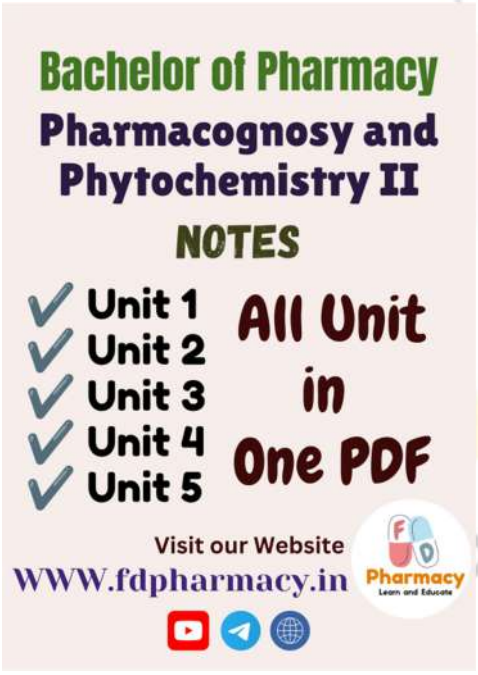
WELCOME

TO


Bachelor of Pharmacy
Pharmaceutical Jurisprudence
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate


Bachelor of Pharmacy
Industrial Pharmacy I
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate


Bachelor of Pharmacy
Medicinal Chemistry II
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate


Bachelor of Pharmacy
Pharmacognosy and Phytochemistry II
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate


Bachelor of Pharmacy
Pharmacology II
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate

MEDICINAL CHEMISTRY - II

UNIT 3

TOPIC :

- **Drugs used in Congestive Heart Failure :** Digoxin, Digitoxin, Nesiritide,Bosentan, Tezosentan.

Drugs Used in Congestive Heart Failure (CHF)

- Congestive Heart Failure (CHF) is a clinical condition where the heart fails to pump sufficient blood to meet the metabolic demands of the body.
- It results from systolic dysfunction (reduced contractility) or diastolic dysfunction (impaired filling).
- Drugs in CHF aim to:
    1. Reduce preload and afterload
    2. Increase cardiac contractility (inotropes)
    3. Control symptoms like edema and dyspnea
    4. Prevent disease progression and mortality

Classification of Drugs in CHF

A. Positive Inotropic Agents (Increase cardiac contractility)

1. Cardiac Glycosides
    - Example: Digoxin
    - Mechanism: Inhibits Na^+/K^+-ATPase → ↑ intracellular Na^+ → ↑ Ca^{2+} influx → ↑ contractility
    - Use: Systolic CHF, atrial fibrillation with CHF
    - Adverse Effects: Arrhythmias, nausea, visual disturbances, digoxin toxicity
2. Phosphodiesterase Inhibitors (PDE-III inhibitors)
    - Examples: Milrinone, Amrinone
    - Mechanism: ↑ cAMP in cardiac muscle → ↑ Ca^{2+} → ↑ contractility; also cause vasodilation
    - Use: Acute decompensated CHF (short-term IV use)
    - Adverse Effects: Arrhythmias, hypotension, thrombocytopenia

B. Vasodilators (Reduce preload and afterload)

1. ACE Inhibitors (Angiotensin-Converting Enzyme Inhibitors)
    - Examples: Enalapril, Lisinopril, Captopril
    - Mechanism: ↓ Angiotensin II → ↓ vasoconstriction and aldosterone → ↓ preload & afterload
    - Use: CHF with reduced ejection fraction, hypertension
    - Adverse Effects: Cough, hyperkalemia, hypotension, angioedema
2. Angiotensin Receptor Blockers (ARBs)
    - Examples: Losartan, Valsartan
    - Mechanism: Block AT_1 receptors → ↓ vasoconstriction, ↓ aldosterone
    - Use: Alternative to ACE inhibitors if intolerant
    - Adverse Effects: Hyperkalemia, hypotension
3. Direct Vasodilators
    - Examples: Hydralazine (arterial), Isosorbide dinitrate (venous)
    - Use: CHF in patients intolerant to ACE inhibitors; combination therapy in African-American patients
    - Adverse Effects: Hypotension, headache, reflex tachycardia

C. Diuretics (Reduce fluid overload)

- Examples: Furosemide (loop diuretic), Hydrochlorothiazide (thiazide), Spironolactone (potassium-sparing)
- Mechanism: Increase sodium and water excretion → ↓ preload, relieve pulmonary and peripheral edema
- Use: Symptomatic relief in CHF
- Adverse Effects: Electrolyte imbalance (hypokalemia, hyponatremia), dehydration

D. Beta-Blockers (Reduce sympathetic overactivity)

- Examples: Carvedilol, Metoprolol succinate, Bisoprolol
- Mechanism: Block β_1 receptors → ↓ heart rate, ↓ myocardial oxygen demand, ↓ remodeling
- Use: Chronic stable CHF with reduced ejection fraction
- Adverse Effects: Bradycardia, hypotension, fatigue

E. Aldosterone Antagonists

- Examples: Spironolactone, Eplerenone
- Mechanism: Block aldosterone → ↓ sodium retention, ↓ cardiac remodeling
- Use: Severe CHF (NYHA class III-IV), post-MI CHF
- Adverse Effects: Hyperkalemia, gynecomastia (spironolactone)

F. Other Agents

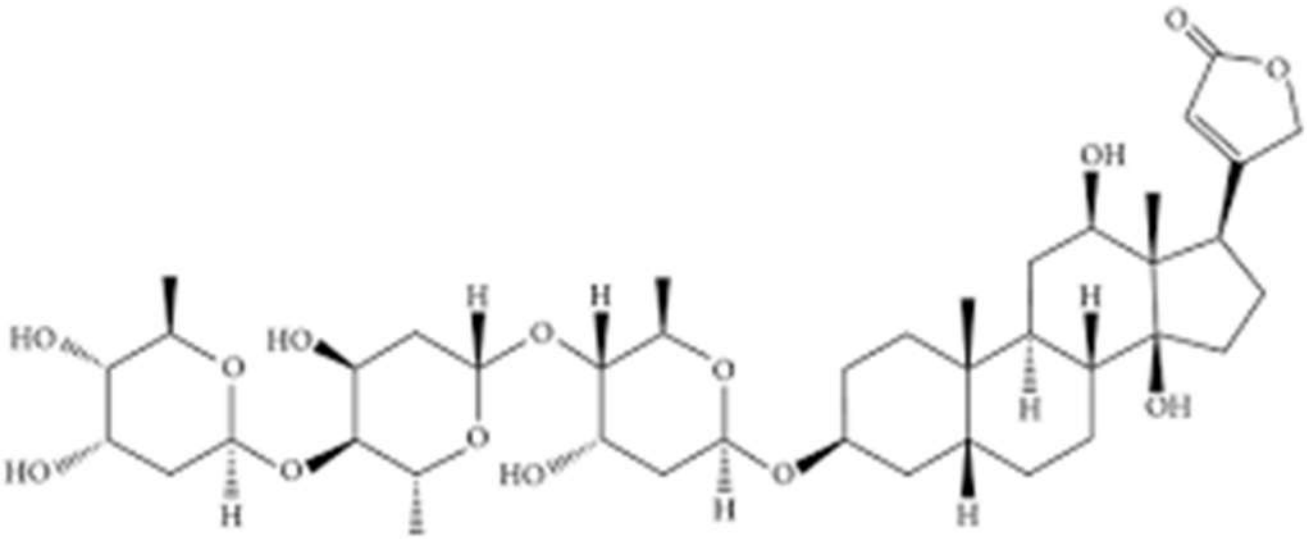
1. Natriuretic Peptides
    - Example: Nesiritide
    - Mechanism: ↑ cGMP → vasodilation, natriuresis
    - Use: Acute decompensated CHF
2. Ivabradine
    - Mechanism: Selective If channel inhibitor → reduces heart rate without affecting contractility
    - Use: CHF patients with sinus rhythm and HR >70 bpm despite beta-blockers
    - Adverse Effects: Bradycardia, visual disturbances

Digoxin

- Digoxin is a cardiac glycoside derived from the leaves of Digitalis lanata (foxglove).
- It is used for heart failure and atrial arrhythmias due to its positive inotropic and negative chronotropic effects.
- Digoxin increases cardiac contractility while slowing heart rate, making it useful in systolic heart failure and atrial fibrillation.
- It has a narrow therapeutic index, so careful dose monitoring is essential to avoid toxicity.

Chemical Structure

- Chemical name: (3β,5β,12β)-3-[(O-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1→4)-O-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-ribo-hexopyranosyl)oxy]-12,14-dihydroxy-card-20(22)-enolide
- Molecular formula: $C_{41}H_{64}O_{14}$
- Molecular weight: 780.94 g/mol
- Chemical class: Cardiac glycoside (steroid nucleus + sugar moieties)
- Structural



Mechanism of Action

Primary Target: Na^+/K^+-ATPase pump in cardiac myocytes
Stepwise Mechanism:

1. Digoxin inhibits Na^+/K^+-ATPase → intracellular Na^+ increases.
2. Elevated Na^+ reduces Na^+/Ca^{2+} exchanger activity, leading to increased intracellular Ca^{2+}.
3. Increased Ca^{2+} → enhanced myocardial contractility (positive inotropic effect).
4. Digoxin also stimulates vagus nerve → decreases SA node firing and AV node conduction (negative chronotropic and dromotropic effects).

Synthesis

- Starting material: Digitoxigenin (steroidal aglycone from plant or synthetic sources)
- Glycosylation:
  - Digitoxigenin is glycosylated with three digitoxose residues using glycosyl donors under acidic catalysis.
- Purification:
  - Crystallization yields pure digoxin suitable for pharmaceutical use.

Uses

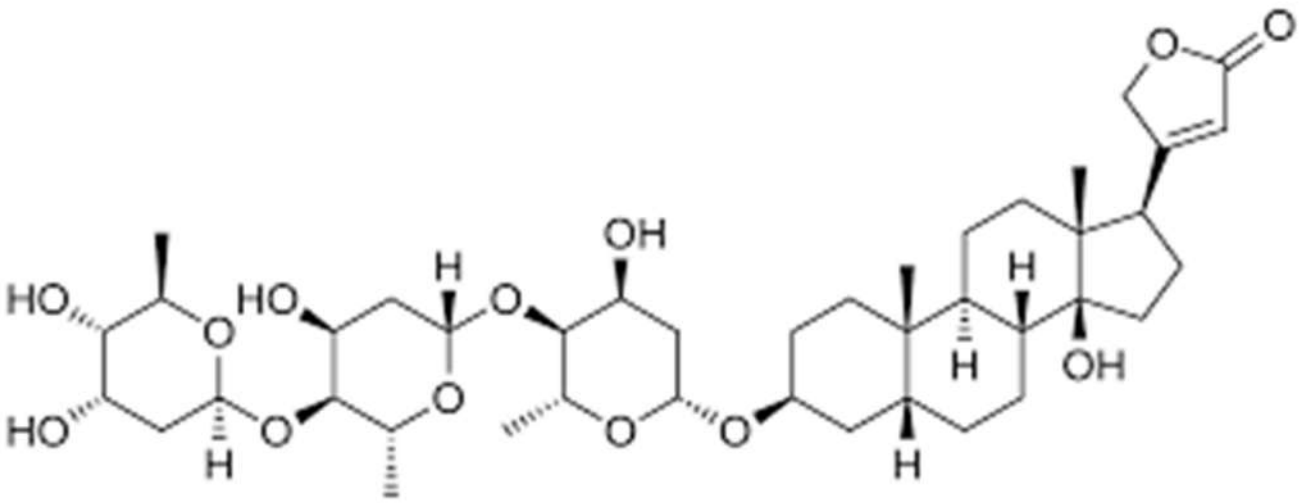
- Therapeutic Uses:
  1. Heart failure: Improves symptoms, exercise tolerance, and cardiac output
  2. Atrial fibrillation and flutter: Rate control and rhythm stabilization
  3. Paroxysmal supraventricular tachycardia (PSVT): Adjunct therapy

Digitoxin

- Digitoxin is a cardiac glycoside obtained from the leaves of Digitalis purpurea.
- Similar to digoxin, it is used in heart failure and certain arrhythmias but differs in pharmacokinetics:
  - Longer half-life (~7 days)
  - Primarily hepatic metabolism (digoxin is mostly renally excreted)
- Digitoxin increases cardiac contractility while slowing heart rate (positive inotropic, negative chronotropic effects).
- Narrow therapeutic index; careful dosing and monitoring required.

Chemical Structure

- Chemical name: (3β,5β,12β)-3-[(O-3,6-dideoxy-β-D-ribo-hexopyranosyl-(1→4)-O-3,6-dideoxy-β-D-ribo-hexopyranosyl-(1→4)-3,6-dideoxy-β-D-ribo-hexopyranosyl)oxy]-12,14-dihydroxy-card-20(22)-enolide
- Molecular formula: $C_{41}H_{64}O_{13}$
- Molecular weight: 764.93 g/mol
- Chemical class: Cardiac glycoside (steroidal aglycone + sugar residues)
- Structural



Mechanism of Action

Primary Target: Na^+/K^+-ATPase pump in cardiac myocytes
Stepwise Mechanism:

1. Inhibits Na^+/K^+-ATPase → intracellular Na^+ rises.
2. Reduced Na^+/Ca^{2+} exchange → increased intracellular Ca^{2+}.
3. Elevated Ca^{2+} → enhanced myocardial contractility (positive inotropic effect).
4. Stimulates vagus nerve → slows SA node firing and AV node conduction (negative chronotropic/dromotropic effects).

Synthesis

- Starting material: Digitoxigenin (steroidal aglycone)
- Glycosylation:
  - Attach three digitoxose sugar residues at C3 via glycosyl donor reaction under acidic catalysis
- Purification:
  - Crystallization yields digitoxin

Uses

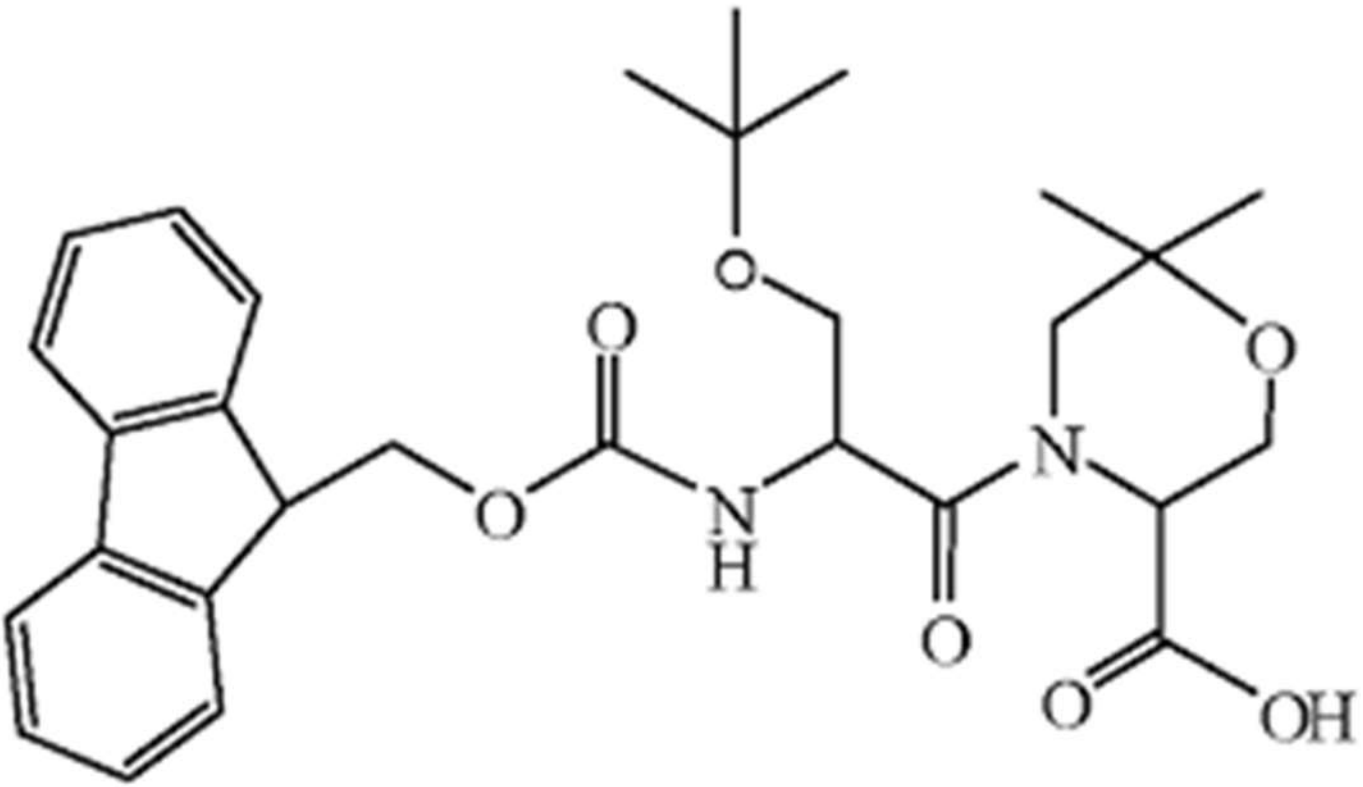
- Therapeutic Uses:
  1. Chronic heart failure (especially when renal excretion is impaired)
  2. Atrial fibrillation and atrial flutter → rate control
  3. Less commonly used for paroxysmal supraventricular tachycardia

Nesiritide

- Nesiritide is a recombinant human B-type natriuretic peptide (BNP).
- It is used primarily in acute decompensated heart failure (ADHF) with dyspnea at rest or minimal exertion.
- Nesiritide acts as a vasodilator and diuretic, reducing preload and afterload, improving cardiac output, and decreasing pulmonary capillary wedge pressure (PCWP).
- Administered intravenously, it is a rapid-acting therapeutic used in hospital settings.

Chemical Structure

- Chemical nature: Recombinant peptide, identical to human BNP
- Amino acid sequence: 32 amino acids, single-chain polypeptide
- Molecular formula: $C_{164}H_{265}N_{47}O_{52}S_2$ (approximate)
- Molecular weight: ~3.5 kDa
- Structural



Mechanism of Action

- Target receptor: Natriuretic peptide receptor-A (NPR-A) on vascular smooth muscle and kidney cells

Stepwise Mechanism:

1. Nesiritide binds NPR-A, a guanylyl cyclase-linked receptor.
2. Activation of NPR-A → ↑ intracellular cyclic GMP (cGMP).
3. Increased cGMP causes:
    - Vasodilation → reduces preload and afterload
    - Natriuresis and diuresis → promotes sodium and water excretion
    - Inhibition of renin-angiotensin-aldosterone system (RAAS)
4. Net effect: Reduced cardiac filling pressures, improved cardiac output, and symptom relief in heart failure.

Synthesis

- Recombinant DNA technology:
    1. Gene encoding human BNP is cloned into an expression vector.
    2. Expressed in E. coli or mammalian cells.
    3. Purification of the peptide from culture media.
    4. Folding and formation of disulfide bond to yield biologically active nesiritide.

Uses

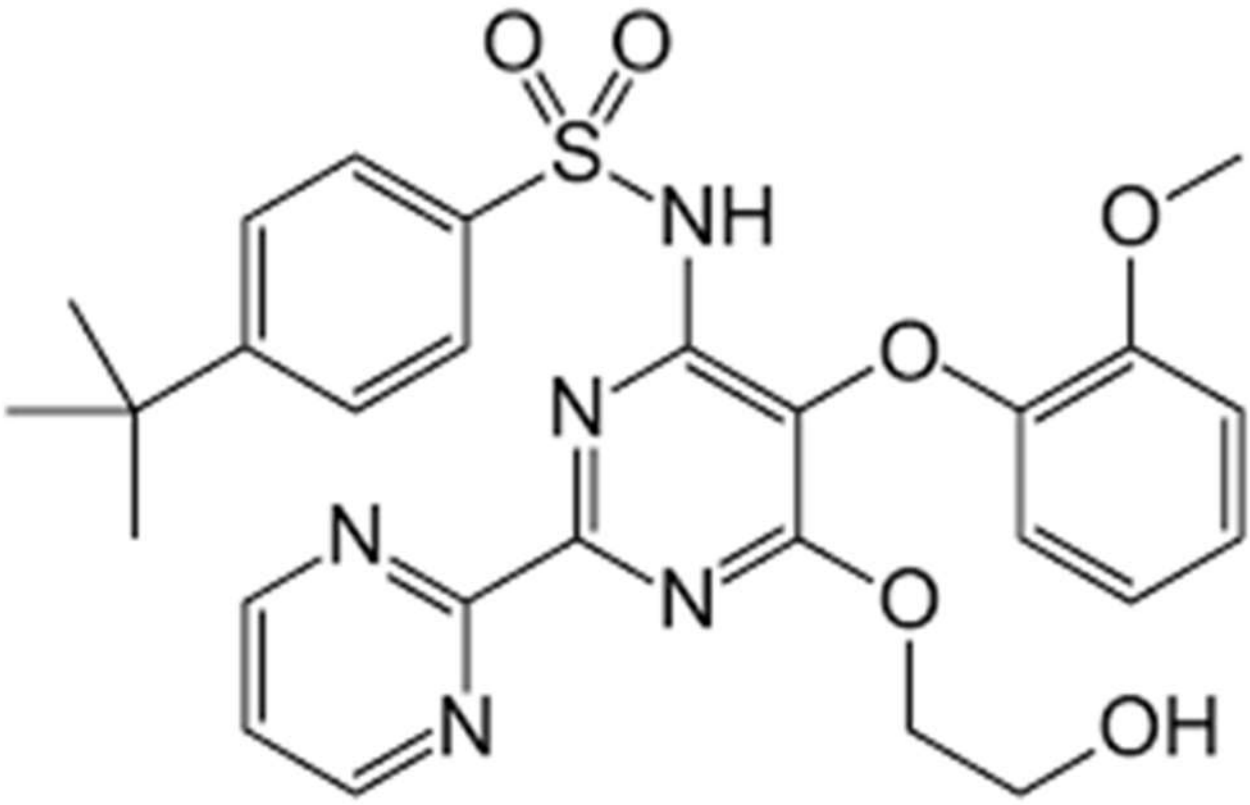
- Therapeutic Uses:
    1. Acute decompensated heart failure (ADHF): Rapid symptomatic relief
    2. Dyspnea at rest or minimal activity associated with heart failure
    3. Sometimes used in acute management of left ventricular dysfunction

Bosentan

- Bosentan is a dual endothelin receptor antagonist (ERA), targeting endothelin-A (ET-A) and endothelin-B (ET-B) receptors.
- It is primarily used in the treatment of pulmonary arterial hypertension (PAH) to reduce pulmonary vascular resistance and improve exercise capacity.
- Bosentan is orally active, metabolized in the liver, and requires monitoring of liver function due to potential hepatotoxicity.

Chemical Structure

- Chemical name: N-[5-(4-bromophenyl)-6-[2-(2-hydroxyethoxy)ethoxy]-4-pyrimidinyl]-4-(tetrahydro-2H-pyran-4-ylamino)benzenesulfonamide
- Molecular formula: $C_{26}H_{29}BrN_6O_4S$
- Molecular weight: 573.2 g/mol
- Chemical class: Endothelin receptor antagonist; sulfonamide derivative
- Structural



Mechanism of Action

- Target: Endothelin-1 (ET-1) receptors (ET-A and ET-B) on vascular smooth muscle and endothelium

Stepwise Mechanism:

1. ET-1 is a potent vasoconstrictor peptide, elevated in pulmonary hypertension.
2. Bosentan competitively blocks ET-A and ET-B receptors, preventing ET-1 binding.
3. Inhibition of ET-A → prevents vasoconstriction and vascular proliferation.
4. Inhibition of ET-B → reduces ET-1-mediated effects on endothelial cells (less ET-1 clearance, but overall vasodilatory effect predominates).
5. Net effect: pulmonary vasodilation, reduced pulmonary arterial pressure, and improved cardiac output.

Synthesis

1. Starting materials: Aromatic sulfonamide derivatives and substituted pyrimidine intermediates
2. Condensation and substitution reactions:
    - Formation of sulfonamide linkage with substituted pyrimidine
    - Introduction of ethoxyethanol side chain and bromophenyl substitution
3. Purification:
    - Crystallization to obtain pure bosentan suitable for oral formulation

Uses

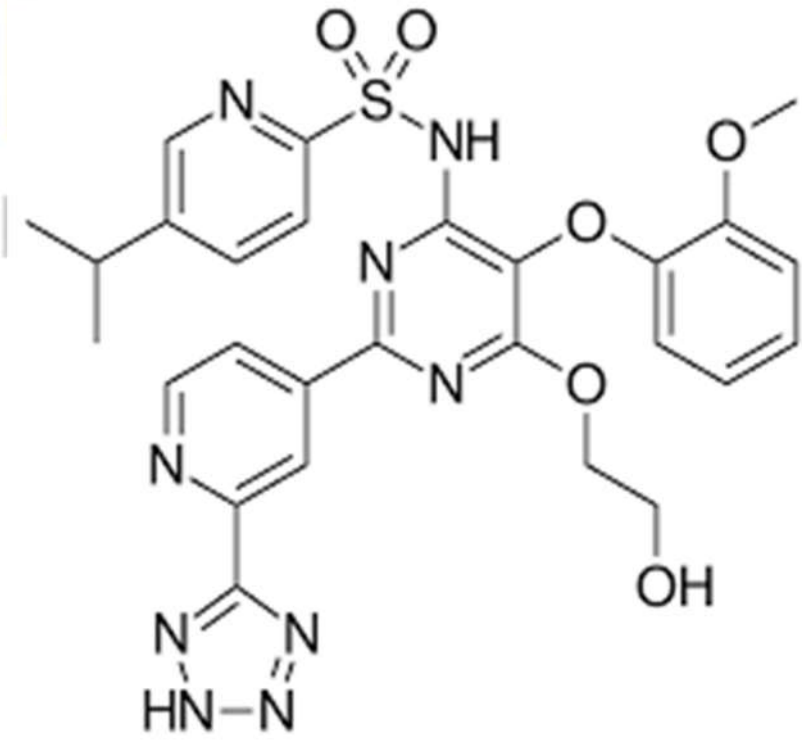
- Therapeutic Uses:
    1. Pulmonary arterial hypertension (PAH) – WHO Group I
    2. Treatment of idiopathic or heritable PAH to improve exercise tolerance and hemodynamics
    3. Sometimes used in connective tissue disease–associated PAH

Tezosentan

- Tezosentan is a non-selective endothelin receptor antagonist (ERA), blocking both ET-A and ET-B receptors.
- It is used primarily in experimental and clinical settings for acute heart failure (AHF) and pulmonary hypertension.
- Administered intravenously, Tezosentan is a rapid-acting vasodilator that reduces pulmonary vascular resistance and systemic vascular resistance.
- Unlike Bosentan, Tezosentan is used in acute settings rather than chronic therapy.

Chemical Structure

- Chemical name: N-(4-chloro-3-methoxyphenyl)-5-(2,3-dimethylmorpholino)pyridine-2-sulfonamide
- Molecular formula: $C_{19}H_{22}ClN_3O_4S$
- Molecular weight: 417.9 g/mol
- Chemical class: Sulfonamide-based endothelin receptor antagonist
- Structural



Mechanism of Action

- Target: Endothelin-1 (ET-1) receptors (ET-A and ET-B) on vascular smooth muscle and endothelium

Stepwise Mechanism:

1. ET-1 binds ET-A and ET-B receptors → potent vasoconstriction and vascular proliferation.
2. Tezosentan competitively blocks ET-A and ET-B receptors, preventing ET-1 binding.
3. Inhibition of ET-A → reduces vasoconstriction in arteries.
4. Inhibition of ET-B → modulates endothelial effects and prevents further vasoconstriction.
5. Net effect: systemic and pulmonary vasodilation, reduced pulmonary and systemic vascular resistance, improved cardiac output.

Synthesis

1. Starting materials: Substituted pyridine and sulfonamide derivatives
2. Substitution reactions:
    - Attach chloro-methoxyphenyl group to pyridine
    - Morpholine ring introduced at position 5 of pyridine
3. Sulfonamide formation:
    - Sulfonyl chloride reacts with aniline derivative to yield Tezosentan
4. Purification: Crystallization to obtain pure intravenous-grade compound

Uses

- Therapeutic Uses:
    1. Acute decompensated heart failure (ADHF) – intravenous therapy to reduce preload/afterload
    2. Pulmonary arterial hypertension (experimental/acute use)
    3. Clinical research for acute left ventricular dysfunction