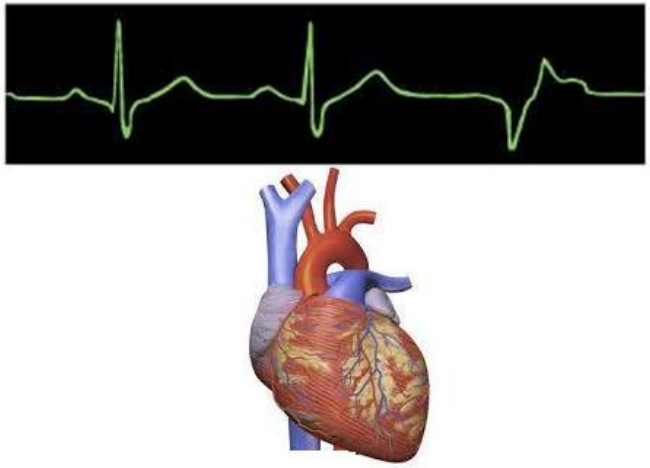
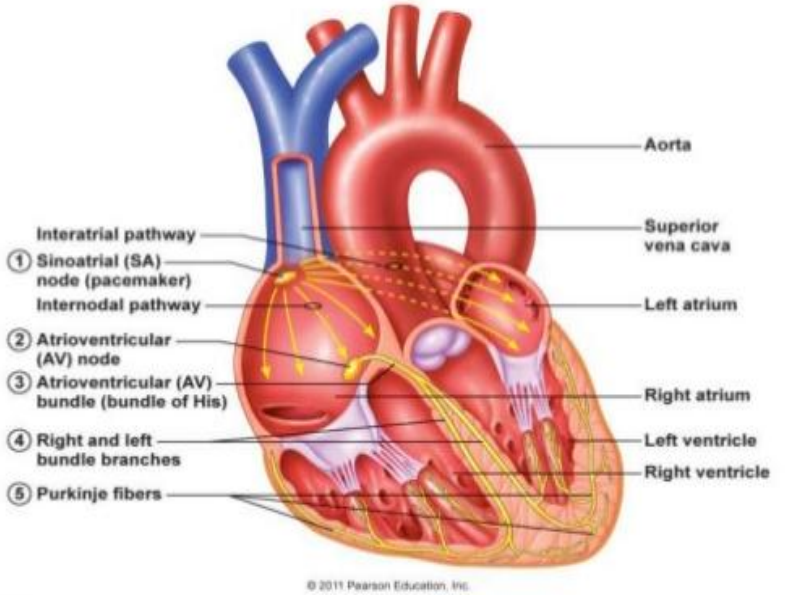
Antiarrhythmic Drugs



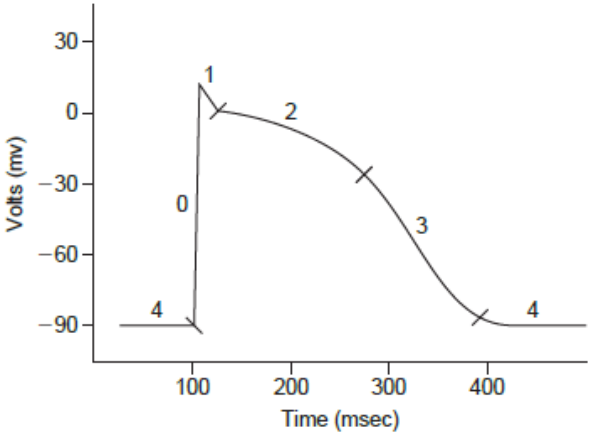
Arrhythmia

Arrhythmia is an alteration in the normal sequence of electrical impulse rhythm that leads to contraction of the myocardium. It is manifested as an abnormality in the rate, in the site from which the impulses originate, or in the conduction through the myocardium. The rhythm of the heart normally is determined by a pacemaker site called the SA node, which consists of specialized cells that undergo spontaneous generation of action potentials at a rate of 100 to 110 action potentials ("beats") per minute. This intrinsic rhythm is strongly influenced by the vagus nerve, overcoming the sympathetic system at rest. This "vagal tone" brings the resting heart rate down to a normal sinus rhythm of 60 to 100 beats per minute. Sinus rates below this range are termed "sinus bradycardia," and sinus rates above this range are termed "sinus tachycardia." The sinus rhythm normally controls both atrial and ventricular rhythm. Action potentials generated by the SA node spread throughout the atria, depolarizing this tissue and causing atrial contraction. The impulse then travels into the ventricles via the AV node. Specialized conduction pathways within the ventricle rapidly conduct the wave of depolarization throughout the ventricles to elicit ventricular contraction. Therefore, normal cardiac rhythm is controlled by the pacemaker activity of the SA node. Abnormal or irregular cardiac rhythms (heartbeats) can occur when the SA node fails to function normally, when other pacemaker sites (e.g., ectopic pacemakers) trigger depolarization, or when a dysfunction occurs along the normal conduction pathways.



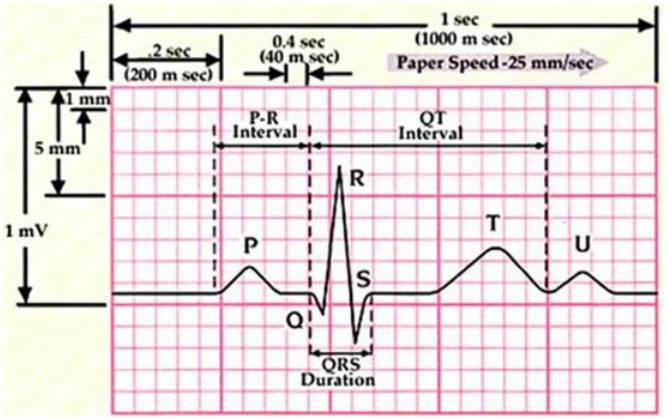
•If the arrhythmia arises from atria, SA node, or AV node it is called supraventricular arrhythmia

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



Cardiac action potential recorded from a Purkinje fiber

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)

Tachycardia (mostly seen)

Bradyarrhythmia ⟹ for therapy Atropine (parasymphatolytic)

β-mimetics: Efedrine

Isoprenaline

Metaproterenol

Terbutaline

Antiarrhythmic Drugs

- Causes of arrhythmia
- Arteriosclerosis
- Coronary artery spasm
- Heart block
- Myocardial ischemia

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

Classification of antiarrhythmics (based on mechanisms of action)

Summary of the Cardiac Physiologic Effects of the Antiarrhythmic Drugs

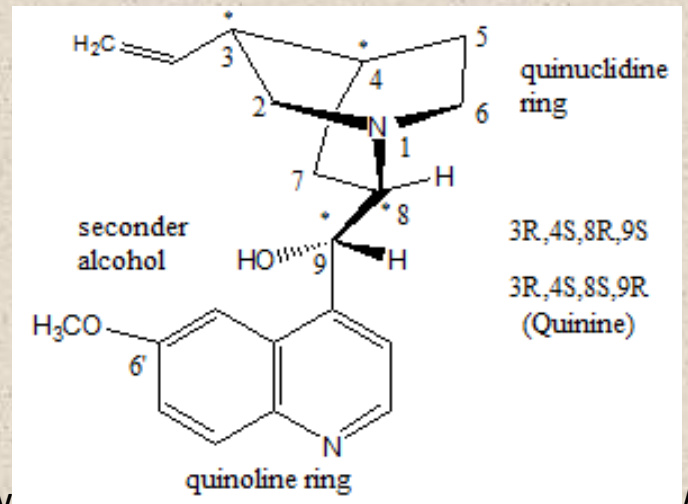
Classification	Mechanism of Action	Primary Sites of Action	Drug Examples
Class IA	Na^+ channel blockade		Quinidine
	Intermediate rate of dissociation from sodium channels		Procainamide
	Slows phase 0 depolarization	Atrial and ventricular tissue	Disopyramide
	Prolongs action potential duration		
	Slows conduction		
Class IB	Na^+ channel blockade		Lidocaine
	Rapid rate of dissociation from sodium channels		Mexiletine
	Shortens phase 3 repolarization	Ventricular tissue	Phenytoin
	Shortens action potential duration		Tocainide
Class 1C	Na^+ channel blockade	Ventricular tissue	Flecainide
	Slows rate of dissociation from sodium channels		Encainide
	Markedly slows phase 0 depolarization		Propafenone
	Slows conduction		Moricizine
Class II	Blocks sympathetic stimulation of β_1-adrenergic receptors	SA node	Propranolol
	Slows phase 4 depolarization	AV node	Sotalol
	Slows firing of SA node and conduction through AV node, prolonging repolarization		β_1-Blockers
Class III	K^+ channel blockade (block delayed rectifier current)	Atrial and ventricular tissue	Amiodarone
	Prolongs phase 3 repolarization		Dronedarone Sotalol
	Prolongs duration of action potential, which prolongs refractory period		Bretylium
Class IV	Ca^{+2} channel blockade	SA node	Verapamil
	Slows phase 4 depolarization	AV node	Diltiazem
	Slows firing of SA node and conduction through AV node, prolonging repolarization of AV node		

AV, atrioventricular; SA, sinoatrial.

Class IA Antiarrhythmic Drugs

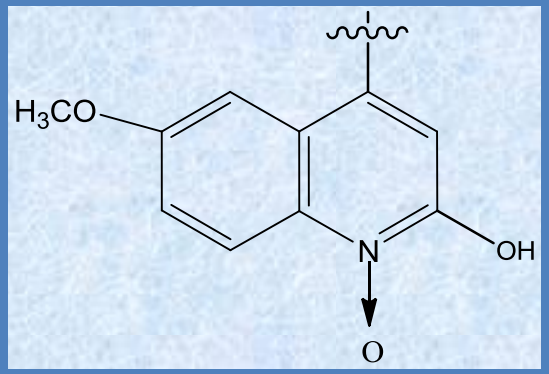
- Na Channel Blockade
- Cause moderate Phase 0 depression
- Prolong repolarization
- Increased duration of action potential.

Quinidine



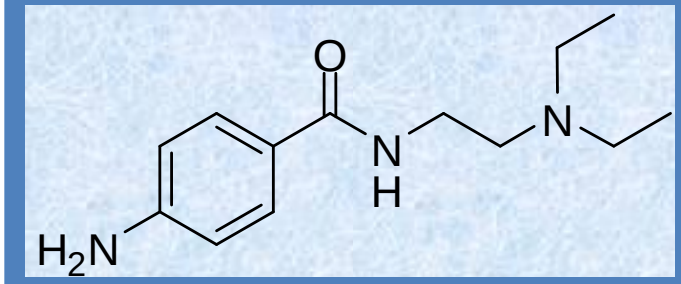
* Two basic nitrogen and basic character (Water-soluble salt forms).

***2. Position aromatic hydroxylation**
***O-Demethylation**
***N-Oxidation**
***3. Position allylic hydroxylation**



Quinidine → alkaloid from Cinchona officinalis L. bark

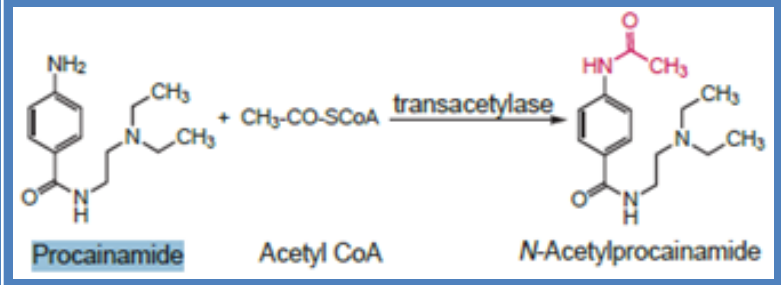
Procainamide (Pronestyl)



4-amino-N-(2-(diethylamino)ethyl)benzamide

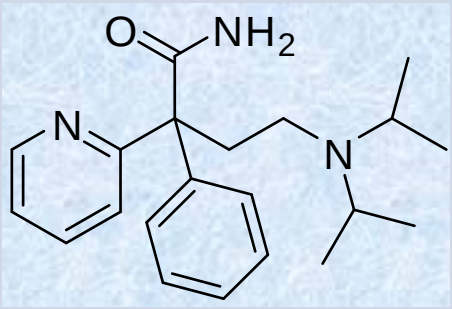
-Similarity to local anesthetic procaine (ester bio-isostere of procainamide)
- More resistant to both enzymatic and chemical hydrolysis
- Limited local anesthetic activity

Metabolism : via N-Acetyl transferase



25% activity

Disopyramide (Norpace, Rythmodul)



4-(diisopropylamino)-2-phenyl-2-(pyridin-2-yl)butanamide

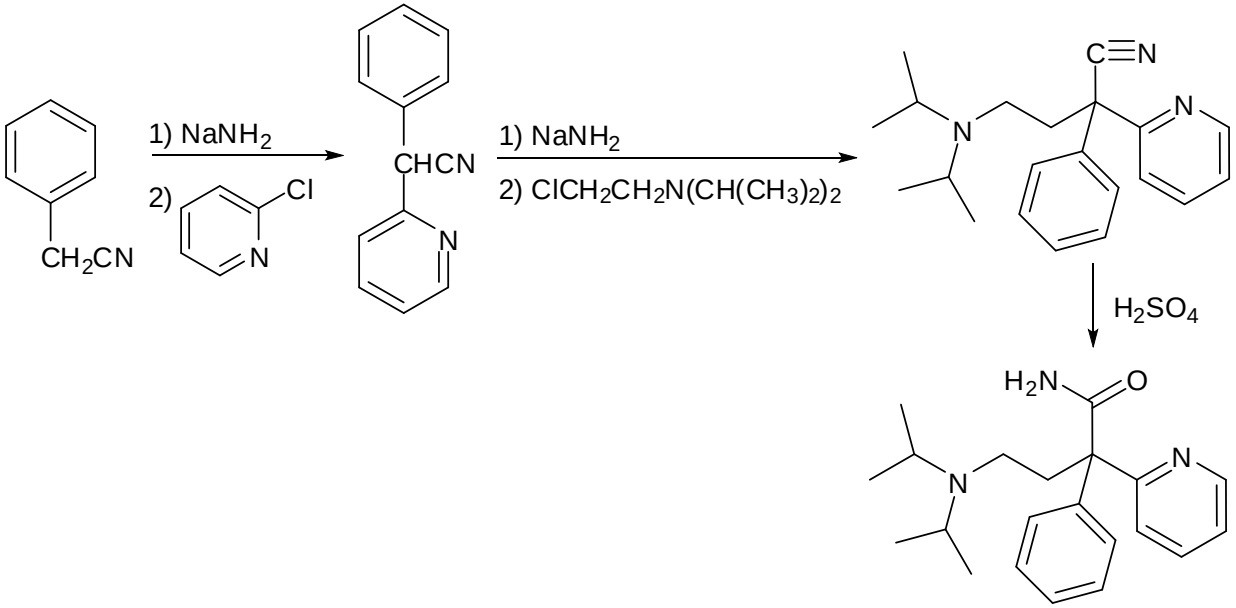
- Cardiac effects are very similar to procainamide
-Used orally for treatment of ventricular and atrial arrhythmias

Metabolism: N-dealkylation (50% activity)

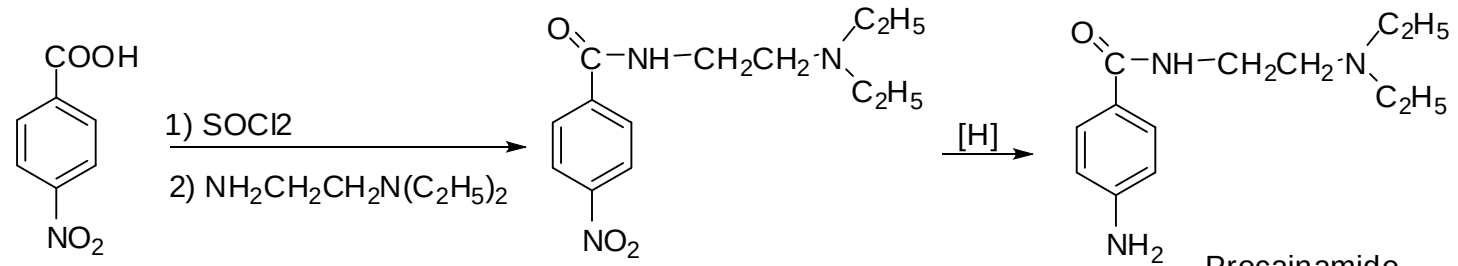
Adverse effects are primarily Anticholinergic ; dry mouth, blurred vision, constipation, and urinary retention

Synthesis

Disopramide:



Procainamide:

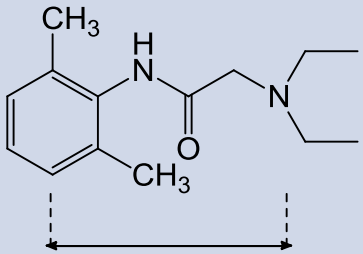
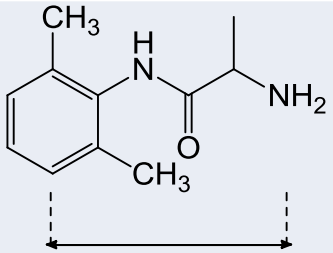
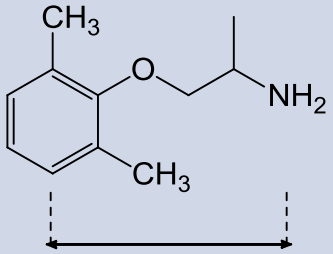


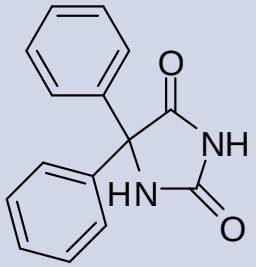
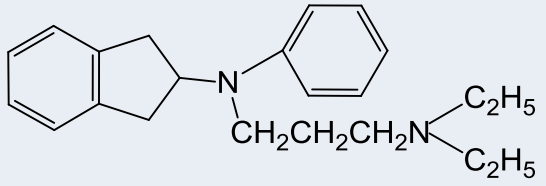
4-Nitrobenzoic acid

Procainamide

Class IB Antiarrhythmic Drugs :

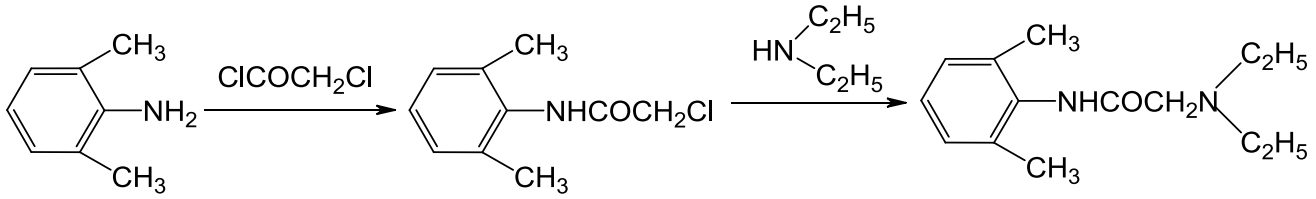
Used especially vetricular arrhythmias (VA)
(m-xylene is the common structure)

Compound	Formula	
Lidocaine (Aritmal, Jetokain simpleks, Dolocain) 2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide *Orally inactive-oxidative dealkylation		Typically the drug of choice for emergency treatment of VA
Tocainide (Xyloton) 2-amino-N-(2,6-dimethylphenyl)propanamide		
Mexiletine (Mexitil) 1-(2,6-dimethylphenoxy)propan-2-amine (can be used orally)		

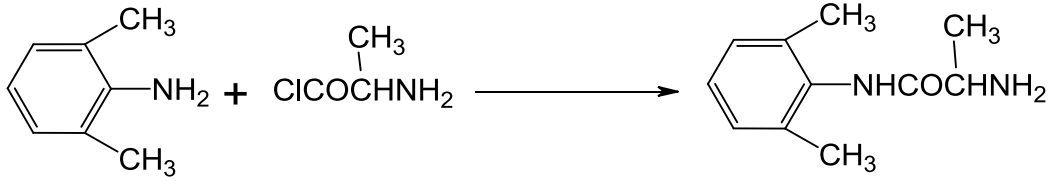
Compound	Formula
Phenytoin 5,5-diphenylimidazolidine-2,4-dione Used in epilepsy with grand mal seizure Useful for Digitalis toxicity arrhytmias	
Aprindine N^1-(2,3-dihydro-1H-inden-2-yl)-N^3,N^3-diethyl-N^1-phenylpropane-1,3-diamine	

Synthesis

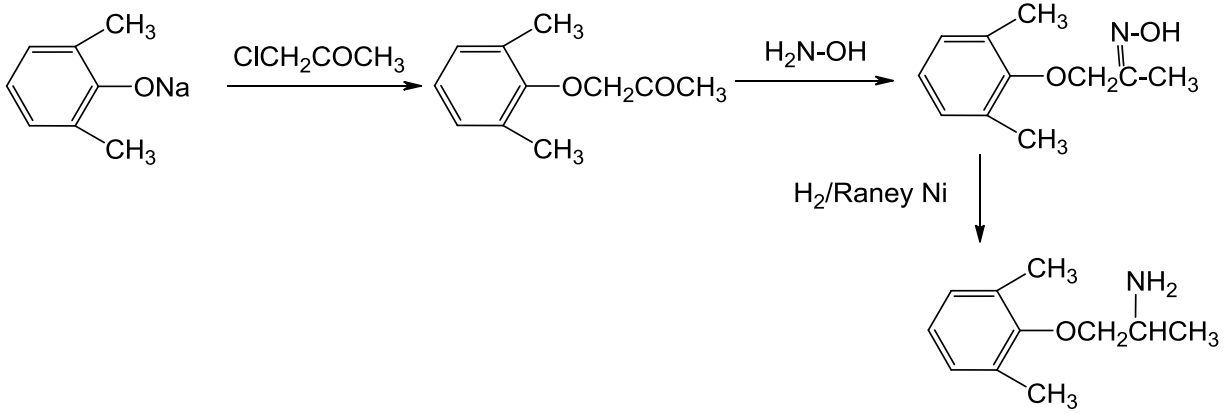
Lidocaine :



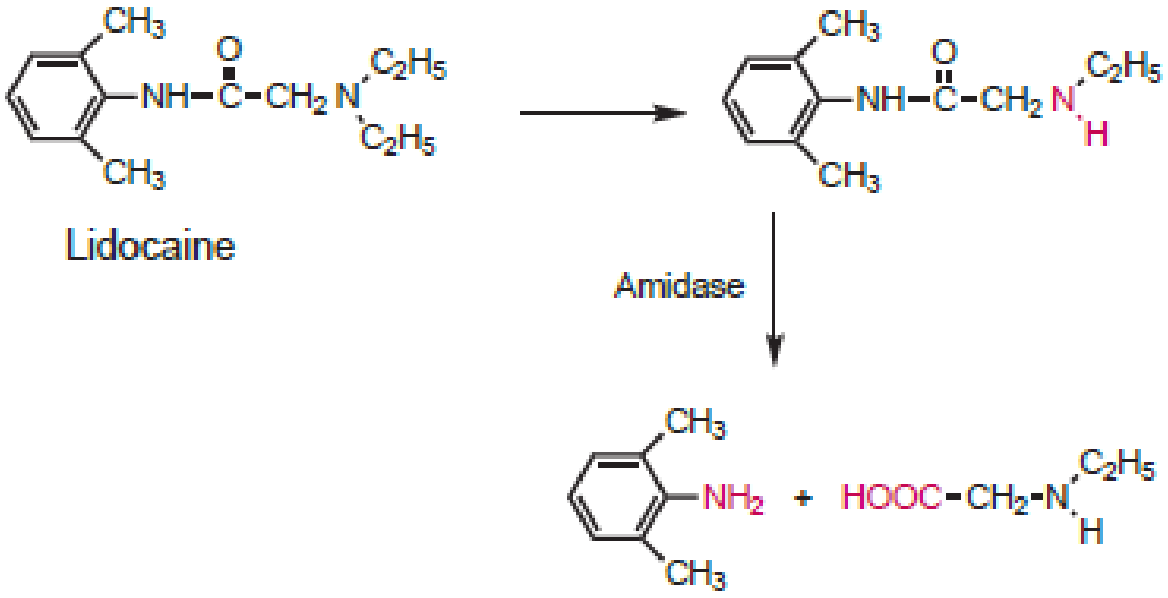
Tocainide:



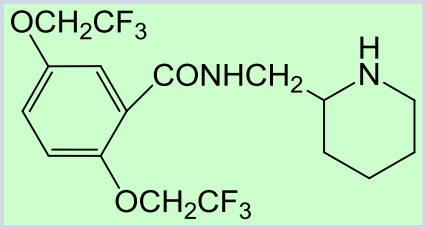
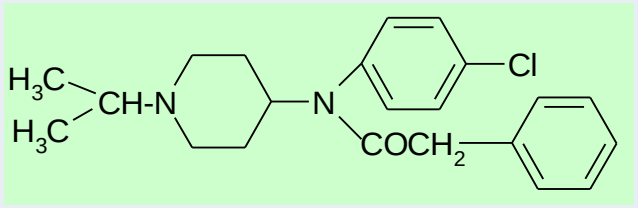
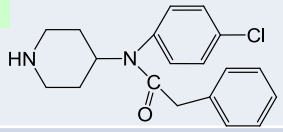
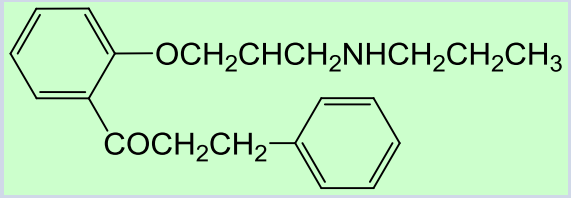
Mexiletine:



Metabolism

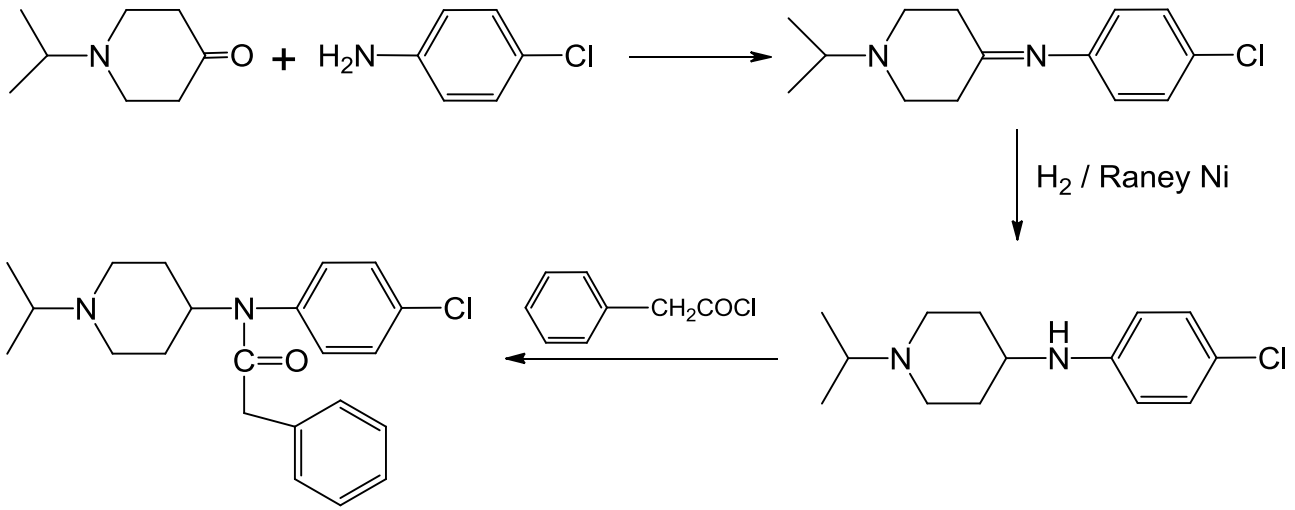

CH3
O
NH
C
CH2
N
C2H5
C2H5
CH3
Lidocaine
CH3
O
NH
C
CH2
N
C2H5
H
CH3
Amidase
CH3
NH2
+
HOOC
CH2
N
C2H5
H
CH3

Class IC Antiarrhythmic Drugs：mainly used in ventricular arrhythmia

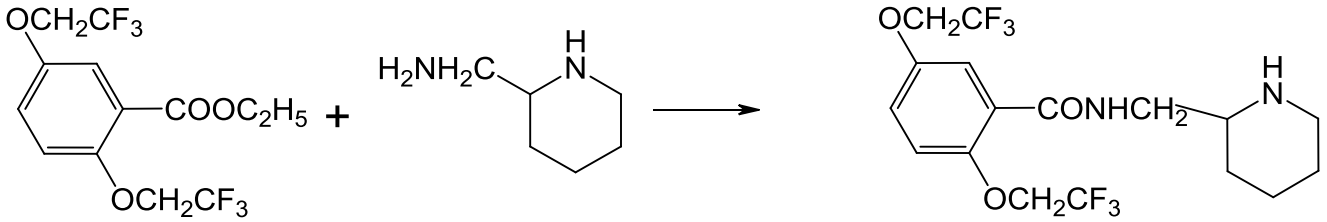
Compound	Formula
Flecainide N-(piperidin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide	
Lorcainide N-(4-chlorophenyl)-N-(1-isopropylpiperidin-4-yl)-2-phenylacetamide *Lorcainide and nor-lorcainide are equipotent	 
Propafenon 1-(2-(2-hydroxy-3-(propylamino)propoxy)phenyl)-3-phenylpropan-1-one *limited use because of central nervous system side effects.	 *poor β-blockade, poor Ca^{++} channel blockade

Synthesis

Lorcainide:

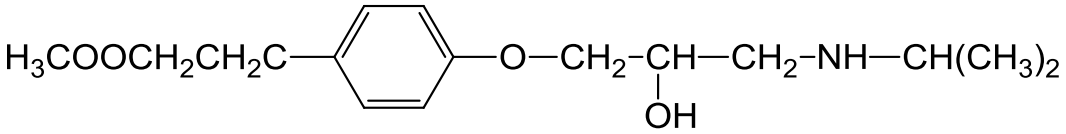


Flecainide:



CLASS II ANTIARRHYTHMIC DRUGS : β-adrenergic receptor blockers

Mostly used:
- Propranolol
- Acebutolol → Metabolised to Diacetolol (active form).
- Esmolol
- Metoprolol
- Timolol

Esmolol 

Methyl 3-(4-(2-hydroxy-3-(isopropylamino)propoxy)phenyl)propanoate

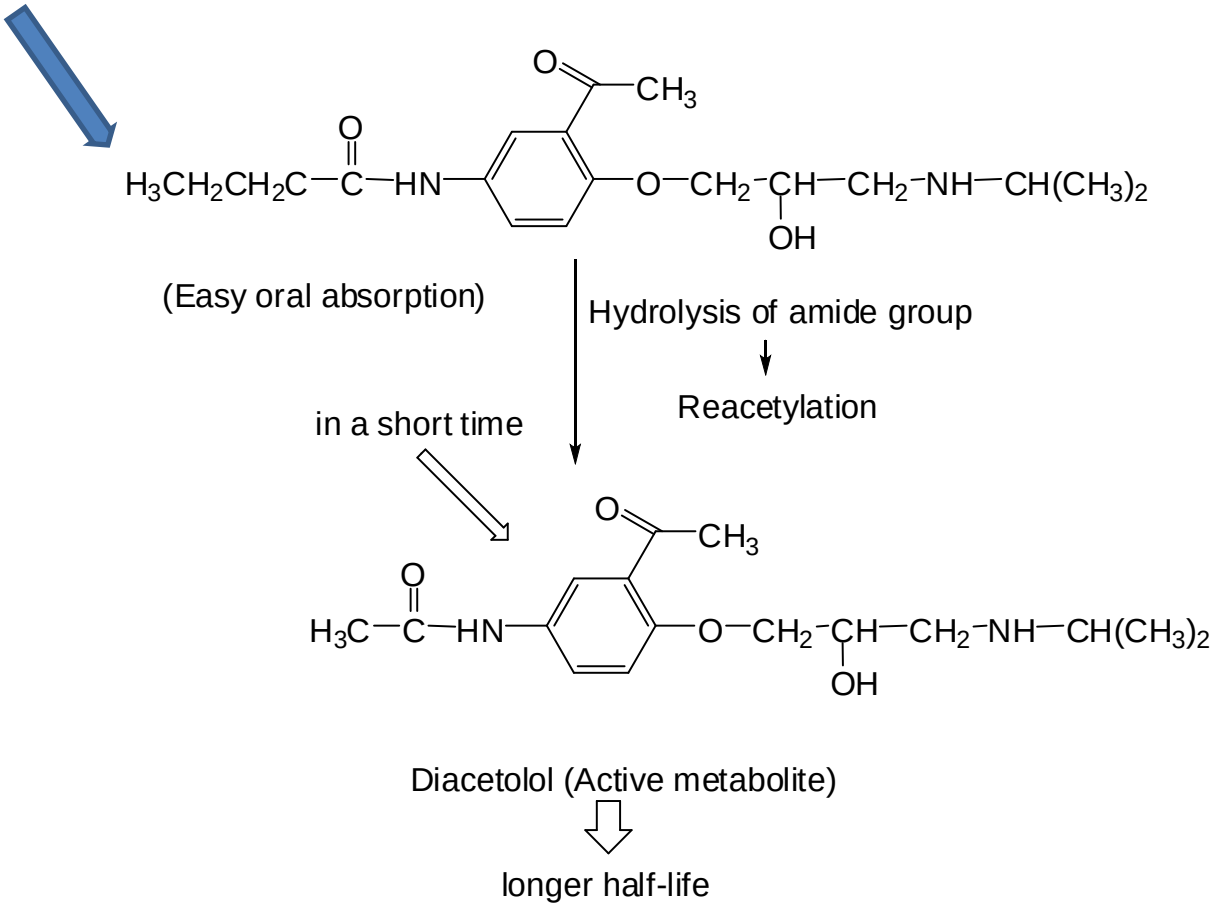
Cardioselective β_1- receptor blocker with rapid onset, a very short duration of action (9 min.), and no significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages.

Decreases the force and rate of heart contractions by blocking beta-adrenergic receptors of the sympathetic nervous system, which are found in the heart and other organs of the body. Prevents the action of two naturally occurring substances: epinephrine and norepinephrine.

Incompatible with $NaHCO_3$

Used for acut supraventricular tachycardia treatment

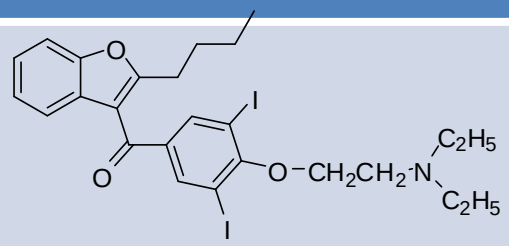
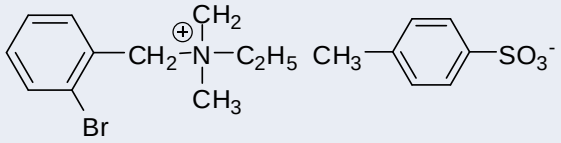
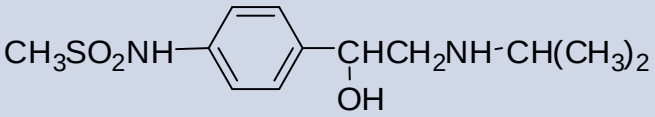
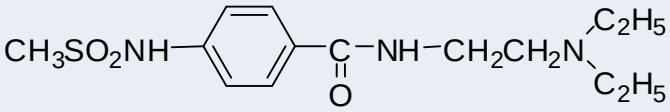
Acebutolol is used to treat ventricular ve atrial arrhythmia



Cardioselective β_1- adrenergic receptor blocker.

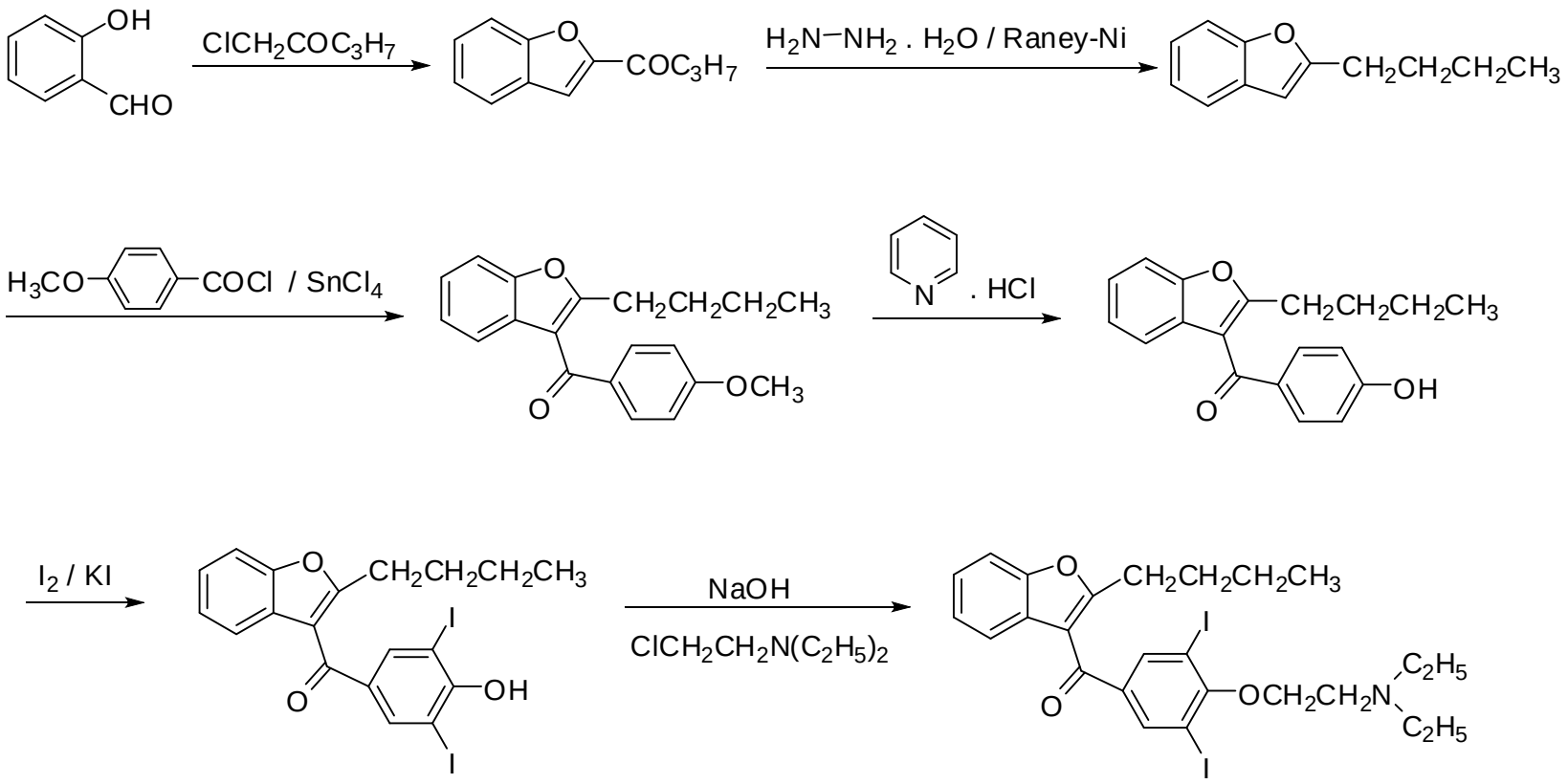
Because of the intrinsic sympathomimetic activity acebutolol can be used safely for patient with asthma and chronic obstructive pulmonary disease

Class III Antiarrhythmic Drugs :

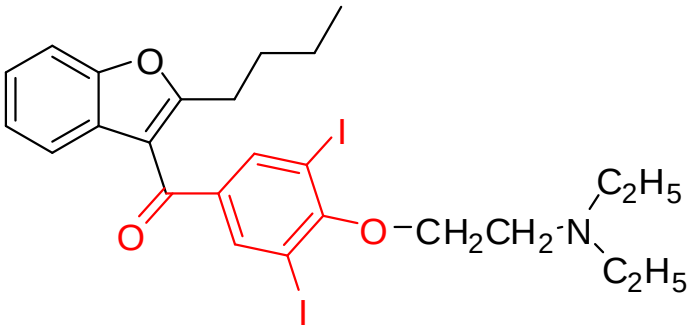
Compound	Formula
Amiodarone (2-butylbenzofuran-3-yl)(4-(2-(diethylamino)ethoxy)-3,5-diiodophenyl)methanone	
Bretylium tosylate (2-bromophenyl)methyl-ethyl-dimethylazanium; 4-methylbenzenesulfonate adrenergic antagonist ***Quaternary ammonium derivative, adrenergic neuron blocker. Antihypertansive.*	 **This drug is used to treat and suppress ventricular arrhythmias, particularly ventricular fibrillation and ventricular tachycardia especially *unresponsive to lidocaine and procainamide*
Sotalol N-(4-(1-hydroxy-2-(isopropylamino)ethyl)phenyl) methanesulfonamide (Non selective beta blocker)	 Used to treat serious Ventricular fibrillation and Ventricular tachycardia (VT) .
Sematilide N-(2-(diethylamino)ethyl)-4-(methylsulfonamido) benzamide	

Synthesis

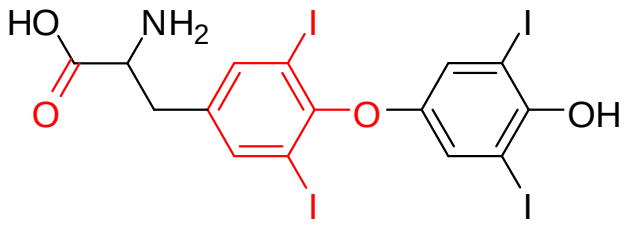
Amiodarone:



- Amiodarone is used in the treatment of a wide range of cardiac tachyarhthmias, including both ventricular and supraventricular (atrial) arrhythmias.
- It has numerous other effects however, including actions that are similar to those of antiarrhythmic classes Ia, II, and IV.
- It has the potential for severe adverse effects including pulmonary toxicity, hepatic dysfunction, neuromuscular symptoms (e.g., peripheral neuropathy or proximal muscle weakness), photosensitivity, hypo- or hyperthyroidism (associated with the structural similarity to thyroid hormones), and QT prolongation.



Amiodarone



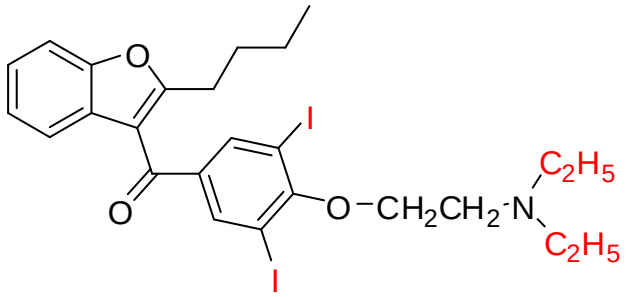
Levothyroxine

Metabolism

- The major metabolite, N-desethylamiodarone (DEA), is formed by N-deethylation. DEA also has antiarrhythmic properties. The elimination half-life of DEA is equal to or longer than that of the parent drug.

- A minor metabolite of amiodarone, di-N-desethylamiodarone

- Amiodarone and N-desethylamiodarone may undergo deiodination to form deiodoamiodarone and deiodo-N-desethylamiodarone, respectively.



Grapefruit juice can enhance the drug toxicity for antiarrhythmic agents, such as

- amiodarone,
- quinidine,
- disopyramide, or
- propafenone and
- for congestive heart failure drug carvedilol.

Class IV Antiarrhythmic Drugs :

Calcium Channel Blockers:

Causes a prolongation of the refractory period in the AV node and the atria and, thus, are very effective in treating supraventricular arrhythmias.

Verapamil and Diltiazem are prototype drug of this class, but dihydropyridine drugs are less effective in cardiac tissues.

Magnesium is natural CCB and used to treat VT/VF.