BIOINFORMATION
Discovery at the interface of physical and biological sciences

OPEN ACCESS GOLD

BIOMEDICAL INFORMATICS

www.bioinformation.net
Volume 17(1)

Research Article

Molecular docking of potential inhibitors with the mTOR protein

JH Shazia Fathima[1], Jayaraman Selvaraj J[2*], Venkatacalam Sivabalan[3], Umapathy Vidhya Rekha[4], Rajagopal Ponnulakshmi[5], Veeraraghavan Vishnupriya[2], Malathi Kullappan[6], Radhika Nalinakumari Sreekandan[7], Surapaneni Krishna Mohan[8], Periyasamy Vijayalakshmi[9]

[1]Department of Oral and Maxillofacial Pathology, Ragas Dental College and Hospitals, Chennai, India; [2]Department of Biochemistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai - 600 077, India [3]Department of Biochemistry, KSR Institute of Dental Sciences and Research, Thiruchengodu-637215, India; [4]Department of Public Health Dentistry, Sree Balaji Dental College and Hospital, Pallikaranai, Chennai-600 100, India; [5]Central Research Laboratory, Meenakshi Academy of Higher Education and Research (Deemed to be University), Chennai-600 078, India; [6]Department of Research, Panimalar Medical College Hospital & Research Institute, Varadharajapuram, Poonamallee, Chennai - 600 123, India; [7]Department of Clinical Skills & Simulation, Panimalar Medical College Hospital & Research Institute, Varadharajapuram, Poonamallee, Chennai - 600 123, India; [8]Department of Biochemistry and Department of Clinical Skills & Simulation, Department of Research, Panimalar Medical College Hospital & Research Institute, Varadharajapuram, Poonamallee, Chennai - 600 123; [9]DBT-BIF Centre, PG & Research Department of Biotechnology & Bioinformatics, Holy Cross College (Autonomous), Trichy, Tamilnadu, India; ***Corresponding Author:** Dr. Jayaraman Selvaraj - E-mail: jselvaendo@gmail.com

Author contacts:
Shazia Fathima JH-shaziafathimarizwan@gmail.com; Selvaraj Jayaraman - jselvaendo@gmail.com; Umapathy Vidhya Rekha-drvidhyarekha@gmail.com; Venkatacalam Sivabalan-biosivabalan@gmail.com; Rajagopal Ponnulakshmi-ramgslaks@gmail.com; Veeraraghavan Vishnupriya-drvishnupriyav@gmail.com; Malathi Kullappan-malak.hari@gmail.com; Radhika Nalinakumari Sreekandan-niharakrishna21@gmail.com; Surapaneni Krishna Mohan -krishnamohan.surapaneni@gmail.com

Received December 29, 2020; Revised December 31, 2020; Accepted January 26, 2021, Published January 31, 2021

DOI: 10.6026/97320630017212

Declaration on Publication Ethics:
The author's state that they adhere with COPE guidelines on publishing ethics as described elsewhere at https://publicationethics.org/. The authors also undertake that they are not associated with any other third party (governmental or non-governmental agencies) linking with any form of unethical issues connecting to this publication. The authors also declare that they are not withholding any information that is misleading to the publisher in regard to this article.

Author responsibility:
The authors are responsible for the content of this article. The editorial and the publisher have taken reasonable steps to check the content of the article in accordance to publishing ethics with adequate peer reviews deposited at PUBLONS.

Declaration on official E-mail:
The corresponding author declares that official e-mail from their institution is not available for all authors

©Biomedical Informatics (2021)

BIOINFORMATION
Discovery at the interface of physical and biological sciences

OPEN ACCESS GOLD
OPEN ACCESS GOLD
OPEN ACCESS GOLD
OPEN ACCESS GOLD

Abstract:
The mTOR (mammalian or mechanistic Target of Rapamycin) is linked with oral cancer. Therefore, it is of interest to study the molecular docking-based binding of paclitaxel (a FDA approved drug for oral cancer) and its analogues with mTOR. Hence, we report the binding features of 10-Deacetyltaxol, 7-Epi-10-deacetyltaxol, 7-Epi-Taxol and 6alpha-Hydroxypaclitaxel with mTOR for further consideration.

Keywords: mTOR, paclitaxel, analogues, molecular docking, oral cancer.

Background:
The mTOR (mammalian or mechanistic Target of Rapamycin) is linked with oral cancer **[1-8].** Therefore, it is of interest to study the molecular docking-based binding of paclitaxel (a FDA approved drug for oral cancer) and its analogues with mTOR.

Materials and Methods

Ligand preparation
Structure of paclitaxel and its 10 analogues were downloaded from PUBCHEM database in SDF format (Table 1).

Protein Preparation
A crystal structure of mTOR (PDB ID: 4JSV) was downloaded from the Protein Data Bank (PDB).

Molecular Docking
Molecular docking analysis has been performed using the Autodock module available in PyRx Version 0.8 [9-10] and visualized by PyMOL [11].

Table 1: List of selected paclitaxel analogues

S. No	Compound Name
1	6alpha-Hydroxypaclitaxel
2	7-Epi-10-deacetyltaxol
3	7-Epi-Taxol
4	10-Deacetyltaxol
5	Cabazitaxel
6	docetaxel trihydrate
7	Larotaxel
8	Paclitaxel-d5
9	Taxol C
10	Taxotere

Table 2: Molecular docking results of paclitaxel and its analogues

S. No	Compound Name	Binding energy kcal/mol	Hydrogen bond interaction	Distance A°
1	Paclitaxel	-6.8	GLY-2203	2
			ARG-2224	2.3
			THR-2207	2.5
Selected best analogues				
1	10-Deacetyltaxol	6.7	THR-2207	2.3
			SER-2221	2.5
			ARG-2224	2.6
2	7-Epi-10-deacetyltaxol	-6.6	SER-2221	2.4
			ARG-2224	2.1
			LYS-2352	2.8
3	7-Epi-Taxol	-5.8	ASP-2212	2
			THR-2214	1.7
4	6alpha-Hydroxypaclitaxel	-5.4	SER-2221	2.4
			ARG-2224	2.2

©Biomedical Informatics (2021)

BIOINFORMATION
Discovery at the interface of physical and biological sciences

OPEN ACCESS GOLD

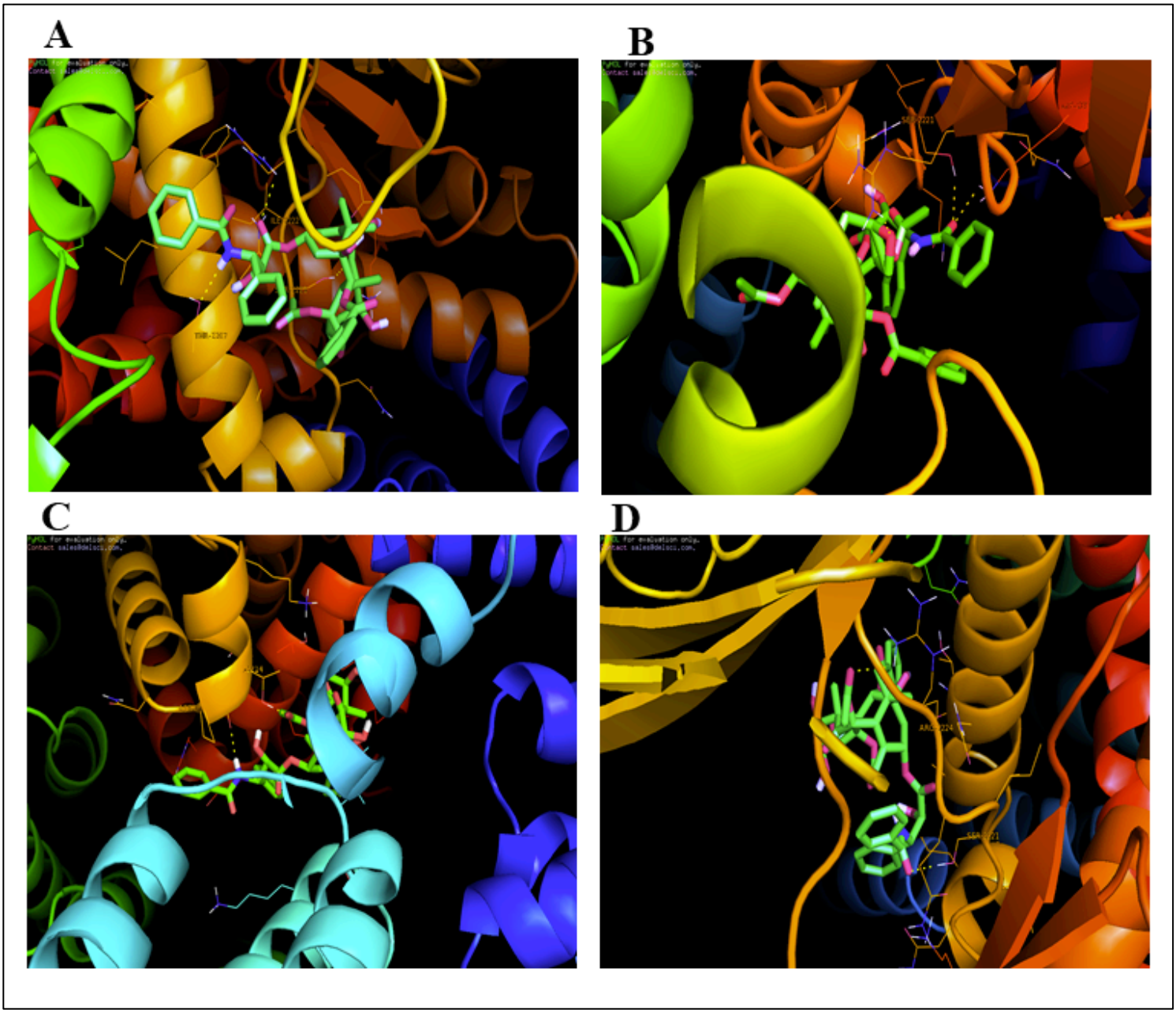


Figure 1: Molecular docking interaction of mTOR with (a) 10-deacetyltaxol; (b) 7-epi-10-deacetyltaxol; (c) 7-epi-taxol; (d) 6-alpha-hydroxypaclitaxel

©Biomedical Informatics (2021)

BIOINFORMATION
Discovery at the interface of physical and biological sciences

OPEN ACCESS GOLD

Results and Discussion:

Paclitaxel and its 10 analogues were docked to the active site of mTOR and the desirable conformations of the studied ligands were identified. It is observed that the ligands were appropriately bound to the active site and in some instances has identical orientations and is equivalent to the typical drug used as control. The values of the binding energies are given in Table 2. These analogues were arranged in order based on binding energies; 10-Deacetyltaxol>7-Epi-10-deacetyltaxol>7-Epi-Taxol>6alpha-Hydroxypaclitaxel. GLY-2203, THR-2207, ASP-2212,T HR-2214, SER-2221, ARG-2224, ARG-2234, LYS-2352 were the residues for hydrogen bond interactions with the ligands. This is similar to the interaction with paclitaxel. The binding energy of -6.8kcal/mol was shown by the docked findings of Paclitaxel with mTOR protein and the three hydrogen bond interaction was formed with GLY-2203, ARG-2224&THR-2207 amino acid residues. Of the ten analogues, 10-Deacetyltaxol, 7-Epi-10-deacetyltaxol, 7-Epi-Taxol, and 6alpha-Hydroxypaclitaxel showed comparable effects to Paclitaxel as compared with other analogues.

10-Deacetyltaxol was chosen as the best ligand docked on the active mTOR segment with a binding energy of -6.7 kcal/mol (Table 2). This docking showed that 10-Deacetyltaxol was observed to be binding on the protein in the active segment due to the formation of three hydrogen bonds with THR-2207, SER-2221, ARG-2224 at a distance of 2.3A°, 2.5A°, 2.6A° and 2.3A° respectively (Figure 1). The best compound 10-Deacetyltaxol selected also showed the very same interaction of the hydrogen bond with THR-2207, almost equivalent to Paclitaxel with ARG-2224. The results obtained from molecular docking indicate that selected active compound 10-Deacetyltaxol can inhibit the growth of the cancer cell lines by inhibiting the mTOR. Orientation, and interaction of the ligand with the mTOR protein, paclitaxel, the standard FDA-approved drug used for the treatment of oral cancer, was docked. There were some good similarities when comparing the position, orientation, and interaction of the ligand (paclitaxel) with the topmost docked ligand conformation (10-Deacetyltaxol). This study showed that all paclitaxel analogues are more effective in targeting mTOR, particularly 10-Deacetyltaxol with binding energy, than the standard drug paclitaxel.

Conclusion:

We report the binding features of 10-Deacetyltaxol, 7-Epi-10-deacetyltaxol, 7-Epi-Taxol and 6alpha-Hydroxypaclitaxel with mTOR for further consideration.

Conflict of interest: Nil

References:

[1] Roy NK et al. *Biomolecules*. 2019, 9(7): 253. [PMID: 31252679]
[2] El-Naggar MH et al. *Nat Prod Res*. 2019 1-12. [PMID: 31526148]
[3] Bray F *et al. CA Cancer J Clin*. 2018 68: 394-424. [PMID: 30207593]
[4] Hashim D *et al. Ann Oncol*. 2019 30:744-756. [PMID: 30840052]
[5] Behera AK *et al. Oncotarget*. 2019 10:3709-3724 [PMID: 31217904]
[6] Monisha J *et al. Cancers (Basel)*. 2018 10; 10:228. [PMID: 29996471]
[7] Vander Broek R, *et al. Oral Dis*. 2015 21:815-25. [PMID: 24219320]
[8] Clark CA *et al. Cancer Prev Res (Phila)*. 2010 3:1586-95. [PMID: 20851953]
[9] Trott O et al. *J Comput Chem*. 2010; 31(2): 455-461. [PMID: 19499576]
[10] Morris GM *et al. J Comput Chem*. 2009; 30:2785-91. [PMID: 19399780]
[11] Lill MA *et al. J Comput Aided Mol Des*. 2011 25:13-9[PMID: 21053052]

Edited by P Kangueane
Citation: Fathima ***et al.*** Bioinformation 17(1): 212-217 (2021)
License statement: This is an Open Access article which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. This is distributed under the terms of the Creative Commons Attribution License

BIOINFORMATION
Discovery at the interface of physical and biological sciences

OPEN ACCESS GOLD
OPEN ACCESS GOLD
OPEN ACCESS GOLD
OPEN ACCESS GOLD

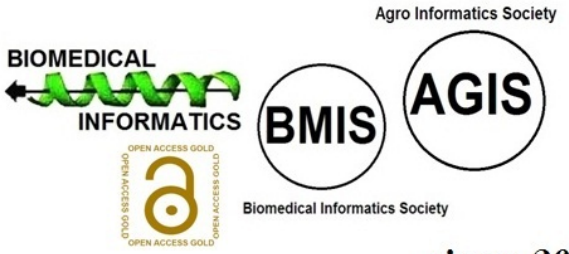
Articles published in BIOINFORMATION are open for relevant post publication comments and criticisms, which will be published immediately linking to the original article for FREE of cost without open access charges. Comments should be concise, coherent and critical in less than 1000 words.

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 17(1): 212-217 (2021)

©Biomedical Informatics (2021)

BIOINFORMATION
Discovery at the interface of physical and biological sciences

OPEN ACCESS GOLD



since 2005

BIOINFORMATION
Discovery at the interface of physical and biological sciences

indexed in

©Biomedical Informatics (2021)