Docking studies of benzimidazole derivatives on Telomerase target for screening of anti-cancer activity

Vidya K.Magar[1*], Karna Khavane[2], Pallavi Bhosale[1], Suvarna Bhokare[1], Anita Wagh[1], Poonam Sable[1], Prashant Jadhav[1], Monika Madibone[1]

1. Srinath College of Pharmacy, Chh. Sambhajinagar (Aurangabad), Maharashtra, India.
2. Dr.Vedprakash Patil Pharmacy College, Chh.Sambhajinagar (Aurangabad), Maharashtra, India.

Correspondence Author:
Dr.Vidya K.Magar,
Srinath college of Pharmacy,
Bajaj Nagar, Waluj, Aurangabad, Wadgaon Kolhati, Maharashtra 431136

Abstract:

The telomere is a functional complex situated on the tip of chromosomes in eukaryotic organisms that includes tandem repeat DNA sequences together with associated proteins. Straight eukaryotic genomes have to maintain their structural integrity and stability. Telomere length tracking and oversight. play a role in both normal cell ageing and disease progression in humans. Docked structures have been employed for finding significant interactions between ligands and proteins, including as hydrogen bonds, hydrophobic interactions, and electrostatic interactions.

Interactions between ligands may demonstrate their processes of action and aid in structural optimisation. According to ligand docking tests, the binding pocket contains the amino acids ARG486, ILE550, MET482, ILE497, TYR551, LEU554, and PHE494. These compounds have

favourable interactions with telomerase and may be utilised in the future to develop innovative, less harmful

Introduction:

In recent years, molecular docking has been recognised as an essential component of in-silico development of drugs. The approach involves predicting the atomic interaction of a small biological molecule with a protein.[1]

Modern docking systems effectively in search high-dimensional subjects by employing a scoring algorithm commonly to accurately evaluate potential dockings. Docking may be used for conducting simulated displays on massive collections of compounds, grade the findings, and produce structural recommendations about how the ligands block the target, which is particularly valuable in lead development..[2]

Cancer is essentially an age-related genetic illnesses which happens when normal cells undergo genomic instability over time and obtain the ability to spread continuously. Telomere attrition occurs after repeated cell divisions, increasing chromosomal instability and significantly contributing to genomic rearrangements that might contribute to developing cancer.[3]

Telomerase expression is tightly controlled in normal cells. On the one conjunction, by transcription management, alternative translation, and environmental modification; on the different hand, by limitations on access to the chromosomal ends.[4]

Telomerase is a unique reverse transcriptase which needs the following two parts: the RNA templates (hTR) and the subunit responsible for catalysis (hTERT). Both components have been utilised as telomerase inhibitors. The first significant example has been presented in 1995, when a type of RNA called antisense addressing the first 185 nucleotide of the hTR molecule had been introduced into HeLa cells, causing forward-looking telomere shortening and ultimately cell a tragedy.[5]

Benzimidazoles are important intermediates in the production of new chemical substances with biological or therapeutic properties. Substituted benzimidazole derivatives have been developed.

Biological activities include antitumor, antimicrobial, anthelmintic, antibacterial, analgesic, and anti-inflammatory defining features.[6-11]

Material and Method:

The telomerase a type of ribonucleoprotein (RNP) reverse transcriptase, duplication chromosomal ends and guarantees genomic integrity. The tcTERT structure is composed of four individual domains (TRBD, fingers, palm, and thumb) organised in a ring, giving a large central cavity for RNA template and telomeric DNA binding during chromosome extension.[12]

The three-dimensional crystal arrangement of telomerase (PDB ID: 5CQG) utilised during assessment was extracted from the RCSB proteins database.

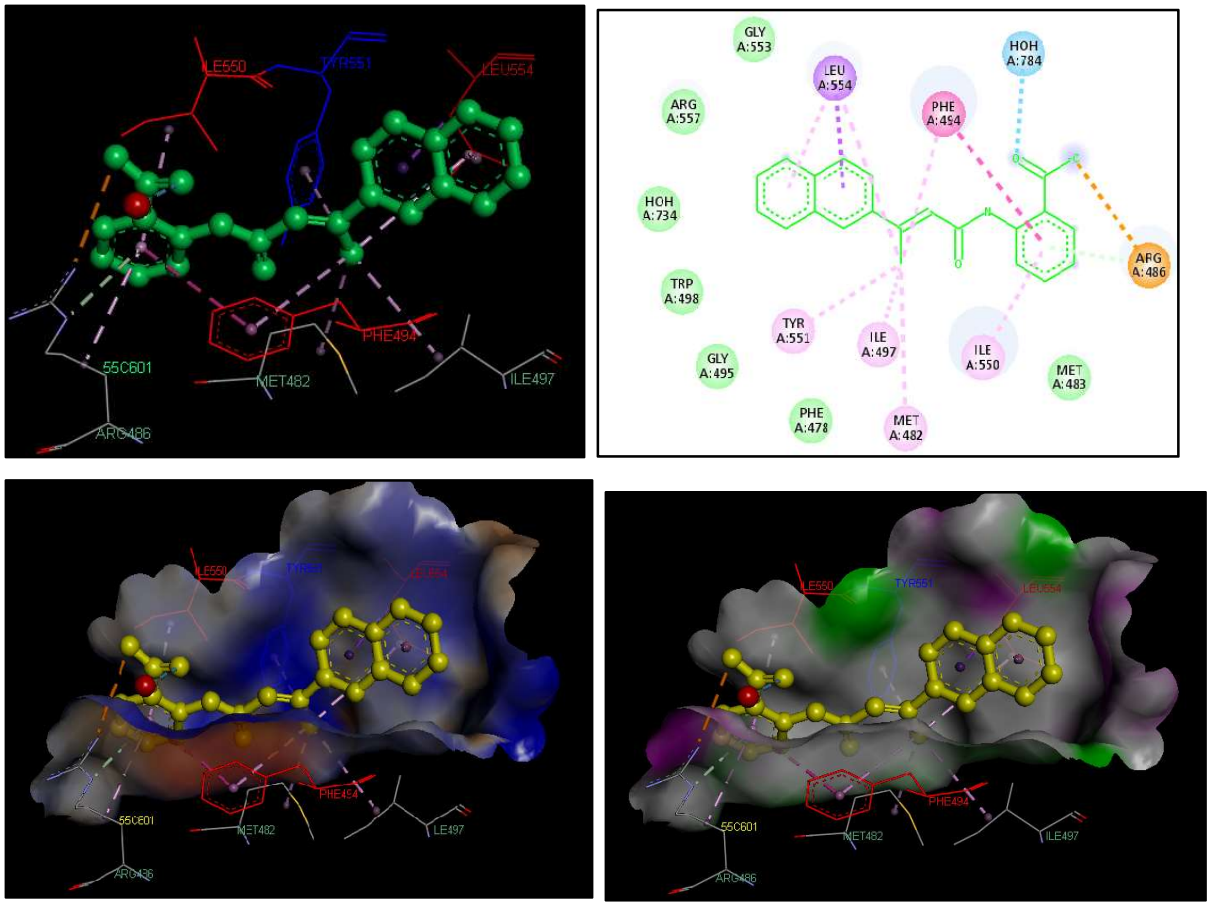


Fig.1. 5CQG Structure of Tribolium telomerase in complex with the highly specific inhibitor BIBR1

1. Preparation of protein structure

Proteins preparations are the process of improving a protein's structure so that it may be employed in precision docking simulations. It's an essential the stage in the molecule docking process. The protein structure must either be retrieved from a database, such as the Protein Databank (PDB), or developed with molecular modelling software, such as SWISS MODELLER. The assembly is then completed by adding the remaining atoms or residues. The protein is after that subjected to energy minimisation in order to relax its structure and eliminate steric hindrance. The protonation statuses of ionisable residues are subsequently evaluated in order to ensure correct electrostatic interactions during docking. To simplify the system even further, water molecules and unimportant ligands are removed from the protein structure. To precisely characterise the protein's behaviours when docking.[13]

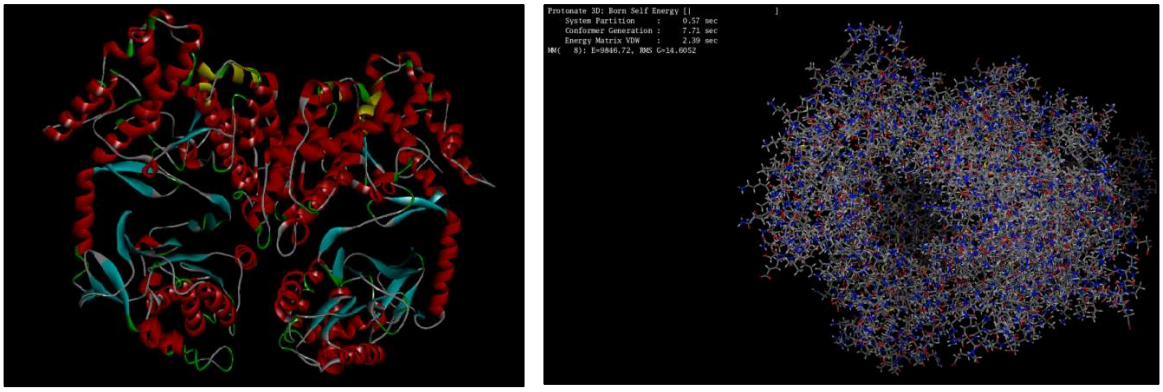
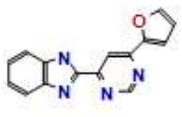
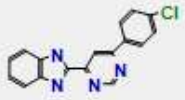
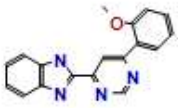
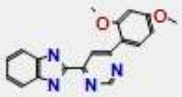
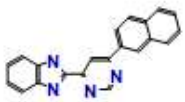


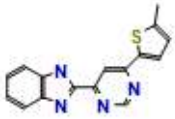
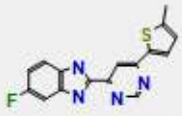
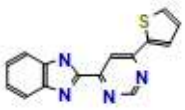
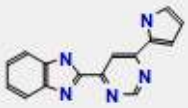
Fig.2. Protein Preparation in MOE

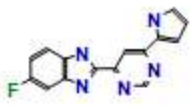
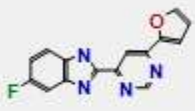
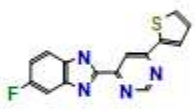
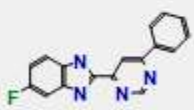
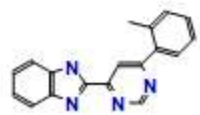
Preparation of the ligand structures

All benzimidazole derivatives have been generated in ChemDraw and saved in mol format, adhering to which a new database had been established with all structures added and energy reduced.

Table.1. Physicochemical Properties

	mol	a_acc	a_don	logP(o...	Weight
1		4.000	2.0000	1.9311	262.272
2		4.000	2.0000	3.8081	306.756
3		5.000	2.0000	3.1701	302.337
4		6.000	2.0000	3.1631	332.363
5		4.000	2.0000	4.4751	322.371

6		5.000	2.0000	2.1406	273.299
7		4.000	2.0000	2.9231	292.366
8		4.000	2.0000	3.1131	310.356
9		4.000	2.0000	2.7461	278.339
10		4.000	3.0000	2.3076	261.288

11		4.000	3.0000	2.4976	279.278
12		4.000	2.0000	2.1211	280.262
13		4.000	2.0000	2.9361	296.329
14		4.000	2.0000	3.4061	290.301
15		4.000	2.0000	3.5121	286.338

Binding site prediction

They are basically hydrophobic pockets inside a protein or enzyme that hold side chain atoms. They act resemble a pocket, allowing ligands to bind and respond in curing illnesses. Protein 3D structure prediction is critical for determining active sites. An active site consists of both the binding site and the catalytic side.

Active Site Determination with MOE Site Finder

To locate active sites in proteins, the minimal interaction energy between receptors and ligands or probes must be calculated. This requires assigning proton locations and partial charges to receptors, which can be challenging. To address this, we have discussed the Geometry Method.

a. Identify the areas where atoms are firmly packed.

b. Remove locations that are highly exposed to solvents.

c. Use hydrophobic and hydrophilic categories.

d. Avoid using grid-based approaches as they are memory-intensive and not rotation-invariant.

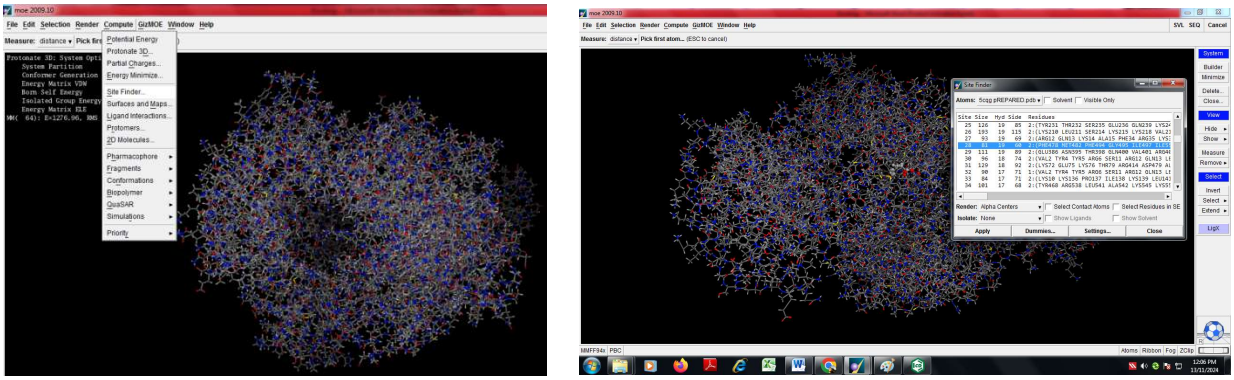


Fig.3. Active site determination

Result and Discussion:

Molecular Docking:

The ligand is docked against the protein, and its interactions are investigated. The scoring function generates a score based on the best-docked ligand complex identified. After docking the ligands to the protein, the outcomes are evaluated to choose the most promising candidates for further exploration. Each ligand's binding affinity has been calculated using the expected interaction energy, and the ligands are ranked proportionally. The docked structures are further investigated to discover significant connections between ligands and proteins, such as hydrogen bonds, hydrophobic interactions, and electrostatic interactions. These

interactions might offer insight into the ligands' strategies of action and enable further structural optimisation.[14-15]

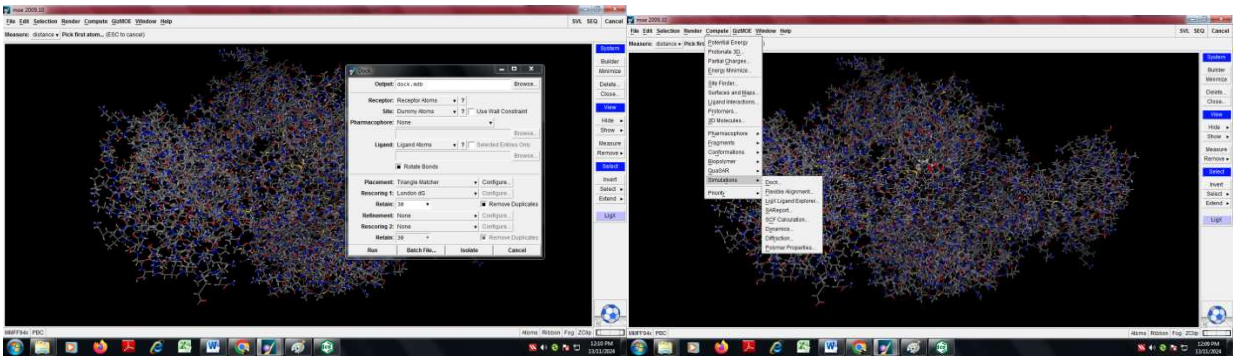


Fig.4. Molecular Docking with Dock Module in MOE

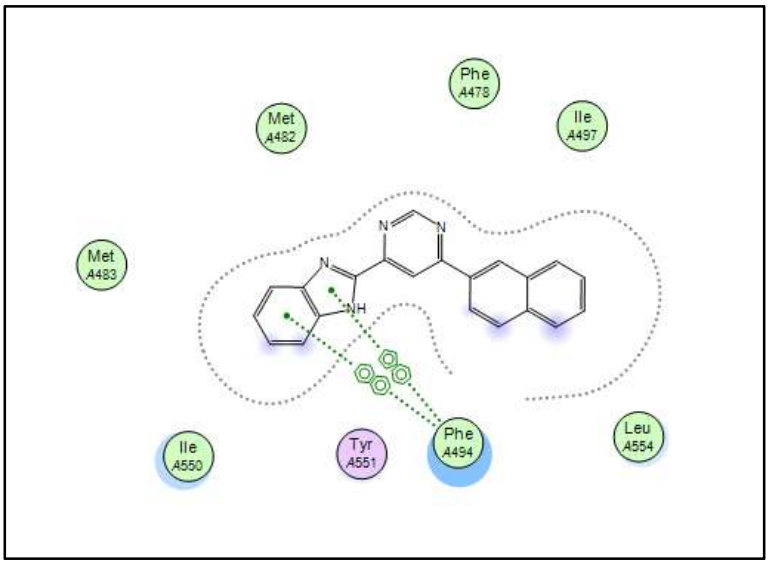
Table.2. Docking Score

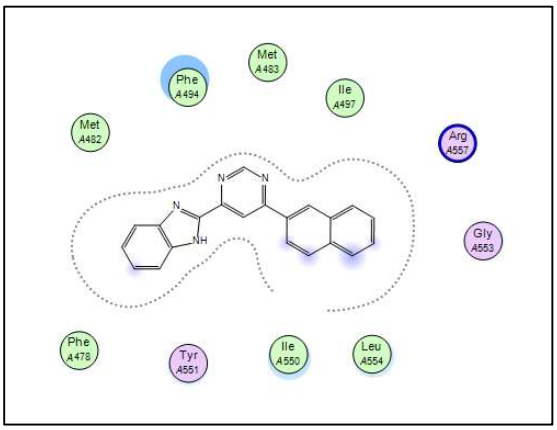
Mol. No	Docking Score
1.	-11.04874
2.	-12.46449
3.	-11.49572
4.	-11.9465
5.	-12.65881
6.	-11.32641
7.	-11.61937
8.	-12.07358
9.	-11.0653
10.	-11.35336
11.	-11.7648
12.	-11.79228
13.	-11.69419
14.	-12.0047
15.	-11.8939

Inbound Ligand	-12.33

5. Docking Interaction:

The basic purpose of molecular docking is to design a ligand-receptor complex with the best shape and lowest binding free energy. The predicted binding free energy (ΔGbind) is based on numerous properties, 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 change of predicted binding free energy (ΔGbind) can provide insight into the interactions that lead to molecular docking.[16]





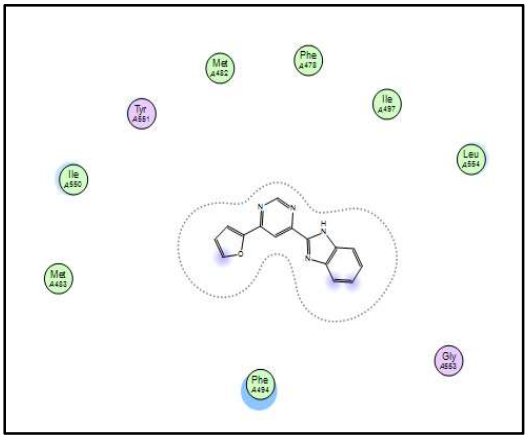


Fig .5. Interaction of Inbound Ligand and New Derivatives with 5cqg

Conclusion:

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, and they may be used in the future to generate novel, less toxic, and more effective cancer treatments.

References:

1. AGU, P. C., et al. Molecular docking as a tool for the discovery of molecular targets of nutraceuticals in diseases management. *Scientific Reports*, 2023, 13.1: 13398.
2. Morris GM, Lim-Wilby M. Molecular docking. Methods Mol Biol. 2008;443:365-82. doi: 10.1007/978-1-59745-177-2_19. PMID: 18446297.
3. Jafri, M.A., Ansari, S.A., Alqahtani, M.H. *et al.* Roles of telomeres and telomerase in cancer, and advances in telomerase-targeted therapies. *Genome Med* **8**, 69 (2016). https://doi.org/10.1186/s13073-016-0324-x
4. PHILIPPI, C., et al. Telomerase as an emerging target to fight cancer—Opportunities and challenges for nanomedicine. *Journal of controlled release*, 2010, 146.2: 228-240.
5. HSU, Yi-hsin; LIN, Jing-jer. Telomere and telomerase as targets for anti-cancer and regeneration therapies. *Acta Pharmacologica Sinica*, 2005, 26.5: 513-518.
6. Galal SA, Abdelsamie AS, Rodriguez ML, Kerwin SM, El Diwani HI. Synthesis and studying the antitumor activity of novel 5-(2-methylbenzimidazol-5-yl)- 1,3,4-oxadiazole-2(3H)-thiones. Eur J Chem 2010;1:67–72.
7. Nguyen PT, Baldeck JD, Olsson J, Marquis RE. Antimicrobial actions of benzimidazoles against oral streptococci. Oral Microbiol Immunol 2005:93–100.
8. Townsend L, Wise D. The synthesis and chemistry of certain anthelmintic benzimidazoles. Parasitol Today 1990;6:107–12.
9. Hasan K, Riza D, Nihat S, Gunal S. Synthesis of some benzimidazole derivatives and their antibacterial and antifungal activities. Asian J Chem 2009;21:6181–9.
10. Dixit S, Kumar Sharma P, Kaushik N. Synthesis of novel benzimidazole derivatives: as potent analgesic agent. Med Chem Res 2013;22:900–4.

11. Desai NC, Dodiya AM, Shihory NR. A search of novel antimicrobial based on benzimidazole and 2-pyridone heterocycles. Med Chem Res 2012;21:2579–86.
12. Bryan C, Rice C, Hoffman H, Harkisheimer M, Sweeney M, Skordalakes E. Structural Basis of Telomerase Inhibition by the Highly Specific BIBR1532. Structure. 2015 Oct 6;23(10):1934-1942. doi: 10.1016/j.str.2015.08.006. Epub 2015 Sep 10. PMID: 26365799; PMCID: PMC4598299.
13. Chaudhary, K. K. & Mishra, N. A review on molecular docking: Novel tool for drug discovery. *JSM Chem.* **4**(3), 1029 (2016).
14. Torres, P. H. M., Sodero, A. C. R., Jofily, P. & Silva-Jr, F. P. Key topics in molecular docking for drug design. *Int. J. Mol. Sci.* **20**(18), 4574 (2019).
15. Pinzi, L. & Rastelli, G. Molecular docking: Shifting paradigms in drug discovery. *Int. J. Mol. Sci.* **20**, 4331 (2019).
16. Agarwal S, Chadha D, Mehrotra R (2015) Molecular modeling and spectroscopic studies of semustine binding with DNA and its comparison with lomustine–DNA adduct formation. J Biomol Struct Dyn 33: 1653-1668.
17. Agu PC, Afiukwa CA, Orji OU, Ezeh EM, Ofoke IH, Ogbu CO, Ugwuja EI, Aja PM. Molecular docking as a tool for the discovery of molecular targets of nutraceuticals in diseases management. Scientific Reports. 2023 Aug 17;13(1):13398.
18. Skariyachan S, Garka S. Exploring the binding potential of carbon nanotubes and fullerene towards major drug targets of multidrug resistant bacterial pathogens and their utility as novel therapeutic agents. InFullerens, Graphenes and Nanotubes 2018 Jan 1 (pp. 1-29). William Andrew Publishing.
19. Morris GM, Lim-Wilby M. Molecular docking. Molecular modeling of proteins. 2008:365-82.