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Adrenergic Antagonists

Presented By;-

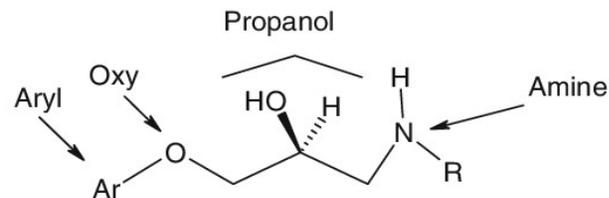
Mr. Samarpan Mishra (Assistant Professor)

Specialization:- Pharmaceutical Chemistry

Adrenergic Antagonists

- ▶ Adrenergic antagonists are drugs that **block α or β adrenergic receptors**, inhibiting the effects of endogenous catecholamines (**norepinephrine, epinephrine**) and sympathetic stimulation.
- ▶ They reduce **heart rate, blood pressure, vasoconstriction**, and other sympathetic actions.
- ▶ They are widely used in **hypertension, angina, arrhythmias, pheochromocytoma, BPH**, and glaucoma.

SAR of beta blockers



Structural Part	Description / Modification	Effect on Activity	Examples
Aryl Ring (Ar-)	Aromatic or heteroaromatic ring attached through oxy linkage	Essential for β -blocking activity; determines potency	Propranolol, Metoprolol
Substitution on Aryl Ring	Para-substitution (e.g., $-\text{OCH}_3$, $-\text{CONH}_2$, $-\text{CN}$)	Increases β_1 -selectivity	Atenolol, Metoprolol, Bisoprolol
	Bulky aromatic groups (naphthalene, bicyclic rings)	\uparrow Lipophilicity, \uparrow potency, more CNS penetration	Propranolol
Oxy Linkage (Ar-O-CH₂-)	Ether linkage between aryl and propanol chain	Required for β -blocking activity; replacing O with CH ₂ \rightarrow loss of activity	All classical β -blockers
Propanol Chain (-CH₂-CH(OH)-CH₂-)	3-carbon chain with β -OH group	Maintains correct distance for receptor binding; β -OH must be S-configuration for high activity	All β -blockers
β-OH Group	Chiral hydroxyl at β -position	S-enantiomer is 50–100 \times more potent than R-form	S-propranolol, S-metoprolol
Amine Group (-NH-R)	Secondary amine required	Essential for binding; primary/tertiary amines reduce activity	All β -blockers
N-Substituent (R group)	Bulky alkyl groups (isopropyl, tert-butyl)	\uparrow β -selectivity; larger groups \rightarrow intrinsic sympathomimetic activity (ISA)	Pindolol, Oxprenolol

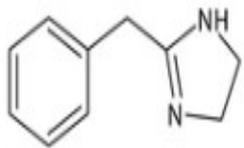
Classification of Adrenergic Antagonists

Classification Adrenergic Antagonists

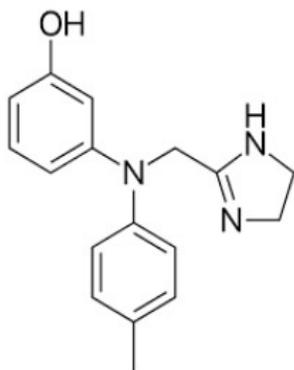
- ❑ **Alpha adrenergic blockers:-** Tolazoline*, Phentolamine, Phenoxybenzamine, Prazosin, Dihydroergotamine, Methysergide.
- ❑ **Beta adrenergic blockers:-** Propranolol*, Metibranolol, Atenolol, Betazolol, Bisoprolol, Esmolol, Metoprolol, Labetolol, Carvedilol.

Alpha adrenergic blockers

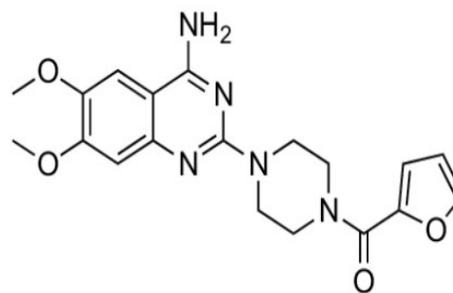
Drug	Introduction	Mechanism of Action (MOA)	Uses
Tolazoline*	Non-selective α -adrenergic antagonist; imidazoline derivative.	Blocks $\alpha_1 + \alpha_2$ receptors, causing vasodilation; also has some histamine-releasing and parasympathomimetic actions.	Peripheral vasospasm (e.g., Raynaud's disease), pulmonary hypertension in newborns (historical), diagnostic aid in pheochromocytoma.
Phentolamine	Short-acting, competitive non-selective α -blocker.	Reversibly blocks $\alpha_1 + \alpha_2$ receptors, leading to vasodilation and fall in BP; increases NE release (due to α_2 block).	Hypertensive crisis due to pheochromocytoma, local anesthesia extravasation, ED (with papaverine), diagnosis of pheochromocytoma.
Phenoxybenzamine	Long-acting, irreversible non-selective α -blocker.	Irreversibly blocks $\alpha_1 \gg \alpha_2$ receptors via covalent bonding \rightarrow long-lasting vasodilation.	Preoperative management of pheochromocytoma, Raynaud's disease, autonomic hyperreflexia.
Prazosin	Selective α_1 -adrenergic blocker; quinazoline derivative.	Selectively blocks α_1 receptors, causing arteriolar + venous dilation with minimal reflex tachycardia.	Hypertension (2nd line), Benign Prostatic Hyperplasia (BPH), PTSD-related nightmares (off-label).
Dihydroergotamine	Ergot alkaloid derivative; partial agonist/antagonist at adrenergic & serotonergic receptors.	Acts mainly on 5-HT _{1D} receptors, causing cranial vasoconstriction; partial α -blocker.	Acute migraine, cluster headache.
Methysergide	Semi-synthetic ergot derivative; serotonergic antagonist.	Blocks 5-HT ₂ receptors \rightarrow reduces vasospasm; mild partial agonist at other 5-HT receptors.	Migraine prophylaxis, cluster headache prophylaxis (rarely used due to fibrosis risk).



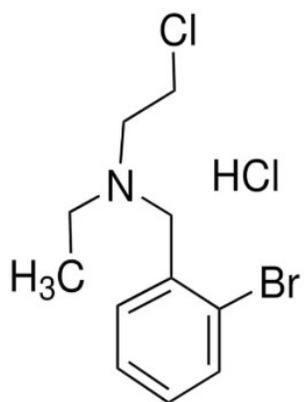
Tolazoline



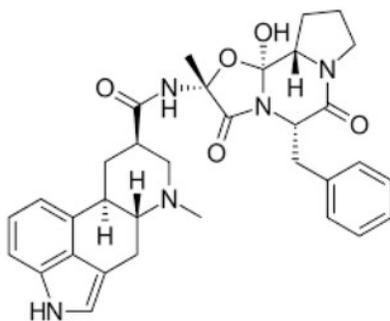
Phentolamine



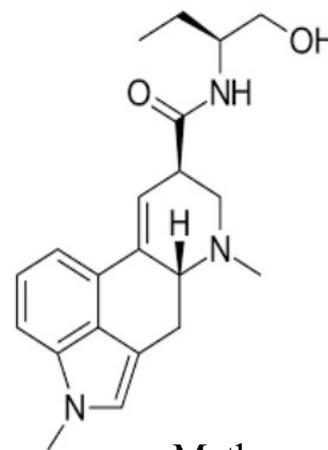
Prazosin



Phenoxybenzamine

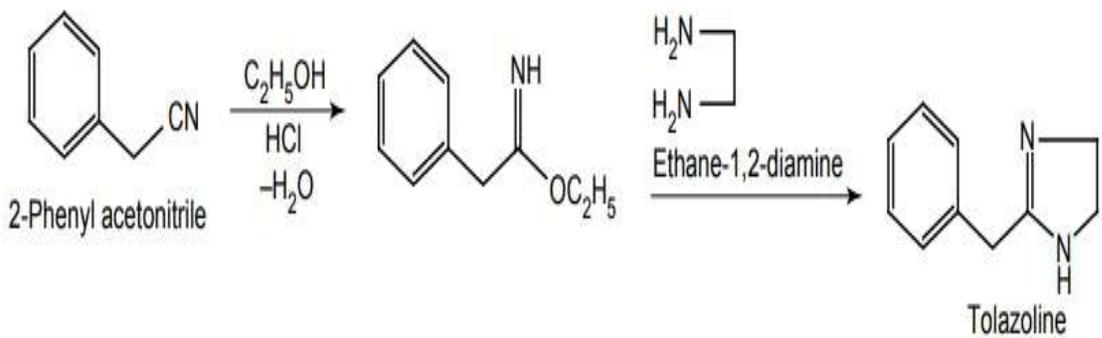


Dihydroergotamine



Methysergide

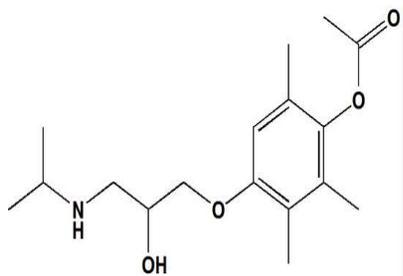




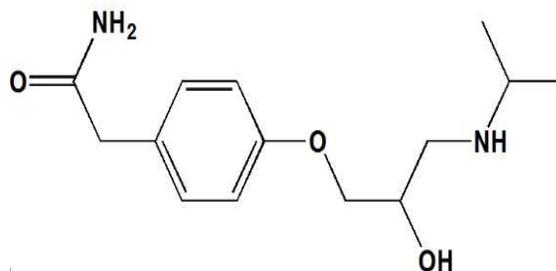
Synthesis of Tolazoline

Beta adrenergic blockers

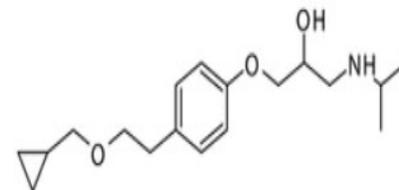
Drug	Introduction	Mechanism of Action (MOA)	Uses
Propranolol*	First-generation non-selective β -blocker	Blocks β_1 & β_2 receptors \rightarrow \downarrow heart rate, \downarrow contractility, \downarrow renin release	Hypertension, angina, arrhythmias, migraine prophylaxis, hyperthyroidism, essential tremor
Metipranolol (Metibranolol)	Non-selective β -blocker	Inhibits β_1 & $\beta_2 \rightarrow \downarrow$ aqueous humor production	Glaucoma (topical)
Atenolol	Second-generation β_1 -selective blocker	Selective β_1 block $\rightarrow \downarrow$ cardiac output, \downarrow BP	Hypertension, angina, post-MI, arrhythmias
Betaxolol	β_1 -selective blocker; available systemic/topical	Blocks $\beta_1 \rightarrow \downarrow$ HR & \downarrow aqueous humor	Hypertension, glaucoma
Bisoprolol	Highly β_1 -selective blocker	Selective β_1 inhibition $\rightarrow \downarrow$ myocardial O_2 demand	Hypertension, heart failure, stable angina
Esmolol	Ultra-short acting β_1 blocker (IV)	β_1 blockade with very short half-life (9 min)	Acute arrhythmias, intraoperative hypertension, thyrotoxicosis crisis
Metoprolol	β_1 -selective blocker	\downarrow HR, \downarrow contractility, \downarrow renin secretion	Hypertension, angina, MI, CHF (succinate)
Labetalol	Mixed $\alpha_1 + \beta$ blocker	Blocks $\alpha_1 \rightarrow$ vasodilation; blocks $\beta \rightarrow \downarrow$ HR	Hypertensive emergencies, pregnancy-induced HTN
Carvedilol	Non-selective β blocker + α_1 blocker + antioxidant	\downarrow HR + vasodilation + \downarrow oxidative stress	Heart failure, post-MI LV dysfunction, hypertension



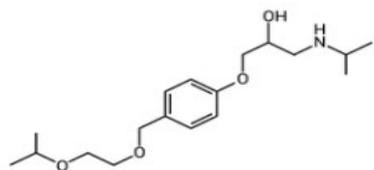
Metibranolol



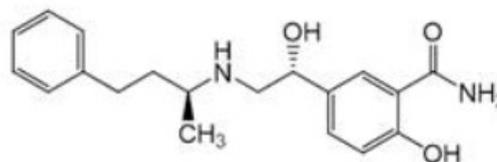
Atenolol



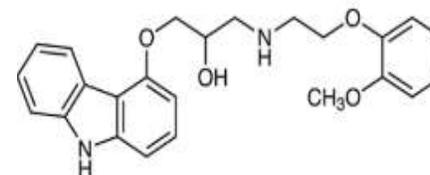
Betazolol



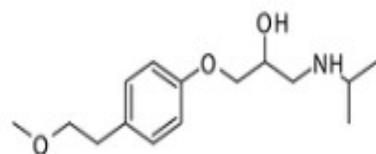
Bisoprolol



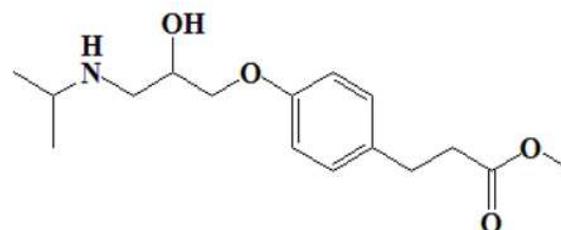
Labetolol



Carvedilol

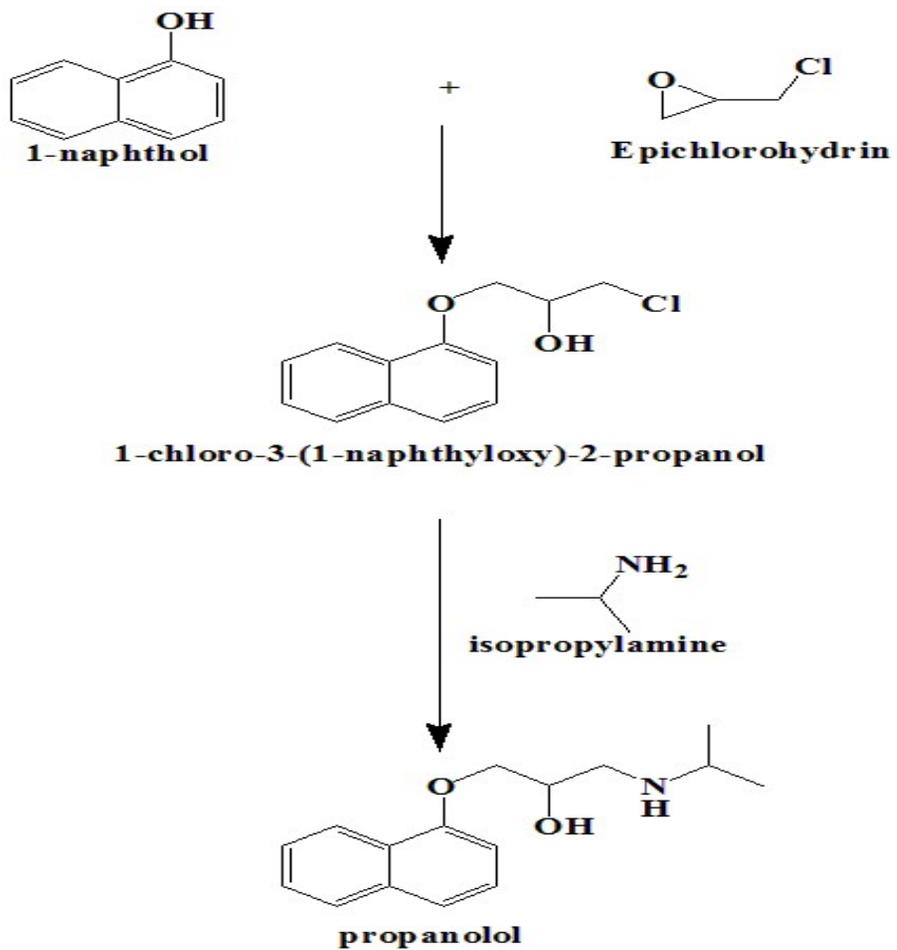


Metoprolol



Esmolol

Synthesis of Propranolol





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