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Research Article

Molecular Docking: A Technique For Discovering Telomerase Inhibitors For Cancer Treatment

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ABSTRACT

Background:
The telomere is a distinct functional complex found at the ends of linear eukaryotic chromosomes, consisting of tandem repeat DNA sequences and related proteins. It is critical that linear eukaryotic genomes remain intact and stable. Telomere length maintenance and regulation have a function in both normal cell ageing and illness in humans.

Aim:
The primary goal of molecular docking is to achieve a ligand-receptor complex with optimal shape and lower binding free energy.

Method:
Predicts a ligand's binding affinity to a target protein molecule. It is a critical step in the in-silico drug design process, giving information regarding protein-ligand interactions in the form of binding affinity scores and binding poses.

Result:
The ligand docking tests indicated that the binding pocket comprises the amino acid residues ARG486, ILE550, MET482, ILE497, TYR551, LEU554, and PHE494.Finally, these compounds have demonstrated favorable interactions with telomerase.

Conclusion:
These findings suggest these derivatives might be used in future studies to develop novel anticancer drugs.

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INTRODUCTION

Molecular docking is an appealing scaffold to understand drug-bimolecular interactions for rational drug design and discovery, as well as in the mechanistic study by placing a molecule (ligand) into the preferred binding site of the target specific region of the DNA/protein (receptor) primarily in a non-covalent fashion to form a stable complex of potential efficacy and more specificity.1, 2 The telomere is a unique functional complex located at the ends of linear eukaryotic chromosomes that is composed of tandem repeat DNA sequences along with associated proteins. It is important to maintain the integrity and stability of linear eukaryotic genomes. Telomere length maintenance and control have a role in both normal cellular ageing and disease in humans. Telomeres are primarily synthesized by the cellular reverse transcriptase telomerase, an RNA-dependent DNA polymerase that adds telomeric DNA to telomeres. Cell immortalization and long-term tumour development typically require telomerase expression. Telomerase activity in humans is carefully regulated throughout development and oncogenesis. Telomerase activity regulation may thus have significant consequences for antiaging and anticancer therapy. 3 Telomeres are composed of up of a capping structure, which is a specialized nucleoprotein structure that includes DNA and shelterin protein complexes. Telomeric DNA has a variable number of G-rich, non-coding tandem repeats (10-15 kb in humans at birth) of double-stranded DNA sequence, 5′-(TTAGGG) n -3′, followed by a terminal 3′ G-rich single-stranded overhang (150-200 nucleotides long). The 3′ G-rich overhang helps telomeric DNA form a higher-order structure in which the 3′ single-stranded overhang folds back and invades the homologous double-stranded TTAGGG region, forming a telomeric loop (T-loop) that protects the 3′-end by sequestering it from recognition by the DDR machinery.4

Molecular Docking Study:

5CQG Structure of Tribolium telomerase in complex with the highly specific inhibitor BIBR1 BIBR1532 inhibits telomerase with excellent specificity, although the chemical mechanism remains unexplained. We describe the crystal structure of BIBR1532 bonded to Tribolium castaneum for catalytic activity. The telomerase component (tcTERT). BIBR1532 interacts with a conserved hydrophobic pocket (FVYL motif) on the thumb domain's outer surface. The FVYL motif is found near TRBD residues that bind to the activation domain (CR4/5) of hTER. In vitro, RNA binding experiments indicate that the human TERT (hTERT) thumb domain binds to the P6.1 stem loop of CR4/5. hTERT mutations in the FVYL pocket disrupt wild-type CR4/5 binding and result in cell telomere erosion. The hTERT FVYL variants V1025F, N1028H, and V1090M have been linked to dyskeratosis congenita and aplastic anaemia, highlighting their biological and clinical importance.5 Pyrimidine, a nitrogen-containing synthetic and physiologically relevant heterocyclic ring system, has both biological and pharmacological activity and is classified as an aromatic six heterocyclic with one and three nitrogen atoms in the ring. The preparation of pyrimidine via various methods is important in the disciplines of medical chemistry and chemistry. Pyrimidines and its derivatives operate as anti-inflammatory, anti-malarial, anti-tumor, cardiovascular agents, anti-neoplastic, anti-tubercular, anti-HIV, diuretic, antiviral, antimicrobial, and analgesic.6

MATERIALS AND METHODS:

1. Protein Preparation:

Protein preparation is the process of optimizing the protein structure and making it suitable for precision docking simulations. It is an important

stage in the molecular docking process. The protein structure is first retrieved from a database such as Protein Databank (PDB) or generated using molecular modeling software such as SWISS MODELLER. The structure is then finished by adding any remaining atoms or residues. The protein is then subjected to energy minimization to relax its structure and eliminate any steric interference. The protonation states of ionizable residues are then determined in order to provide appropriate electrostatic contacts during docking. To simplify the system further, water molecules and unnecessary ligands are removed from the protein structure. To accurately portray the protein's behavior during docking.7

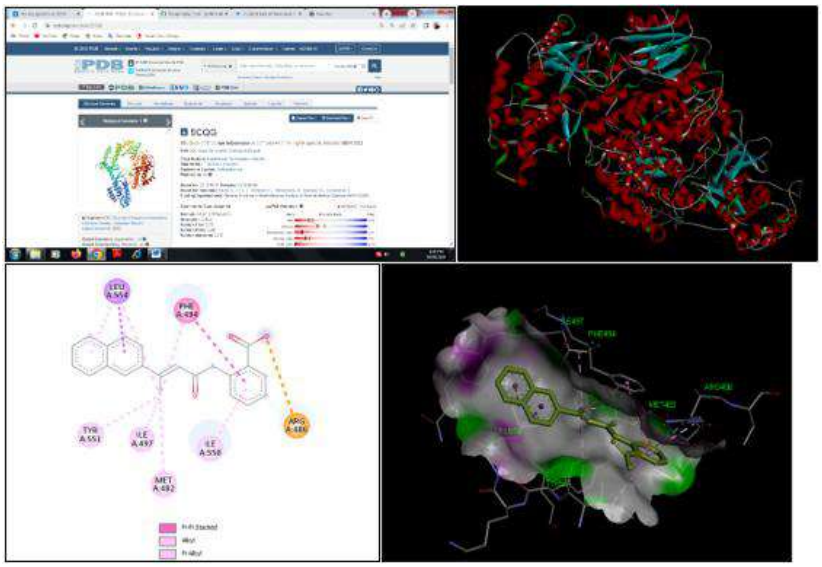


Figure 1: 5cqg obtained from Protein Databank (PDB)

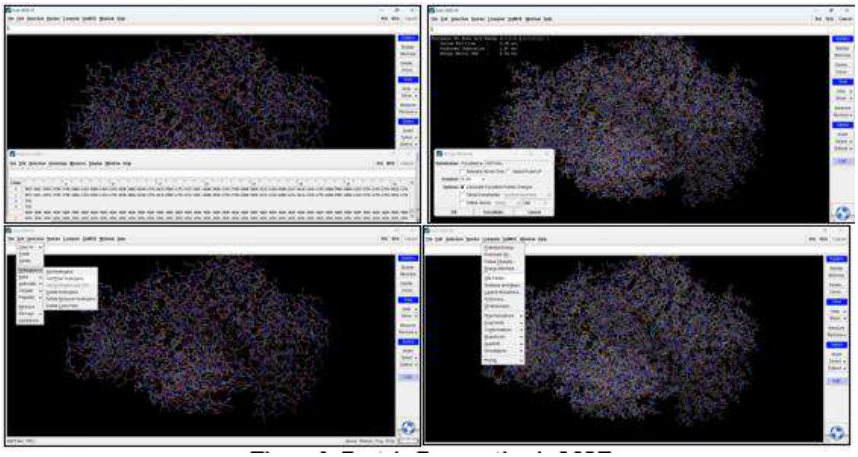


Figure 2: Protein Preparation in MOE

2. Active site: Determination in MOE

The binding pockets can be defined before docking. As a result, three distinct ways to validating the binding pocket of interest during molecular docking can be proposed 8, as shown below.

i. **Site-directed docking.**

First, locate the protein-ligand binding site, and then dock the ligand.

ii. **Blind docking**.

The docked ligand is placed directly onto the entire receptor structure, with no prior knowledge of the binding site. 9

iii. **Docking with the standard**

Here, you dock the protein with the test ligands and/or standard small molecule(s). The standard ligand aids in the prediction of the appropriate binding pocket.10

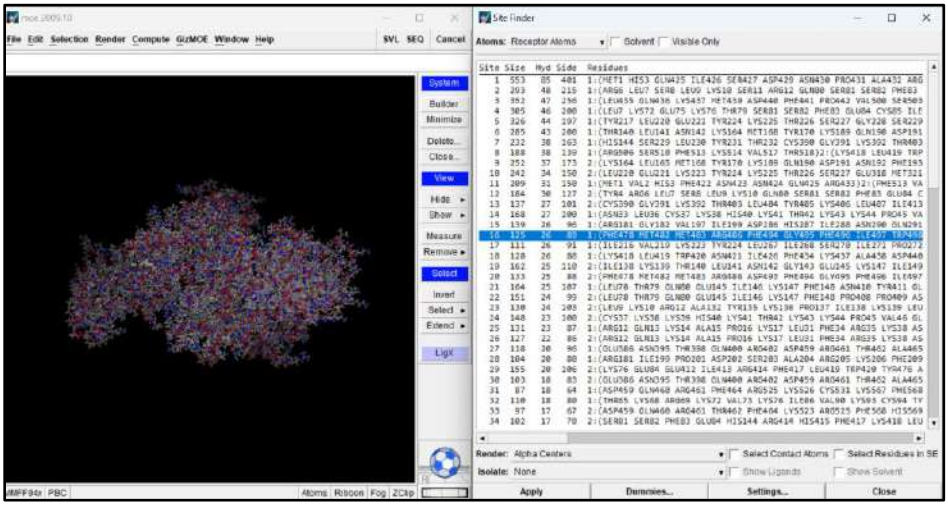


Figure 3:Active site determination

3. Preparation of Ligand:

All chalcone derivatives were sketched in a chem draw and saved in mol format, then a new database was created, and all structures were added and energy was minimized.

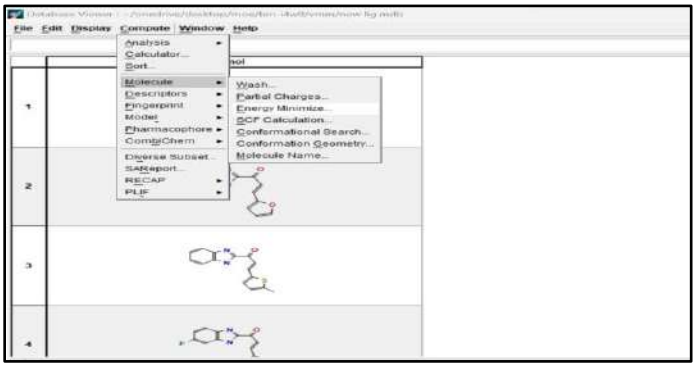
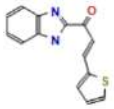
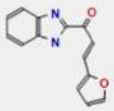
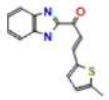
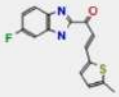
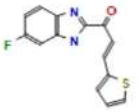
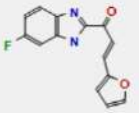
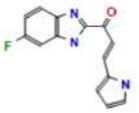
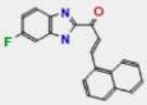
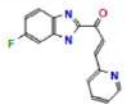
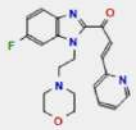
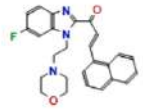
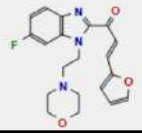
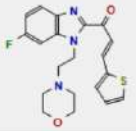


Figure 4: Preparation of Ligand

Table 1: Physicochemical Properties

	mol	a_acc	a_don	SlogP	Weight
1		3.0000	2.0000	3.5205	254.313
2		3.0000	2.0000	3.0520	238.246
3		3.0000	2.0000	3.8289	268.340
4		3.0000	2.0000	3.9680	286.330
5		3.0000	2.0000	3.6596	272.303
6		3.0000	2.0000	3.1911	256.236
7		3.0000	3.0000	2.9262	255.252
8		3.0000	2.0000	4.7513	316.335

9		4.0000	2.0000	2.9931	267.263
10		5.0000	0.0000	3.0651	380.423
11		4.0000	0.0000	4.8233	429.495
12		4.0000	0.0000	3.2631	369.396
13		4.0000	1.0000	2.9982	368.412
14		4.0000	0.0000	3.7316	385.463
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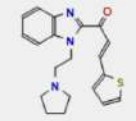
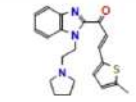
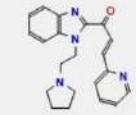
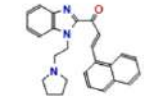
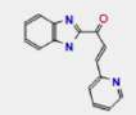
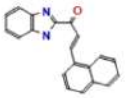
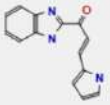
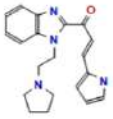
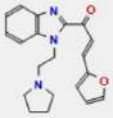
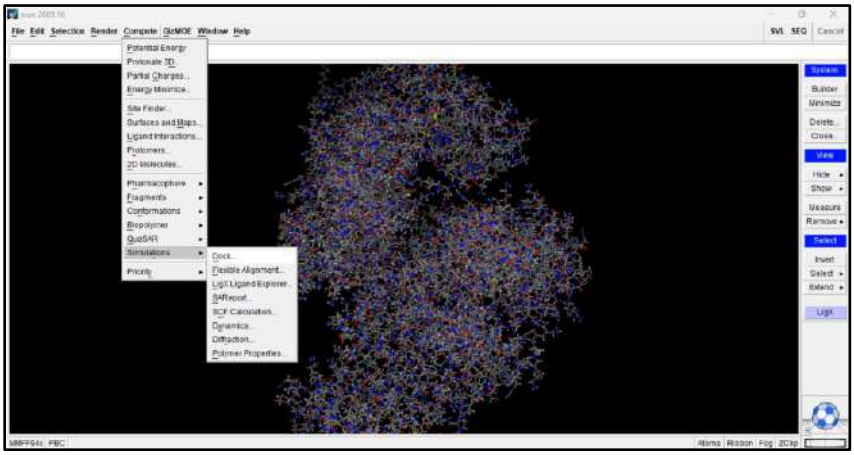
16		3.0000	0.0000	4.3561	351.474
17		3.0000	0.0000	4.6645	365.501
18		4.0000	0.0000	3.6896	346.434
19		3.0000	0.0000	5.4478	395.506
20		4.0000	2.0000	2.8540	249.273

21		3.0000	2.0000	4.6122	298.345
22		3.0000	3.0000	2.7871	237.262
23		3.0000	1.0000	3.6227	334.423
24		3.0000	0.0000	3.8876	335.407

RESULT AND DISCUSSION:

Docking Score:

The ligand is docked against the protein and its interactions are examined. The scoring function returns a score based on the best-docked ligand complex selected.11 After the ligands have been docked to the protein, the findings are analyzed to determine the most promising candidates for future research. Each ligand's binding affinity is computed using the expected interaction energy, and the ligands are ordered accordingly. The docked structures are also examined to determine important interactions between the ligands and the protein, such as hydrogen bonds, hydrophobic interactions, and electrostatic interactions. These interactions can provide insights into the ligands' mechanisms of action and enable further optimization of their structure.12



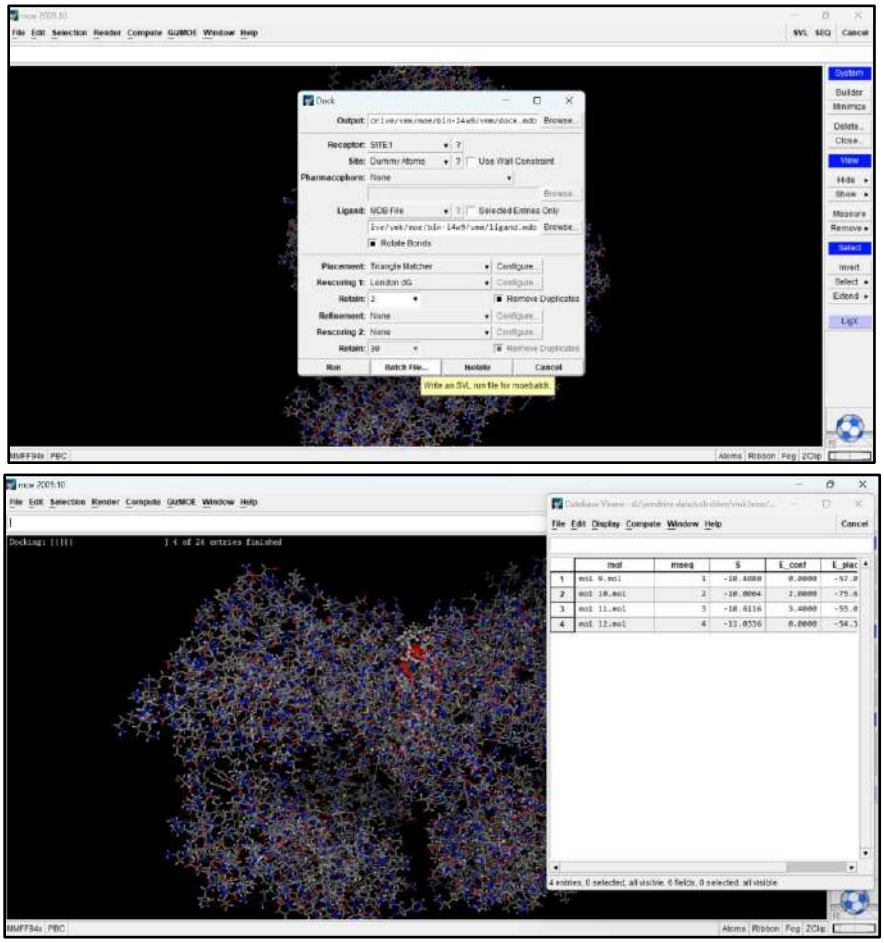


Figure 5: Molecular Docking with Dock Module in MOE

Table 2: Docking Score

Mol. No	Docking Score
1	10.243
2	-10.656
3	-11.102
4	-11.169
5	-10.579
6	-10.533
7	-10.977
8	**-12.396**
9	-10.867
10	-11.517
11	**-12.053**
12	-11.314
13	-11.170
14	-11.475
15	-11.109
16	-11.017
17	-11.512
18	-10.760
19	-11.463
20	-10.775

21	-11.208
22	-10.098
23	-10.822
24	-11.129
Inbound Ligand	-12.33

5. Docking Interaction:

The primary goal of molecular docking is to achieve a ligand-receptor complex with optimal shape and lower binding free energy. The anticipated binding free energy (ΔGbind) is based on several characteristics, including hydrogen bond (ΔGhbond), electrostatic (ΔGelec), torsional free energy (ΔGtor), dispersion and repulsion (ΔGvdw), desolvation (ΔGdesolv), total internal energy (ΔGtotal), and unbound system's energy (ΔGunb). Understanding the ethics of anticipated binding free energy (ΔGbind) can shed light on the nature of interactions that contribute to molecular docking.13

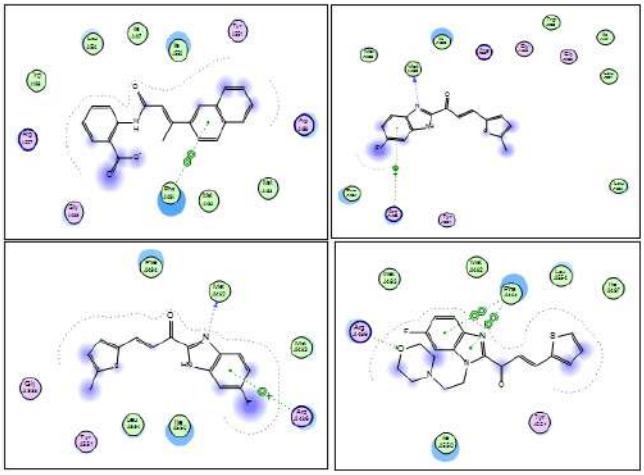


Figure 6: Interaction of Inbound Ligand and New Derivatives with 5cqg

CONCLUSION:

The ligand docking experiments revealed that the binding pocket contains the amino acid residues ARG486, ILE550, MET482, ILE497, TYR551, LEU554, PHE494.Finally, these derivatives have shown good interactions with telomerase, and in the future, it can be considered for synthesis in the development of new, less toxic, and more effective drugs for the treatment of cancer.

ACKNOWLEDGEMENT:

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