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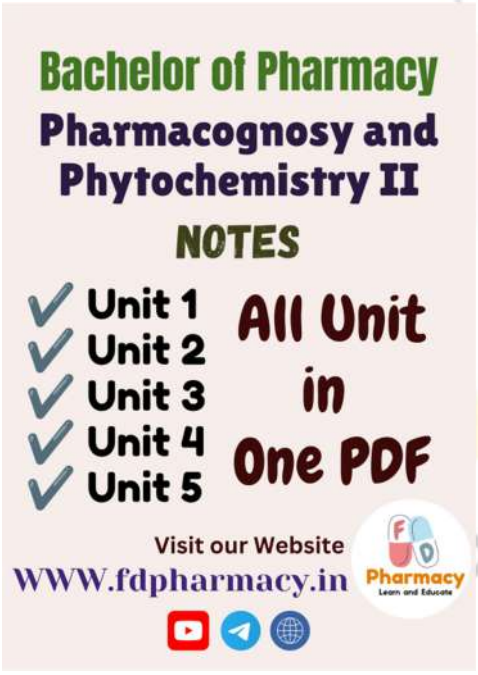
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MEDICINAL CHEMISTRY - II

UNIT 2

TOPIC :

- **Anti-hypertensive Agents :** Timolol, Captopril, Lisinopril, Enalapril, Benazepril hydrochloride, Quinapril hydrochloride, Methyldopate hydrochloride,*Clonidine hydrochloride, Guanethidine monosulphate, Guanabenz acetate, Sodium nitroprusside, Diazoxide, Minoxidil, Reserpine, Hydralazine hydrochloride.

ANTIHYPERTENSIVE AGENTS

Antihypertensive agents are a class of medications used for the treatment of hypertension, which is persistently elevated blood pressure.

These drugs work through different mechanisms to:

- Lower blood pressure
- Reduce cardiac workload
- Prevent complications associated with chronic hypertension, such as:
    - Cardiovascular events (heart attack, stroke)
    - Renal damage (chronic kidney disease)
    - Retinopathy (damage to retinal vessels)

The choice of an antihypertensive agent depends on the patient's age, comorbidities, and severity of hypertension.

Mechanism of Action

Antihypertensive agents reduce blood pressure by acting on:

1. Blood volume – by promoting excretion of sodium and water (Diuretics)
2. Cardiac output – by reducing heart rate and contractility (Beta-blockers)
3. Peripheral vascular resistance – by relaxing vascular smooth muscle (CCBs, ACE inhibitors, ARBs, Direct vasodilators)
4. Renin-angiotensin-aldosterone system (RAAS) – by inhibiting angiotensin formation or action (ACE inhibitors, ARBs, Renin inhibitors)
5. Sympathetic nervous system – by reducing sympathetic tone (Central acting agents, Alpha-blockers)

Clinical Uses

- Essential hypertension (primary)
- Secondary hypertension (renal, endocrine, cardiovascular)
- Heart failure management (ACE inhibitors, Beta-blockers, Diuretics)
- Post-myocardial infarction (Beta-blockers, ACE inhibitors)
- Chronic kidney disease (ACE inhibitors, ARBs)
- Acute hypertensive emergencies (IV agents like Nitroprusside, Labetalol)

Examples

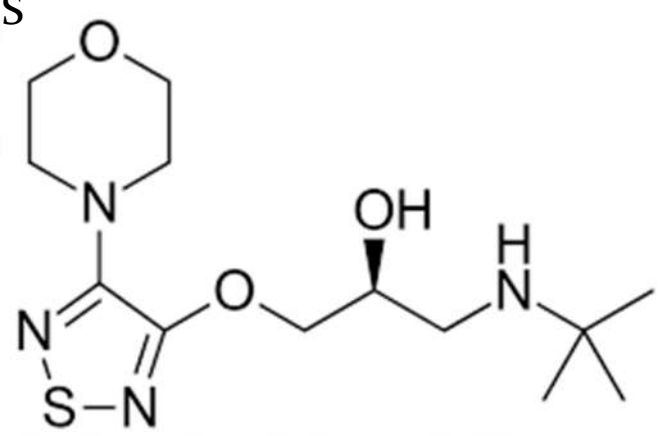
- Timolol,
- Captopril,
- Lisinopril,
- Enalapril,
- Benazepril hydrochloride,
- Quinapril hydrochloride,
- Methyldopate hydrochloride,
- Clonidine hydrochloride,
- Guanethidine monosulphate,
- Guanabenz acetate,
- Sodium nitroprusside,
- Diazoxide,
- Minoxidil,
- Reserpine,
- Hydralazine hydrochloride

Timolol

- Timolol is a non-selective beta-adrenergic receptor blocker (β-blocker).
- Used primarily in ophthalmology to reduce intraocular pressure (IOP) in glaucoma.
- Also used systemically in hypertension, angina pectoris, and cardiac arrhythmias.
- Available as ophthalmic solution (eye drops) and oral tablets.

Chemical Structure

- IUPAC Name: (S)-1-(tert-butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol
- Molecular Formula: $C_{13}H_{22}N_2O_3S$
- Molecular Weight: 316.39 g/mol
- Structural



Mechanism of Action

- Site of action: β-adrenergic receptors in ciliary body of the eye and heart.
- MOA:
  1. Ocular effect:
     - Blocks β-receptors in ciliary epithelium → ↓ aqueous humor production → ↓ intraocular pressure.
  2. Systemic effect:
     - Non-selective β1 and β2 blockade → ↓ heart rate, myocardial contractility, and cardiac output → ↓ blood pressure.
- Effect: Reduces IOP in glaucoma and systemic blood pressure in hypertension.

Synthesis

- Starting material: Substituted epichlorohydrin and isopropylamine derivatives.
- Steps:
    1. Preparation of the propanolamine intermediate.
    2. Etherification with substituted thiadiazole moiety.
    3. Formation of the final Timolol structure.
    4. Purification and crystallization → yields Timolol.

Uses

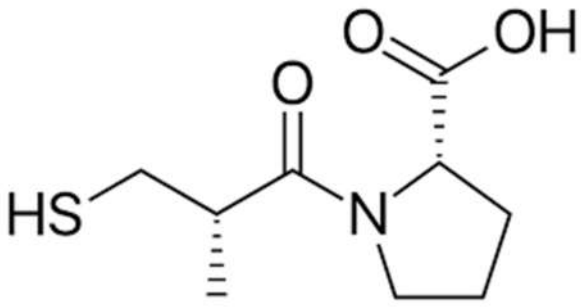
- Ophthalmology:
    - Primary open-angle glaucoma (POAG)
    - Ocular hypertension
- Cardiovascular:
    - Hypertension
    - Angina pectoris
    - Cardiac arrhythmias
    - Prevention of myocardial infarction (secondary prevention)

Captopril

- Captopril is the first orally active angiotensin-converting enzyme (ACE) inhibitor.
- Used primarily for hypertension, congestive heart failure, and diabetic nephropathy.
- Reduces angiotensin II levels, leading to vasodilation and reduced aldosterone secretion.
- Administered orally as tablets.
- Rapid onset of action; short half-life (~2–3 hours) requiring 2–3 doses per day.

Chemical Structure

- IUPAC Name: (2S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl]pyrrolidine-2-carboxylic acid
- Molecular Formula: $C_9H_{15}NO_3S$
- Molecular Weight: 217.29 g/mol
- Structural



Mechanism of Action

- Site of action: Angiotensin-converting enzyme (ACE) in the lungs and vascular endothelium.
- MOA:
  1. Inhibits ACE → prevents conversion of angiotensin I → angiotensin II.
  2. Reduced angiotensin II:
     - Vasodilation → ↓ systemic vascular resistance → ↓ blood pressure
     - ↓ Aldosterone secretion → ↑ sodium and water excretion
  3. Prevents breakdown of bradykinin → contributes to vasodilation
- Effect: Lowers blood pressure, reduces cardiac workload, and protects kidneys.

Synthesis

- Starting materials: L-proline and suitable thiol-containing acyl intermediates.
- Steps:
    1. Formation of thiol-substituted acyl intermediate.
    2. Coupling with L-proline derivative to form the amide linkage.
    3. Purification and crystallization → yields Captopril.

Uses

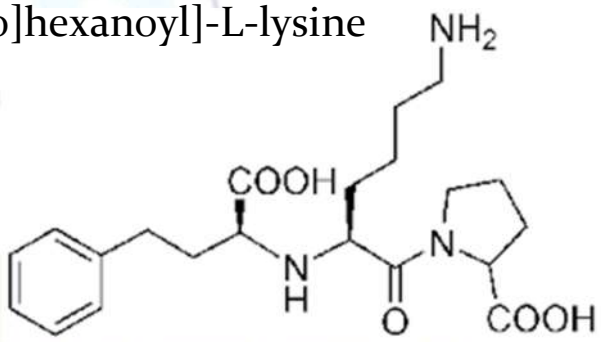
- Hypertension (first-line or in combination therapy).
- Congestive heart failure (reduces afterload and cardiac remodeling).
- Diabetic nephropathy (protects renal function, reduces proteinuria).
- Post-myocardial infarction (reduces mortality and ventricular remodeling).

Lisinopril

- Lisinopril is an angiotensin-converting enzyme (ACE) inhibitor, like Captopril.
- Used for hypertension, congestive heart failure (CHF), and post-myocardial infarction therapy.
- Unlike Captopril, Lisinopril does not contain a thiol group; it is a lysine derivative.
- Administered orally, with longer half-life (~12 hours) → usually once daily dosing.
- Improves survival in heart failure and prevents renal complications in diabetes.

Chemical Structure

- IUPAC Name: (2S)-1-[(2S)-6-amino-2-{[(1-carboxy-3-phenylpropyl)amino]acetyl}amino]hexanoyl]-L-lysine
- Molecular Formula: $C_{21}H^{31}N_3O_5$
- Molecular Weight: 405.5 g/mol
- Structural



Mechanism of Action

- Site of action: Angiotensin-converting enzyme (ACE) in lungs and vascular endothelium.
- MOA:
  1. Inhibits ACE → prevents angiotensin I → angiotensin II conversion.
  2. Reduced angiotensin II:
     - Vasodilation → lowers blood pressure
     - Decreased aldosterone → promotes sodium and water excretion
  3. Prevents bradykinin degradation → additional vasodilation
- Effect: Lowers BP, reduces cardiac workload, protects kidneys.

Synthesis

- Starting materials: Lysine derivatives and suitable acyl intermediates.
- Steps:
    1. Formation of dipeptide-like intermediate with carboxylic acid functionalities.
    2. Coupling with phenylpropylamine derivative to produce Lisinopril backbone.
    3. Purification and crystallization → yields Lisinopril tablets.

Uses

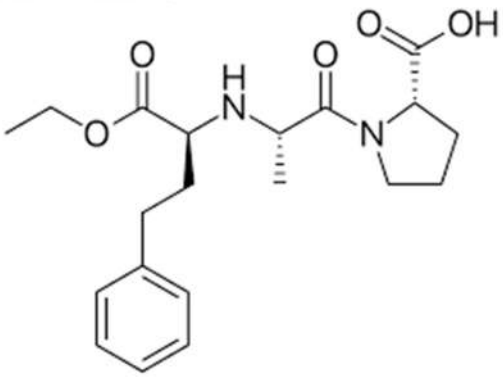
- Hypertension (first-line or combination therapy).
- Congestive heart failure (improves survival and reduces symptoms).
- Post-myocardial infarction (reduces mortality and ventricular remodeling).
- Diabetic nephropathy (reduces proteinuria and protects renal function).

Enalapril

- Enalapril is an angiotensin-converting enzyme (ACE) inhibitor.
- Used for hypertension, congestive heart failure (CHF), and diabetic nephropathy.
- Administered orally as Enalapril maleate; longer duration of action than Captopril.
- It is a prodrug, metabolized in the liver to Enalaprilat, the active ACE inhibitor.
- Reduces angiotensin II levels → vasodilation, decreased aldosterone, and renal protection.

Chemical Structure

- IUPAC Name: (S)-1-[(2S)-2-[(1-ethoxycarbonyl-3-phenylpropyl)amino]propanoyl]pyrrolidine-2-carboxylic acid
- Molecular Formula: $C_{20}H_{28}N_2O_5$
- Molecular Weight: 376.45 g/mol
- Structural



Mechanism of Action

- Site of action: Angiotensin-converting enzyme (ACE) in vascular endothelium and lungs.
- MOA:
  1. Enalapril → hydrolyzed to Enalaprilat (active form).
  2. Inhibits ACE → prevents conversion of angiotensin I → angiotensin II.
  3. Reduced angiotensin II:
     - Vasodilation → ↓ blood pressure
     - ↓ Aldosterone → ↑ sodium and water excretion
  4. Bradykinin degradation is inhibited → vasodilation
- Effect: Lowers BP, reduces cardiac workload, protects kidneys.

Synthesis

- Starting materials: L-proline derivatives and substituted phenylpropyl amine intermediates.
- Steps:
    1. Formation of the amide bond between proline and phenylpropylamine.
    2. Esterification to produce the prodrug Enalapril.
    3. Purification and crystallization → yields Enalapril maleate.

Uses

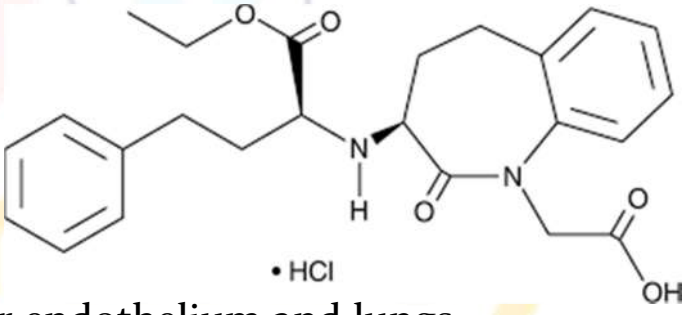
- Hypertension (monotherapy or combination).
- Congestive heart failure (reduces afterload and improves survival).
- Post-myocardial infarction (reduces mortality and ventricular remodeling).
- Diabetic nephropathy (reduces proteinuria, renal protection).

Benazepril Hydrochloride

- Benazepril Hydrochloride is an angiotensin-converting enzyme (ACE) inhibitor.
- Used primarily for hypertension and heart failure, and sometimes for renal protection in diabetic nephropathy.
- Administered orally; it is a prodrug that is converted to benazeprilat, the active ACE inhibitor.
- Produces long-acting antihypertensive effects → usually once daily dosing.

Chemical Structure

- IUPAC Name: (3S)-1-[(2S)-2-ethoxy-2-oxo-1-[(phenylmethyl)amino]ethyl]-3-phenylpropyl-L-lysine hydrochloride
- Molecular Formula: $C_{27}H_{31}N_3O_5 \cdot HCl$
- Molecular Weight: 493.0 g/mol
- Structural



Mechanism of Action

- Site of action: ACE in vascular endothelium and lungs.
- MOA:
  1. Benazepril → hydrolyzed in liver to benazeprilat (active form).
  2. Inhibits ACE → prevents conversion of angiotensin I → angiotensin II.
  3. Reduced angiotensin II:
     - Vasodilation → lowers systemic vascular resistance
     - ↓ Aldosterone → promotes sodium and water excretion
  4. Inhibits bradykinin breakdown → additional vasodilation
- Effect: Lowers blood pressure, reduces cardiac workload, protects kidneys.

Synthesis

- Starting materials: Lysine derivatives and substituted phenylpropylamine intermediates.
- Steps:
    1. Formation of amide bond between lysine derivative and phenylpropylamine.
    2. Esterification to form prodrug Benazepril.
    3. Conversion to hydrochloride salt for oral formulation.
    4. Purification and crystallization → yields Benazepril HCl.

Uses

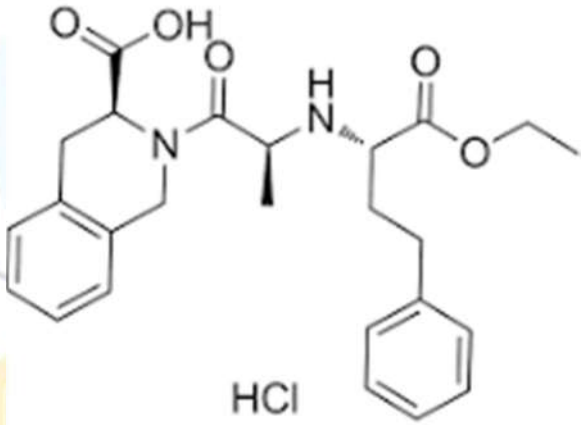
- Hypertension (first-line therapy or combination therapy).
- Heart failure (adjunct to standard therapy).
- Diabetic nephropathy (reduces proteinuria and protects renal function).
- Post-myocardial infarction (to reduce cardiac remodeling).

Quinapril Hydrochloride

- Quinapril Hydrochloride is an angiotensin-converting enzyme (ACE) inhibitor.
- Used primarily for hypertension and congestive heart failure (CHF).
- Administered orally; it is a prodrug, metabolized in the liver to quinaprilat, the active ACE inhibitor.
- Long-acting antihypertensive effect → usually once or twice daily dosing.

Chemical Structure

- IUPAC Name: (3S)-2-[2-ethoxy-1-[(1S)-1-carboxy-3-phenylpropyl]amino]acetyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid hydrochloride
- Molecular Formula: $C_{23}H_{28}N_2O_5 \cdot HCl$
- Molecular Weight: 472.0 g/mol
- Structural



Mechanism of Action

- Site of action: ACE in vascular endothelium and lungs.
- MOA:
  1. Quinapril → hydrolyzed in liver to quinaprilat (active form).
  2. Inhibits ACE → prevents conversion of angiotensin I → angiotensin II.
  3. Reduced angiotensin II:
     - Vasodilation → ↓ systemic vascular resistance
     - ↓ Aldosterone → ↑ sodium and water excretion
  4. Inhibits bradykinin degradation → additional vasodilation
- Effect: Lowers blood pressure, reduces cardiac workload, protects kidneys.

Synthesis

- Starting materials: Isoquinoline derivatives and phenylpropylamine intermediates.
- Steps:
    1. Formation of amide bond between isoquinoline derivative and phenylpropylamine.
    2. Esterification to form prodrug Quinapril.
    3. Conversion to hydrochloride salt for oral formulation.
    4. Purification and crystallization → yields Quinapril HCl.

Uses

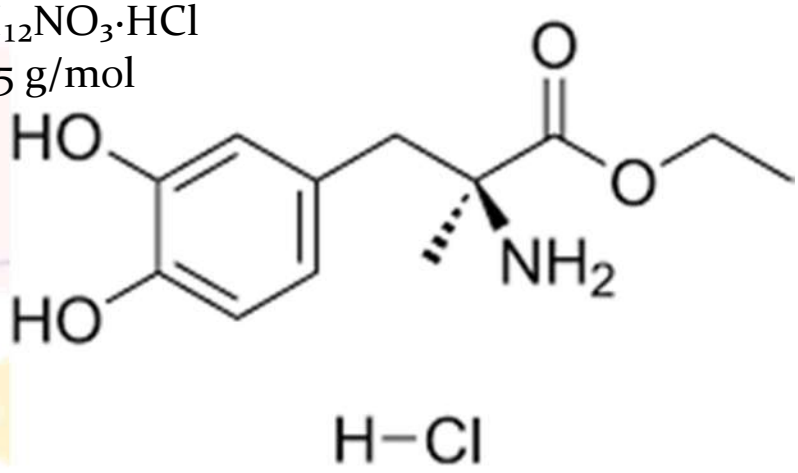
- Hypertension (monotherapy or combination therapy).
- Congestive heart failure (CHF) (reduces afterload and improves survival).
- Post-myocardial infarction (reduces mortality and cardiac remodeling).
- Diabetic nephropathy (renal protective effects, reduces proteinuria).

Methyldopa Hydrochloride

- Methyldopa Hydrochloride is a centrally acting antihypertensive drug.
- It is a prodrug, converted in the CNS to α-methyl norepinephrine, which acts as a false neurotransmitter.
- Used primarily for hypertension, especially in pregnancy (drug of choice for gestational hypertension and preeclampsia).
- Administered orally as tablets or orally disintegrating tablets; also available as IV for emergency use.

Chemical Structure

- IUPAC Name: (±)-α-methyl-3-hydroxy-DL-phenylalanine hydrochloride
- Molecular Formula: $C_9H_{12}NO_3 \cdot HCl$
- Molecular Weight: 213.65 g/mol
- Structural



Mechanism of Action

- Site of action: Central nervous system, primarily CNS adrenergic neurons.
- MOA:
  1. Methyldopa → converted to α-methyl norepinephrine in CNS.
  2. Acts as a false neurotransmitter → stimulates central α_2-adrenergic receptors.
  3. Reduces sympathetic outflow → decreased peripheral vascular resistance and cardiac output.
- Effect: Lowers blood pressure without significant reduction in renal blood flow.

Synthesis

- Starting material: L-tyrosine.
- Steps:
    1. Alpha-methylation of L-tyrosine to form α-methyl-L-tyrosine.
    2. Hydroxylation on the aromatic ring → forms α-methyl-3-hydroxy-phenylalanine.
    3. Formation of hydrochloride salt → Methyldopa HCl.
    4. Purification and crystallization to obtain pure compound.

Uses

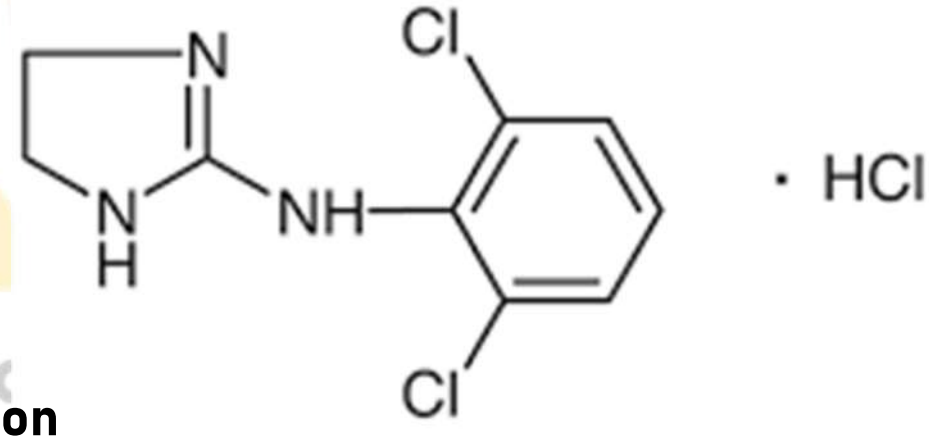
- Hypertension (chronic, mild to moderate).
- Hypertension in pregnancy (drug of choice due to fetal safety).
- Adjunct therapy in combination with diuretics or other antihypertensives.
- Occasionally used in pheochromocytoma-induced hypertension.

Clonidine Hydrochloride

- Clonidine Hydrochloride is a centrally acting antihypertensive agent.
- Belongs to the imidazoline derivative class and acts as an α_2-adrenergic receptor agonist in the CNS.
- Used for hypertension, attention-deficit hyperactivity disorder (ADHD), withdrawal symptoms in opioid dependence, and sometimes in migraine prophylaxis.
- Available as oral tablets, transdermal patches, and injectable formulations.

Chemical Structure

- IUPAC Name: N-(2,6-dichlorophenyl)-4,5-dihydro-1H-imidazol-2-amine hydrochloride
- Molecular Formula: $C_9H_9Cl_2N_3 \cdot HCl$
- Molecular Weight: 230.6 g/mol
- Structural



Mechanism of Action

- Site of action: Central nervous system (medullary vasomotor center).
- MOA:
  1. Stimulates central α_2-adrenergic receptors → reduces sympathetic outflow.
  2. ↓ Peripheral vascular resistance → ↓ blood pressure.
  3. ↓ Heart rate and cardiac output → contributes to antihypertensive effect.
- Effect: Lowers blood pressure with minimal effect on renal blood flow.

Synthesis

- Starting materials: 2,6-dichloroaniline and glyoxal derivatives.
- Steps:
    1. Formation of imidazoline ring via cyclization with amino precursors.
    2. Coupling with 2,6-dichlorophenyl derivative to form Clonidine backbone.
    3. Conversion to hydrochloride salt → improves solubility and stability.
    4. Purification and crystallization to obtain pure Clonidine HCl.

Uses

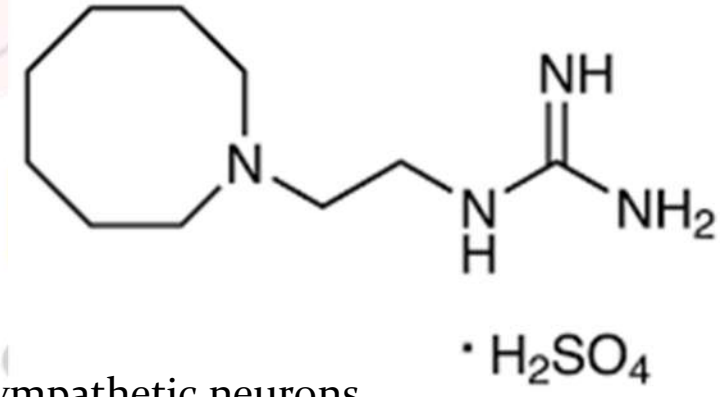
- Hypertension (alone or in combination with other antihypertensives).
- ADHD (as adjunct therapy, often with stimulants).
- Opioid withdrawal and nicotine withdrawal (reduces sympathetic symptoms).
- Migraine prophylaxis (off-label in some cases).
- Glaucoma (topical α_2 agonist reduces intraocular pressure).

Guanethidine Monosulphate

- Guanethidine Monosulphate is a peripherally acting antihypertensive agent.
- Belongs to the adrenergic neuron-blocking agent class.
- Used primarily for moderate to severe hypertension, especially in patients unresponsive to other antihypertensives.
- Administered orally as tablets; also available in some regions as injectable forms.
- Acts by depleting norepinephrine from sympathetic nerve endings, reducing sympathetic tone and lowering blood pressure.

Chemical Structure

- IUPAC Name: (2-aminoethyl)guanidinium sulfate (monosulphate)
- Molecular Formula: $C_2H_8N_4 \cdot H_2SO_4$
- Molecular Weight: 168.2 g/mol (free base)
- Structural



Mechanism of Action

- Site of action: Peripheral sympathetic neurons.
- MOA:
  1. Taken up by postganglionic adrenergic neurons via norepinephrine transporter.
  2. Displaces norepinephrine from storage vesicles → depletion of NE in synaptic cleft.
  3. Reduces sympathetic stimulation of blood vessels → decreased peripheral resistance.
  4. Result: Slow-onset reduction of blood pressure.
- Effect: Long-term antihypertensive action; minimal CNS effects.

Synthesis

- Starting materials: Aminoethylguanidine derivatives.
- Steps:
    1. Preparation of guanidine compound.
    2. Formation of monosulphate salt to enhance solubility.
    3. Purification and crystallization → yields Guanethidine Monosulphate.

Uses

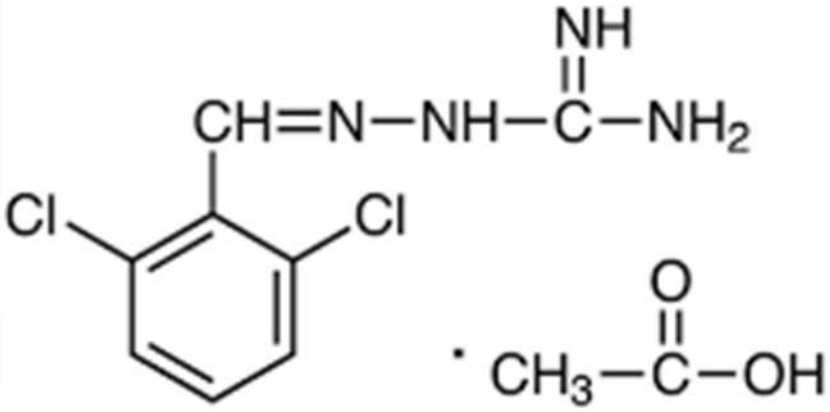
- Moderate to severe hypertension (especially resistant cases).
- Sometimes used in combination with diuretics or other antihypertensives.
- Rarely used now due to availability of safer alternatives.

Guanabenz Acetate

- Guanabenz Acetate is a centrally acting antihypertensive agent.
- Belongs to the imidazoline derivative class, similar to Clonidine.
- Used primarily for hypertension.
- Administered orally as tablets.
- Acts by stimulating central α_2-adrenergic receptors, which reduces sympathetic outflow, thereby lowering blood pressure.

Chemical Structure

- IUPAC Name: 2,6-dichloro-N-(2-ethylphenyl)-4,5-dihydro-1H-imidazol-2-amine acetate
- Molecular Formula: $C_{12}H_{14}Cl_2N_2 \cdot C_2H_4O_2$ (acetate salt)
- Molecular Weight: 270.12 g/mol (free base)
- Structural



Mechanism of Action

- Site of action: Central nervous system (medullary vasomotor center).
- MOA:
  1. Stimulates α_2-adrenergic receptors in the CNS → decreases sympathetic outflow.
  2. ↓ Peripheral vascular resistance → ↓ blood pressure.
  3. ↓ Heart rate and cardiac output → contributes to antihypertensive effect.
- Effect: Lowers blood pressure with minimal impact on renal blood flow.

Synthesis

- Starting materials: 2,6-dichloroaniline and imidazoline precursors.
- Steps:
    1. Formation of imidazoline ring via cyclization.
    2. Coupling with 2-ethylphenyl derivative.
    3. Formation of acetate salt → Guanabenz Acetate.
    4. Purification and crystallization to obtain pure drug.

Uses

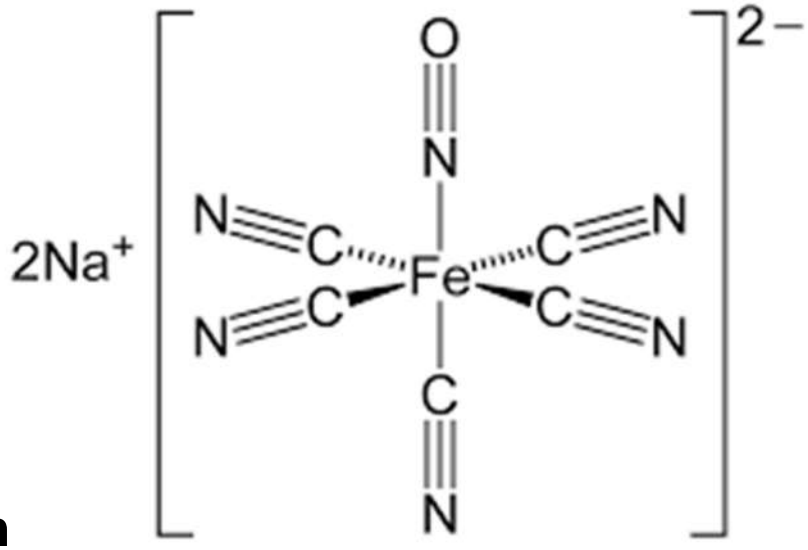
- Hypertension (monotherapy or combination therapy).
- Sometimes used in adjunct therapy for sympathetic overactivity conditions.
- Off-label use: certain pain disorders (rare, centrally mediated).

Sodium Nitroprusside

- Sodium Nitroprusside (SNP) is a direct-acting vasodilator.
- Used for hypertensive emergencies, acute heart failure, and controlled hypotension during surgery.
- Administered intravenously due to rapid onset of action.
- Produces both arterial and venous dilation, reducing afterload and preload, leading to rapid blood pressure reduction.
- Very short-acting; effects are quickly reversible when infusion is stopped.

Chemical Structure

- IUPAC Name: Sodium pentacyanonitrosylferrate(II)
- Molecular Formula: $Na_2[Fe(CN)_5NO]\cdot 2H_2O$
- Molecular Weight: 297.95 g/mol
- Structural



Mechanism of Action

- Site of action: Vascular smooth muscle.
- MOA:
  1. Releases nitric oxide (NO) upon entering vascular smooth muscle.
  2. NO → activates guanylate cyclase → ↑ cyclic GMP (cGMP).
  3. cGMP → smooth muscle relaxation → vasodilation.
- Effect: Rapid reduction in arterial and venous pressure, decreases cardiac preload and afterload.

Synthesis

- Starting materials: Sodium ferrocyanide, nitric oxide donor reagents.
- Steps:
    1. Formation of pentacyanonitrosylferrate complex.
    2. Sodium salt formation → enhances water solubility.
    3. Purification and crystallization → yields Sodium Nitroprusside.

Uses

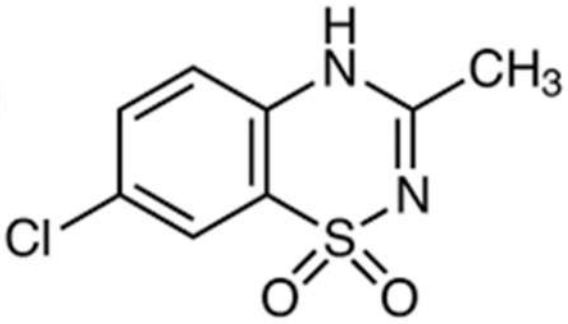
- Hypertensive emergencies (rapid BP control).
- Acute decompensated heart failure (reduces afterload and preload).
- Controlled hypotension during surgery to minimize blood loss.
- Occasionally used in cardiogenic shock under ICU supervision.

Diazoxide

- Diazoxide is a potent, direct-acting vasodilator and antihypertensive agent.
- Primarily used for acute hypertensive crises and management of hypoglycemia due to insulinoma.
- Administered intravenously for rapid action or orally in chronic conditions.
- Produces arterial vasodilation, reducing peripheral resistance and lowering blood pressure.

Chemical Structure

- IUPAC Name: 7-chloro-3-methyl-4H-1,2,4-benzothiadiazine 1,1-dioxide
- Molecular Formula: $C_8H_8ClN_2O_2S$
- Molecular Weight: 210.68 g/mol
- Structural



Mechanism of Action

- Site of action: Vascular smooth muscle and pancreatic beta cells (for insulin release).
- MOA (antihypertensive):
  1. Activates ATP-sensitive K^+ channels in vascular smooth muscle.
  2. Causes membrane hyperpolarization → closes voltage-gated Ca^{2+} channels.
  3. ↓ Intracellular Ca^{2+} → smooth muscle relaxation → arterial vasodilation.
- MOA (hyperinsulinemia/insulinoma):
  - Inhibits insulin secretion by opening K^+ channels in pancreatic beta cells.
- Effect: Rapid reduction of blood pressure; can control hypoglycemia in insulinoma.

Synthesis

- Starting materials: Chlorobenzenes and thiadiazine precursors.
- Steps:
    1. Formation of benzothiadiazine nucleus.
    2. Introduction of chlorine and methyl substituents at appropriate positions.
    3. Formation of sulfonamide group to complete Diazoxide.
    4. Purification and crystallization to obtain pure drug.

Uses

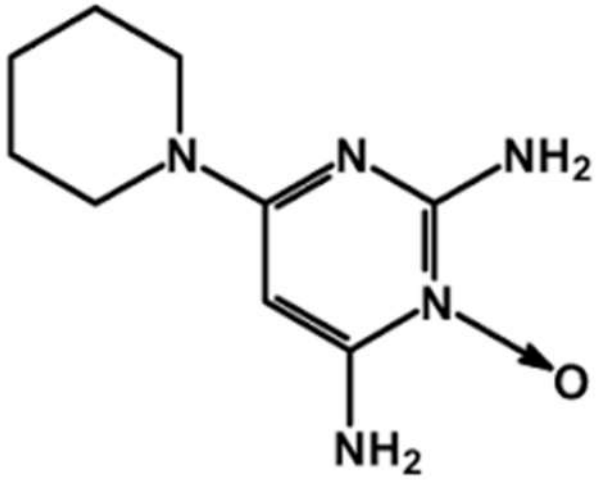
- Hypertensive emergencies (rapid IV control of blood pressure).
- Chronic hypertension (oral, less common).
- Hypoglycemia due to insulinoma (inhibits insulin secretion).
- Sometimes used as adjunct in congenital hyperinsulinism.

Minoxidil

- Minoxidil is a direct-acting arteriolar vasodilator.
- Used primarily for severe, refractory hypertension (usually in combination with a diuretic and beta-blocker).
- Topically, it is widely used for androgenic alopecia (hair regrowth).
- Administered orally for antihypertensive therapy and topically for hair loss treatment.
- Produces potent arterial dilation with minimal venous effects.

Chemical Structure

- IUPAC Name: 6-(1-piperidinyl)-2,4-pyrimidinediamine 3-oxide
- Molecular Formula: $C_9H_{15}N_5O$
- Molecular Weight: 209.25 g/mol
- Structural



Mechanism of Action

- Site of action: Vascular smooth muscle (arterioles).
- MOA:
  1. Activates ATP-sensitive K^+ channels in vascular smooth muscle.
  2. Causes membrane hyperpolarization → closes voltage-gated Ca^{2+} channels.
  3. ↓ Intracellular Ca^{2+} → relaxation of arteriolar smooth muscle.
- Effect: Arteriolar dilation → ↓ peripheral resistance → ↓ blood pressure.
- Hair growth action: Possibly enhances blood flow to hair follicles and prolongs anagen phase of hair cycle (topical use).

Synthesis

- Starting materials: Pyrimidine derivatives and piperidine intermediates.
- Steps:
    1. Formation of pyrimidine-2,4-diamine nucleus.
    2. Introduction of piperidinyl substituent at position 6.
    3. Oxidation to N-oxide form → active Minoxidil.
    4. Purification and crystallization to obtain the pure compound.

Uses

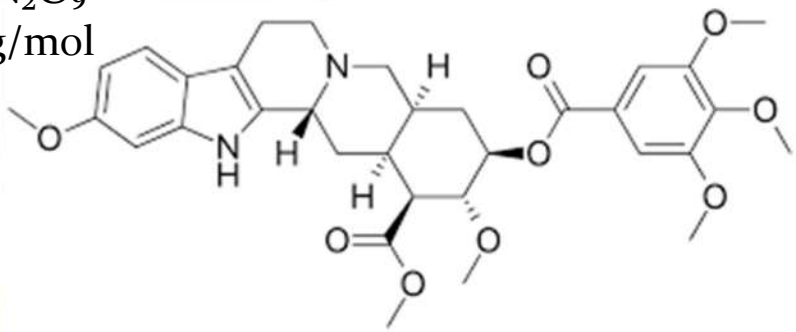
- Severe or refractory hypertension (oral, usually with diuretic and beta-blocker).
- Topical therapy for androgenic alopecia (male and female pattern baldness).
- Occasionally investigated for wound healing and alopecia areata (off-label).

Reserpine

- Reserpine is a peripherally acting antihypertensive and sedative agent.
- It is an alkaloid obtained from Rauwolfia serpentina (Indian Snakeroot).
- Used for mild to moderate hypertension, psychotic disorders, and adjunct therapy in heart failure (historically).
- Administered orally as tablets.
- Acts by depleting catecholamines (norepinephrine, dopamine) from peripheral sympathetic neurons, reducing vascular tone.

Chemical Structure

- IUPAC Name: Methyl (1S,2R,3R,5S,7S,15R,16R)-10,17-dimethoxy-3-(3,4,5-trimethoxybenzoyl) yohimban-16-carboxylate
- Molecular Formula: $C_{31}H_{40}N_2O_9$
- Molecular Weight: 608.66 g/mol
- Structural



Mechanism of Action

- Site of action: Peripheral sympathetic nerve endings (adrenergic neurons).
- MOA:
  1. Irreversibly binds to vesicular monoamine transporter (VMAT) → prevents uptake of norepinephrine, dopamine, and serotonin into synaptic vesicles.
  2. Neurotransmitters are degraded by monoamine oxidase (MAO) → depletion in nerve endings.
  3. ↓ Sympathetic tone → vasodilation → ↓ peripheral resistance → ↓ blood pressure.
  4. Also exerts central sedative effects due to CNS catecholamine depletion.

Synthesis

- Source: Naturally extracted from Rauwolfia serpentina roots.
- Steps (simplified):
    1. Extraction of alkaloid fraction from roots using alcohol/water.
    2. Purification and crystallization of Reserpine.
    3. Conversion to pharmaceutical grade tablets for oral administration.

Uses

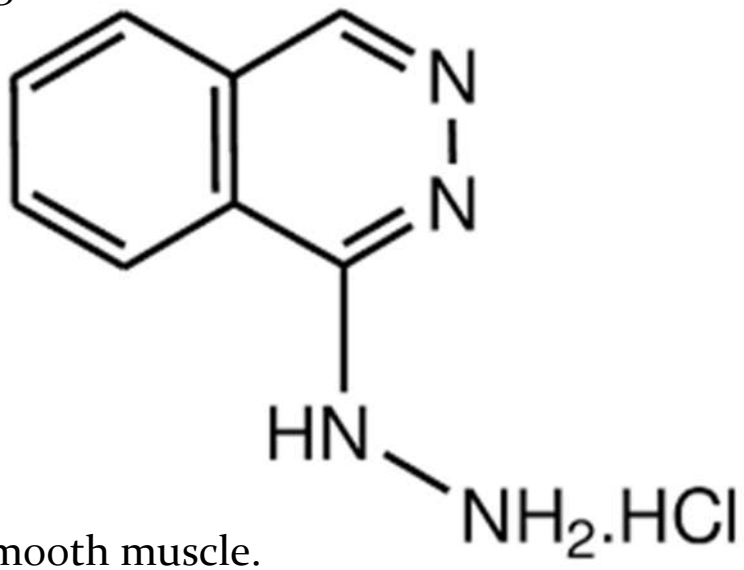
- Hypertension: Mild to moderate cases, often in combination with other antihypertensives.
- Psychiatric disorders: Sedative and tranquilizing effects historically used for schizophrenia or anxiety.
- Adjunct therapy: Occasionally in heart failure (reduces sympathetic overactivity).

Hydralazine Hydrochloride

- Hydralazine Hydrochloride is a direct-acting arterial vasodilator.
- Used for hypertension, heart failure (adjunct therapy), and hypertensive emergencies (IV form).
- Acts mainly on arterioles, causing reduction in peripheral resistance with minimal venous dilation.
- Administered orally as tablets or intravenously in emergencies.
- Often combined with beta-blockers and diuretics to prevent reflex tachycardia and fluid retention.

Chemical Structure

- IUPAC Name: 1-hydrazinophthalazine hydrochloride
- Molecular Formula: $C_8H_8N_4 \cdot HCl$
- Molecular Weight: 182.63 g/mol
- Structural



Mechanism of Action

- Site of action: Arteriolar smooth muscle.
- MOA:
  1. Direct relaxation of vascular smooth muscle (mainly arterioles).
  2. Exact mechanism is not fully understood, but may involve:
     - Interference with calcium metabolism in smooth muscle
     - Modulation of intracellular cGMP levels
  3. ↓ Peripheral resistance → ↓ blood pressure
- Effect: Minimal effect on venous tone → mild reduction in preload; decreases afterload significantly.

Synthesis

- Starting materials: Phthalazine derivatives and hydrazine.
- Steps:
    1. Formation of phthalazine nucleus.
    2. Introduction of hydrazine group at position 1.
    3. Formation of hydrochloride salt → Hydralazine Hydrochloride.
    4. Purification and crystallization to obtain pure drug.

Uses

- Hypertension: Mild to moderate (oral therapy).
- Hypertensive emergencies: IV form for rapid BP control.
- Heart failure: Adjunct therapy in combination with nitrates (esp. in patients intolerant to ACE inhibitors).
- Occasionally used in pregnancy-induced hypertension (with caution).