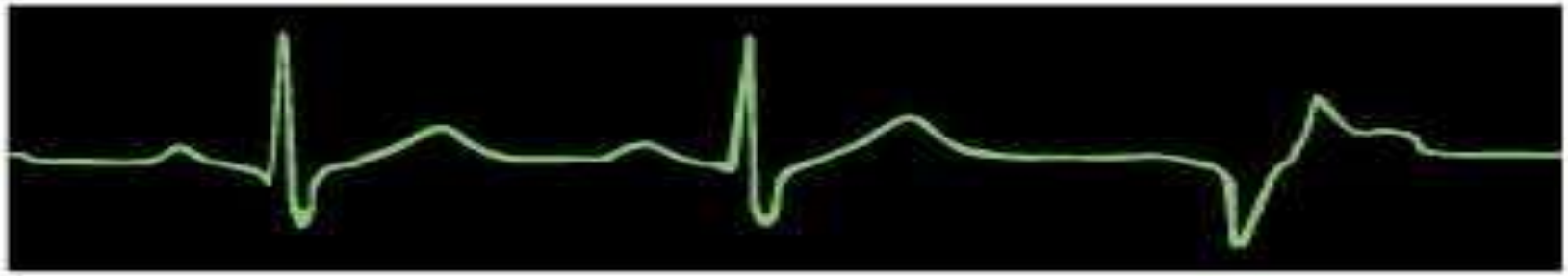
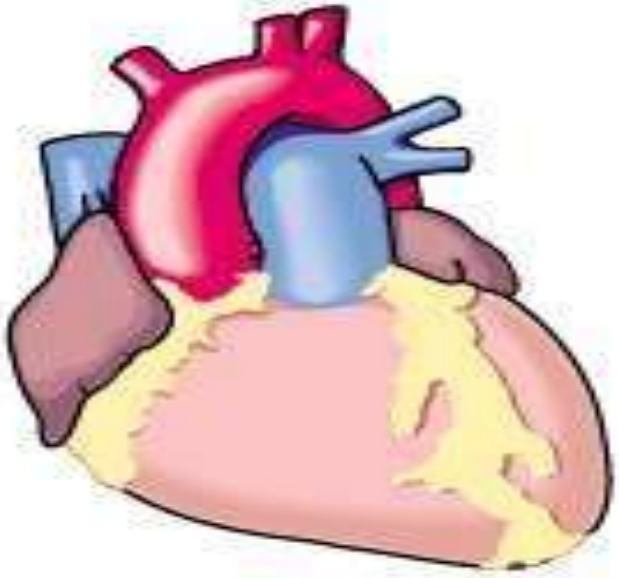
Antiarrhythmic Drugs





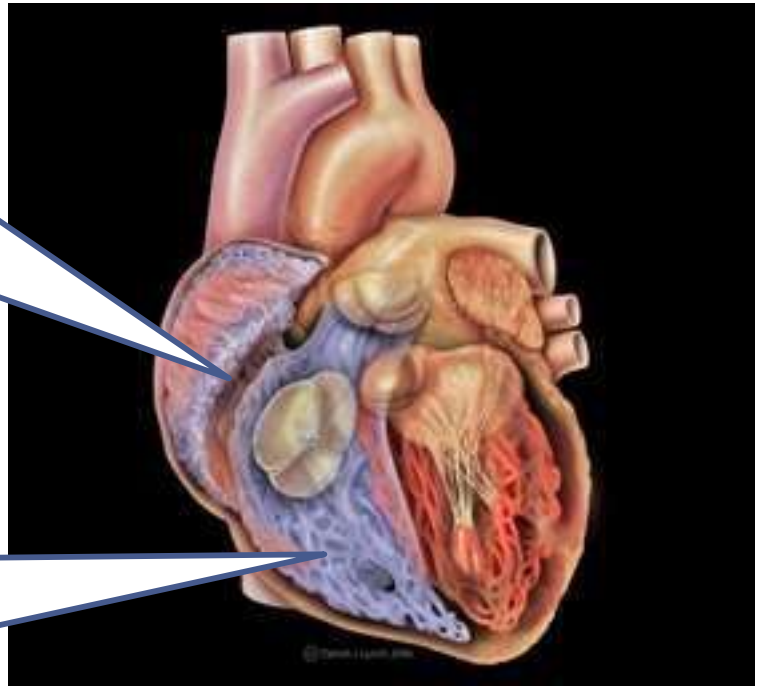
Arrhythmia

- Heart condition where disturbances in
  - Pacemaker impulse formation
  - Contraction impulse conduction
  - Combination of the two

Results in rate and/or timing of contraction of heart muscle that is insufficient to maintain normal cardiac output (CO)

Arrhythmia /dysrhythmia: abnormality in the site of origin of impulse, rate, or conduction

If the arrhythmia arises from atria, SA node, or AV node it is called supraventricular arrhythmia



If the arrhythmia arises from the ventricles it is called ventricular arrhythmia

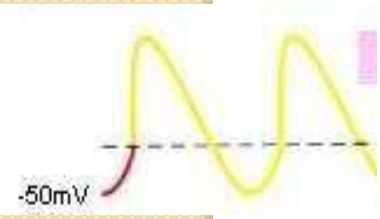
Causes of arrhythmia

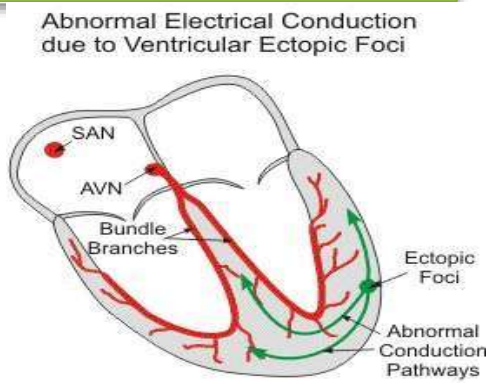
- arteriosclerosis
- Coronary artery spasm
- Heart block
- Myocardial ischemia

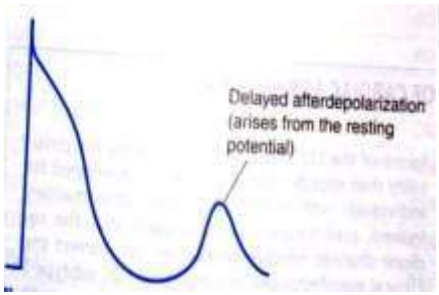
Mechnisms of Arrhythmogenesis

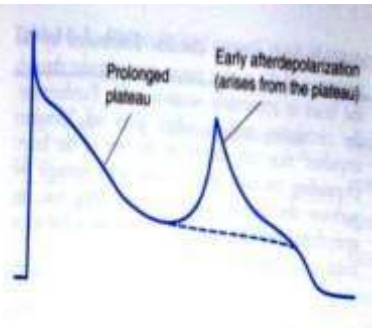
1- Abnormal impulse generation

- Automatic rhythms
  - Enhanced normal automaticity
    - ↑AP from SA node
  - Ectopic focus
    - AP arises from sites other than SA node
- Triggered rhythms
  - Delayed afterdepolarization
  - Early afterdepolarization





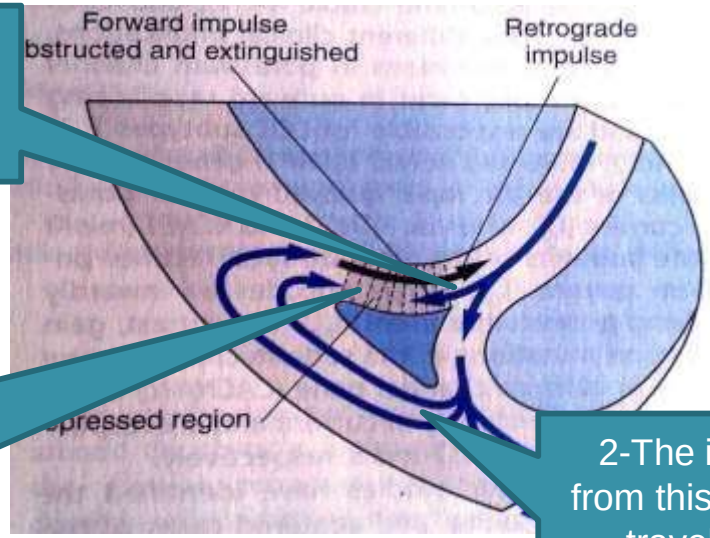




- 2-Abnormal conduction
  - Conduction block
    - 1st degree
    - 2nd degree
    - 3rd degree
  - Reentry
    - Circus movement
    - Reflection

This is when the impulse is not conducted from the atria to the ventricles

1-This pathway is blocked



3-So the cells here will be reexcited (first by the original pathway and the other from the retrograde)

2-The impulse from this pathway travels in a retrograde fashion (backward)

Antiarrhythmic drugs

Most antiarrhythmic drugs are pro-arrhythmic (promote arrhythmia)

- They are classified according to ***Vaughan William*** into four classes according to their effects on the cardiac action potential

class	mechanism	action	notes
I	Na^+ channel blocker	Change the slope of phase 0	Can abolish tachyarrhythmia caused by reentry circuit
II	β blocker	↓heart rate and conduction velocity	Can indirectly alter K and Ca conductance
III	K^+ channel blocker	1. ↑action potential duration (APD) or effective refractory period (ERP). 2.Delay repolarization.	Inhibit reentry tachycardia
IV	Ca^{++} channel blocker	Slowing the rate of rise in phase 4 of SA node(slide 12)	↓conduction velocity in SA and AV node

Classification of antiarrhythmics
(based on mechanisms of action)

Class I – membrane depressant drugs

blocker's of fast Na^+ channels

Subclass IA

Cause moderate Phase 0 depression
Prolong repolarization
Increased duration of action potential.

Examples

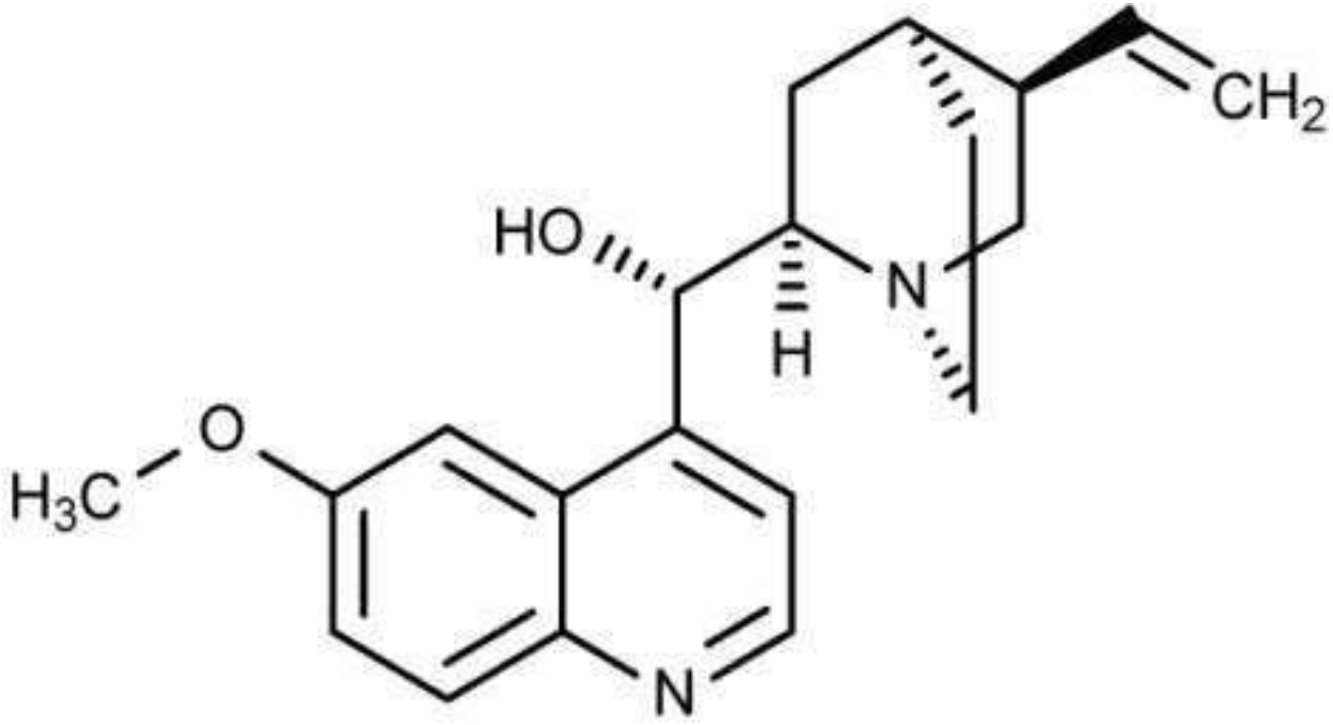
Quinidine

Procainamide

Phenytoin

Quinidine

1st antiarrhythmic used, treat both atrial and ventricular arrhythmias, increases refractory period..

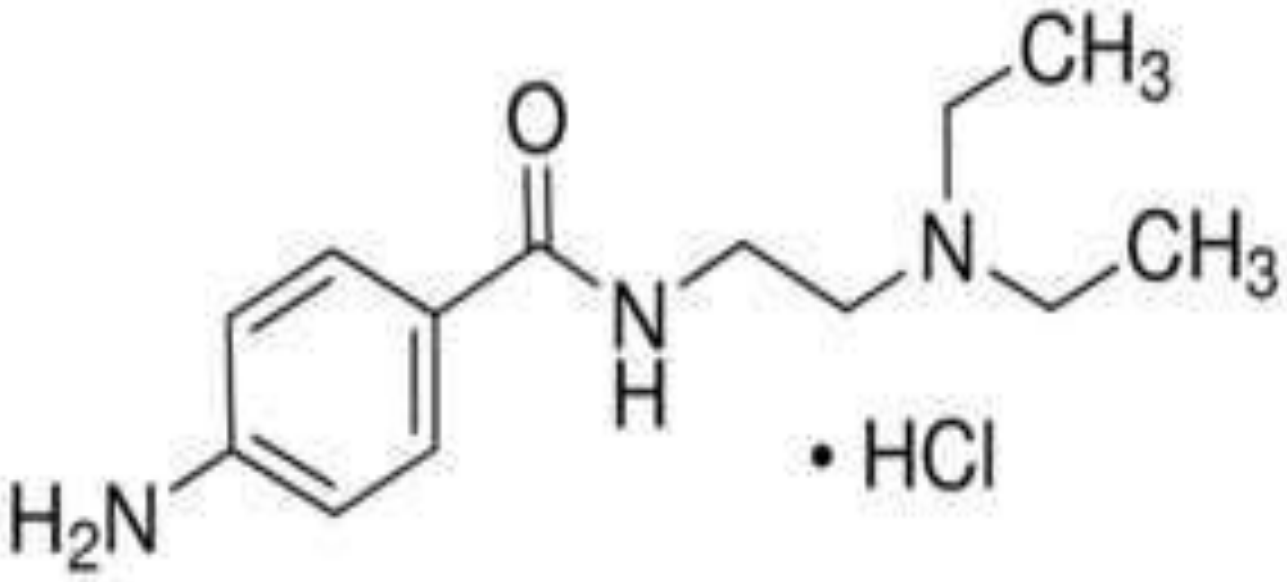


MOA

Quinidine blocks myocardia Na+ channel in the open state
Reduces automaticity and maximal rate
0 phase depolarization
In a frequency dependent manner

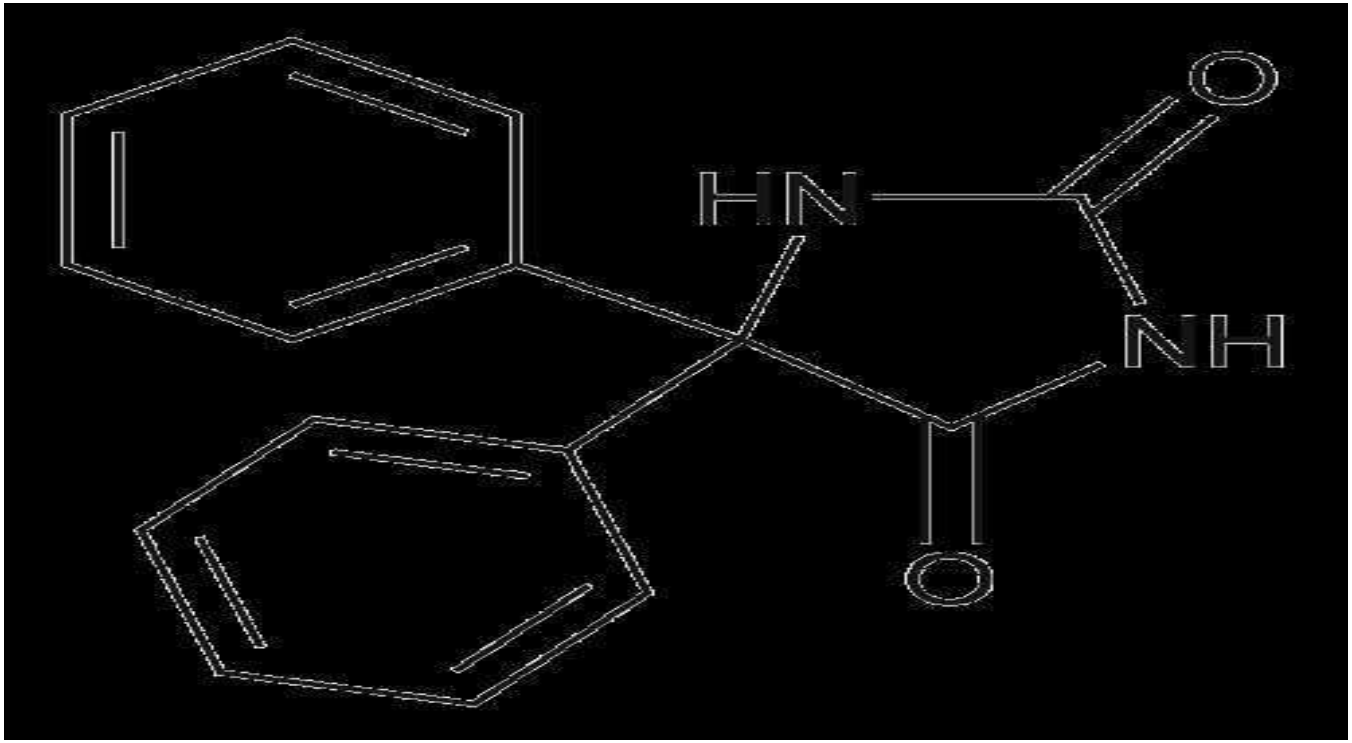
Procainamide

increases refractory period



Phenytoin

anticonvulsant that also works as antiarrhythmic similar to lidocaine.



Class II – β–adrenergic blockers

Based on two major actions

1)blockade of myocardial β–adrenergic receptors

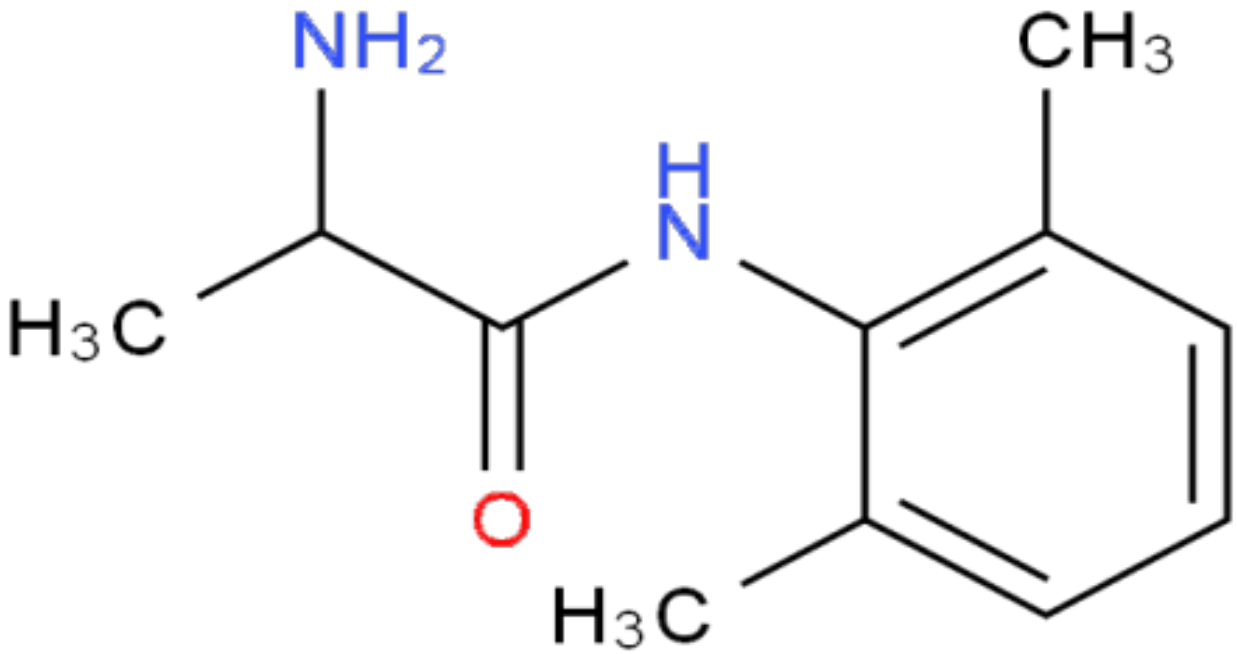
2)Direct membrane-stabilizing effects related to Na^+ channel blockade

Example

Tocainide

propranolol

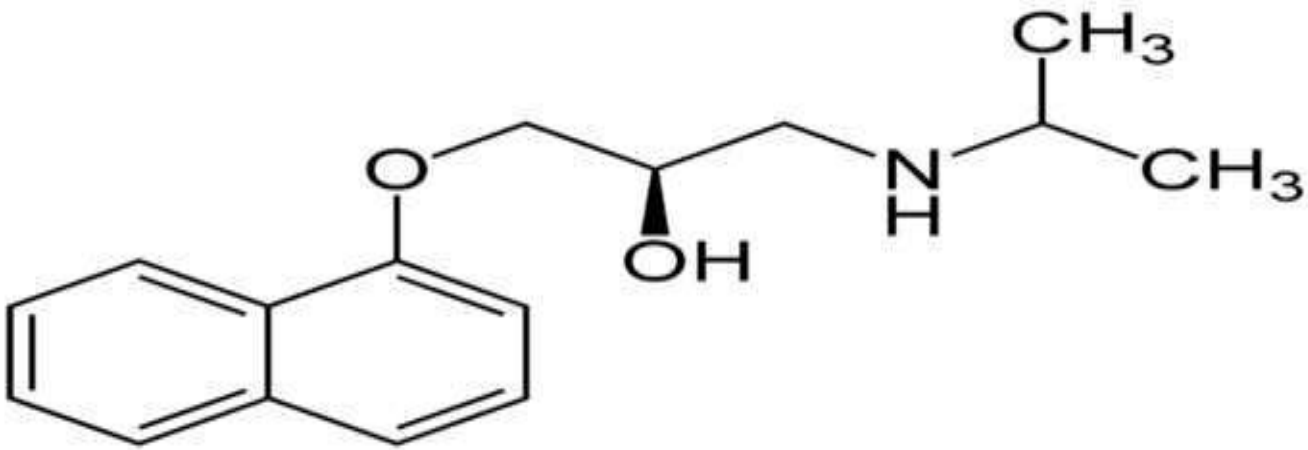
Tocainide



Propranolol

causes both myocardial β–adrenergic blockade and membrane-stabilizing effects
Slows SA node and ectopic pacemaking
Can block arrhythmias induced by exercise or apprehension
Other β–adrenergic blockers have similar therapeutic effect..

Propranolol



Class III–Repolarization prolongators

K^+ channel blockers

Developed because some patients negatively sensitive to Na channel blockers (they died!)

Cause delay in repolarization and prolonged refractory period.

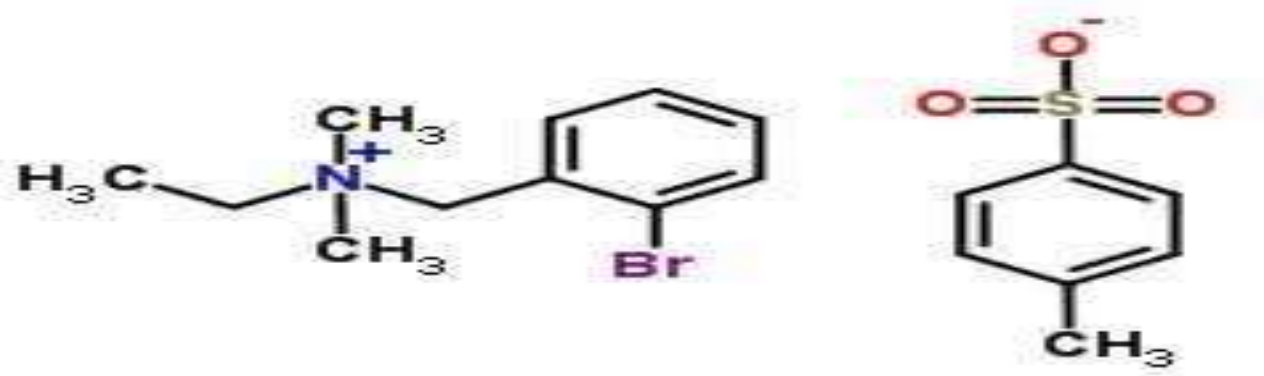
Examples

Bretylium

Amiodarone

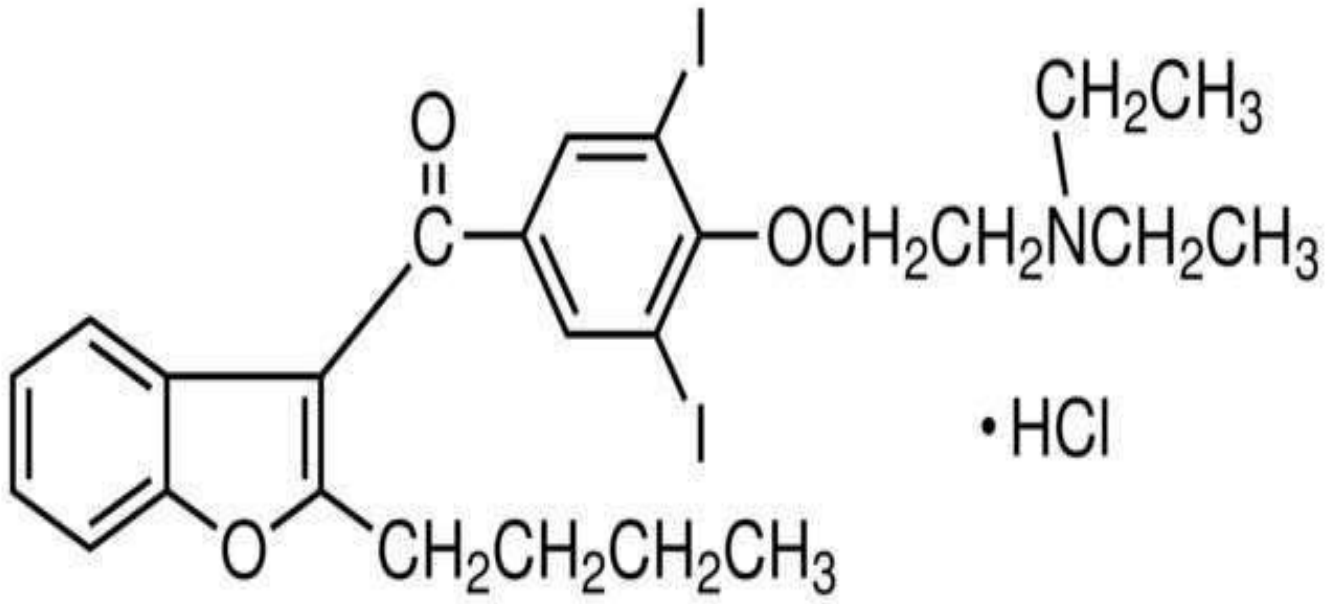
Bretylium Tosylate

first developed to treat hypertension but found to also suppress ventricular fibrillation associated with myocardial infarction



Amiodarone

prolongs action potential by delaying K^+ efflux but many other effects characteristic of other classes



Class IV – Ca^{2+} channel blockers

slow rate of AV-conduction in patients with atrial fibrillation

Examples

Diltiazem

Verapamil

Verapamil

blocks Na^+ channels in addition to Ca^{2+}; also slows SA node in tachycardia

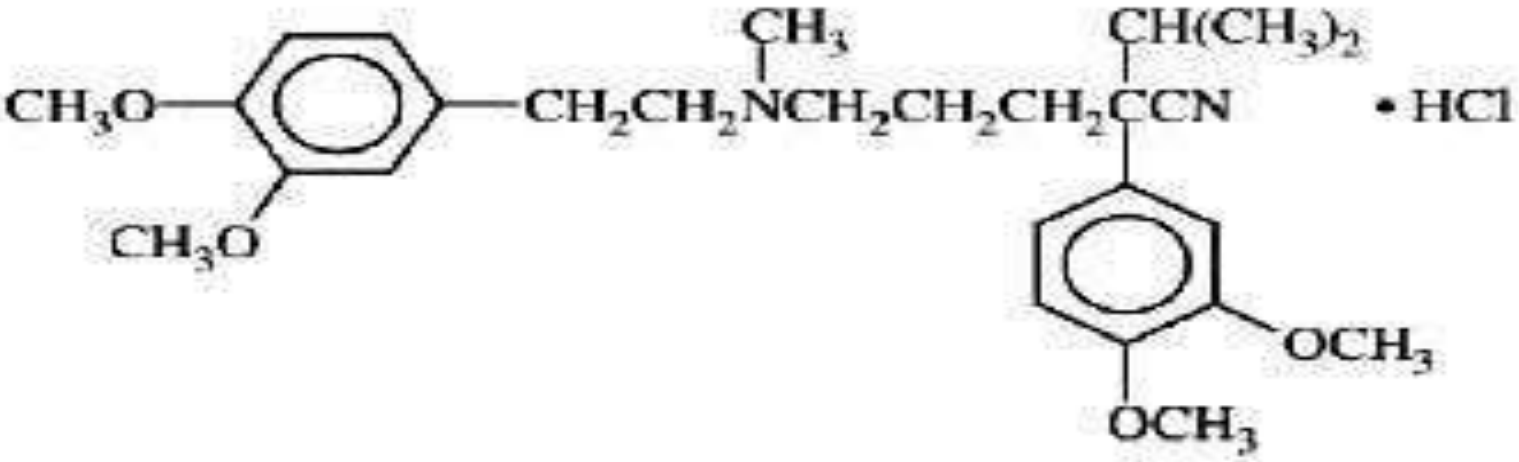
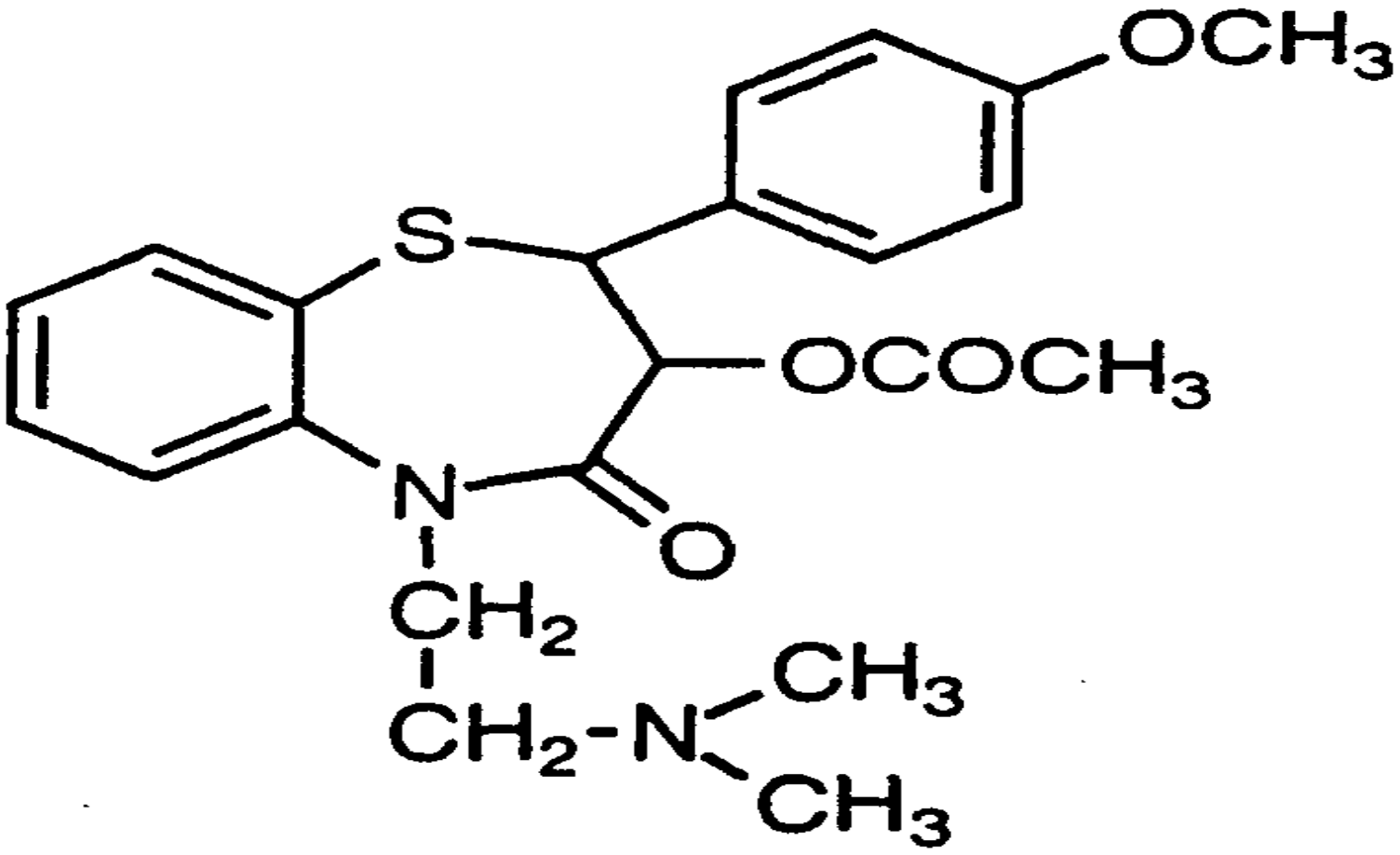


Fig. 1. Structural formula of verapamil hydrochloride.

Diltiazem



DISOPYRAMIDE PHOSPHATE

Synthesis