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6-OXA-3-THIAOCTANOIC ACID HAS POTENTIAL INHIBITORS AGAINST THYROID CANCER- *IN-SILICO* ANALYSIS

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Keywords:

Thyroid cancer, Thyroid hormone receptor alpha1 (TRα1), *Andrographis paniculata*, Molecular Docking

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ABSTRACT: Cancer is an uncontrollable incurable disease with abnormal growth and proliferation of cells. Thyroid cancer is caused due to the thyroid hormone effects on growth, development and homeostasis in mammals. Thyroid cancer is the most common endocrine malignancy. Thyroid hormone is encoded by two types of thyroid receptors that are TRα and TRβ. TRα is functionally divided in two types TRα1 and TRα2. TRα1 is expressed first during fetal development and is widely expressed in adult tissues. Over-expression of TRα1 has shown its ability to trigger hyper-proliferation and to accelerate the tumeorigenic process in developing intestinal cancer. The novelty of our approach is to demonstrate the inhibitory activity of a plant extract compound against TRα1 using *In-silico* methods. *Andrographis paniculata* plant leaf is extracted with Methanol and three compounds were identified from GC-MS analysis. The 3D crystal structure of the thyroid cancer for Thyroid hormone receptor alpha1 (ID: 1NAV) were retrieved from the Protein Data Bank (PDB) and was used for carrying out the molecular docking calculation. The result shows that, of three compounds extracted from *A. paniculata* leaves, compound 6-Oxa-3-thiaoctanoic acid exhibits potential inhibitory activity against TRα1.

INTRODUCTION: Thyroid cancer (TC) is one of the most common cancer in all primary endocrine cancers in the world [1]. Thyroid cancer is the endocrine malignancy. The cancer statistics estimate that 62,980 patients will be diagnosed with thyroid cancer in the United States in 2014, with the largest annual incidence rise among all cancers [2]. In 1973 and 2002, there was an average increase in thyroid cancer incidence of 67% in females and 48% of males in 19 countries across the Americas, Asia, Europe, and Oceania [3]. The thyroid cancer in women is higher than in men and it comprises 2.7% of all cancers in females. It is the ninth most common cancers [5].

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Thyroid cancer is discovered with synchronous metastases, which will progress quickly with a worse survival [6-9]. Although the incidence of thyroid cancer is low (only approximately 1% of all tumors) and the prognosis is better, it accounts for more than 90% of all endocrine cancers, and it contributes to more than 50% of deaths from endocrine cancers [10-12]. Most thyroid cancer patients do not have a history of radiation exposure and not all individuals exposing to radiation develop thyroid cancer, which indicates that genetic factors also play an important role in the development of thyroid cancer [13, 14]. Thyroid hormone effects on growth, development and homeostasis in mammals [15].

Thyroid hormone Receptors (TRs) are transcription factors that belong to the nuclear receptor super family [16]. The synthesis of Thyroid Hormones (THs) is regulated through the hypothalamus, pituitary thyroid axis [17].

The thyroid gland predominantly secretes Thyroxine (T4) and Triiodothyronine (T3). Triiodothyronine (T3) is the most active TH, since it has a higher affinity by the nuclear TRs, which mediate most actions of these hormones [18]. T3 exerts its actions by translocation into the nucleus of target cells and binding to the Ligand Binding Domain (LBD) of TRs [19] and it regulates important genes in intestinal, skeletal, and cardiac muscles as well as in the liver, and the central nervous system [20]. The TRs encoded by two genes with THRA and THRB are located on two different chromosomes. Classically, TRs bind to specific DNA sequences on the promoter of T3-target genes TREs to activate or repress basal gene transcription are two genes for TRs are TRα and TRβ, that give rise to an ensemble of four different isoform by means of alternative splicing or differential promoter usage: TRα1, TRα2, TRβ1, and TRβ2 [19, 21]. TRα1 is expressed first during fetal development and is widely expressed in adult tissues; TRβ1 appears later in development and displays highest expression in the adult liver, kidney, and lung [22].

Thyroid hormone receptor alpha1 also known as nuclear receptor subfamily, group A, member 1(NR1A1), is a nuclear receptor protein that in humans is encoded by the THRA gene it's a several receptors for thyroid hormone, and has been shown to mediate the biological activities of TR [23, 24]. TRα1 and TRβ1 vary from 400 to 500 amino acids in size, having abundantly homologous LBD. TRα isoforms α1, α2 and α3, are encoded by the TRα gene. These isoforms vary in their carboxyl termini due to alternative splicing. TRα1 has a binding capacity for T3, which leads to activation or repression of target genes, whereas TRα2 and TRα3 are non-T3 binding products and inhibit T3 functions [25].

TRα is the main isoform expressed in the heart and mediates many of the effects of the THs in this organ [26-28]. TRα function is cardiomyocyte growth [29], for suppression of MHC-β expression [30], and whereas mice in which TRα has been genetically inactivated shown a markedly decreased heart rate, mice with deletion of TRβ have a normal heart rate. Furthermore, TRα KO mice show increased relaxation time and decreased tension development [31]. TRα is predominant in the hepatocyte precursor, the stellate cells, and this isoform could play a critical role in hepatocyte maturation during the perinatal period [32]. TH controls the proliferation of the intestinal epithelial progenitors during the postnatal maturation steps in both amphibians and mammals. Moreover, this process is strongly correlated with a set of common, regulated TH-target genes and signaling pathways, although important differences also exist [33]. Both TRα and TRβ are expressed in intestinal epithelial cells [34], but the proliferation of epithelial cells depends mainly on the TRα1 receptor involves the regulation of cell cycle control genes and of the Wnt/β-catenin pathway, a key modulator of cell proliferation in the intestinal epithelium. Liganded TRα1 increases expression of both β-catenin and secreted frizzled-related protein-2 (sFRP2), resulting in expression Wnt target genes and in the stimulation of epithelial progenitor proliferation [35, 36].

For recent year researches have aimed at identifying and validating plant derived substances for the treatments are 25% of modern medicines are directly and indirectly derived from plants [37-39] the natural plant compounds or phytomedicines used for various diseases [40, 41]. *A. Paniculata* is used in traditional Siddha and Ayurvedic medicine as well as in tribal medicine in India and some other countries for multiple clinical applications. The plant extracts exhibited anti-typhoid, anti-fungal, anti-hepatotoxic, anti-biotic, anti-malarial [42], and anti-cancer activities [43]. This study was an attempt to identify bioactive compounds from *A. Paniculata* plant leaves using GC-MS analysis and molecular docking study were carried out.

MATERIAL AND METHODS:

Collection and Preparation of Sample: The *Andrographis paniculata* leaves were collected from Annamalai University, Annamalai Nagar, Chidhambaram, and Tamilnadu. The plant leaves were collected in the morning session (during 8am-10am) and were packed new polyethylene bags. The samples were transported to the Laboratory at Annamalai University and kept at room temperature for further processing. The leaves were washed and shade dried leaves of *Andrographis paniculata* were then pulverized into powder and kept an airtight container for using further process.

Extraction of Leaves: The powder leaves of *Andrographis paniculata* (100g) were extracted with methanol (500 ml) for 48 hours at temperatures ranging between 60-65^{0}C from using a soxhlet extractor. The solvent was evaporated by rotary evaporator to obtain viscous semisolid masses. The semi dry methanol crude extract (30g) was suspended in water. The crude extract was filtered separately through Whatman No: 4, filter paper to obtained dust free plant crude extract. This dust free plant crude extract was used to carry out GC-MS analysis.

GC-MS Analysis: The GC-MS analysis of organic methanol extracts isolated from leaves *Andrographis paniculata*. Joel GC-MS, GC-Mate II (IIT Chennai) Helium was used as the carrier gas at a flow rate of 1 ml/min. The temperature was programmed at a flow rate of 1ml/min. The temperature was programmed at 80^{0}C for 5min then increased up to 300^{0}C at the rate of 15^{0}C/min. The temperature of injector and E1 detector (70ev) was 280^{0}C and 300^{0}C, respectively 2µl of plant extract was injected with GC-MS manually.

Preparation of protein structure: The 3D structure of Thyroid hormone receptor alpha1 (PDB I.D: 1NAV) was downloaded from the Protein Data Bank (PDB) (http://www.rcsb. org/pdb/). The structural information of the macromolecules determined by X-ray crystallographic and NMR methods is available in the PDB. The water molecules were removed from the protein structure (1NAV) before docking.

Preparation of Ligand structures: The identified Chemical compound 6-Oxa-3-thiaoctanoic acid was derived from *Andrographis paniculata* plant leaves and its structural properties were retrieved from the PubChem. ChemSketch (Chemically intelligent drawing interface freeware developed by Advance Chemistry Development, Inc., (http:// www.acdlabs.com) was used to construct the structure of the ligand and to determine the basic properties.

The ligand molecule was generated and the three dimensional optimizations were done and finally the optimized file was saved. MOL file (a file format for holding information about the atoms, bonds, connects and coordinates of a molecule).

Docking analysis: The docking analysis was performed by Discover Studio Version 4.5 (Biovia Dassault system, Inc. USA) for the Thyroid hormone receptor alpha1 protein against the compound 6-Oxa-3-thiaoctanoic acid.

RESULT: The *Andrographis paniculata* plant leaves (**Fig. 1**), the methanolic extract of plant leaf was used for GC-MS analysis by using Joel GC-MS, GC-Mate II (IIT Chennai). The result of GC-MS analysis produce a chromatogram with three retention peak (**Fig. 2**) and compound structure identified were standard compound library (**Fig. 3**). Retention time, compound name and properties are shown in (**Table 1**).

Molecular docking study was performed, based on the Lipinski´s rule ligand molecules are selected. The intestinal thyroid cancer responsible protein Thyroid hormone receptor alpha1 protein was retrieved from Protein Data Bank (PDB ID: 1NAV) it's used as target protein the structure and Ramachandran plot were shown in (**Fig. 4**) visualized by Discover studio v4.5. The 6-Oxa-3-thiaoctanoic acid compound linear and 3D structures were shown as (**Fig. 5**).

The 6-Oxa-3-thiaoctanoic acid was docked with Intestinal thyroid cancer protein by using Discover Studio v4. 5 (Biovia Dassault system, Inc. USA). The TRα1 protein and 6-Oxa-3-thiaoctanoic acid compound strongly interacts with each other by hydrogen bond interaction. Two hydrogen bond interactions were formed between Protein-ligand complex the hydrogen bond interaction was denoted by green dots (**Fig. 6**), 2D interaction structure were shown in (**Fig. 7**). The binding region amino acids are shown in the histogram (**Fig. 8).**

This histogram denotes the corresponding amino acids are involved in hydrogen bond formation between target and bioactive compound the amino acids are respectively SER277, GLY278, the Protein–Ligand docking was performed and the Libdock score value 72.05. The electrostatic potential surface was also created (**Fig. 9**). This computational technique strongly supports and helps to identify the novel and more potent inhibitors through Ligand-Receptor interaction.

Plant leaf structure:

FIG. 1: *ANDROGRAPHIS PANICULATA* PLANT

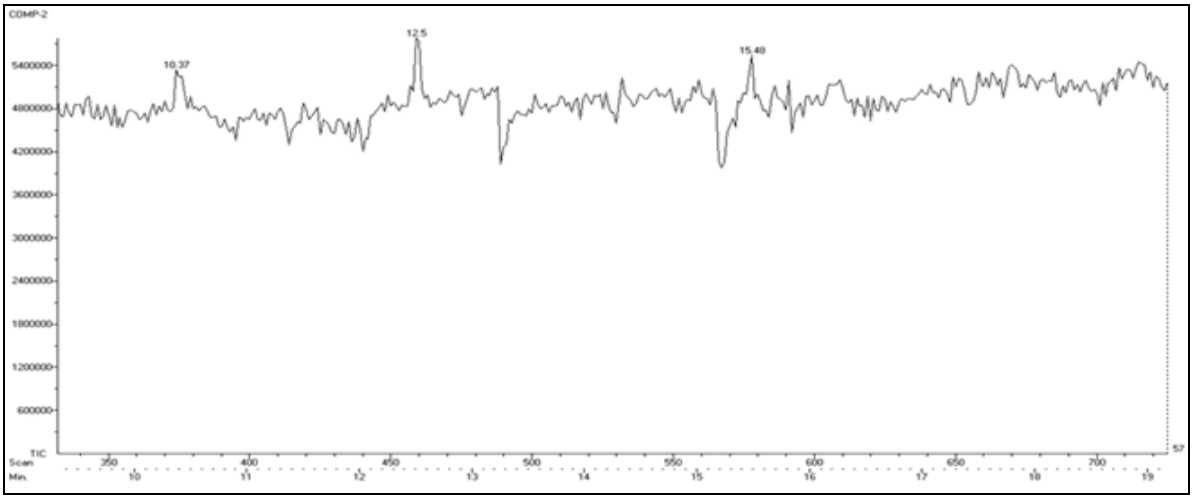

FIG. 2: GC-MS ANALYSIS OF *ANDROGRAPHIS PANICULATA* EXTRACT

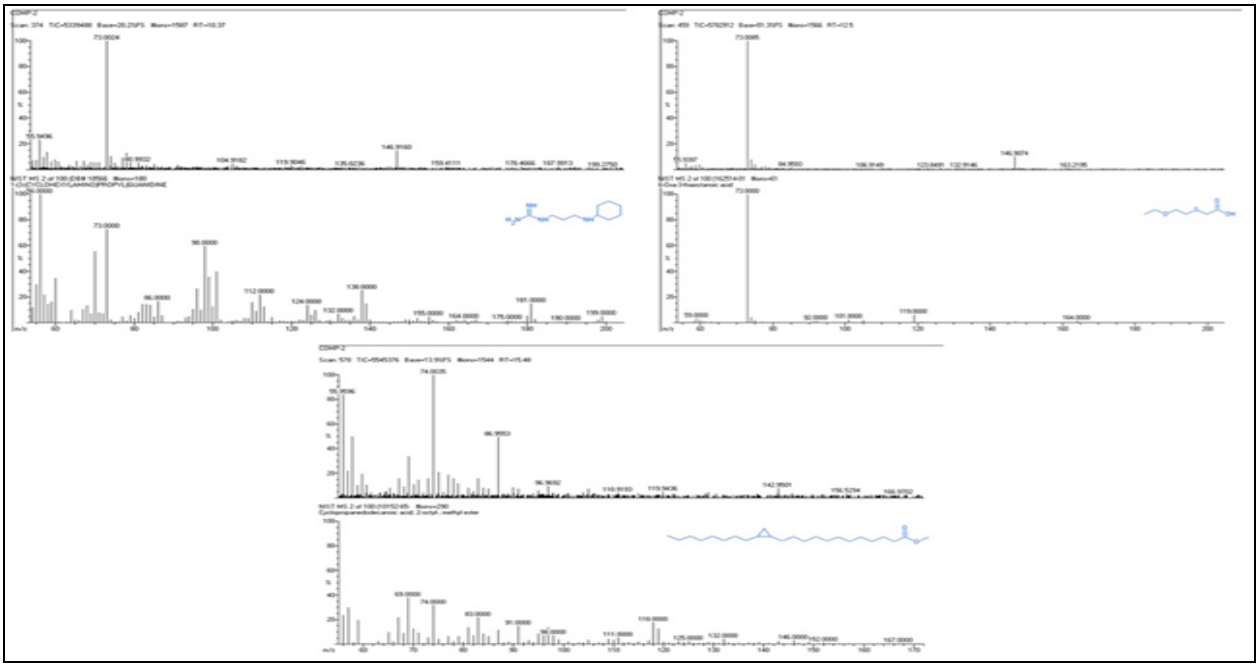

FIG. 3: BIOACTIVE COMPOUNDS FROM GC-MS ANALYSIS.

GC-MS analysis:

TABLE 1: PROPERTIES OF METHANOLIC EXTRACT COMPOUND

S. No	Retention Time	Compound Name	Molecular Formula	Molecular Weight g/mol	H Donor and Acceptor
1.	10.37	1-[3-[cyclohexyl amino]propyl]guanidine	$C_{12}H_{26}N_4$	226.36164	2,2
2.	12.5	6-Oxa-3-thiaoctanoic acid	$C_6H_{12}O_3S$	164.22268	1,4
3.	15.48	Cyclopropaneoctanoic acid, 2-octyl-, methyl ester	$C_{20}H_{38}O_2$	310.51452	0,2

Protein structure:

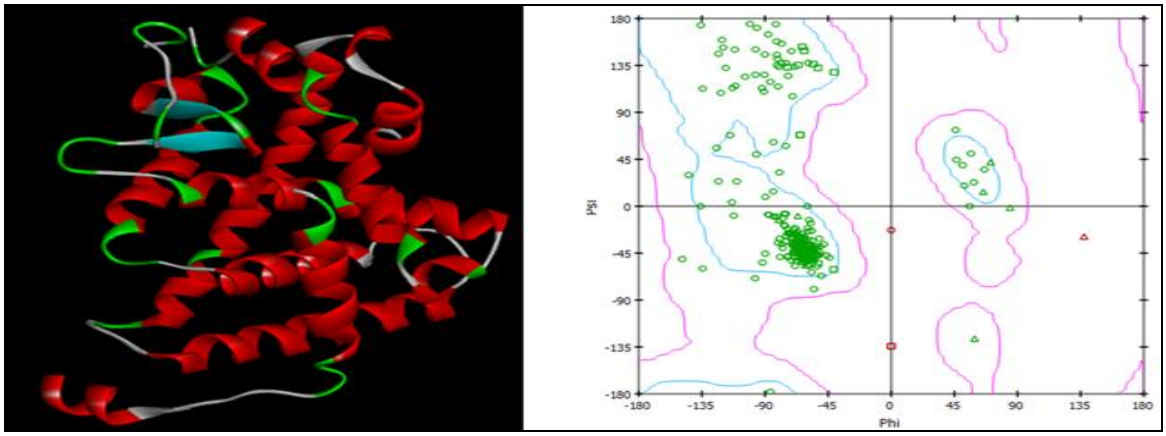

FIG. 4: STRUCTURE OF THYROID HORMONE RECEPTOR ALPHA 1 AND RAMACHANDRAN PLOT

Compound structure:

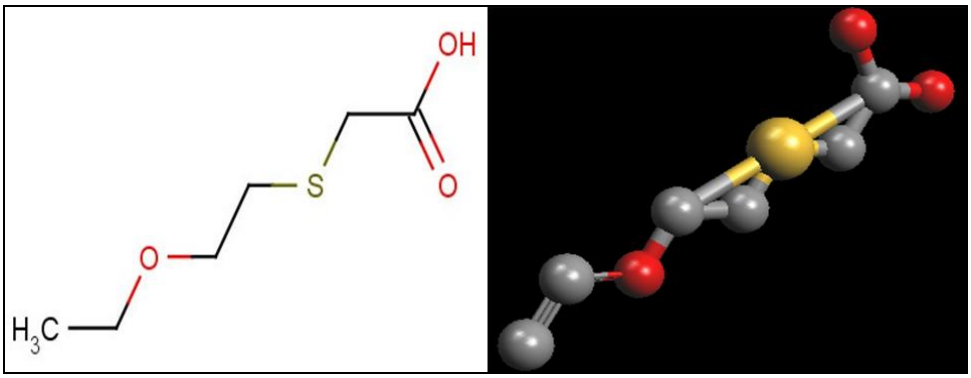

FIG. 5: LINEAR AND 3D STRUCTURE OF 6-OXA-3-THIAOCTANOIC ACID

Docking analysis:

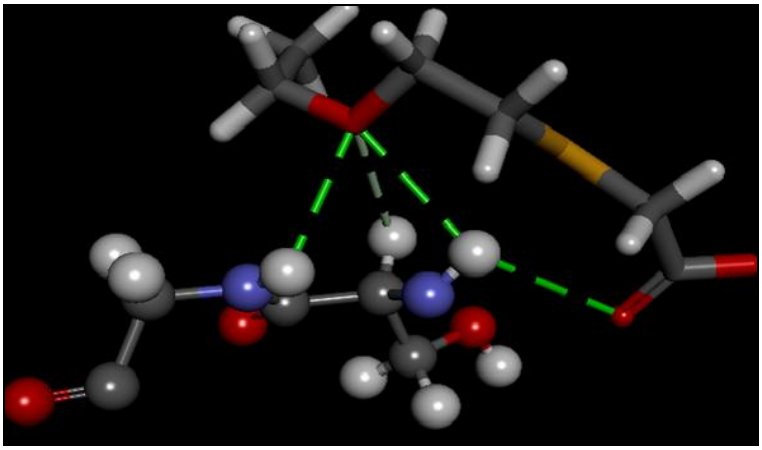

FIG. 6: INTERACTION OF ACTIVE SITE REGION BETWEEN THYROID HORMONE RECEPTOR ALPHA1 AND 6-OXA-3-THIAOCTANOIC ACID

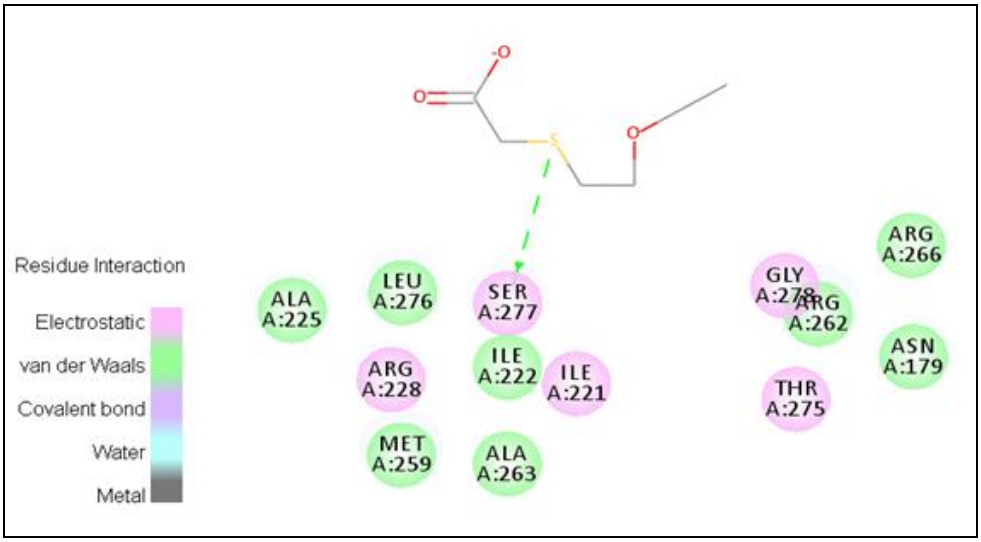

FIG. 7: 2D INTERACTION OF THE ACTIVE SITE REGION BETWEEN THYROID HORMONE RECEPTOR ALPHA1 AND 6-OXA-3-THIAOCTANOIC ACID

Amino acid binding site:

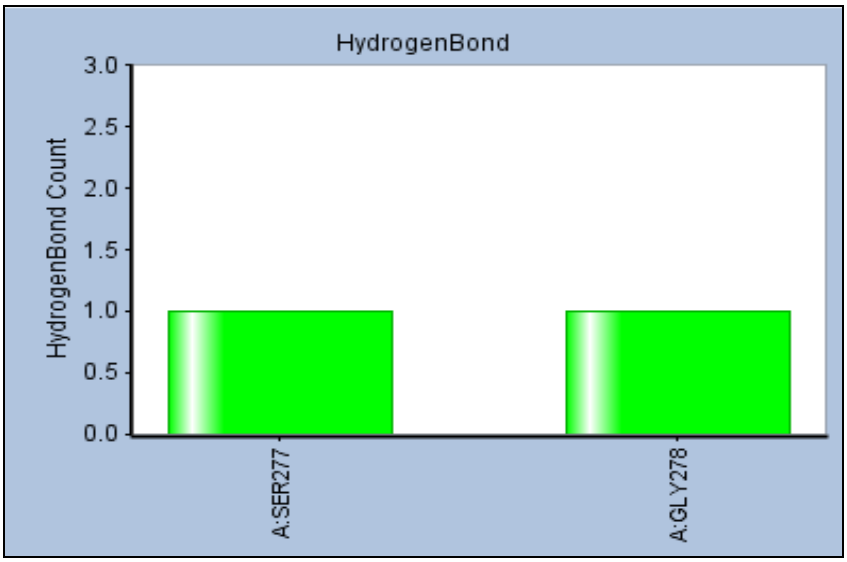

FIG. 8: HISTOGRAM OF BINDING REGION AMINO ACID

Electrostatic surface:

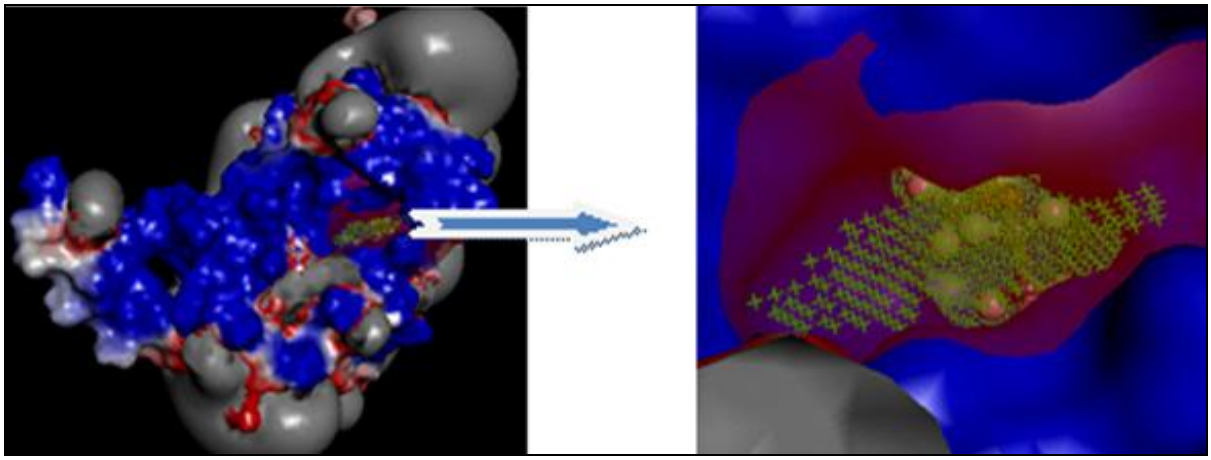

FIG. 9: ELECTROSTATIC POTENTIAL SURFACES

DISCUSSIONS: Hebraism has a long tradition of use of outside of conventional medicine. It is becoming more mainstream as improvements in analysis and quality control along with advances in clinical research. Molecular Docking is important methods in computerized drug designing for different targeted disease, including cancer [44]. The *Andrographis paniculata* plant Tamil name nilavembu it's commonly called medicinal plant it has pharmaceutical important and also used as chemotherapeutic agents in the treatment of several types of cancers [43] is the study was structured-based drug design for thyroid cancer, here we used GC-MS analyzed compound identified from *A. paniculata* plant leaf 6-Oxa-3-thiaoctanoic acid inhibiting thyroid hormone receptor alpha1 (TRα1) responsible to thyroid cancer. 6-Oxa-3-thiaoctanoic acid compound has stronger and higher binding affinity.

There are 2 hydrogen bond interactions resulting with corresponding amino residues for SER277, GLY278 and the libdock score value is 72.05. The present study proves the *A. paniculata* plant leaf compound 6-Oxa-3-thiaoctanoic acid as the potential ability to inhibiting Thyroid cancer. Our *In Silico* study strongly supports for further researchers in clinical trials to test its effectiveness and for social benefit thus reducing the time and cost of the drug discovery.

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