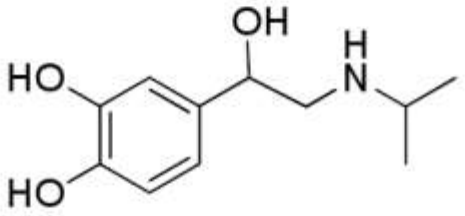
β- Antagonists

SAR of β- Blockers

Modification of ISOproterenol **(Adr. Agonist structure)**

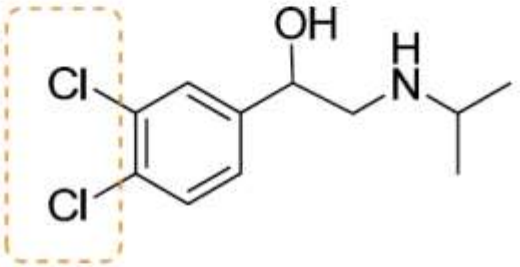


isoproterenol

1) 3'4'-di-OH groups have been replaced by two chloro groups

Dichloroisoproterenol

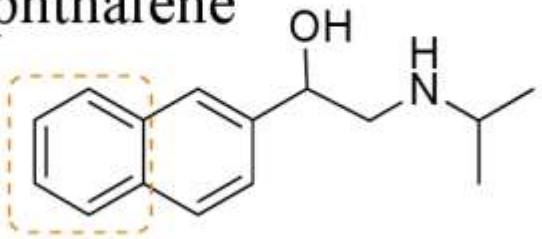
partial agonist (not a pure antagonist)



2) Catechol group have been replaced by naphthalene

Pronethalol

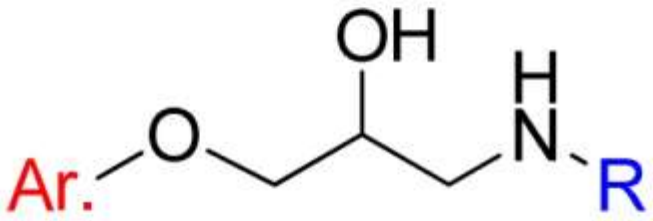
weak antagonist but much side effect



β- Antagonists

SAR of β- Blockers

Aryloxypropanolamines



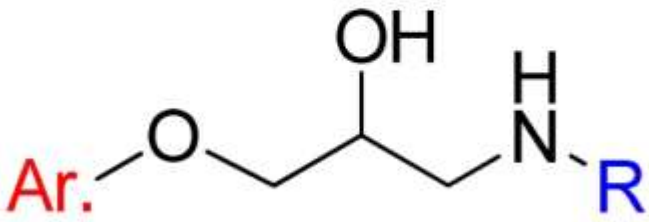
1. secondary amine for optimal activity

2. β-OH-substituted carbon must be in the *S* absolute configuration

3. an -OCH_2- group (oxymethylene bridge) has been incorporated between the aromatic ring and the ethylamino side chain. (gives affinity to drug) → more potent β-blockers

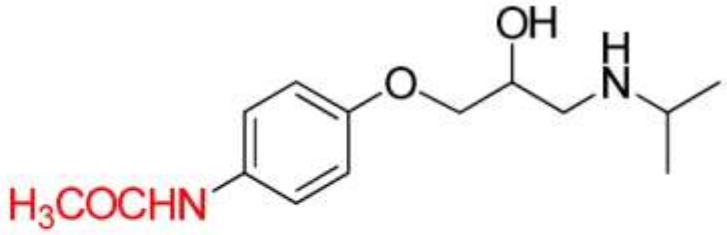
β- Antagonists

Aryloxypropanolamines



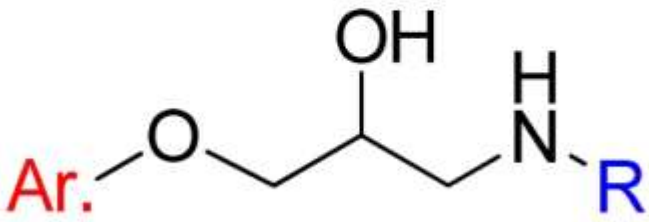
3. nature of the aromatic ring

- affects the ADME
- the presence of a *para*-substituent of sufficient size on the aromatic ring along with the absence of meta-substituents. → β_1-selectivity
- E.g. Practolol



β- Antagonists

Aryloxypropanolamines



4. nature molecule

lipophilic nature → **CNS side effects**, such as, confusion, depression

→ primarily cleared by the **liver** (doses adjusted in patients with liver disease)

E.g. Propranolol

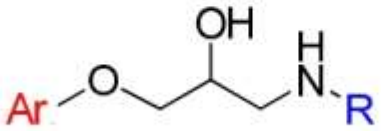
hydrophilic drugs → no CNS side effects

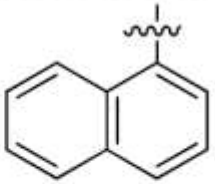
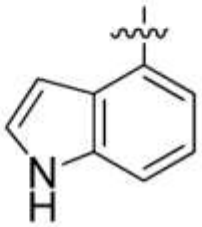
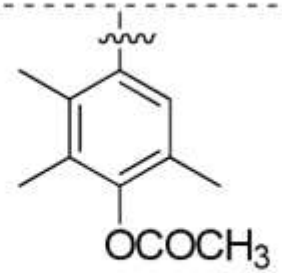
→ cleared by the **kidney** (doses adjusted in renal failure)

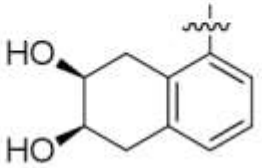
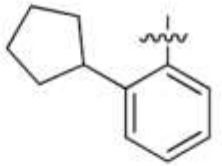
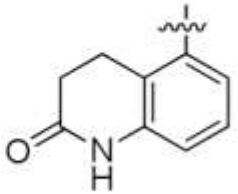
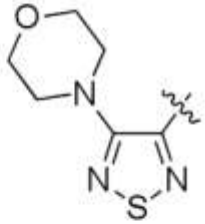
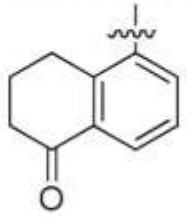
E.g. atenolol

β- Antagonists

First Generation



	Ar	R
(1) Propranolol		
(2) Pindolol		
(3) Metipranolol		

	Ar.	R
(4) Nadolol		
(5) Penbutolol		
(6) Carteolol		
(7) Timolol		
(8) *Levo*bunolol		

β- Antagonists

First Generation

Antihypertensive drugs used for the treatment of hypertension

- Propranolol, Nadolol, Penbutolol, Pindolol, Carteolol, Timolol

intrinsic β -agonistic activity (ISA), Partial agonist
(used when little cardiac ↓ HR needed)

Drugs used in glaucoma

- Carteolol, timolol, levobunolol, and metipranolol are used topically to treat open-angle glaucoma.
- they may reduce the production of aqueous humor.

β- Antagonists

First Generation

Other uses

- angina pectoris , myocardial infarction , migraine prophylaxis

Contraindication

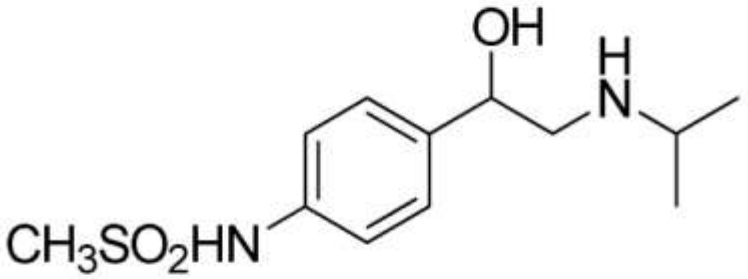
- exhibits no selectivity for β-receptors, it is contraindicated in the presence of conditions such as asthma and bronchitis.

β- Antagonists

First Generation

(9) Sotalol

- Phenylethylamine derivative
- Antiarrythmic drug



- blocks K^+ channels → stop the inward K^+ current that delays cardiac repolarization → treatment ventricular arrhythmias and atrial fibrillation

β- Antagonists

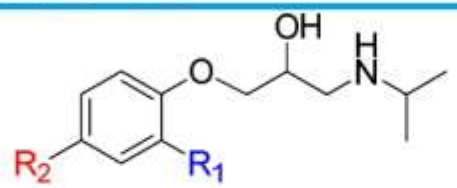
Second Generation

- Cardioselective β_1 – antagonist

- Adv. = lack of a blocking effect on the β_2 -receptors in the bronchi
  → safe for use in patients who have bronchitis or bronchial asthma.

β- Antagonists

Second Generation



- Use: the treatment of hypertension

angina pectoris &
myocardial infarction

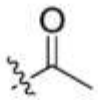
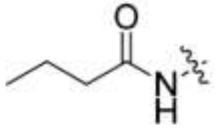
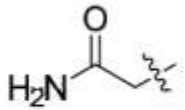
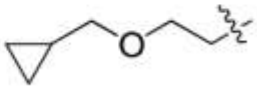
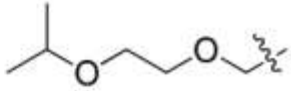
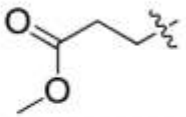
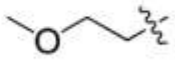
- Atenolol and metoprolol

Glaucoma

- Betaxolol

Cardiac arrhythmias

- Esmolol and acebutolol

	R_1	R_2
(1) Acebutolol		
(2) Atenolol	H	
(3) Betaxolol	H	
(5) Bisoprolol	H	
(6) Esmolol	H	
(7) Metoprolol	H	

β- Antagonists

Third Generation

(1) Labetalol

- phenylethanolamine derivative
- β 1.5 > α_1 blocking activities
- used as racemate

  (1*R*,1'*R*) isomer [Dilevalol] → β –blocker

  (1*S*,1'*R*) isomer → Powerful α_1 -blocker

  (1*S*,1'*S*) isomer & (1*R*,1'*S*) isomer → no blocking activity

Use: management of hypertension

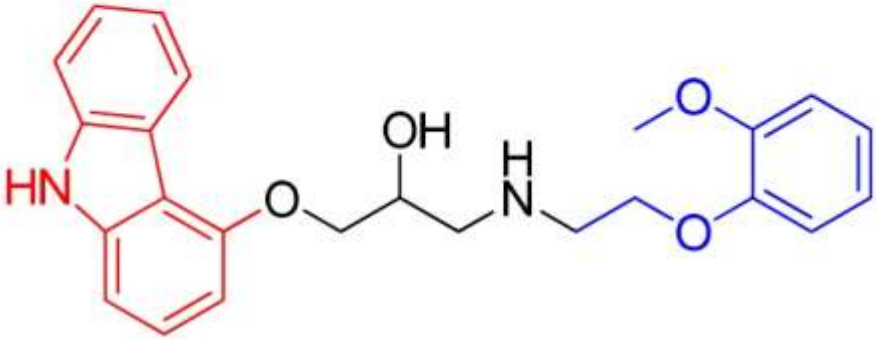
α_1 –blocking effects produce vasodilation

β – blocking effects prevent the reflex tachycardia

β- Antagonists

Third Generation

(2) Carvedilol



- phenylethanolamine derivative
- β 10 *to* 100 > α_1 blocking activities
- used as racemate

  R isomer → α_1 -blocker

  S isomer → β –blocker + α_1 –blocker

- It possesses antioxidant activity and an antiproliferative effect on vascular smooth muscle cells.

Use:

- Treatment of hypertension and congestive heart failure

End of the topic

Reference:

Textbook of org. medi. and ph'cal chem. – Wilson and Giswolds

Principles of medicinal chemistry – W. C. Foye