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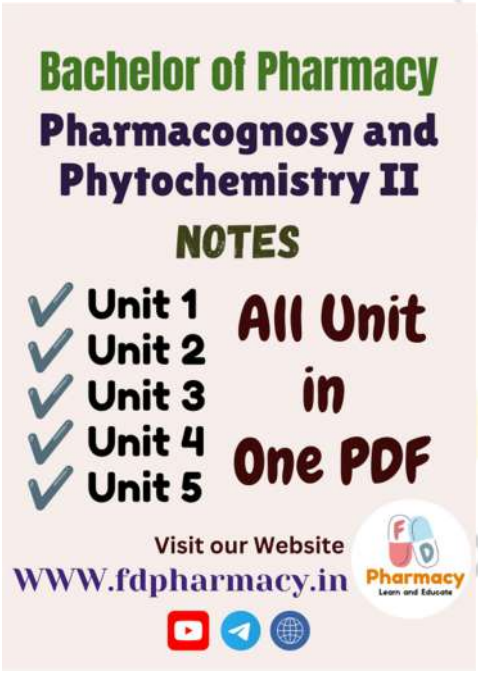
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MEDICINAL CHEMISTRY - II

UNIT 4

TOPIC :

- **Thyroid and antithyroid drugs :** L-Thyroxine, L-Thyronine, Propylthiouracil, Methimazole.

Thyroid and Antithyroid Drugs

- Thyroid hormones (T_3 – triiodothyronine, T_4 – thyroxine) regulate growth, development, metabolism, and thermogenesis.
- Antithyroid drugs are used to treat hyperthyroidism, particularly Graves' disease.
- Understanding these drugs is essential in B.Pharm pharmacology, as they influence metabolism, cardiovascular system, and endocrine balance.

Thyroid Drugs (Hormone Replacement Therapy)

Drugs

1. Levothyroxine (T_4)
2. Liothyronine (T_3)
3. Liotrix (T_4 + T_3 mixture)

Mechanism of Action

- Thyroid hormones enter cells → converted (T_4 → T_3 if needed)
- Bind nuclear thyroid hormone receptors (TRα, TRβ) → modulate transcription of target genes
- Increase basal metabolic rate, oxygen consumption, and heat production
- Promote protein synthesis, carbohydrate metabolism, and lipid metabolism

Uses

- Hypothyroidism (primary or secondary)
- Myxedema
- Thyroid cancer (suppression therapy with levothyroxine)

Adverse Effects

- Overdose → thyrotoxicosis symptoms: palpitations, weight loss, heat intolerance, nervousness, insomnia

Pharmacokinetics

- Levothyroxine: oral absorption 60–80%, long half-life ~7 days
- Liothyronine: faster onset, shorter half-life, more potent

Antithyroid Drugs

A. Thioamides (Thionamides)

- Drugs: Methimazole, Carbimazole (prodrug of methimazole), Propylthiouracil (PTU)
- Mechanism of Action:
  1. Inhibit thyroid peroxidase (TPO) → blocks iodination of tyrosine → ↓ T_3/T_4 synthesis
  2. PTU additionally inhibits peripheral T_4 → T_3 conversion
- Uses:
  - Hyperthyroidism (Graves' disease, toxic multinodular goiter)
  - Preoperative preparation before thyroidectomy
  - Thyroid storm (especially PTU)
- Adverse Effects:
  - Rash, urticaria
  - Agranulocytosis (rare but serious)
  - Hepatotoxicity (PTU more than methimazole)
  - Arthralgia, lupus-like syndrome

B. Iodine and Iodide Preparations

- Drugs: Lugol's solution, Potassium iodide (KI)
- Mechanism:
  - Large doses → Wolff–Chaikoff effect → inhibit organification of iodide → ↓ thyroid hormone synthesis
  - Short-term use only (used preoperatively or in thyroid storm)
- Adverse Effects: Rash, metallic taste, salivary gland swelling

C. Radioactive Iodine (^{131}I)

- Taken orally → concentrated in thyroid → beta emission destroys thyroid tissue
- Used in hyperthyroidism (especially in adults)
- Avoid in pregnancy and breastfeeding

D. Beta-Blockers (Adjunct Therapy)

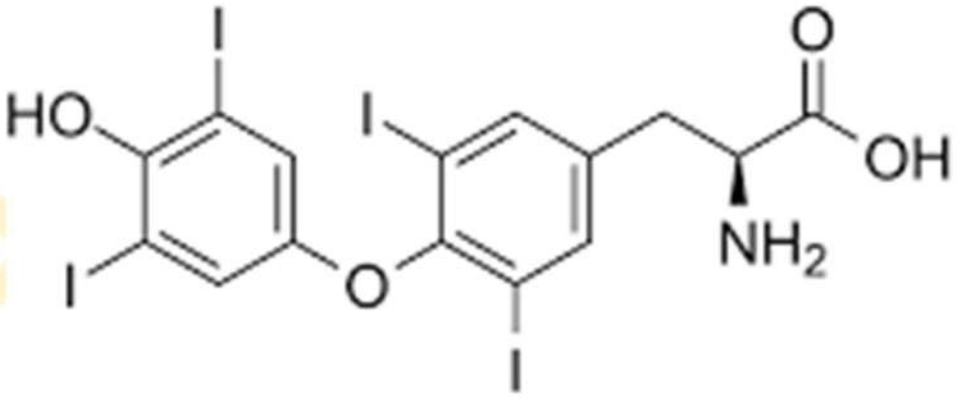
- Drugs: Propranolol, Atenolol
- Mechanism: Symptomatic relief (↓ tachycardia, palpitations, tremor)
- Additional effect: Propranolol inhibits peripheral T_4 → T_3 conversion

L-Thyroxine (Levothyroxine)

- L-Thyroxine (T_4) is a synthetic form of the thyroid hormone thyroxine, naturally produced by the thyroid gland.
- It is the prohormone of the biologically active triiodothyronine (T_3).
- Used to treat hypothyroidism, goiter, and certain thyroid cancers.
- Administered orally or intravenously.
- It plays a critical role in metabolism, growth, and development.

Chemical Structure

- Chemical name: (2S)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propanoic acid
- Molecular formula: $C_{15}H_{11}I_4NO_4$
- Molecular weight: 776.87 g/mol
- Chemical class: Iodinated tyrosine derivative; thyroid hormone
- Structural



Mechanism of Action

- Target: Nuclear thyroid hormone receptors (TR) in almost all body cells

Stepwise Mechanism:

1. L-Thyroxine is converted peripherally to T_3 (triiodothyronine) by deiodinases.
2. T_3 binds to thyroid hormone receptors (TR) in the nucleus, forming a hormone-receptor complex.

3. The complex binds thyroid hormone response elements (TREs) on DNA, regulating transcription of target genes.
4. Physiological effects:
    - Metabolic: Increases basal metabolic rate (BMR), oxygen consumption, and thermogenesis
    - Cardiovascular: Increases heart rate, cardiac output
    - Growth & Development: Promotes CNS development, bone maturation, and protein synthesis
    - Lipid & Carbohydrate Metabolism: Enhances lipolysis and gluconeogenesis

Synthesis

1. Starting material: L-Tyrosine or iodinated tyrosine derivatives
2. Step 1: Iodination at specific positions on phenolic rings
3. Step 2: Coupling of two iodinated tyrosine units via ether linkage
4. Step 3: Purification and crystallization → pharmaceutical-grade L-Thyroxine

Uses

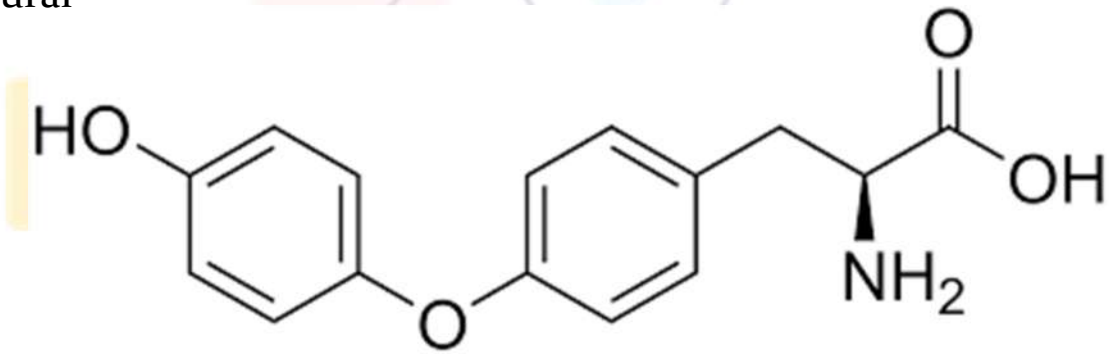
- Therapeutic Uses:
    1. Hypothyroidism (congenital or acquired)
    2. Goiter (iodine deficiency or nodular goiter)
    3. Myxedema
    4. Thyroid hormone replacement post-thyroidectomy
    5. Management of certain thyroid cancers (suppression therapy)

L-Thyronine (Triiodothyronine, T3)

- L-Thyronine (T_3) is the active thyroid hormone, produced by the thyroid gland and also generated peripherally from L-Thyroxine (T_4) via deiodination.
- It is more potent than T_4, with faster onset of action.
- T_3 regulates metabolic rate, growth, development, and cardiovascular function.
- Clinically used for hypothyroidism, myxedema, and certain thyroid hormone replacement therapies.
- Administered orally or intravenously.

Chemical Structure

- Chemical name: 3,5,3'-triiodo-L-thyronine
- Molecular formula: $C_{15}H_{12}I_3NO_4$
- Molecular weight: 650.97 g/mol
- Chemical class: Iodinated tyrosine derivative; thyroid hormone
- Structural



Mechanism of Action

- Target: Nuclear thyroid hormone receptors (TR) in almost all body cells

Stepwise Mechanism:

1. L-Thyronine (T_3) binds directly to thyroid hormone receptors (TR) in the nucleus.

2. Forms a hormone-receptor complex that binds thyroid hormone response elements (TREs) on DNA.
3. Modulates transcription of target genes → physiological effects:
    - Metabolic: Increases basal metabolic rate (BMR), oxygen consumption, and thermogenesis
    - Cardiovascular: Increases heart rate, cardiac output
    - Growth & Development: Promotes CNS development, bone maturation, and protein synthesis
    - Lipid & Carbohydrate Metabolism: Enhances lipolysis and gluconeogenesis

Synthesis

1. Starting material: L-Tyrosine or iodinated tyrosine derivatives
2. Step 1: Iodination at specific positions on phenolic rings (3,5,3' positions)
3. Step 2: Coupling of iodinated tyrosine units via ether bond
4. Step 3: Purification and crystallization → pharmaceutical-grade L-Thyronine

Uses

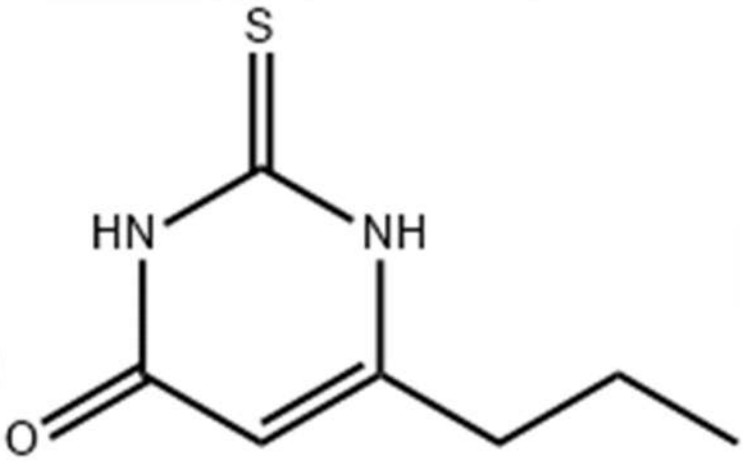
- Therapeutic Uses:
    1. Hypothyroidism (especially in T4-resistant cases or rapid onset required)
    2. Myxedema
    3. Post-thyroidectomy thyroid hormone replacement
    4. Certain thyroid hormone tests (diagnostic use)
    5. Management of cretinism in children (less commonly, due to T4 preference)

Propylthiouracil (PTU)

- Propylthiouracil (PTU) is an antithyroid drug belonging to the thiouracil class.
- It is primarily used to treat hyperthyroidism, particularly in Graves' disease, thyroid storm, and preoperative preparation for thyroid surgery.
- PTU is administered orally.
- It works by inhibiting thyroid hormone synthesis and peripheral conversion of T4 to T3.

Chemical Structure

- Chemical name: 6-propyl-2-thiouracil
- Molecular formula: $C_7H_{10}N_2OS$
- Molecular weight: 170.23 g/mol
- Chemical class: Thiouracil derivative; antithyroid agent
- Structural



Mechanism of Action

- Target: Thyroid peroxidase enzyme (TPO) and peripheral tissues

Stepwise Mechanism:

1. PTU inhibits thyroid peroxidase (TPO) → blocks iodination of tyrosine residues in thyroglobulin → inhibits synthesis of T3 and T4.

2. PTU inhibits 5'-deiodinase in peripheral tissues → reduces conversion of T4 to active T3.
3. Overall Effect:
    - Decreased production of thyroid hormones
    - Reduced peripheral effects of T3

Pharmacodynamic Note:

- Slower onset of action due to existing thyroid hormone stores in the gland.

Synthesis

1. Starting material: Thiourea or substituted uracil derivatives
2. Step 1: Alkylation at C6 with propyl halide → introduces propyl group
3. Step 2: Purification → crystallization to obtain pharmaceutical-grade PTU

Uses

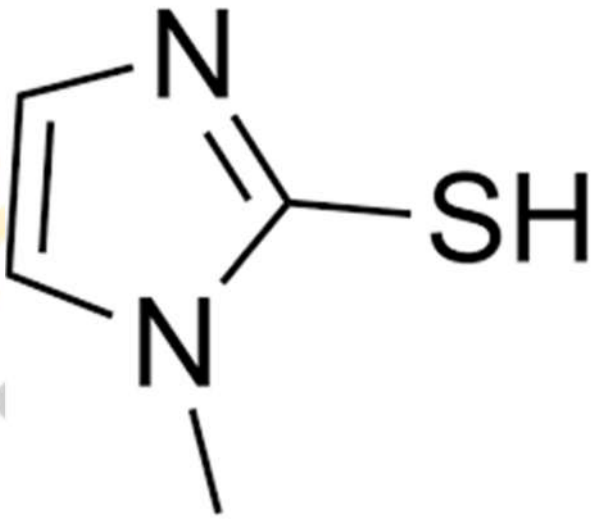
- Therapeutic Uses:
    1. Hyperthyroidism (Graves' disease, toxic multinodular goiter)
    2. Thyroid storm (acute management)
    3. Preoperative preparation before thyroidectomy
    4. Alternative to methimazole in first trimester of pregnancy (preferred due to lower teratogenic risk)

Methimazole

- Methimazole (also called Thiamazole) is an antithyroid drug of the thioimidazole class.
- It is primarily used to treat hyperthyroidism, including Graves' disease, thyroid storm, and preoperative preparation for thyroid surgery.
- Administered orally and is considered first-line therapy in adults.
- Less preferred in first trimester of pregnancy due to teratogenic risk; Propylthiouracil (PTU) is preferred then.

Chemical Structure

- Chemical name: 1-methyl-2-mercaptoimidazole
- Molecular formula: $C_4H_6N_2S$
- Molecular weight: 114.16 g/mol
- Chemical class: Thioimidazole derivative; antithyroid agent
- Structural



Mechanism of Action

- Target: Thyroid peroxidase enzyme (TPO)

Stepwise Mechanism:

1. Methimazole inhibits thyroid peroxidase (TPO) → blocks iodination of tyrosine residues in thyroglobulin → prevents formation of T3 and T4.

2. Does not inhibit peripheral conversion of $T_4 \rightarrow T_3$ (unlike PTU).
3. Overall Effect:
    - Decreased thyroid hormone synthesis
    - Reduced hyperthyroid symptoms

Pharmacodynamic Note:

- Onset is slower because existing stores of T_3 and T_4 in the thyroid gland must be depleted.

Synthesis

1. Starting material: Thiourea or imidazole derivatives
2. Step 1: Cyclization to form imidazole ring
3. Step 2: Methylation at N1 → introduces N-methyl group
4. Step 3: Purification → crystallization to obtain pharmaceutical-grade Methimazole

Uses

- Therapeutic Uses:
    1. Hyperthyroidism (Graves' disease, toxic nodular goiter)
    2. Thyroid storm (acute management)
    3. Preoperative preparation before thyroidectomy
    4. Alternative to radioactive iodine therapy in certain patients