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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 $T_4 \rightarrow T_3$ 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)

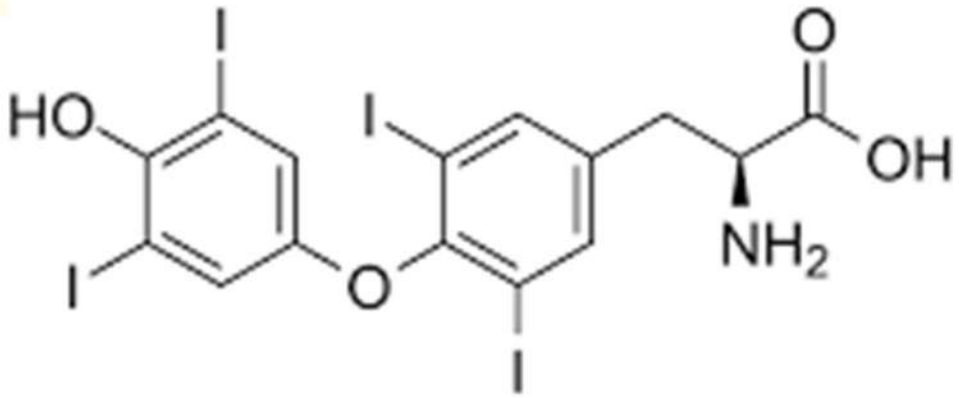
- Additional effect: Propranolol inhibits peripheral $T_4 \rightarrow T_3$ conversion

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. T3 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

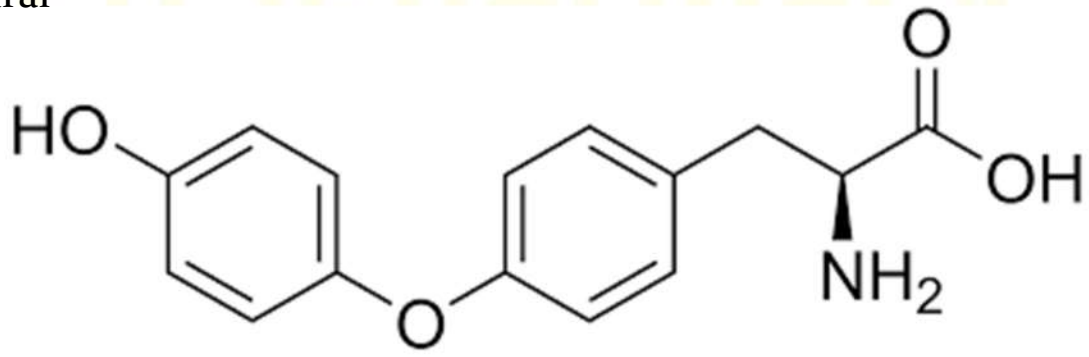
- **Therapeutic Uses:**
    1. **Hypothyroidism** (congenital or acquired)
    2. **Goiter** (iodine deficiency or nodular goiter)
    3. **Myxedema**
    4. **Thyroid hormone replacement post-thyroidectomy**
    5. **Management of certain thyroid cancers** (suppression therapy)

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

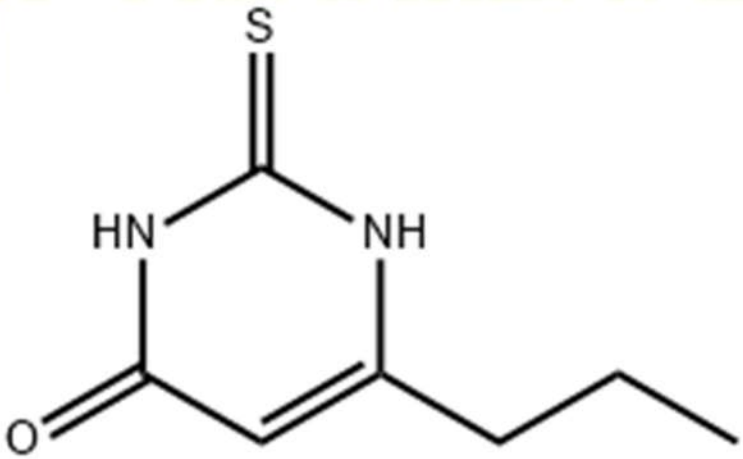
- **Therapeutic Uses:**
    1. **Hypothyroidism** (especially in T4-resistant cases or rapid onset required)
    2. **Myxedema**
    3. **Post-thyroidectomy thyroid hormone replacement**
    4. **Certain thyroid hormone tests** (diagnostic use)
    5. **Management of cretinism in children (less commonly,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

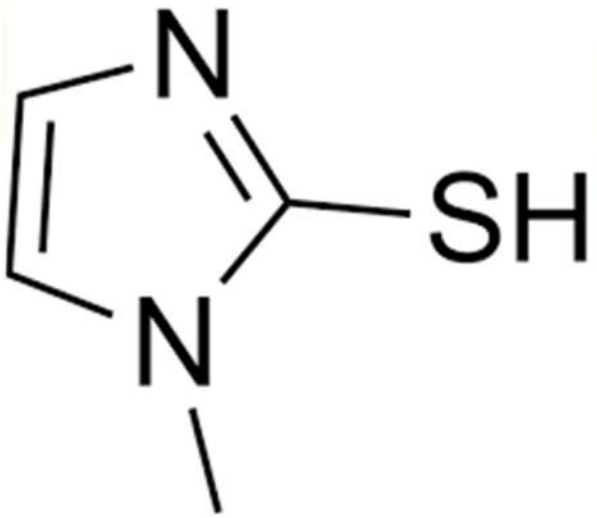
- **Therapeutic Uses:**
    1. **Hyperthyroidism** (Graves' disease, toxic multinodular goiter)
    2. **Thyroid storm** (acute management)
    3. **Preoperative preparation** before thyroidectomy
    4. **Alternative to methimazole** in first trimester of pregnancy (preferred due to lower teratogenic 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 T_3 and T_4.
2. Does not inhibit peripheral conversion of T_4 → 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