CHAPTER 11

Thyroid and Antithyroid Drugs

The thyroid gland present in the human body regulates and maintains the normal growth and maturation by releasing thyroid hormones. The important and the major kind of two thyroid hormones are T_3—tri-iodothyronine (most active form) and T_4—tetraiodothyronine (thyroxine). The other hormone is calcitonin, secreted by the parathyroid gland or parathyroid follicular cells. Thyroxine was first obtained by Kendall as a crystalline powder in 1915. Later, it was synthesized by Harington and Barger in England.

SYNTHESIS AND SECRETION

Thyroid hormones are synthesized by thyroid glands and stored in thyroid follicles. The main source of thyroid is iodine in diet.

Various steps involved in the synthesis of thyroid hormones are depicted as follows.

1. **Iodine uptake:** Thyroid cells uptake plasma iodide by active transport process along with the help of sodium–iodide symporter.
2. **Oxidation of iodide:** The iodide gets oxidized to iodinium ion by the enzyme thyroperoxidase with the usage of hydrogen peroxide. The formed iodinium ion combined with the tyrosine residues of thyroglobulin (TG) leads to the formation of monoiodotyrosine (MIT) and di-iodotyrosine (DIT).
3. **Coupling reaction:** Pairs of MIT and DIT are coupled to generate T_3(MIT + DIT). Coupling of pairs of DIT + DIT leads to the formation of T_4. The entire reaction is catalyzed by the enzyme peroxidase.
4. **Storage and release:** TG containing iodinated tyrosine residues are stored in the follicle and released in to the circulation.

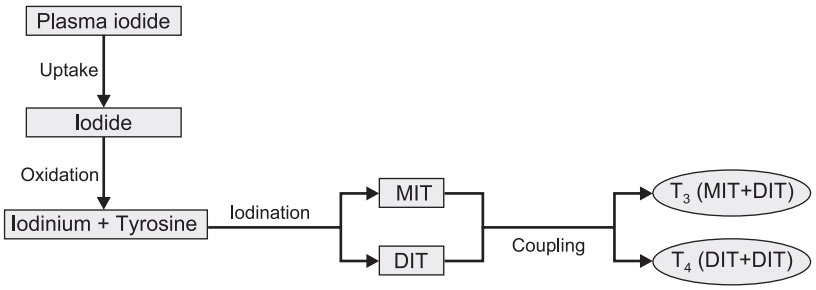


Figure 11.1: Formation of thyroid hormones.

Regulation of secretion

The secretion of thyroid hormone is regulated by TSH (secreted by anterior pituitary) and TRH (secreted from hypothalamus). Normally, 15–30 mcg of T_3 and 70–90 mcg of T_4 secreted in our body daily. Maximum amount of T_4 is converted into T_3, in the peripheral tissues.

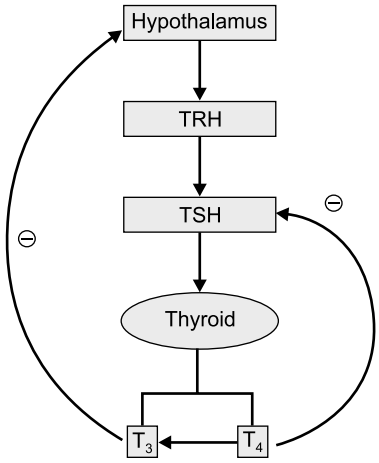


Figure 11.2: Feedback mechanism of thyroid hormone.

Mechanism of action

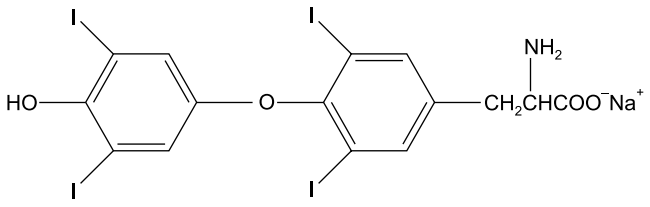
Thyroid hormones acts on the specific receptors, known as nuclear receptors or steroid receptors.

Thyroid Diseases: There are two types of diseases related to thyroid gland.

1. **Hypothyroidism:** Inadequate secretion of thyroid hormones, known as hypothyroidism. It leads to bradycardia, mental and growth retardation, dwarfism, etc. The therapeutic use of thyroid hormones is for hormone replacement therapy in patients with hypothyroidism or cretinism and for TSH suppression therapy in patients with thyroid cancer.
2. **Hyperthyroidism:** Excess secretion of thyroid hormones and circulation, known as hyperthyroidism. It leads to tachycardia, excess heat production, tremor and cardiac arrythmias. Antithyroid drugs propylthiouracil, methimazole and carbimazole are used to treat this condition.

Thyroid Drugs: Drugs which are used for the treatment of hypothyroidism are called thyroid drugs. They are as follows:

L-Thyroxine or Levothyroxine (T_4)



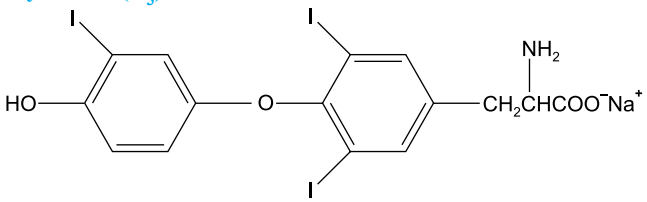
O-[4[Hydroxy-3,5-diiodophenyl]-3,5-diiodo-2-tyrosine]monosodium salt

Properties: It is slightly yellow colour, odourless and tasteless powder. It is hygroscopic in nature, hence stored in dark coloured bottles to prevent spontaneous deiodination. The levo isomer is the active form of the drug.

Uses: It is the drug of choice for the replacement therapy in hypothyroidism. It is also used for the treatment of chronic lymphocytic thyroiditis, non-epidemic goiter, etc. IV administration of T_4 is used to treat myxoedema coma.

Dose: Oral route: 50–100 mg daily, for IV route – 1.5 to 5 ml solution, 100 µg/ml.

L-Thyronine or Liothyronine (T_3)



Properties: It is light-tan colour, odourless and tasteless crystalline powder. It is slightly soluble in water.

Uses: It is the drug of choice for the replacement therapy in hypothyroidism. It is also used for the treatment of male infertility, metabolic insufficiency and some kind of metabolic disorders.

Liver is the major site of non-deiodinative degradation of thyroid hormones; T_4 and T_3 are conjugated with glucuronic and sulfuric acids through the phenolic hydroxyl group and excreted into the bile. Some amount of thyroid hormones are liberated by hydrolysis of the conjugates in the intestine and reabsorbed.

ANTITHYROID DRUGS

Introduction

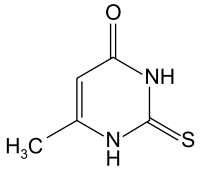
Antithyroid drugs are compounds that act within the thyroid gland to inhibit the biosynthesis of the thyroid hormones. Excessive amount of thyroid hormones in the circulation is associated with a number of diseased states, including Graves disease, toxic adenoma, goitre, and thyroidities among others.

Classification

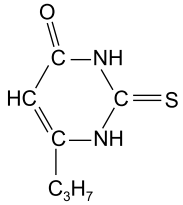
Antithyroid drugs are classified as follows:

I. Thioureylenes

i. Thiouracil derivatives

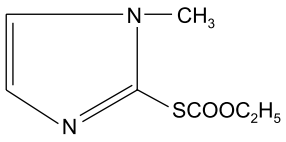


Methylthiouracil

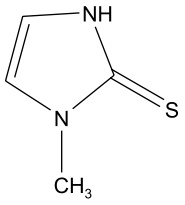


Propylthiouracil

ii. Imidazoles

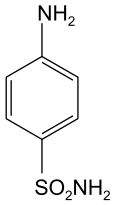


Carbimazole

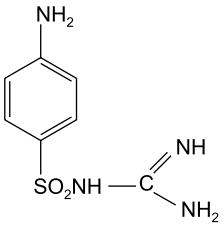


Methimazole

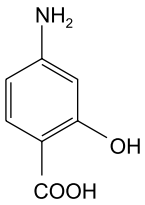
iii. Aniline derivatives



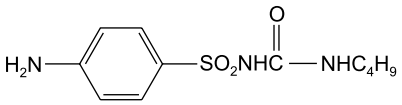
Sulphanilamide



Sulphaguanidine



p-Aminosalicylic acid

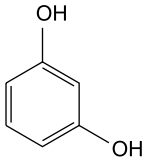


Carbutamide

Mode of action: These agents interfere with some of the process catalyzed by thyroid peroxidase, such as iodide oxidation, organification, and coupling of iodotyrosines.

II. Polyhydric Phenols

i. Resorcinol



Mode of action: The only clinical agent from this category is resorcinol. It possesses same mechanism of action similar to that of thioamides.

III. Ionic Inhibitors

(a) Potassium perchlorate
(b) Thiocynate

Mode of action: These anions resemble iodide ions and affect the power of thyroid gland to accumulate iodine.

IV. Miscellaneous Agents

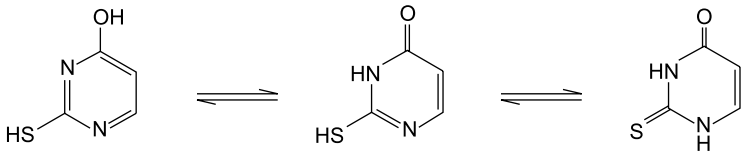
(a) Lithium carbonate
(b) Adrenergic blockers

SYNTHESIS AND DRUG PROFILE

I. Thioureylenes

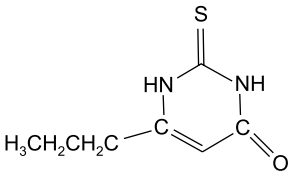
Mode of action: Thiourea and thiouracil derivatives are among the primary drugs to treat thyroid hyperactivity. Methyl and propylthiouracil derivatives are effective drugs in the treatment of thyroid-related problems. They prevent iodine incorporation into the organic form perhaps by antagonizing the iodide oxidation by peroxidase. They are also found to prevent coupling of iodotyrosines to form iodothyronines.

The 2-thiouracil derivatives, that is, 4-keto-2-thio pyrimidines, are undoubtedly tautomeric compounds and can be represented as follows:



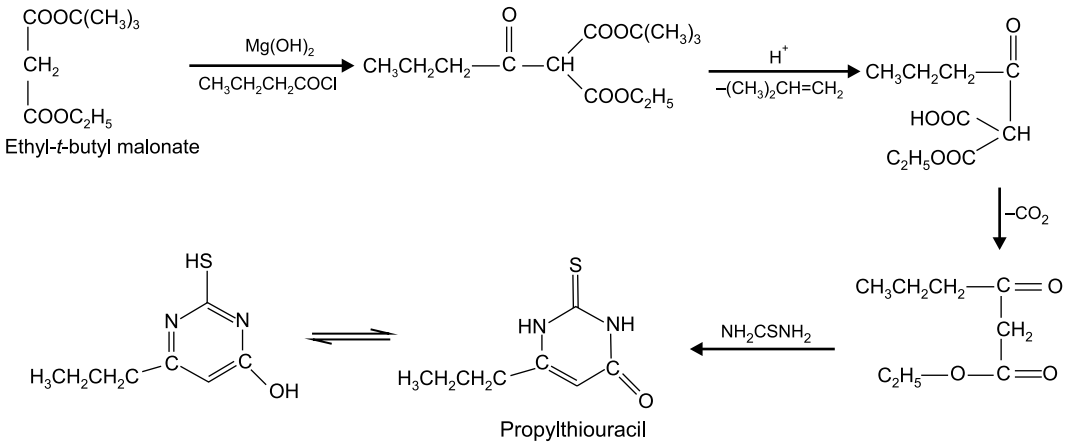
Some 300-related structures have been evaluated for antithyroid activity, but, of these, only the 6-allyl-2-thiouracil and closely related structure possess useful clinical activity. The most serious adverse effect of thiouracil therapy is agranulocytosis.

i. Propylthiouracil (Tietil)



6-Propyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one

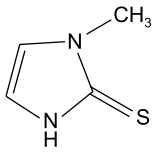
Synthesis



Properties and uses: It is a white powdery crystalline substance with bitter taste, soluble in water, alcohol, chloroform, and ether. Used in the management of hyperthyroidism.

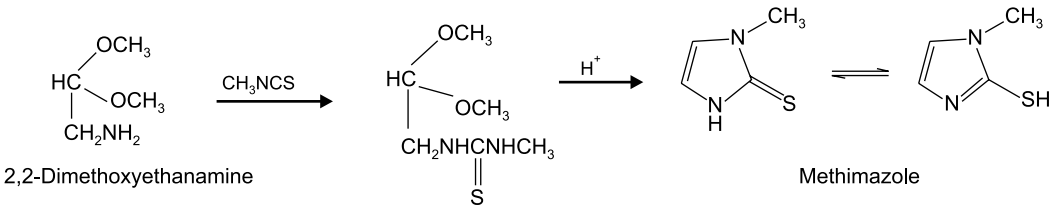
Dose: For hyperthyroidism, the dose for adults initially is 200–300 mg per day in divided doses. When the patient attains normal basal metabolic rate (euthyroidism), the dose is usually reduced to a maintenance dose of 50–75 mg per day in two-to-three divided doses. In children, over 10-years old, initial dose is 150–300 mg per day in four divided doses until the child becomes euthyroid, then, usually, 100 mg daily is given in two divided doses, for maintenance.

ii. Methimazole (Tapazele)



3-Methyl-1H-imidazole-2(3*H*)-thione

Synthesis

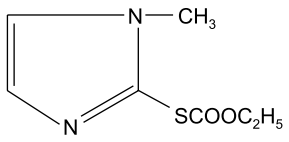


2,2-Dimethoxyethanamine Methimazole

Properties and uses: It exists as white to pale-buff colour solid with characteristic odour and soluble in water. The drug is more potent, more prompt, and has more prolonged action than propylthiouracil. It is indicated in the treatment of hyperthyroidism.

Dose: Usual initial dose is 5–20 mg every 8 hrs. When condition is stabilized (1–2 months), the dose is reduced to a maintenance dose of 5–15 mg per day. For children, the initial dose is 400 µg/kg body weight per day in divided doses.

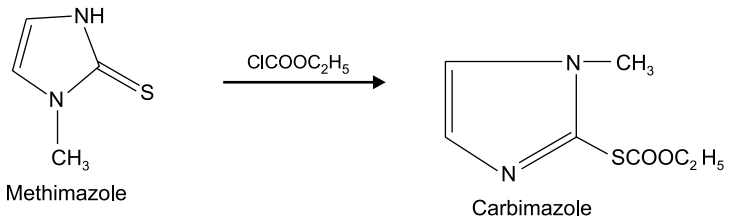
iii. Carbimazole



1-Methyl-2-thioxo-1,2-dihydroimidazole-3-ethyl carboxylate

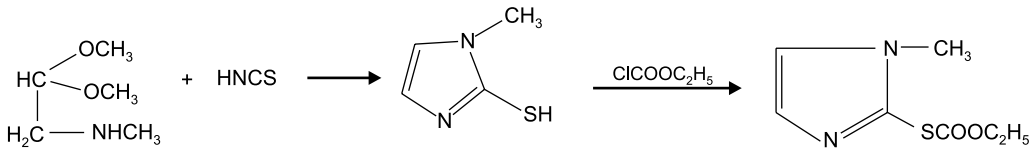
Synthesis

Route I: From: Methimazole



Methimazole — Carbimazole

Route II. From: N-Methylamino acetal



N-Methylamino acetal — 1-Methyl-2-mercapto imidazole — Carbimazole

PROBABLE QUESTIONS

1. Define and classify antithyroid agents and write the synthesis and uses of any two of them.
2. Write the synthesis and uses of methylthiouracil and propylthiouracil.