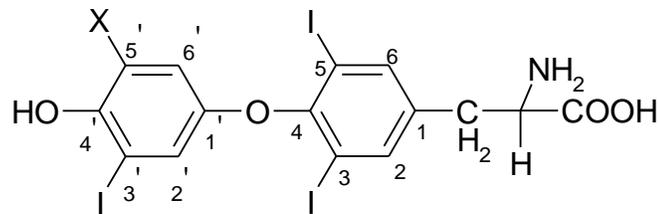


THYROID AND ANTITHYROID AGENTS

- The thyroid gland is a large endocrine gland weighing about 20gm in adults. It is found located deep in the neck, close to the trachea.
- Desiccated defatted thyroid substance has been used for as replacement therapy in thyroid gland deficiency. The efficacy of whole gland is now known to depend on its thyroglobulin contents. This is an Iodine-containing globulin.
- The most important thyroid hormones are L-thyroxine (T₄) and triiodothyronine (T₃) which are iodine containing derivative of L-Thyronine.
- Thyroxine is 3,5,3',5' tetraiodothyronine and the triiodo analogue is 3,5,3' triiodothyronine. The metabolic activity of L-triiodothyronine is 3 to 5 times that of L-thyroxine.

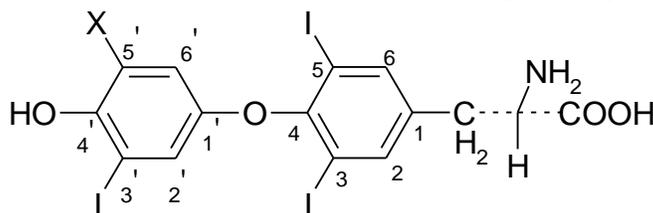


Thyroxine X=I

Triiodothyronine X=H

- The biosynthesis of the thyroid hormones by the thyroid glands depends on the adequate supply of dietary iodide ion-iodide is actively transported into the gland.
- This transport is stimulated by thyroid stimulating hormones (TSH, thyrotrophin) and is also controlled by an autoregulatory mechanism. The transport is inhibited by ions, such as thiocyanate (SCN^-) and perchlorate (ClO_4^-).
- The iodide undergoes oxidation by a membrane bound enzyme thyroid peroxidase.
- The secretion of thyroid hormones is proteolytic enzymes from lysosomes which completely breakdown the thyroglobulin into its constituent amino acids releasing L-thyroxine and L-triiodothyronine into the circulation. The proteolysis is stimulated by TSH.
- The thyroid hormones are transported in the blood in strong but non-covalent association with certain plasma proteins. Thyroxine-binding globulin (TBG) is the major carrier of thyroid hormones thyroxine-binding prealbumin (TBPA) and albumin are the other carrier proteins less than 0.05% of L-thyroxine and 0.5% of L-triiodothyronine exist in free unbound state. The stereochemistry of the thyroid hormones plays an important role in defining the hormonal activity. Because of the steric effect of the large iodine atoms in position-3 and position-5, the planes of the two aromatic rings are perpendicular to each other and separated by oxygen atom which holds the rings at an angle of about 120°.

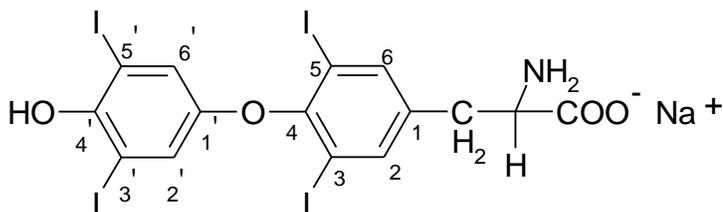
The amino acid side chain, in energetically most favoured conformation, has carbonyl group at the maximum distance from the aromatic ring bearing the side chain.



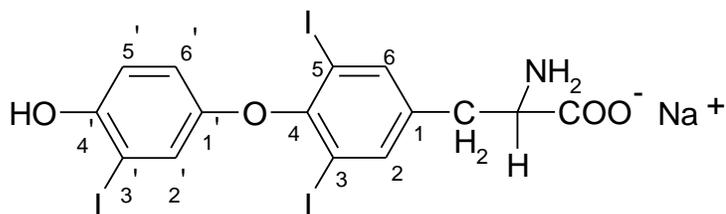
Thyroxine (conformational shape)

Note=> SAR-

- If the ether oxygen can be replaced isosterically by sulphur or methylene which also provide an angle of approximately 120°. These does not impair the thyromimetic activity.
 - A phenolic hydroxyl at 4'-postion is important for hydrogen bonding to transport protein.
 - If can, however, be replaced by isosteric group like NH₂ or by a group that can generate a hydroxyl group after metabolism (OCH₃ or OCOCH₃) but such change results in reduce hormonal activity.
 - Thyroid hormones are used in the treatment of hypothyroidism.
 - Drug used in hypothyroidism +>
- a) Levothyroxine sodium => Levothyroxin sodium is the sodium salt of the levo isomer of thyroxine.

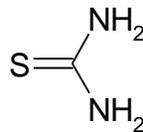


- b) Liothyronine sodium => Liothyronine sodium is the sodium salt of L-3,3',5-triiodothyronine.

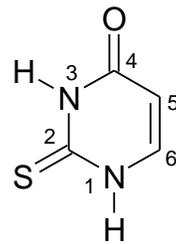


Antithyroid drugs

- Antithyroid drugs are used for the control of hyperthyroidism.
- Thiourea and related compounds shows an antithyroid activity , but they are too toxic for clinical use.
- More useful drugs are 2-thiouracil derivatives and a closely related 2-thioimidazole derivative. Have a similar mechanism of action (i.e. prevention of the iodination of the precursors of the thyronine and triiodothyronine).
- The main difference in the compounds contains in their relative toxicity.



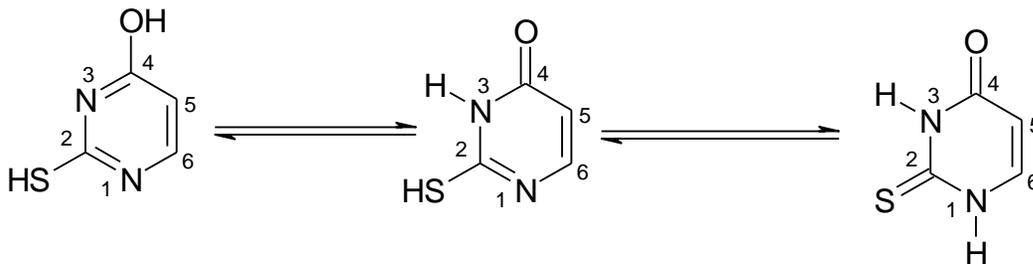
Thiourea



2-Thiouracil

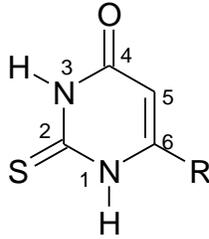
Note-

- The most serious adverse effect of thiouracil therapy is agranulocytosis.
- Tautomerism



Antithyroid drugs may be divided into three categories =>

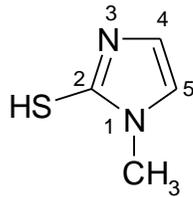
- A) Thiourenes =>
 - 1) Thiouracil derivative –



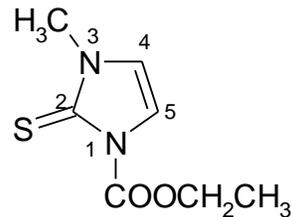
S.NO.	NAME OF DRUG	R
1.	Methylthiouracil	CH ₃
2.	Propylthiouracil	CH ₂ CH ₂ CH ₃

2) Imidazole derivative –

Exa-



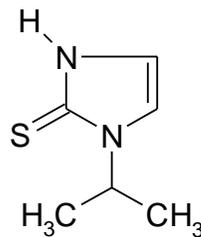
Methimazole



Carbimazole

Note- These drugs act by inhibiting the formation of thyroid hormones by interfering with the incorporation of iodine into tyrosyl residue of thyroglobulin, they also inhibit the coupling of these iodotyrosyl residue to form Iodothyronine.

- Centimzone (Antithyroid drug was discovered at CDRI LKO)



B) Ionic inhibitors => Ionic inhibitors are the substances which block the iodine transport mechanism.

Exa- Thiocyanate ion (SCN⁻)

Perchlorate ion (ClO₄⁻)

Note- Potassium and perchlorate used to control hyperthyroidism. But they can cause fetal plastic anaemia.

C) Radioactive Iodine => Used mainly isotopes of iodine (Mostly used = ^{131}I)

Note- radioactive Iodine in the form of Sodium Iodide (^{131}I) use in the treatment of hyperthyroidism.