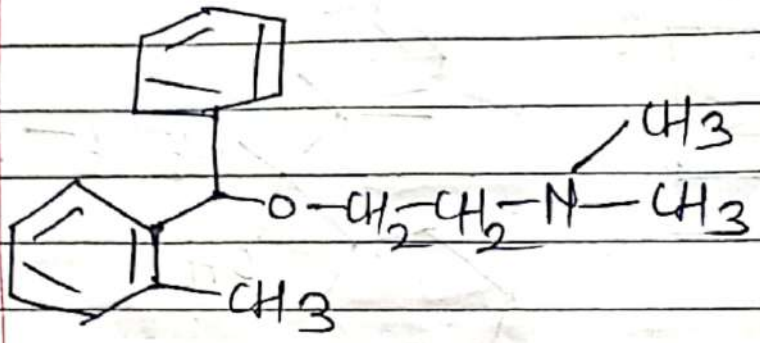
Cyclopentolate



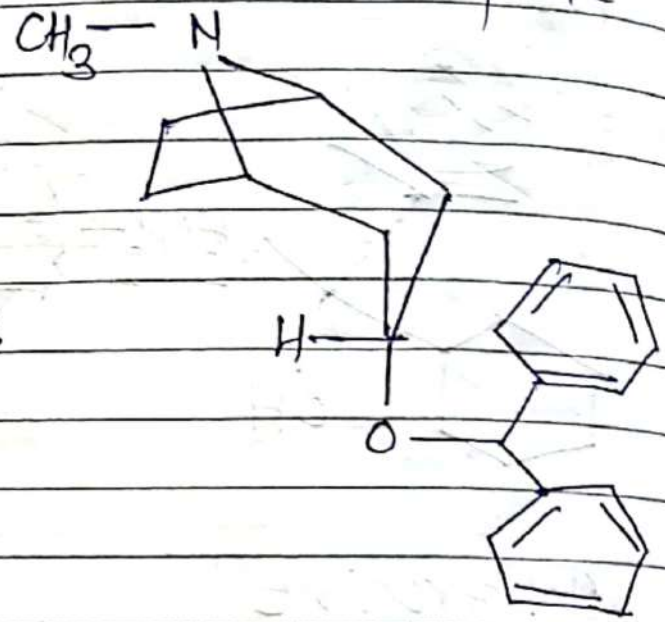
(Amino ester)

Amino Ethers :→

Orphenadrine

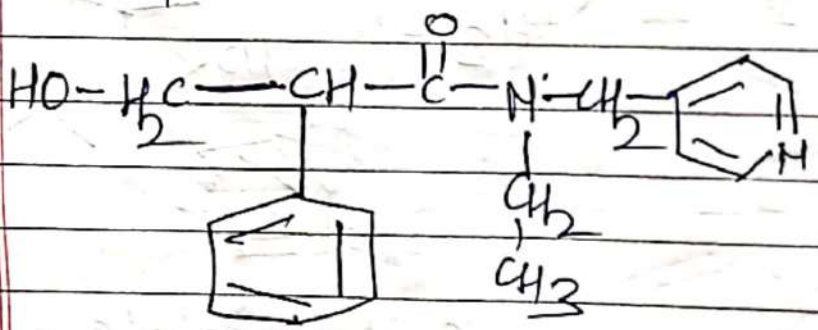


Benztropine

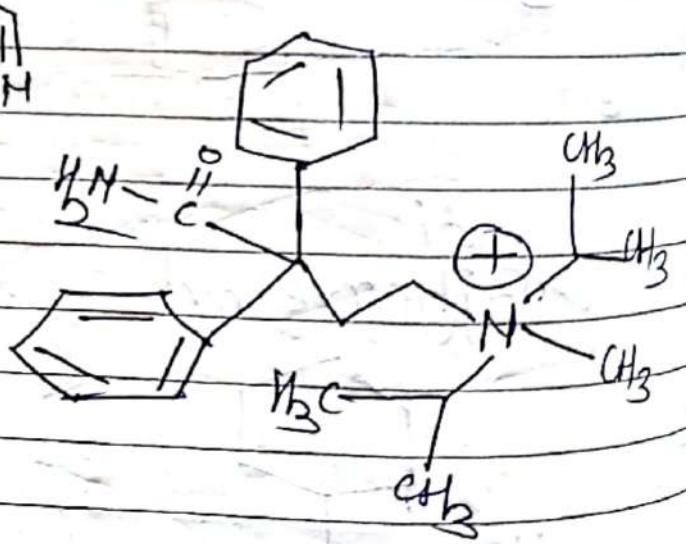


Amino Amides :→

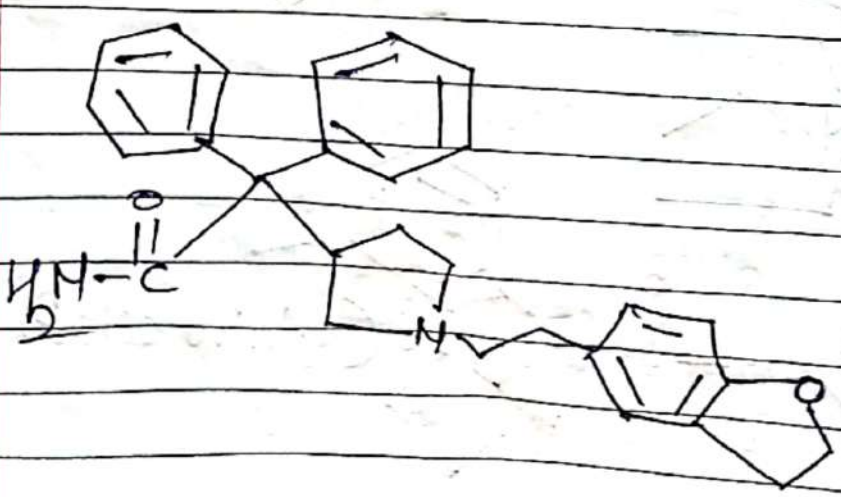
Tropicamide



Isopropamide

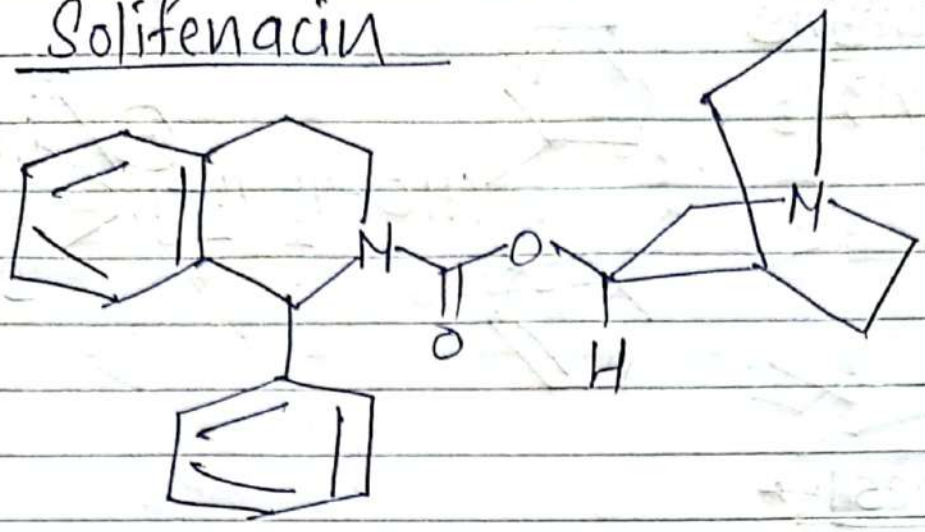


Darifenacin

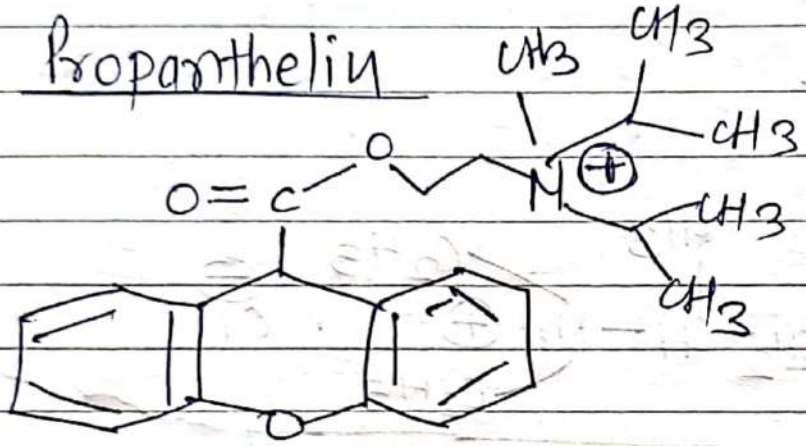


Amino esters :-

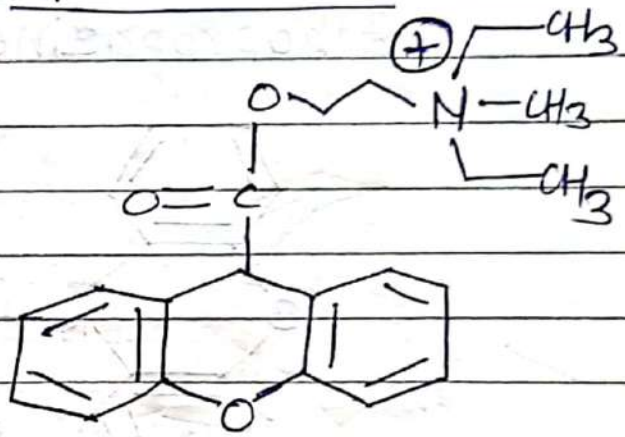
Solifenacin



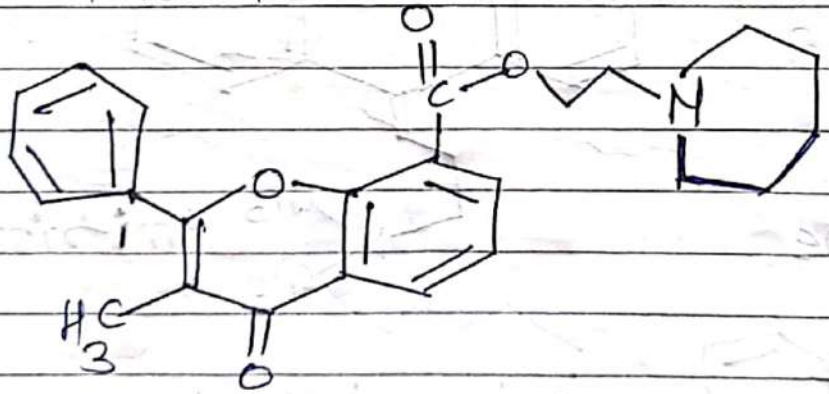
Propanthelin



methanthelin



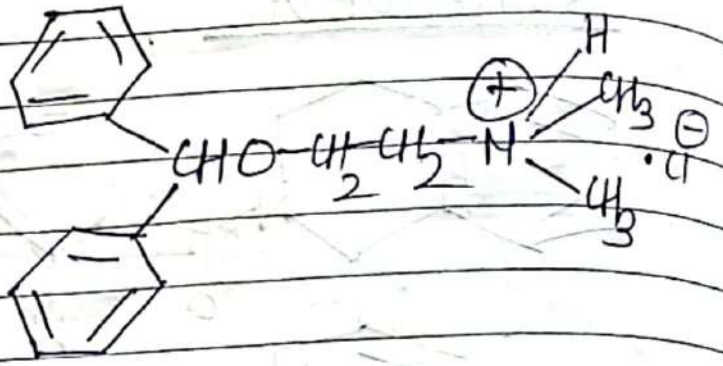
Flavoxate



Miscellaneous

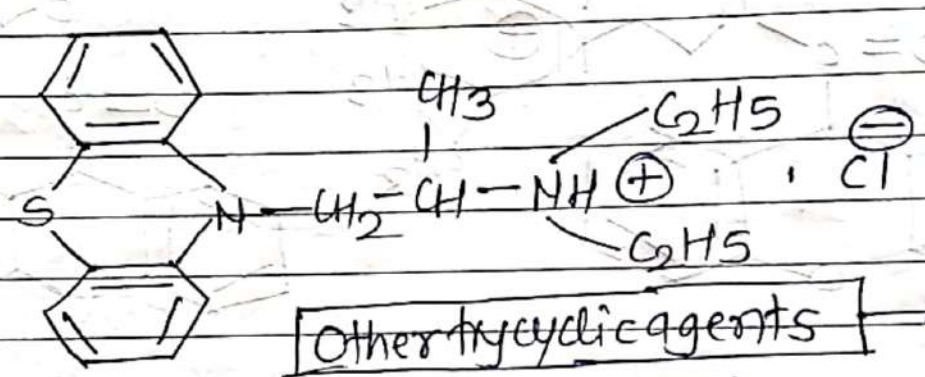
Antihistamine Anticholinergic agent

Diphenhydramine
(Benadryl)

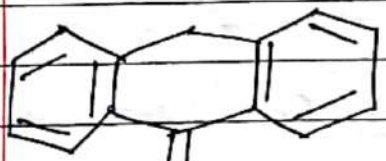


Phenothiazines

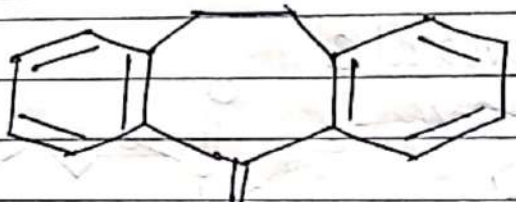
Ethopropazine



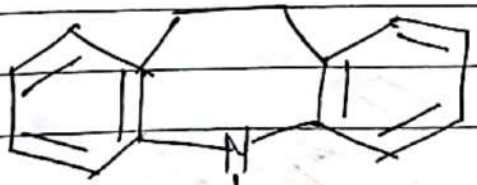
Other tricyclic agents



Nortriptyline



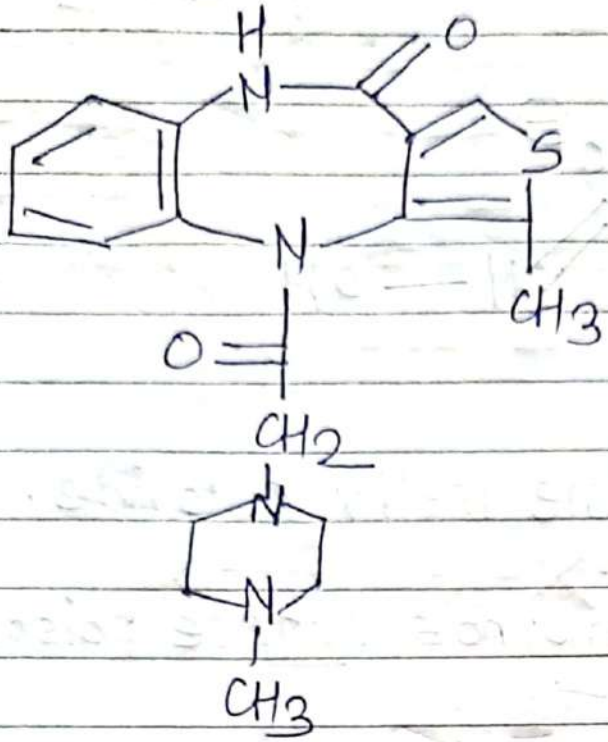
Amitriptyline



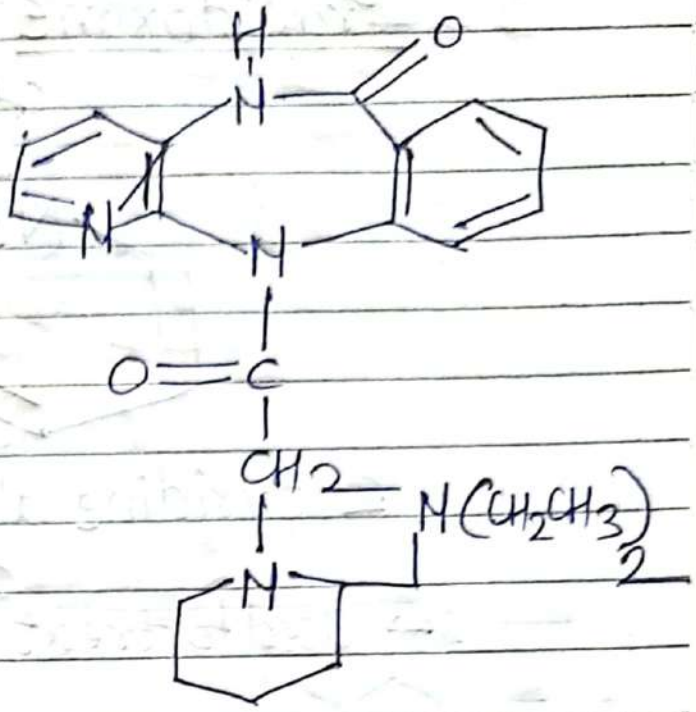
Imipramine

(Dibenzoazepine derivative)

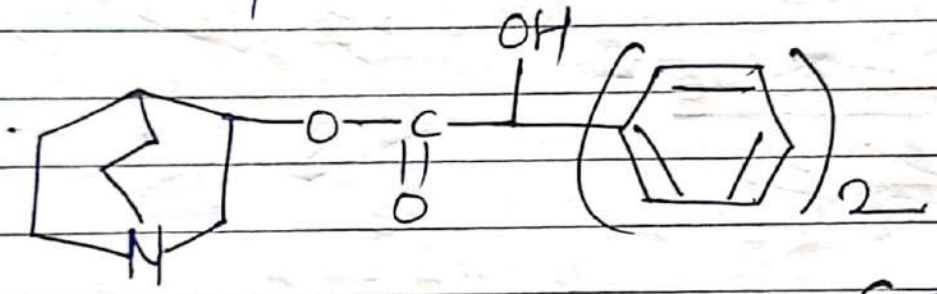
Recent muscarinic antagonists:-



Telenzepine



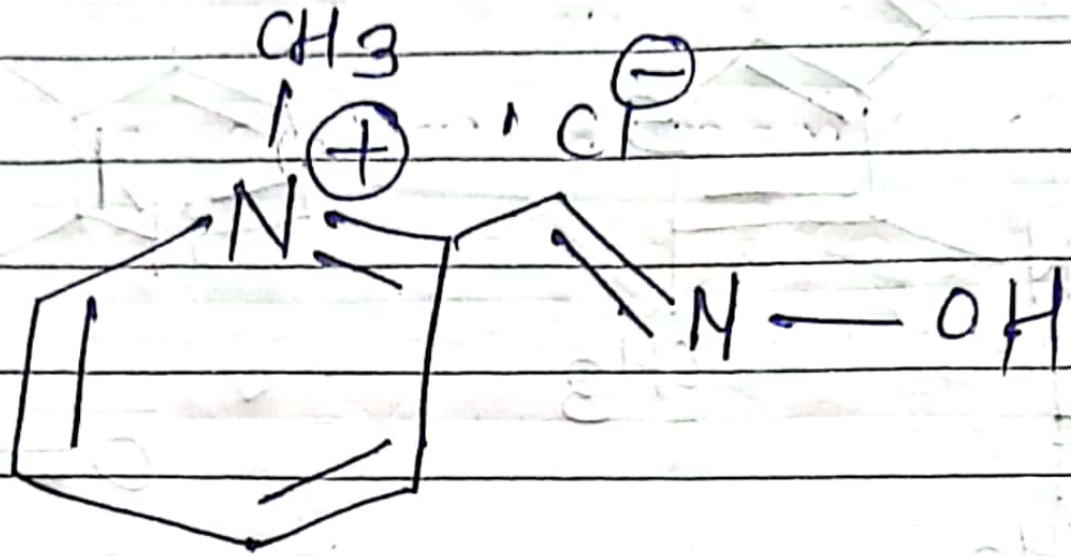
AFDX-116



3-Quinuclidinyl benzilate (QNB)

cholinesterase reactivator:→

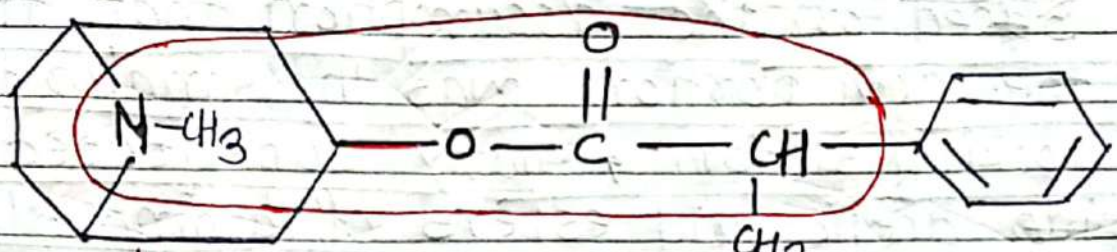
Pralidoxime :→



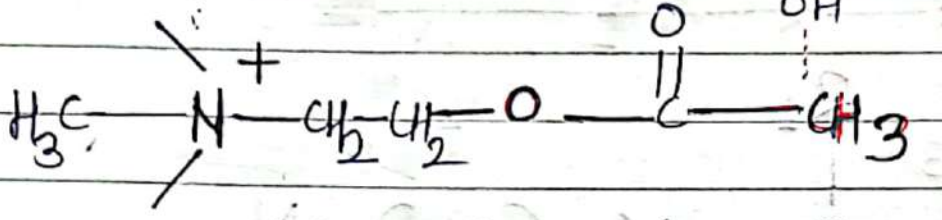
2-pyridine aldoxime methyl chloride.

→ used to treat Organophosphatase poisoning

SAR of Anticholinergic drugs :-
(SAR of muscarinic antagonists)



Atropine



Acetylcholine

- Atropine is prototype anticholinergic agent, provided the structural model that guided design of synthetic muscarinic antagonists for almost 70 years.
- Circled portion of atropine resembles with the Acetylcholine.

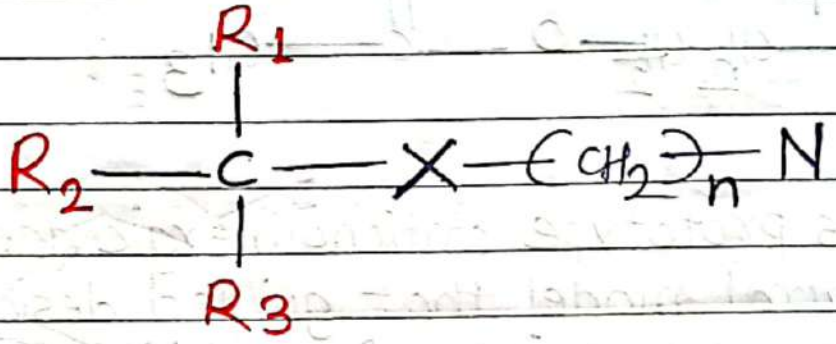
Although amine functional group is seperated from the ester oxygen by more than two carbons, the confirmation assumed by the tropine ring orients these two carbons such that intervening distance is similar to that in acetylcholine.

- One imp. difference - size of acyl portion of the molecules

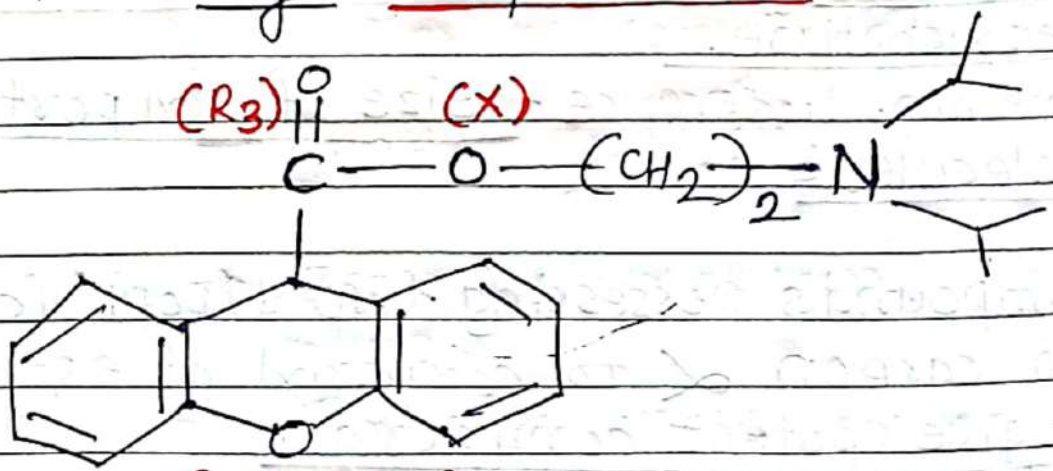
Compounds possessing two lipophilic groups on carbon α to carbonyl of ester moiety give potent compounds.

Atropine and Acetylcholine — Both are esters of amino alcohol.

- — Based on the assumption that the size of the acyl portion was the major factor in blocking action, many substituted amino acetic acid esters of amino alcohol were prepared and evaluated.



- substituents R_1 and R_2 should be carbocyclic or heterocyclic for maximal antagonist potency
  - Rings may be identicle
  - Rings when different → More potency
  - R_1 & R_2 may be combined in tricyclic ring system e.g. Propanthelin

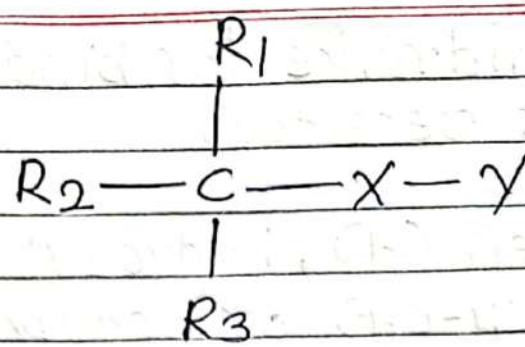


- If R_1 & R_2 → Napthalene ring — inactive compound.

Because of steric hindrance for binding with receptor. (muscarinic receptor)

- R3 may be hydrogen (H), hydroxyl (-OH), hydroxy methyl ($-CH_2-OH$) or carboxamide ($-\overset{O}{\overset{\|}{C}}-NH_2$) or component of the R1 & R2 ring system (one of two)
- If hydroxyl or hydroxy methyl is present → more potent compounds. — increases binding strength — by hydrogen bond interaction at the receptor.
- X-substituent — ester — not absolute necessity for muscarinic antagonist activity. — may be ether oxygen or may be absent completely.
- The N substituent is quaternary ammonium salt in the most potent anticholinergic drugs. Tertiary amines also possess antagonist activity. (binding to receptor in cationic form) The alkyl substituents are usually methyl, ethyl, propyl or isopropyl
- The distance between the ring substituted carbon and the amine nitrogen is apparently not critical. The length of alkyl chain connecting these may be from two to four carbons. Most potent agents have two methylene units in the chain.

I



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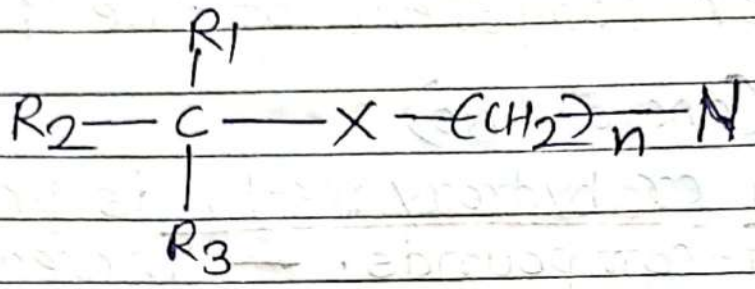

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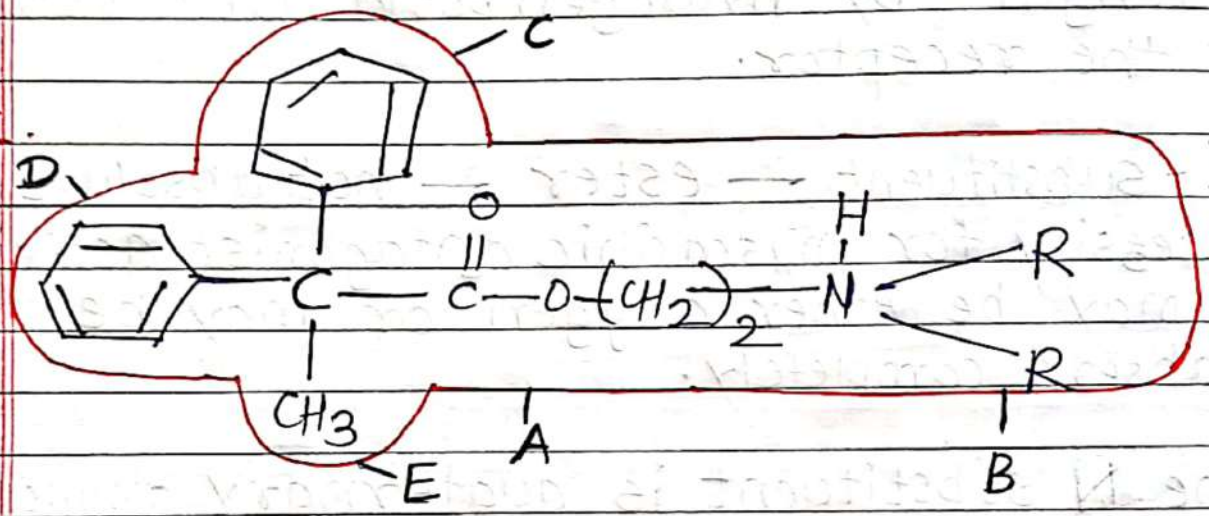

R_1 and R_2 → Cyclic structure (carbocyclic or heterocyclic), may be identical. may be combined.

R_3 → H, OH, $-CH_2OH$, CH_3

X → Ester, ether oxygen, H-bonding group.

Y (N) → Tertiary amine or quaternary ammonium.

A → hydrogen bonding site.
B → Anionic bonding site
D & C → Large hydrophobic area.
E → Small hydrophobic area

- Potent cholinergic blocking agents differ from agonists in three ways :-

I. Antagonist may contain larger groups than methyl on the nitrogen atom. (No larger than butyl)

II. Nitrogen atom in antagonist is not always quaternary as pH at receptor is below 7, this amino group is protonated and carries positive (+ve) charge that interacts with anionic site of receptor.

III. The acyl group in antagonist is always larger than . The larger acyl groups ensure that the compound is partial agonist.