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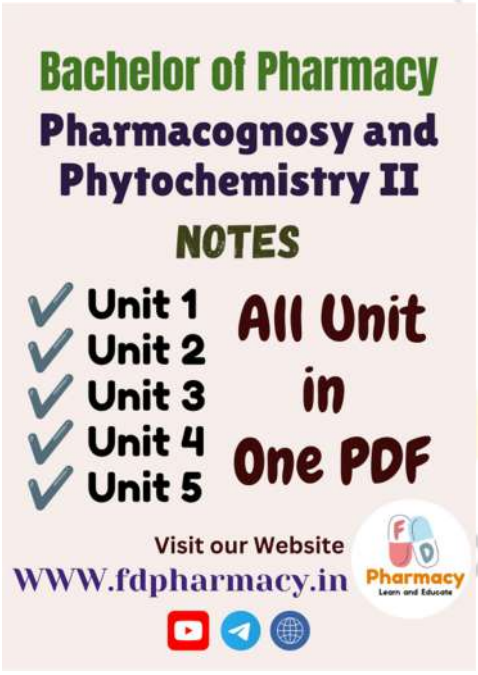
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MEDICINAL CHEMISTRY - II

UNIT 4

TOPIC :

- **Drugs acting on Endocrine system**

  Nomenclature, Stereochemistry and metabolism of steroids

Drugs Acting on the Endocrine System

The endocrine system controls physiological processes via hormones secreted by glands such as pituitary, thyroid, adrenal, pancreas, parathyroid, and gonads.

- Drugs targeting the endocrine system are used to:
  1. Replace deficient hormones (hormone replacement therapy)
  2. Inhibit excess hormone production (antagonists or synthesis inhibitors)
  3. Modulate hormone action (receptor agonists/antagonists)
- These drugs are crucial in diabetes, thyroid disorders, adrenal diseases, growth disorders, reproductive disorders, and calcium metabolism disorders.

Classification of Endocrine Drugs

A. Pituitary Hormones and Analogs

Hormone	Examples	Mechanism	Uses
Growth Hormone (GH)	Somatropin	Stimulates growth & metabolism	GH deficiency, Turner syndrome
Antidiuretic Hormone (ADH)	Desmopressin	↑ Water reabsorption in kidneys	Diabetes insipidus, hemophilia A
Oxytocin	Oxytocin	Stimulates uterine contraction & milk ejection	Labor induction, postpartum hemorrhage
Gonadotropins	FSH, LH	Stimulate ovarian/testicular function	Infertility, ovulation induction
Somatostatin analogs	Octreotide, Pegvisomant	Inhibit GH & hormone secretion	Acromegaly, gigantism

B. Thyroid Hormones and Antithyroid Drugs

Drug	Mechanism	Use
Levothyroxine (T_4), Liothyronine (T_3)	Hormone replacement	Hypothyroidism, cretinism
Methimazole, Propylthiouracil (PTU)	Inhibit thyroid hormone synthesis	Hyperthyroidism, Graves' disease
Potassium iodide	Inhibits thyroid hormone release	Thyroid storm, preoperative thyroidectomy

C. Adrenal Drugs

Class	Examples	Mechanism	Use
Glucocorticoids	Prednisone, Dexamethasone	Anti-inflammatory, immunosuppressive	Addison's disease, asthma, autoimmune disorders
Mineralocorticoids	Fludrocortisone	Sodium retention, potassium excretion	Addison's disease
Steroid synthesis inhibitors	Metyrapone, Ketoconazole	Inhibit cortisol synthesis	Cushing's syndrome

D. Pancreatic Hormones / Antidiabetics

Drug	Mechanism	Use
Insulin & analogs	↑ Glucose uptake, ↓ Blood glucose	Type 1 & 2 diabetes
Sulfonylureas	↑ Insulin secretion	Type 2 diabetes
Biguanides (Metformin)	↓ Hepatic glucose production	Type 2 diabetes
Thiazolidinediones	↑ Insulin sensitivity	Type 2 diabetes
SGLT2 inhibitors	↑ Urinary glucose excretion	Type 2 diabetes

E. Sex Hormones and Modulators

Drug	Mechanism	Use
Estrogens	Hormone replacement	Menopause, contraception, osteoporosis
Progestins	Hormone replacement	Contraception, amenorrhea
Androgens	Replace testosterone	Hypogonadism, delayed puberty
SERMs	Tamoxifen, Raloxifene	Modulate estrogen receptor activity
Antiandrogens	Flutamide, Finasteride	Block androgen receptor

F. Parathyroid / Calcium-Regulating Drugs

Drug	Mechanism	Use
Vitamin D & analogs	Calcitriol, Cholecalciferol	↑ Calcium absorption
Calcimimetics	Cinacalcet	Activate Ca^{2+} receptor → ↓ PTH
Calcium salts	Calcium carbonate	Maintain serum calcium

Nomenclature of Steroids

- Steroids are organic compounds derived from the cyclopentanoperhydrophenanthrene nucleus, consisting of four fused rings (A, B, C, D).
  - Rings A, B, C are six-membered; D is five-membered.
- Steroids have 17 carbon atoms numbered C1–C17.
- The nomenclature is based on:
  1. Ring system
  2. Carbon numbering
  3. Functional groups
  4. Saturation (double bonds)
  5. Stereochemistry (α/β orientation)

Steroid Ring System

- Ring labeling: A, B, C, D
- Carbon numbering:
  - Begins at C1 in ring A and continues sequentially through rings B, C, D.
  - Side chains and substituents are numbered from attachment points.

Schematic:

A B C D

_____ _____ _____ ____

C1–C2–C3–C4–C5–C6–C7–C8–C9–C10–C11–C12–C13–C14–C15–C16–C17

Functional Groups

Position	Common Groups	Biological Importance / Examples
C3	Keto (=O), Hydroxyl (OH)	Determines corticosteroid / estrogen activity
C11	Hydroxyl (OH)	Glucocorticoid activity
C17	Hydroxyl (OH), Keto (=O)	Androgen / estrogen activity
C20	Keto (=O)	Progestin activity
Double bonds	Δ4, Δ5	Modify receptor binding and potency

Saturation and Double Bonds

- Saturated steroids: suffix -ane (e.g., pregnane)
- Unsaturated steroids: suffix -ene (e.g., androstenes)
- Multiple double bonds: Δ notation indicates position (Δ4, Δ5, Δ9(11))

Stereochemistry

- α (alpha): Substituent below the plane of the ring
- β (beta): Substituent above the plane of the ring
- Ring junctions:
  - Cis: Flexible
  - Trans: Rigid (common)
- Importance: Stereochemistry is critical for receptor binding and biological activity.
- Example: 17β-OH in testosterone → essential for androgenic activity

Examples of Steroid Nomenclature

Steroid	IUPAC Name	Key Functional Groups
Testosterone	17β-hydroxy-4-androsten-3-one	C3 keto, C17β-OH, Δ4 double bond
Estradiol	17β-estradiol	Aromatic A-ring, C3 OH, C17β-OH
Progesterone	4-pregnene-3,20-dione	C3 keto, C20 keto, Δ4 double bond
Prednisone	17α,21-dihydroxypregna-1,4-diene-3,11,20-trione	C3, C11, C17 OH/keto, Δ1,4 double bonds

Stereochemistry of Steroids

- Steroids are chiral molecules with multiple stereocenters.
- Stereochemistry is crucial because the biological activity of steroids depends on the three-dimensional orientation of functional groups.
- Even small changes in orientation can alter receptor binding, potency, or therapeutic effect.

Ring Junctions

- Steroids have four fused rings (A, B, C, D):
  - A, B, C are six-membered
  - D is five-membered

Ring junction types:

1. Trans junction (common):
   - Rings are rigid and planar
   - Most natural steroids have trans junctions between A/B and C/D rings
2. Cis junction (less common):
   - Rings are more flexible
   - Rare in natural steroids

Substituent Orientation

- Substituents can be above or below the plane of the steroid rings:
  - β (beta): Above the plane
  - α (alpha): Below the plane

Example:

- 17β-OH in testosterone: hydroxyl group above the plane → essential for androgenic activity
- 17α-OH in prednisone: hydroxyl below the plane → modifies glucocorticoid activity

Metabolism of Steroids

Steroid metabolism refers to the biochemical modification of steroid hormones in the body to facilitate their biological activity, inactivation, and excretion.

- Occurs mainly in the liver, but also in kidneys, intestines, and target tissues.
- Metabolism ensures hormone homeostasis and prevents toxicity from excess steroids.

General Pathway

Steroid metabolism generally occurs in two phases:

A. Phase I: Functionalization

- Introduces or exposes polar functional groups (hydroxyl, keto, double bonds) via oxidation, reduction, or hydrolysis.
- Mainly catalyzed by cytochrome P450 enzymes in the liver.

Key reactions:

Reaction Type	Description	Example
Hydroxylation	Addition of OH group	C11 hydroxylation of cortisol
Reduction	Double bond reduction	Δ4–5 reduction in testosterone to dihydrotestosterone
Oxidation	Hydroxyl → keto conversion	C17-OH oxidation in cortisol metabolism
Dehydrogenation	Removal of H	Formation of Δ4 double bonds in progestins

Purpose:

- Increases polarity for subsequent conjugation
- Sometimes activates or inactivates steroids

B. Phase II: Conjugation

- Conjugation with water-soluble moieties like glucuronic acid or sulfate.
- Catalyzed by UDP-glucuronyltransferases or sulfotransferases.

Examples:

Conjugation Type	Enzyme	Product	Excretion Route
Glucuronidation	UDP-glucuronyltransferase	Steroid glucuronides	Urine
Sulfation	Sulfotransferase	Steroid sulfates	Urine / bile

Purpose:

- Makes steroids water-soluble for renal excretion
- Reduces biological activity

Sites of Metabolism

Organ / Tissue	Metabolic Role
Liver	Major site; Phase I & II reactions
Kidney	Minor hydroxylation, conjugation, excretion
Intestine	Enterohepatic recycling (some conjugates hydrolyzed by gut bacteria)
Target tissues	Local activation/inactivation of steroids (e.g., testosterone → DHT in prostate)

Excretion

- Major route: Urinary excretion of conjugated metabolites
- Minor route: Biliary excretion → feces
- Unconjugated steroids are poorly water-soluble and minimally excreted

Clinical Significance

1. Liver disease → impaired metabolism → accumulation → increased steroid effects or toxicity
2. Synthetic modifications (halogenation, methylation, fluorination) → resist metabolism → longer half-life, increased potency
3. Drug interactions: CYP450 inducers/inhibitors can alter steroid metabolism
4. Metabolic diseases: Defects in steroidogenic enzymes (e.g., 21-hydroxylase deficiency) → congenital adrenal hyperplasia