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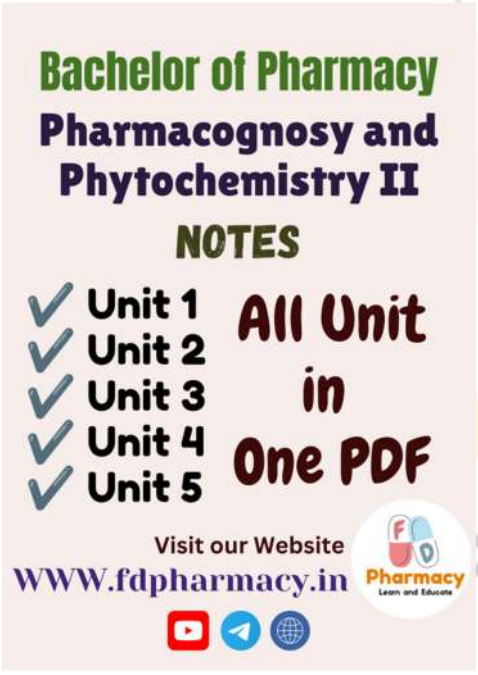
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MEDICINAL CHEMISTRY - II

UNIT 4

TOPIC :

- **Drugs for erectile dysfunction :** Sildenafil, Tadalafil.

Drugs for Erectile Dysfunction

- Erectile dysfunction (ED) is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.
- Causes:
  1. Vascular: Atherosclerosis, hypertension
  2. Neurological: Spinal cord injury, neuropathies
  3. Hormonal: Low testosterone
  4. Psychogenic: Stress, depression
- Drugs used for ED aim to enhance penile blood flow, modulate nitric oxide signaling, or address hormonal deficiencies.

Major Classes of Drugs for ED

A. Phosphodiesterase Type 5 (PDE5) Inhibitors

- Mechanism of Action:
  - Inhibit PDE5 → prevent degradation of cGMP → smooth muscle relaxation in corpora cavernosa → increased blood inflow → erection.
- Drugs:
  1. Sildenafil – rapid onset (30–60 min), lasts ~4–5 hrs
  2. Tadalafil – longer duration (~36 hrs), daily use possible
  3. Vardenafil – similar onset and duration as sildenafil
  4. Avanafil – fast onset (15–30 min), shorter duration
- Uses:
  - Erectile dysfunction due to vascular, diabetic, or idiopathic causes
- Side Effects:
  - Headache, flushing, dyspepsia, nasal congestion, visual disturbances
- Precautions:
  - Contraindicated with nitrates (risk of severe hypotension)

B. Intracavernosal or Intraurethral Agents

1. Alprostadil (Prostaglandin E1)
    - Mechanism: Directly increases cAMP → smooth muscle relaxation → vasodilation
    - Administration:
        - Intracavernosal injection
        - Intraurethral suppository
    - Uses: ED in patients unresponsive to oral PDE5 inhibitors
    - Side Effects: Penile pain, priapism, fibrosis at injection site

C. Hormonal Therapy

- Indicated in hypogonadism (low testosterone levels)
- Drugs:
    - Testosterone enanthate / cypionate / undecanoate (IM injection)
    - Transdermal testosterone (gel or patch)
- Mechanism: Restores normal serum testosterone → improves libido and erectile function
- Side Effects: Acne, polycythemia, prostate enlargement, liver toxicity (oral formulations)

D. Dopaminergic Agents

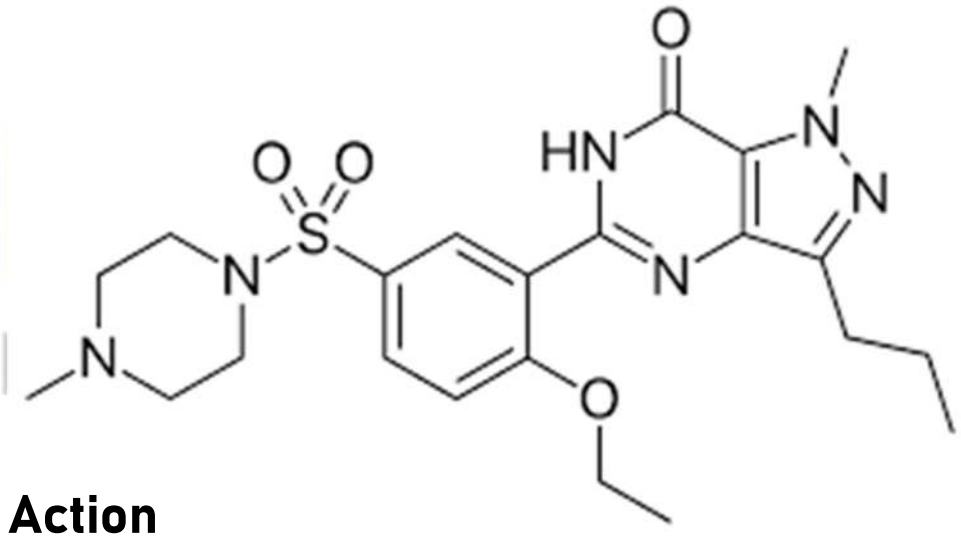
- Example: Apomorphine (subcutaneous or sublingual)
- Mechanism: Stimulates central dopamine receptors → triggers erection via central nervous system pathways
- Uses: Mild to moderate ED
- Side Effects: Nausea, hypotension, dizziness

Sildenafil

- Sildenafil is a phosphodiesterase type 5 (PDE5) inhibitor.
- Developed primarily for the treatment of erectile dysfunction (ED) and pulmonary arterial hypertension (PAH).
- It enhances smooth muscle relaxation and vasodilation in the corpus cavernosum and pulmonary vasculature.
- Administered orally, with rapid onset and good oral bioavailability.

Chemical Structure

- Chemical name: 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine
- Molecular formula: $C_{22}H_{30}N_6O_4S$
- Molecular weight: 474.6 g/mol
- Chemical class: PDE5 inhibitor; pyrazolopyrimidinone derivative
- Structural



Mechanism of Action

- Target: Phosphodiesterase type 5 (PDE5) enzyme in corpus cavernosum and pulmonary vasculature

Stepwise Mechanism:

1. Sexual stimulation → nitric oxide (NO) release in corpus cavernosum

2. NO activates guanylate cyclase, increasing cGMP levels → smooth muscle relaxation
3. Sildenafil inhibits PDE5, the enzyme that degrades cGMP
4. Elevated cGMP → prolonged smooth muscle relaxation → increased blood flow to penis → erection
5. In pulmonary vasculature → decreased pulmonary vascular resistance and improved cardiac output

Synthesis

1. Step 1: Formation of pyrazolopyrimidinone core via cyclization of appropriate hydrazine and diketone precursors
2. Step 2: Substitution at 5-position with 4-ethoxyphenylsulfonyl group
3. Step 3: Coupling with methylpiperazine to yield sildenafil
4. Purification: Crystallization to obtain pharmaceutical-grade sildenafil

Uses

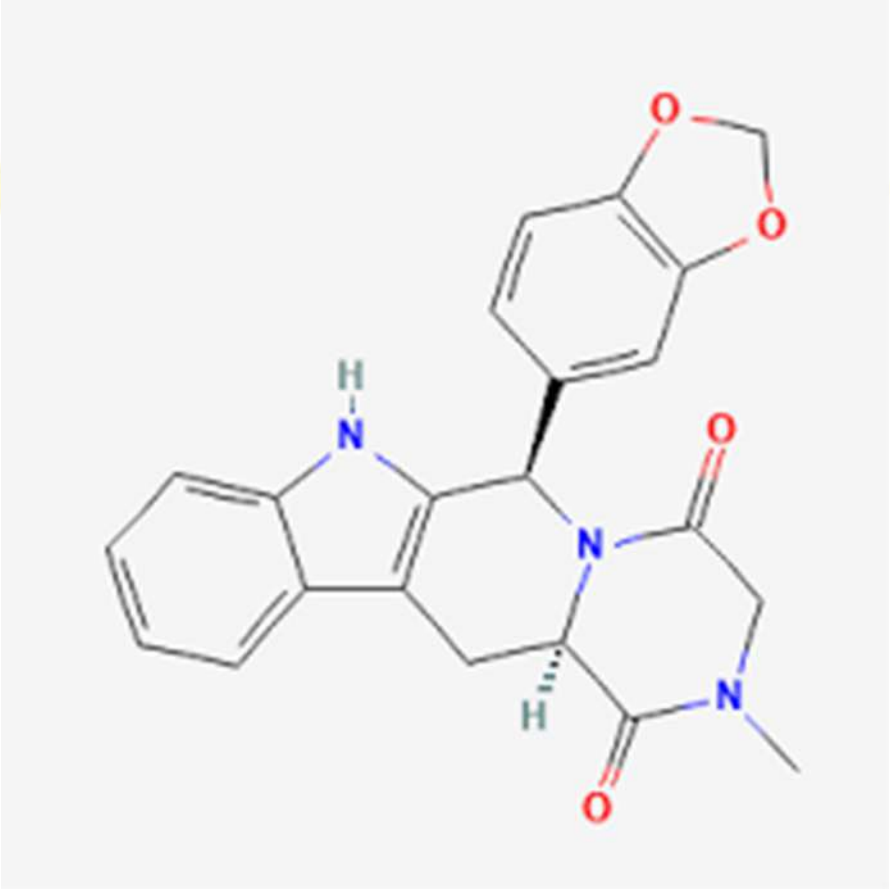
- Therapeutic Uses:
    1. Erectile dysfunction (ED) in men
    2. Pulmonary arterial hypertension (PAH) (under brand name Revatio)
    3. Off-label: Raynaud's phenomenon, high-altitude pulmonary edema (experimental)

Tadalafil

- Tadalafil is a phosphodiesterase type 5 (PDE5) inhibitor, similar to sildenafil, but with a longer duration of action (~36 hours).
- It is used primarily for erectile dysfunction (ED), pulmonary arterial hypertension (PAH), and benign prostatic hyperplasia (BPH) associated LUTS.
- Administered orally, with relatively slow onset but prolonged effect, earning it the nickname “weekend pill”.

Chemical Structure

- Chemical name: (6R,12aR)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1’,2’:1,6]pyrido[3,4-b]indole-1,4-dione
- Molecular formula: $C_{22}H_{19}N_3O_4$
- Molecular weight: 389.4 g/mol
- Chemical class: PDE5 inhibitor; tadalafil is a carboline derivative
- Structural



Mechanism of Action

- Target: Phosphodiesterase type 5 (PDE5) enzyme in corpus cavernosum and pulmonary vasculature

Stepwise Mechanism:

1. Sexual stimulation → NO release in corpus cavernosum
2. NO activates guanylate cyclase, increasing cGMP → smooth muscle relaxation
3. Tadalafil inhibits PDE5, the enzyme that degrades cGMP
4. Elevated cGMP → prolonged smooth muscle relaxation → increased penile blood flow → erection
5. In pulmonary vasculature → decreased pulmonary vascular resistance, improved right ventricular function

Synthesis

1. Formation of pyrido[3,4-b]indole core from tryptamine derivatives
2. Cyclization and introduction of dioxolyl group at position 6
3. Oxidation to introduce dione functionality at 1,4-positions
4. Purification → pharmaceutical-grade tadalafil

Uses

- Therapeutic Uses:
    1. Erectile dysfunction (ED)
    2. Pulmonary arterial hypertension (PAH)
    3. Benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS)
    4. Off-label: Raynaud's phenomenon (experimental)