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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

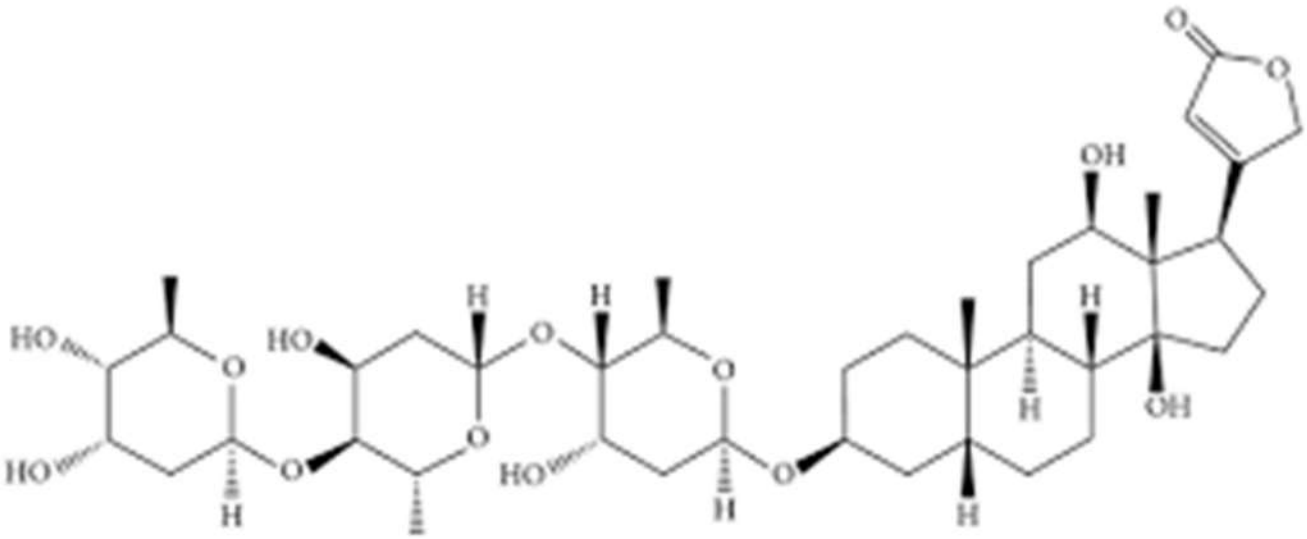
1. **Natriuretic Peptides**
    - **Example:** Nesiritide
    - **Mechanism:** ↑ cGMP → vasodilation, natriuresis
    - **Use:** Acute decompensated CHF
2. **Ivabradine**
    - **Mechanism:** Selective **If channel inhibitor** → reduces heart rate without affecting contractility
    - **Use:** CHF patients 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

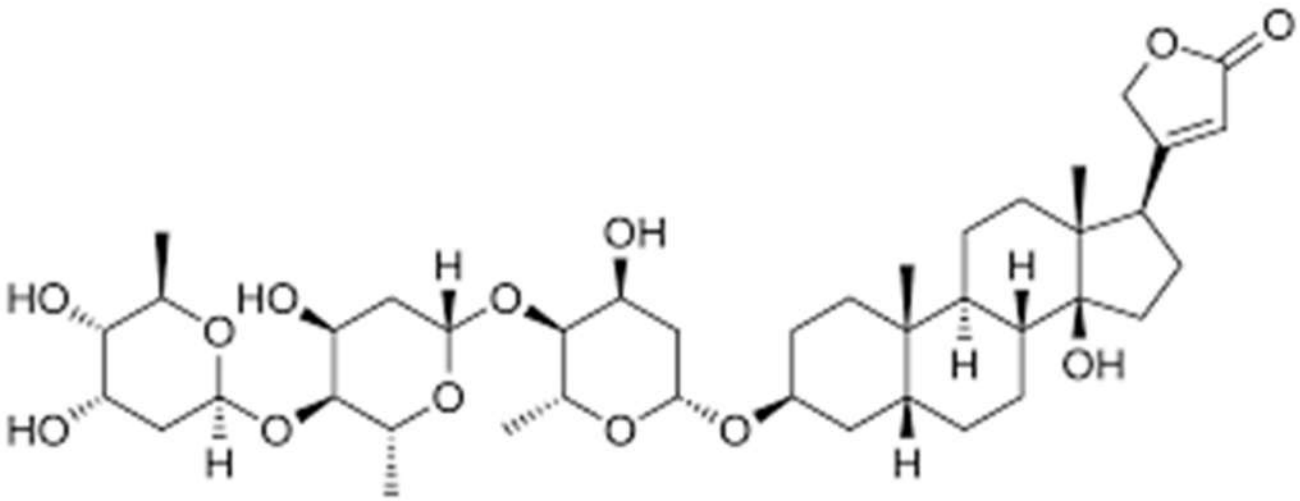
- **Therapeutic Uses:**
  1. **Heart failure:** Improves symptoms, exercise tolerance, and cardiac output
  2. **Atrial fibrillation and flutter:** Rate control and rhythm stabilization
  3. **Paroxysmal supraventricular tachycardia (PSVT):** Adjunct therapy

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**

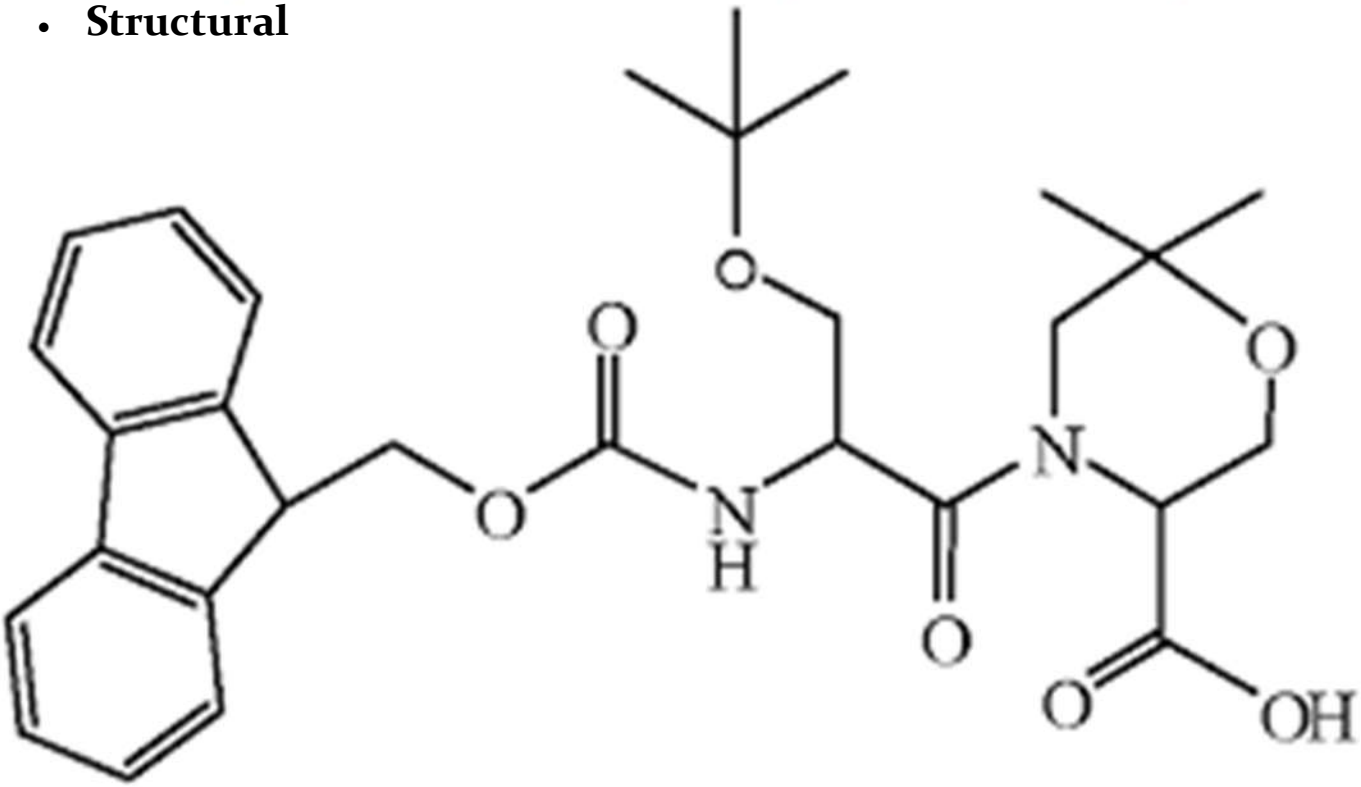
Nesiritide

- **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

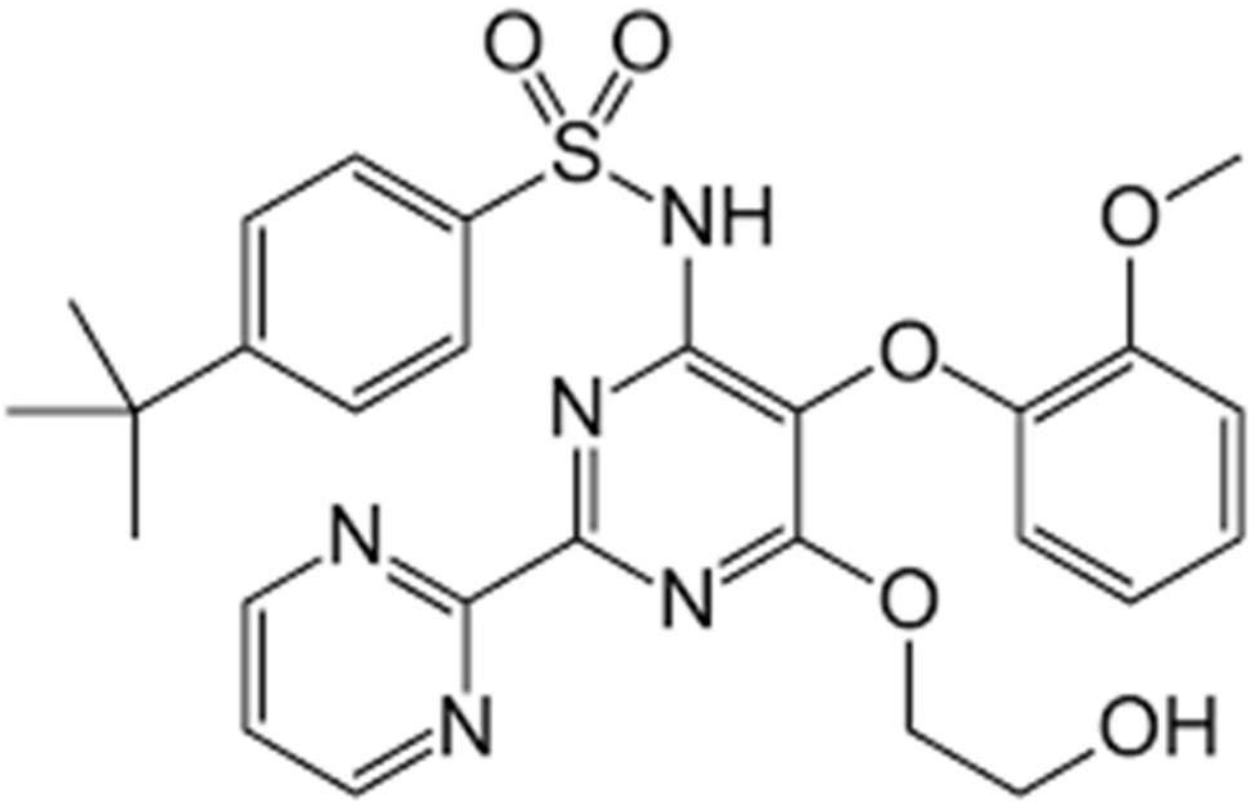
- **Therapeutic Uses:**
    1. **Acute decompensated heart failure (ADHF):** Rapid symptomatic relief
    2. **Dyspnea at rest or minimal activity** associated with heart failure
    3. Sometimes used in **acute management of left ventricular dysfunction**

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

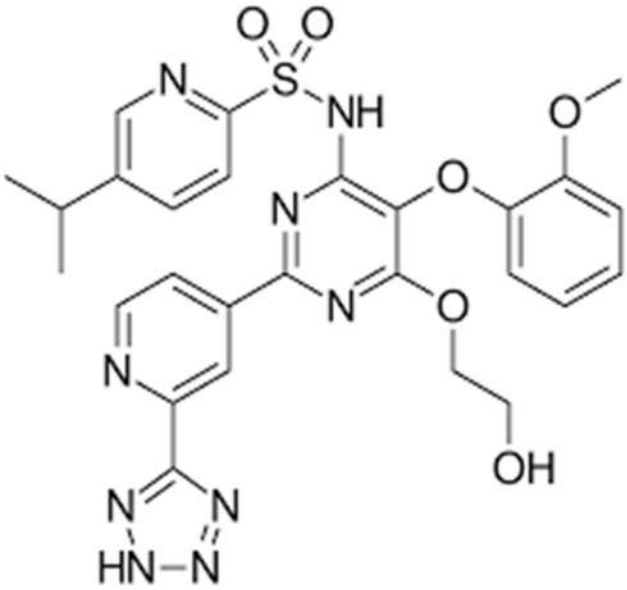
- **Therapeutic Uses:**
    1. **Pulmonary arterial hypertension (PAH)** – WHO Group I
    2. **Treatment of idiopathic or heritable PAH** to improve **exercise tolerance** and **hemodynamics**
    3. Sometimes used in **connective tissue disease–associated PAH**

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**