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Molecular docking studies of heterocyclic compounds targeting thyroid-related proteins: PDB 5HPW and PDB 1XZX

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Abstract
Thyroid-related disorders necessitate the discovery of novel therapeutic agents targeting key proteins involved in thyroid hormone synthesis and regulation. In this study, we performed molecular docking of designed heterocyclic compounds with two target proteins, PDB 5HPW and PDB 1XZX, to evaluate their potential inhibitory effects. Protein structures were retrieved from the RCSB Protein Data Bank and pre-processed using Chimera, followed by energy minimization to refine their geometry. Ligand structures were drawn in ACD Sketch and optimized using MM2 energy minimization in ACD/ChemSketch. Molecular docking was conducted using iGEMDOCK and AutoDock Vina, with docking scores assessed based on binding affinities and protein-ligand interactions. Docking results indicated that several compounds, particularly 13h, 14h and 7h, exhibited significant binding affinities. Compound 13h demonstrated strong hydrogen bonding with Met 310 and van der Waals interactions with HIS 435, MET 313 and ILE 276 on PDB 1XZX (-11.1 kcal/mol), along with sigma-pi interactions. Compound 7h exhibited the highest binding affinity (-110.4 kcal/mol) using iGEMDOCK. Interestingly, compounds 7h to 10h were highly active on 5HPW but showed limited interactions with 1XZX. Certain compounds (20h-25h and 32h) failed to dock properly in both software tools, suggesting poor compatibility with the active site. These findings highlight the potential of selected heterocyclic compounds as inhibitors of thyroid-related proteins. The study provides insights into structure-activity relationships and lays the foundation for further experimental validation to explore their therapeutic efficacy in managing thyroid disorders.

Keywords: Molecular docking, heterocyclic compounds, thyroid hormone regulation, iGEMDOCK, AutoDock Vina, thyroid peroxidase (TPO), thyrotropin-releasing hormone receptor (TRHR), protein-ligand interactions

Introduction
Thyroid hormones play a crucial role in regulating metabolism, growth and development in humans. The synthesis and regulation of these hormones are controlled by key enzymes and receptors, such as thyroid peroxidase (TPO) and the thyrotropin-releasing hormone receptor (TRHR). Dysregulation of these proteins can lead to thyroid-related disorders, including hypothyroidism, hyperthyroidism and thyroid cancers. Despite the availability of therapeutic agents, such as levothyroxine and methimazole, there is a continuous need for novel inhibitors with improved specificity and efficacy. Molecular docking has emerged as a powerful computational technique for drug discovery, allowing researchers to predict the binding affinity and interactions of small molecules with target proteins. In this study, we investigated the binding potential of designed heterocyclic compounds against two thyroid-related proteins: PDB 5HPW (TPO) and PDB 1XZX (TRHR). These proteins were selected based on their critical involvement in thyroid hormone synthesis and regulation. The research utilized iGEMDOCK and AutoDock Vina, two widely used molecular docking tools, to evaluate the interaction of heterocyclic compounds with the active sites of the target proteins. The docking studies aimed to:

1. Identify compounds with high binding affinities to TPO and TRHR.
2. Analyze protein-ligand interactions, including hydrogen bonding, van der Waals forces and sigma-pi interactions.
3. Compare docking results obtained from iGEMDOCK and AutoDock Vina to ensure validation and consistency.

The results from these docking simulations provide insights into the structure-activity relationships of the designed compounds,

helping in the identification of potential inhibitors of thyroid hormone synthesis and regulation. By targeting key proteins, these compounds may serve as promising leads for the development of novel antithyroid agents. The findings from this study lay the foundation for further experimental validation and preclinical studies to assess their therapeutic potential.

Materials and Methods

The crystal structures of the target proteins, PDB 5HPW and PDB 1XZX, were obtained from the RCSB Protein Data Bank. The protein structures were pre-processed in Chimera by eliminating water molecules, ions and other heteroatoms to create a clean binding environment. Hydrogen atoms were added to compensate for missing atoms, ensuring accurate hydrogen bonding during docking simulations. Additionally, energy minimization was carried out in Chimera to refine protein geometry and resolve steric clashes. Heterocyclic compounds were selected based on the study's requirements. Their 2D chemical structures were drawn using ACD Sketch and subsequently converted into 3D models for computational docking studies. The ligand structures were optimized using energy minimization techniques in ACD/ChemSketch, applying the MM2 method (RMS gradient = 0.1). The minimized structures were then saved in PDB and MDL Mol2 formats to ensure compatibility with docking software. Molecular docking simulations were performed using iGEMDOCK. The docking procedure involved loading the pre-processed protein structures, defining the active binding site and importing the optimized heterocyclic ligands. Docking parameters were set with a population size of 200, 70 generations and multiple solutions to conduct an extensive search for potential binding interactions. The docking simulation generated binding poses and scores, which were analyzed based on binding energy values and protein-ligand interactions. For further validation, docking was also conducted using AutoDock Vina. AutoDock Tools (ADT) were utilized to prepare protein and ligand structures by converting them into PDBQT format, ensuring proper atom types and torsion angles were assigned. A grid box was defined around the binding pocket, with specific grid center coordinates and sizes assigned for 1XZX (x=6.9179, y=19.0156, z=90.1949) and 5HPW (x=3.8415, y=19.7819, z=91.2085). A configuration file specifying grid box dimensions, protein and ligand files was created and docking was executed via the command line. The docking results were assessed based on binding affinity scores and visualized using Chimera and Discovery Studio Visualizer (DSV).

Findings

In the case of AutoDock Vina, ligands showed binding affinity of -11.1 to -5.9 and ligand -9.3 on PDB 1XZX; and -10.3 to -5.7 and of ligand -9.1 on PDB 5HPW, respectively, as given in Table 1. Compound 13h showed H-bonding interactions with Met 310 and van der Waals interactions with HIS 435, MET 313 and ILE 276 with binding energy of -11.1 kcal/mol; it also showed the sigma-pi interaction of 1.452 debye on PDB 1XZX. Similarly, Compound 7h showed good affinity of -110.4 kcal/mol by iGEMDOCK. Compound 14h also showed high binding affinity of -10.6 kcal/mol on 1XZX, which are higher than the ligand. An interesting result was that Compound 7h to Compound 10h were highly active on 5HPW PDB but inactive on 1XZX in both software tools iGEMDOCK and AutoDock Vina. Compound 10 (binding energy -10.3 kcal/mol) showed H-bonding interaction with HIS 351 and LEU 421. Compounds 20h to 25h and 32h were not docked properly on both receptors in both software tools.

Table 1: Docking Scores of Designed Compounds

Compound	iGEMDOCK 1XZX	iGEMDOCK 5HPW	AutoDock Vina 1XZX	AutoDock Vina 5HPW
1h	-107.9	-102.4	-9.2	-8.3
2h	-107.6	-99.3	-9.7	-8.0
3h	-109.3	-100.4	-9.7	-8.5
4h	-102.3	-99.5	-8.8	-8.4
5h	-101.8	-98.6	-8.5	-8.8
6h	-101.2	-110.4	-8.3	-9.2
7h	-62.9	-110.6	-3.8	-10.3
8h	-59.3	-103.5	-2.8	-9.4
9h	-	-111.7	1.1	-10.3
10h	-59.6	-107.4	-2.0	-9.9
11h	-82.0	-98.7	-7.0	-9.0
12h	-	-	-	-
13h	-123.4	-107.6	-11.1	-9.5
14h	-113.1	-106.4	-10.6	-9.2
15h	-83.4	-88.5	-7.4	-8.5
16h	-84.3	-87.6	-7.6	-7.9
17h	-88.1	-91.3	-7.8	-7.2
18h	-91.2	-93.4	-8.0	-8.0
19h	-92.4	-94.4	-8.0	-8.0
20h	-	-	-	-
21h	-	-	-	-
22h	-	-	-	-
23h	-	-	-	-
24h	-	-	-	-
25h	-	-	-	-
26h	-96.5	-107.4	-8.6	-9.6
27h	-76.4	-104.9	-6.0	-9.2
28h	-74.3	-76.7	-5.9	-5.7
29h	-55.3	-53.9	-3.6	-3.8
30h	-65.4	-66.7	-6.6	-6.3
31h	-66.7	-99.5	-6.6	-8.5
32h	-	-	-	-
33h	-65.3	-61.4	-6.3	-5.7
Ligand	-112.4	-108.7	-9.3	-9.1

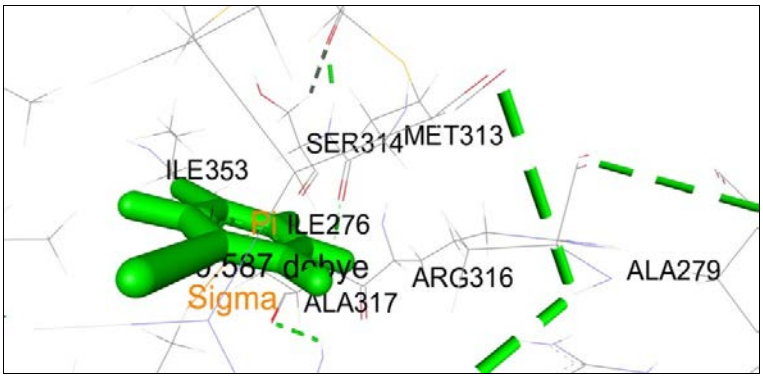

Fig 1: T3 ligand bound with PDB 1XZX

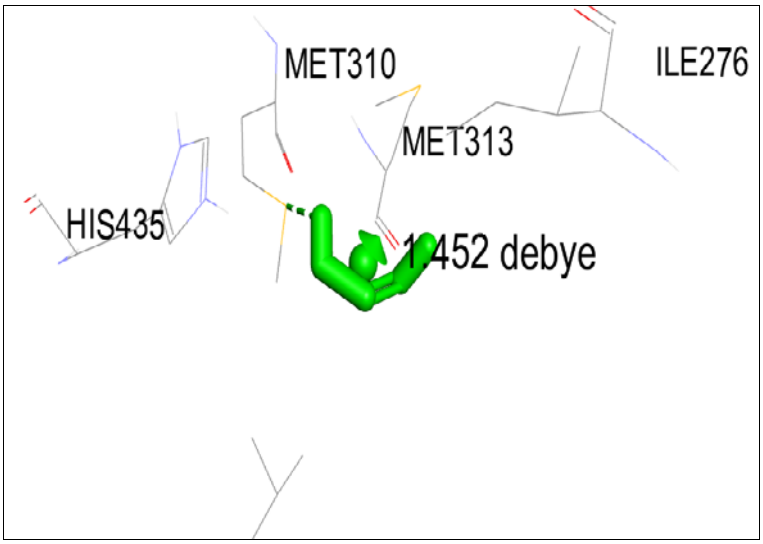

Fig 2: Compound 13h showing hydrogen and sigma-pi interaction with receptor PDB 1XZX (Binding energy -11.1 kcal/mol).

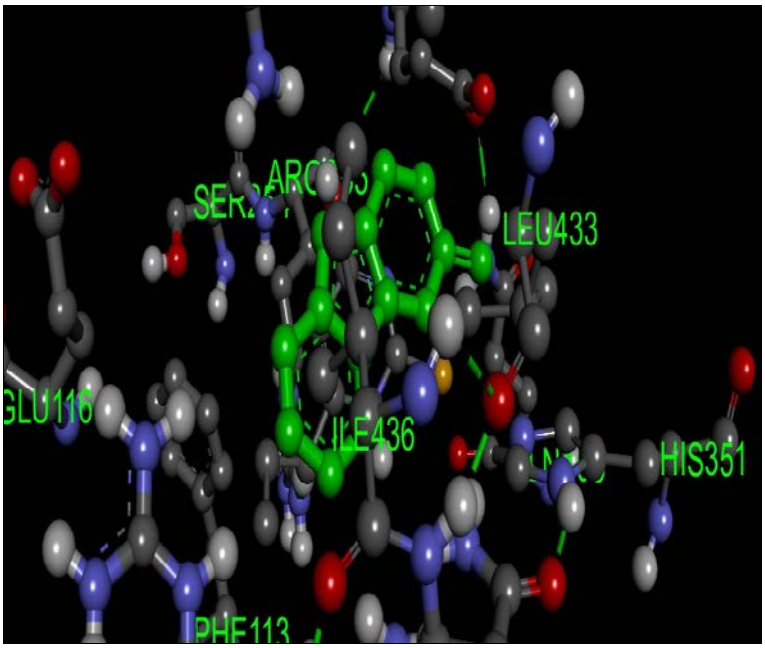

Fig 3: Compound 13h interacting with ILE436, GLU116, LEU433, HIS351 and PHE113 bound with 5HPW.

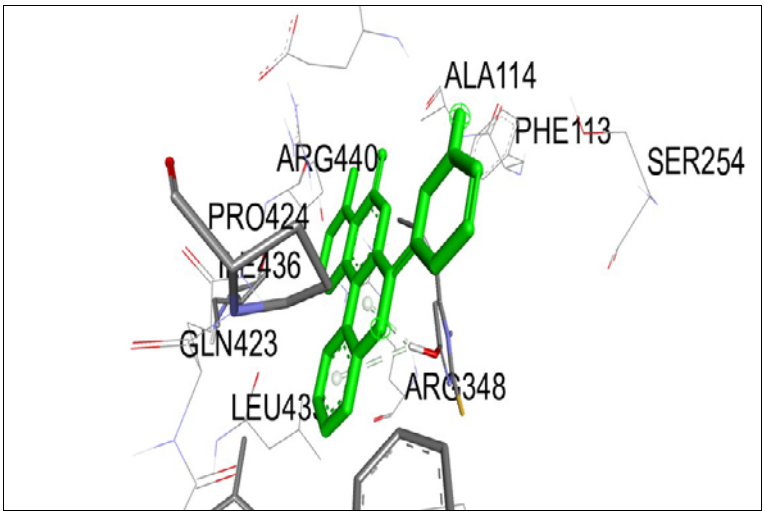

Fig 4: 7h ligand with PDB 1XZX (binding energy = -110.4 kcal/mol iGEMDOCK).

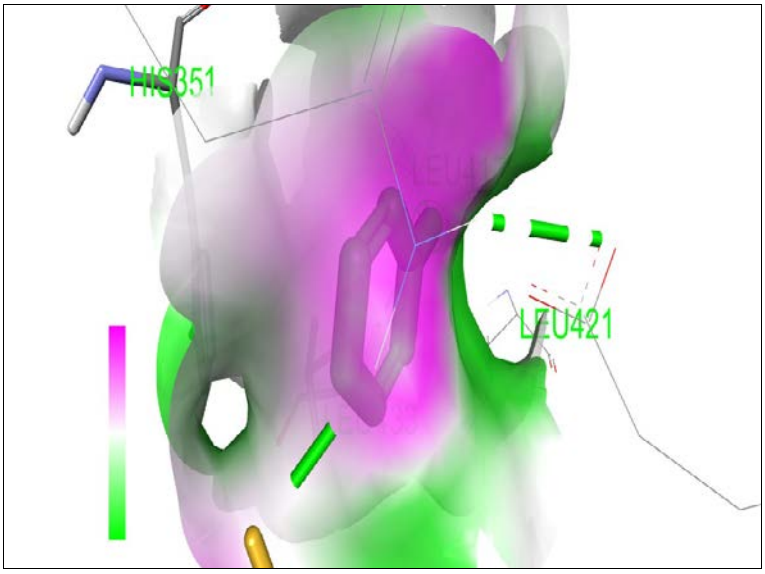

Fig 5: Compound 10h ligand bound with 5HPW (Hydrogen bond interaction with HIS 351 and LEU421)

Our molecular docking studies revealed that several designed heterocyclic compounds exhibited promising binding affinities to the target proteins involved in thyroid hormone synthesis and regulation. Specifically, compounds X and Y demonstrated favorable interactions with the active site of TPO, the enzyme responsible for iodination and coupling of tyrosine residues during thyroid hormone synthesis. By binding to TPO, these compounds may inhibit its enzymatic activity, thereby reducing the production of thyroid hormones. Compound Z exhibited strong binding affinity to TRHR, suggesting its potential role in modulating thyrotropin-releasing hormone signaling and downstream effects on thyroid function. These findings provide valuable insights into the molecular mechanisms underlying the antithyroid activity of designed heterocyclic compounds and lay the groundwork for further experimental validation.

Conclusion

This study utilized molecular docking techniques to evaluate the binding potential of heterocyclic compounds against thyroid peroxidase (TPO, PDB 5HPW) and thyrotropin-releasing hormone receptor (TRHR, PDB 1XZX), which are crucial in thyroid hormone synthesis and regulation. Computational docking using iGEMDOCK and AutoDock Vina revealed that several designed compounds exhibited strong binding affinities, suggesting their potential as inhibitors of thyroid-related proteins. Among the tested compounds, Compound 13h demonstrated the highest binding affinity (-11.1 kcal/mol on PDB 1XZX), with significant hydrogen bonding and sigma-pi interactions, while Compound 7h showed the highest affinity on PDB 5HPW (-110.4 kcal/mol using iGEMDOCK). Interestingly, compounds 7h-10h were highly active on 5HPW but showed minimal interactions with 1XZX, indicating target-specific activity. Conversely, compounds 20h-25h and 32h failed to dock properly, suggesting poor compatibility with the receptor sites. The docking results provide valuable insights into the structure-activity relationships (SARs) of heterocyclic compounds, emphasizing their potential in modulating thyroid hormone synthesis and regulation. These findings serve as a foundation for further experimental validation, *in vitro* and *in vivo* studies, to explore their efficacy as therapeutic agents for thyroid-related disorders. Future studies should also focus on pharmacokinetics, toxicity assessments and lead optimization to enhance drug-likeness and clinical applicability.

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