A comparative study between Propylthiouracil, Carbimazole, Methimazole, Levothyroxine and Myo-inositol against thyroid malfunction and suggestive combination therapy based on Myo-inositol and Iodine.

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Highlights-

- Thyroid gland disorders are a very common public health disorder.
- Amongst the marketed drugs available to treat thyroid disorders the ADMET properties have been compared via online software.
- A novel drug delivery including the combination therapy of myo-inositol and iodine has been suggested.
- The use of this combination therapy can be considered as promising in the treatment of thyroid related abnormalities.

Abstract-

Hypo and hyper thyroidism involves the malfunctioning in Iodine content and regulation of body. The iodine is preliminary constituent activated compound that maintains the T3 & T4 secretion, composition enabling the thyroid hormones to act efficiently. In this study a novel drug delivery involving combination therapy has been suggested to work against the anti-thyroid activity. Myo-inositol administration along with Iodine controls the H_2O_2 activity that meddle with iodine organification along with T3 T4 regulation. Why myo-inositol is being administered as a combination therapy with Iodine has being suggested. It is because of the mechanism of action at cellular level, the control over iodine secretion, regulation and metabolism gives an upper hand. Along with its properties, myo-inositol is also a naturally occurring molecule present in the physiological system gaining positive attribute over other drugs with respect to toxicity and tolerated dose. A comparative study is been done between drugs propylthiouracil, carbimazole, methimazole, levothyroxine and myo-inositol to ensure the best activity and dry-lab study to support the myo-inositol and iodine combination therapy as a better approach against thyroidism.

Keywords- T3:T4, Thyroid gland, myo-inositol, MOA, ADMET.

Abbreviations-

- T3- Triiodothyronine
- T4- Thyroxine
- ADMET- Absorption Distribution Metabolism Elimination Toxicity
- TSH- Thyroid Stimulating Hormone
- TSHRH- Thyroid Stimulating Hormone Releasing Hormone
- DIT – Diiodotyrosine
- MIT- Monoiodotyrosine
- TRH- Thyrotropin-Discharging Hormone
- PDK1- Pyruvate Dehydrogenase Kinase and Isoenzyme 1
- GLUT4- Glucotransporter 4

- T44- Levothyroxine
- PIP - Phosphatidylinositol-3,4,5-phosphate, inositol-1,4,5-triphosphate

Introduction-

The butterfly-shaped organ present below the Adam's apple, along the front of windpipe is the thyroid gland. The thyroid gland is an endocrine gland which has 2 lobes bridged by isthmus. It is a brownish red coloured organ. The thyroid gland absorbs iodine from the food eaten and uses it to make the two main hormones T3 and T4. It is important that the levels of both these hormones are maintained. The pituitary gland and the hypothalamus work together to maintain the levels of T3 and T4. The hypothalamus produces TSHRH (Thyroid Stimulating Hormone Releasing Hormone) which works in signalling the pituitary towards the production of T3 and T4 by manipulating the release of TSH (Thyroid Stimulating Hormone). The disease associated with the thyroid glands are directly related to the imbalance of the iodine in our body. The most common disease encountered are hypothyroidism and hyperthyroidism. This study has shown a comparative work on the basis of cellular mechanism, ADMET studies (The ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties of your molecules are of vital importance. The ability to quickly and accurately predict these properties through software studies simply from the 2D structure of the molecule is extremely helpful.), of 5 molecules towards responsiveness of Iodine-Myo-inositol integrated combination therapy.

Mechanism of action for Propyl Thiouracil[1]

Propylthiouracil represses the creation of new thyroid hormone by an act of restraining the catalyst thyroid peroxidase, which has a primary rule to change over iodide to iodine particle and consolidation of iodine atom into tyrosine [2]. As a result of this production of DIT (diiodotyrosine) and MIT (monoiodotyrosine) ceases, the fundamental constituents for thyroxine (T4) and triiodothyronine (T3) generation. T4 to T3 transformation also gets hindered.

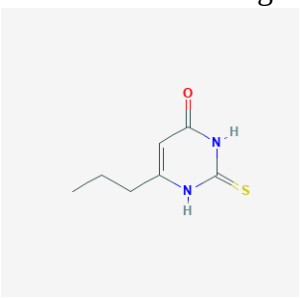

Fig1.Structure of propyl thiouracil[3]

Mechanism of action for Carbimazole[4]

Carbimazole is an antithyroid specialist that diminishes the concentration and uptake of inorganic iodine by thyroid, additionally it lessens the development of di-diiodotyrosine and T4. When changed over to its dynamic step of methimazole (activated form), stopping the coupling of thyroid peroxidase and also it iodinates the tyrosine residues on thyroglobulin, henceforth responsible for subsequent decrease in synthesis of T3 and T4 [5]. It is an imidazole antithyroid specialist. Carbimazole is converted to methimazole, which is answerable for the antithyroid movement in the pathways.

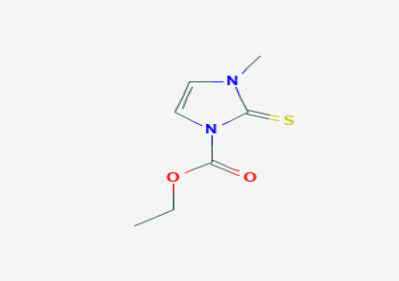

Fig2.Structure of Carbimazole[6]

Mechanism of action for Methimazole[7]

The essential mechanism of action of methimazole is to obstruct the creation in thyroid gland from secreting thyroid hormone. It meddles with the progression that causes the iodination of tyrosine deposits in thyroglobulin, interceded by the catalyst thyroid peroxidase, along these lines forestalling T4 and T3 [5] synthesis. Possibility for iodotyrosyl residues to get coupled can be an additional mechanism. Methimazole may likewise meddle with the oxidation of iodotyrosyl groups and iodide ions. In the long run, thyroglobulin gets drained, following reduction of thyroid hormone levels. Henceforth providing assistance with controlling illnesses by influencing the immune system. Different investigations show that decrease of soluble interleukin 2, intracellular adhesion molecule 1 and anti-thyrotropin receptor antibody with time, immune related hyperthyroid issues [8]. Nonetheless, there is no impact of this medication on the current T4 and T3 in the course or put away in the thyroid organ.

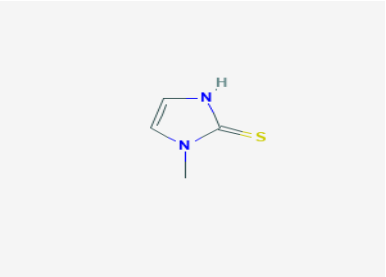

Fig3.Structure of Methimazole[9]

Mechanism of action for Levothyroxine [10]

Levothyroxine (T44) is an engineered form of thyroid hormones: T4. Ordinarily, the nerve center gives access to the hypothalamus for secretion of TRH. The role of TRH is to animates the anterior pituitary gland for emission of thyroid stimulating hormone (TSH), which in this way responsible for stimulation of the thyroid to discharge T4 and 20% T3. Half of T4 at that point gets changed over to its active metabolite of T3. The thyroid hormones at that point work by authoritative to thyroid receptor proteins contained inside the cell core.

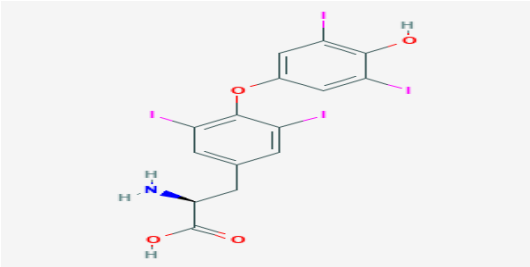

Fig4.Structure of Levothyroxine [13]

Mechanism of action for Myo-inositol [14]

The activity of myo-inositol shows engage with synapse union and it is an antecedent to the phosphatidylinositol cycle. The change that happens in the cycle re-enacts when the postsynaptic receptor is enacted yet without initiating the receptor. This movement incites a phony initiation which directed the action of monoamines and different synapses. The arrangement of inositol hexaphosphate after organization of inositol presents qualities such as antioxidant characters involved by the chelation of ferric particles and concealment of hydroxyl radicals. Myo-inositol controls the activation for pyruvate dehydrogenase kinase and isoenzyme 1 (PDK1) responsible for favouring glucose transport into plasma membrane by acting on glucotransporter 4 (GLUT4) [15].

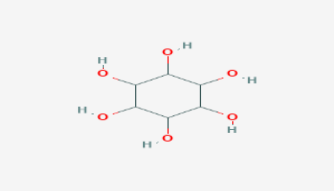

Fig5.Structure of Myo-inositol [14]

Myo- Inositol and Iodine

The thyroid gland releases hormones T3 and T4, and iodine is essential in their synthesis. The T3: T4 ratio in the body is essential for the correct functioning of the thyroid gland. The analysis of the T3: T4 ratio can help determine the iodine levels in the body. According to the study conducted by D. Barbaroet. al [16], myo-inositol being a carbocyclic polyol regulates the generation of hydrogen peroxide (H_2O_2) in thyrocytes. The H_2O_2 is essential for the iodine organification and thyroid hormone biosynthesis. Thus, the combined therapy of iodine and myo-inositol may prove to be crucial in improving the thyroid functionality. The hormones T3 and T4 play an important role in the development of the central nervous system by aiding in cell differentiation at the early stages of life as well as maintain the metabolic homeostasis in the adult life. Initially it is incorporated in the cellular membrane as phosphatidyl-myo-inositol. It is the precursor for several inositol containing compounds involved in signal transduction, membrane biogenesis, vesicle trafficking, and chromatin re-modelling. As myo-inositol plays a crucial role in the regulation of iodine organification, the supplementation may aid in iodine deficiency. Thus, the novel idea of supplying iodine with myo-inositol may also be considered as the treatment in the iodine deficiency. For the synthesis of PIP (Phosphatidylinositol-3,4,5-phosphate, inositol-1,4,5-triphosphate) myo-inositol is a precursor a source of diacylglycerol (secondary messenger). PIP are members of protein kinase family that regulates calcium levels intracellularly. Phosphoinositide, myo-inositol (secondary messenger) involve in cell signalling and activities of TSH, follicle-stimulating hormone (FSH) and insulin [18,19]proved to be effective formulation against hypothyroid patients suffering by Autoimmune Thyroiditis [20,21,22].

Result 1-

Based on the properties like absorption, distribution, metabolism, excretion and toxicity the following drugs are being tested and the result is recorded on the basis of dry-lab studies [17].

Myo-inositol

DRUG	PROPERTY	MODEL NAME	PREDICTED VALUE	UNIT
Myo-Inositol	Absorption	Water Solubility	0.384	Numeric (log mol/L)
Myo-Inositol	Absorption	$CaCO_2$ permeability	-0.579	Numeric (log Papp in 10^{-6} cm/sec)
Myo-Inositol	Absorption	Intestinal Absorption (Human)	20.269	Numeric % absorbed
Myo-Inositol	Absorption	Skin Permeability	-4.149	Numeric (log Kp)
Myo-Inositol	Absorption	P-glycoprotein Substrate	No	Categorical (Yes/No)
Myo-Inositol	Absorption	P-glycoprotein I inhibitor	No	Categorical (Yes/No)
Myo-Inositol	Absorption	P-glycoprotein II inhibitor	No	Categorical (Yes/No)

Myo-Inositol	Distribution	VDss (Human)	-0.419	Numeric (log L/kg)
Myo-Inositol	Distribution	Fraction Unbound (Human)	0.794	Numeric (Fu)
Myo-Inositol	Distribution	BBB permeability	-0.501	Numeric (log BB)
Myo-Inositol	Distribution	CNS Permeability	-6.252	Numeric (log PS)
Myo-Inositol	Metabolism	CYP2D6 Substrate	No	Categorical (Yes/No)
Myo-Inositol	Metabolism	CYP3A4 Substrate	No	Categorical (Yes/No)
Myo-Inositol	Metabolism	CYP1A2 Inhibitor	No	Categorical (Yes/No)
Myo-Inositol	Metabolism	CYP2C19 Inhibitor	No	Categorical (Yes/No)
Myo-Inositol	Metabolism	CYP2C9 Inhibitor	No	Categorical (Yes/No)
Myo-Inositol	Metabolism	CYP2D6 Inhibitor	No	Categorical (Yes/No)
Myo-Inositol	Metabolism	CYP3A4 Inhibitor	No	Categorical (Yes/No)
Myo-Inositol	Excretion	Total Clearance	0.6	Numeric (log ml/min/kg)
Myo-Inositol	Excretion	Renal OCT2 Substrate	No	Categorical (Yes/No)
Myo-Inositol	Toxicity	AMES Toxicity	No	Categorical (Yes/No)
Myo-Inositol	Toxicity	Max. Tolerated Dose (Human)	2.476	Numeric (log mg/kg/day)
Myo-Inositol	Toxicity	hERG I Inhibitor	No	Categorical (Yes/No)
Myo-Inositol	Toxicity	hERG II Inhibitor	No	Categorical (Yes/No)
Myo-Inositol	Toxicity	Oral Rat Acute Toxicity LD_{50}	1.654	Numeric mol/kg
Myo-Inositol	Toxicity	Oral Rat Chronic Toxicity LOAEL	4.343	Numeric (log mg/kg_bw/day)
Myo-Inositol	Toxicity	Hepatotoxicity	Yes	Categorical (Yes/No)
Myo-Inositol	Toxicity	Skin Sensitization	No	Categorical (Yes/No)
Myo-Inositol	Toxicity	T.Pyriformis Toxicity	0.285	Numeric (log ug/L)
Myo-Inositol	Toxicity	Minnow Toxicity	3.908	Numeric (log mM)

Methimazole

DRUG	**PROPERTY**	**MODEL NAME**	**PREDICTED VALUE**	**UNIT**
Methimazole	Absorption	Water Solubility	-1.36	Numeric (log mol/L)
Methimazole	Absorption	$CaCO_2$ permeability	1.444	Numeric (log Papp in 10^{-6} cm/sec)
Methimazole	Absorption	Intestinal Absorption (Human)	97.338	Numeric % absorbed
Methimazole	Absorption	Skin Permeability	-2.736	Numeric (log Kp)
Methimazole	Absorption	P-glycoprotein Substrate	yes	Categorical (Yes/No)
Methimazole	Absorption	P-glycoprotein I inhibitor	no	Categorical (Yes/No)
Methimazole	Absorption	P-glycoprotein II inhibitor	no	Categorical (Yes/No)
Methimazole	Distribution	VDss (Human)	0.173	Numeric (log L/kg)

Methimazole	Distribution	Fraction Unbound (Human)	0.735	Numeric (Fu)
Methimazole	Distribution	BBB permeability	-0.159	Numeric (log BB)
Methimazole	Distribution	CNS Permeability	-2.7	Numeric (log PS)
Methimazole	Metabolism	CYP2D6 Substrate	no	Categorical (Yes/No)
Methimazole	Metabolism	CYP3A4 Substrate	no	Categorical (Yes/No)
Methimazole	Metabolism	CYP1A2 Inhibitor	no	Categorical (Yes/No)
Methimazole	Metabolism	CYP2C19 Inhibitor	no	Categorical (Yes/No)
Methimazole	Metabolism	CYP2C9 Inhibitor	no	Categorical (Yes/No)
Methimazole	Metabolism	CYP2D6 Inhibitor	no	Categorical (Yes/No)
Methimazole	Metabolism	CYP3A4 Inhibitor	no	Categorical (Yes/No)
Methimazole	Excretion	Total Clearance	0.816	Numeric (log ml/min/kg)
Methimazole	Excretion	Renal OCT2 Substrate	no	Categorical (Yes/No)
Methimazole	Toxicity	AMES Toxicity	no	Categorical (Yes/No)
Methimazole	Toxicity	Max. Tolerated Dose (Human)	-0.462	Numeric (log mg/kg/day)
Methimazole	Toxicity	hERG I Inhibitor	no	Categorical (Yes/No)
Methimazole	Toxicity	hERG II Inhibitor	no	Categorical (Yes/No)
Methimazole	Toxicity	Oral Rat Acute Toxicity LD_{50}	2.605	Numeric mol/kg
Methimazole	Toxicity	Oral Rat Chronic Toxicity LOAEL	1.202	Numeric (log mg/kg_bw/day)
Methimazole	Toxicity	Hepatotoxicity	no	Categorical (Yes/No)
Methimazole	Toxicity	Skin Sensitization	yes	Categorical (Yes/No)
Methimazole	Toxicity	T.Pyriformis Toxicity	0.244	Numeric (log ug/L)
Methimazole	Toxicity	Minnow Toxicity	2.579	Numeric (log mM)

Levothyroxine

DRUG	PROPERTY	MODEL NAME	PREDICTED VALUE	UNIT
Levothyroxine	Absorption	Water Solubility	-2.891	Numeric (log mol/L)
Levothyroxine	Absorption	$CaCO_2$ permeability	-0.475	Numeric (log Papp in 10^{-6} cm/sec)
Levothyroxine	Absorption	Intestinal Absorption (Human)	58.699	Numeric % absorbed
Levothyroxine	Absorption	Skin Permeability	-2.735	Numeric (log Kp)
Levothyroxine	Absorption	P-glycoprotein Substrate	yes	Categorical (Yes/No)
Levothyroxine	Absorption	P-glycoprotein I inhibitor	no	Categorical (Yes/No)
Levothyroxine	Absorption	P-glycoprotein II inhibitor	no	Categorical (Yes/No)
Levothyroxine	Distribution	VDss (Human)	-0.069	Numeric (log L/kg)
Levothyroxine	Distribution	Fraction Unbound (Human)	0.492	Numeric (Fu)
Levothyroxine	Distribution	BBB permeability	-1.433	Numeric (log BB)
Levothyroxine	Distribution	CNS Permeability	-2.279	Numeric (log PS)
Levothyroxine	Metabolism	CYP2D6 Substrate	no	Categorical (Yes/No)

Levothyroxine	Metabolism	CYP3A4 Substrate	no	Categorical (Yes/No)
Levothyroxine	Metabolism	CYP1A2 Inhibitor	no	Categorical (Yes/No)
Levothyroxine	Metabolism	CYP2C19 Inhibitor	no	Categorical (Yes/No)
Levothyroxine	Metabolism	CYP2C9 Inhibitor	no	Categorical (Yes/No)
Levothyroxine	Metabolism	CYP2D6 Inhibitor	no	Categorical (Yes/No)
Levothyroxine	Metabolism	CYP3A4 Inhibitor	no	Categorical (Yes/No)
Levothyroxine	Excretion	Total Clearance	-0.387	Numeric (log ml/min/kg)
Levothyroxine	Excretion	Renal OCT2 Substrate	no	Categorical (Yes/No)
Levothyroxine	Toxicity	AMES Toxicity	no	Categorical (Yes/No)
Levothyroxine	Toxicity	Max. Tolerated Dose (Human)	0.505	Numeric (log mg/kg/day)
Levothyroxine	Toxicity	hERG I Inhibitor	no	Categorical (Yes/No)
Levothyroxine	Toxicity	hERG II Inhibitor	no	Categorical (Yes/No)
Levothyroxine	Toxicity	Oral Rat Acute Toxicity LD_{50}	2.451	Numeric mol/kg
Levothyroxine	Toxicity	Oral Rat Chronic Toxicity LOAEL	2.963	Numeric (log mg/kg_bw/day)
Levothyroxine	Toxicity	Hepatotoxicity	no	Categorical (Yes/No)
Levothyroxine	Toxicity	Skin Sensitization	no	Categorical (Yes/No)
Levothyroxine	Toxicity	T.Pyriformis Toxicity	0.285	Numeric (log ug/L)
Levothyroxine	Toxicity	Minnow Toxicity	-0.734	Numeric (log mM)

Carbimazole

DRUG	PROPERTY	MODEL NAME	PREDICTED VALUE	UNIT
Carbimazole	Absorption	Water Solubility	-2.485	Numeric (log mol/L)
Carbimazole	Absorption	$CaCO_2$ permeability	1.708	Numeric (log Papp in 10^{-6} cm/sec)
Carbimazole	Absorption	Intestinal Absorption (Human)	96.104	Numeric % absorbed
Carbimazole	Absorption	Skin Permeability	-2.735	Numeric (log Kp)
Carbimazole	Absorption	P-glycoprotein Substrate	no	Categorical (Yes/No)
Carbimazole	Absorption	P-glycoprotein I inhibitor	no	Categorical (Yes/No)
Carbimazole	Absorption	P-glycoprotein II inhibitor	no	Categorical (Yes/No)
Carbimazole	Distribution	VDss (Human)	-0.306	Numeric (log L/kg)
Carbimazole	Distribution	Fraction Unbound (Human)	0.65	Numeric (Fu)
Carbimazole	Distribution	BBB permeability	-0.197	Numeric (log BB)
Carbimazole	Distribution	CNS Permeability	-3.003	Numeric (log PS)
Carbimazole	Metabolism	CYP2D6 Substrate	no	Categorical (Yes/No)
Carbimazole	Metabolism	CYP3A4 Substrate	no	Categorical (Yes/No)
Carbimazole	Metabolism	CYP1A2 Inhibitor	yes	Categorical (Yes/No)

Carbimazole	Metabolism	CYP2C19 Inhibitor	no	Categorical (Yes/No)
Carbimazole	Metabolism	CYP2C9 Inhibitor	no	Categorical (Yes/No)
Carbimazole	Metabolism	CYP2D6 Inhibitor	no	Categorical (Yes/No)
Carbimazole	Metabolism	CYP3A4 Inhibitor	no	Categorical (Yes/No)
Carbimazole	Excretion	Total Clearance	0.486	Numeric (log ml/min/kg)
Carbimazole	Excretion	Renal OCT2 Substrate	no	Categorical (Yes/No)
Carbimazole	Toxicity	AMES Toxicity	no	Categorical (Yes/No)
Carbimazole	Toxicity	Max. Tolerated Dose (Human)	0.385	Numeric (log mg/kg/day)
Carbimazole	Toxicity	hERG I Inhibitor	no	Categorical (Yes/No)
Carbimazole	Toxicity	hERG II Inhibitor	no	Categorical (Yes/No)
Carbimazole	Toxicity	Oral Rat Acute Toxicity LD_{50}	3.268	Numeric mol/kg
Carbimazole	Toxicity	Oral Rat Chronic Toxicity LOAEL	0.649	Numeric (log mg/kg_bw/day)
Carbimazole	Toxicity	Hepatotoxicity	yes	Categorical (Yes/No)
Carbimazole	Toxicity	Skin Sensitization	yes	Categorical (Yes/No)
Carbimazole	Toxicity	T.Pyriformis Toxicity	0.285	Numeric (log ug/L)
Carbimazole	Toxicity	Minnow Toxicity	1.476	Numeric (log mM)

Propyl thiouracil

DRUG	PROPERTY	MODEL NAME	PREDICTED VALUE	UNIT
Propyl thiouracil	Absorption	Water Solubility	-2.888	Numeric (log mol/L)
Propyl thiouracil	Absorption	$CaCO_2$ permeability	1.208	Numeric (log Papp in 10^{-6} cm/sec)
Propyl thiouracil	Absorption	Intestinal Absorption (Human)	93.101	Numeric % absorbed
Propyl thiouracil	Absorption	Skin Permeability	-3.154	Numeric (log Kp)
Propyl thiouracil	Absorption	P-glycoprotein Substrate	no	Categorical (Yes/No)
Propyl thiouracil	Absorption	P-glycoprotein I inhibitor	no	Categorical (Yes/No)
Propyl thiouracil	Absorption	P-glycoprotein II inhibitor	no	Categorical (Yes/No)
Propyl thiouracil	Distribution	VDss (Human)	0.066	Numeric (log L/kg)
Propyl thiouracil	Distribution	Fraction Unbound (Human)	0.623	Numeric (Fu)
Propyl thiouracil	Distribution	BBB permeability	-0.303	Numeric (log BB)
Propyl thiouracil	Distribution	CNS Permeability	-2.993	Numeric (log PS)
Propyl thiouracil	Metabolism	CYP2D6 Substrate	no	Categorical (Yes/No)
Propyl thiouracil	Metabolism	CYP3A4 Substrate	no	Categorical (Yes/No)

Propyl thiouracil	Metabolism	CYP1A2 Inhibitor	no	Categorical (Yes/No)
Propyl thiouracil	Metabolism	CYP2C19 Inhibitor	no	Categorical (Yes/No)
Propyl thiouracil	Metabolism	CYP2C9 Inhibitor	no	Categorical (Yes/No)
Propyl thiouracil	Metabolism	CYP2D6 Inhibitor	no	Categorical (Yes/No)
Propyl thiouracil	Metabolism	CYP3A4 Inhibitor	no	Categorical (Yes/No)
Propyl thiouracil	Excretion	Total Clearance	0.075	Numeric (log ml/min/kg)
Propyl thiouracil	Excretion	Renal OCT2 Substrate	no	Categorical (Yes/No)
Propyl thiouracil	Toxicity	AMES Toxicity	no	Categorical (Yes/No)
Propyl thiouracil	Toxicity	Max. Tolerated Dose (Human)	0.915	Numeric (log mg/kg/day)
Propyl thiouracil	Toxicity	hERG I Inhibitor	no	Categorical (Yes/No)
Propyl thiouracil	Toxicity	hERG II Inhibitor	no	Categorical (Yes/No)
Propyl thiouracil	Toxicity	Oral Rat Acute Toxicity LD_{50}	2.388	Numeric mol/kg
Propyl thiouracil	Toxicity	Oral Rat Chronic Toxicity LOAEL	1.317	Numeric (log mg/kg_bw/day)
Propyl thiouracil	Toxicity	Hepatotoxicity	yes	Categorical (Yes/No)
Propyl thiouracil	Toxicity	Skin Sensitization	no	Categorical (Yes/No)
Propyl thiouracil	Toxicity	T.Pyriformis Toxicity	-0.04	Numeric (log ug/L)
Propyl thiouracil	Toxicity	Minnow Toxicity	2.037	Numeric (log mM)

Molecules	**Molecular weight**	**Log P**	**Acceptor**	**Donor**
Propylthiouracil	170.237	1.38499	2	2
Carbimazole	186.236	1.56069	5	0
Methimazole	114.173	1.08269	2	1
Levothyroxine	776.872	4.5573	4	3
Myo-inositol	180.156	-3.8346	6	6

Result 2-

On the basis of main function, pathway towards effectivity following are the results for Propylthiouracil, Carbimazole, Methimazole, Levothyroxine and myo-inositol.

Drug	**Main Function**	**Effective control as anti-thyroid**	**Control over Thyroid Mechanism**
Propylthiouracil	Stop production of new thyroid hormone by controlling thyroid peroxidase.	• Stops DIT &MIT production • Stops T_4 & T_3 production • Controls iodide to iodine conversion	Controls thyroid hormone in blood and thyroid gland.

Carbimazole	Reduce the uptake & concentration of inorganic iodine	• Gets converted to methimazole controlling thyroid peroxidase. • Stops di-Diiodo tyrosine & thyroxin production.	No such total control indicated.
Methimazole	Controls the thyroid gland and secretion of thyroid hormone	• Control iodide iodine conversion by ceasing secretion of thyroid peroxidase • Meddle oxidation of iodotyrosyl residue and coupling with iodide.	In case of hyperthyroidism controls the immune system
Levothyroxine	T_4 engineered species conversion into T_3 after discharge.	• Controls DNA transcription. • Gluconeogenesis • Hike in protein amalgamation	Acts as a alternative of naturally occurring T_4 and in the physiological system influence the T_4 activities
Myo-inositol	Acts in cellular mechanic pathway by controlling glucose mechanism and effect in metabolic pathway	• engage with synapse union and neurotransmitter synthesis prior to phosphatidylinositol cycle. • Regulates the activity of monoamines and other neurotransmitters. • Regulates iodine organification	Allows treatment of metabolic disorders such thyroid malfunction.

Discussion-

On the basis of cellular mechanism, the suggestive study shows [16] that involvement of myo-inositol shows great cellular aggressions to regulate iodine organification. Drugs required to solve the problems of anti-thyroid activity must able to regulate the iodine regulation mechanism in cellular body. The drugs used in this case study comprises of propylthiouracil, carbimazole, methimazole, levothyroxine. A comparative ADMET study has been performed to check the status of the drugs taken in the study. Myo-inositol shows an intestinal absorption of 20.269-unit comparative to the other 4 drugs carbimazole shows the best absorption rate of 96.104 unit. On the other hand, myo-inositol provides the best tolerance of 2.476 unit however, methimazole shows a negative maximum tolerance dose of -0.462 unit. The LD_{50} value for myo-inositol also has the least toxic rate of 1.654 units whereas the maximum LD_{50} value signs to carbimazole supporting the fact that myo-inositol must be a better suggestive drug compared to carbimazole. The total clearance rate of myo-inositol is around 0.6 units whereas levothyroxine has a negative clearance rate of -0.387 units. The ADMET studies shows enhanced support on our theory suggestive towards myo-inositol and iodine supplementation a novel pathway as an anti-thyroid treatment. Myo-inositol having negative logP suggests that it is hydrophilic in nature and hence needs to be administered parenterally giving better and immediate results as a drug delivery system.

Propylthiouracil is responsible for iodide to iodine conversion. Carbimazole is responsible for Di-Diiodo tyrosine & thyroxin production. Methimazole ceases iodide iodine conversion. But the control of cellular matters such as DNA transcription, cellular protein activity binding (action), effect at synaptic levels shows prominent features for levothyroxine and myo-inositol. Myo-inositol gains an advantage after administered over iodine showing following effects a) H_2O_2 prime molecule for iodine regulation b) phosphatidyl-myo-inositol. Myo-inositol along with Iodine supplement supports the mechanism hence shows a prominent combination therapy for effectivity against anti-thyroid activity.

Acknowledgement

Foremost we would sincerely like to express our gratitude to our parents Soma and Debasish Guha, Mahuya and Ratan Kumar Das, Prabir Kumar Nandi and Chitra Nandi. We also would love to show our respect to our professors Dr. S. Ganguly, Dr. Venkatesan Jayaprakash**,** Dr B.N Sinha for their support and guidance. We also express our gratitude towards the corona warriors fighting the pandemic and wishing their success.

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