WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 17, 1260-1275. Research Article ISSN 2277–7105

MOLECULAR DOCKING AND PHARMACOKINETIC PROFILING OF 2,4-DISUBSTITUTED FURAN DERIVATIVES AGAINST PROTEIN 7UR3 FOR ANTICANCER ACTIVITY

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Article Received on
18 July 2025,

Revised on 07 August 2025,
Accepted on 27 August 2025

DOI: 10.20959/wjpr202517-38169

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ABSTRACT

Objectives: The present study was undertaken to evaluate the anticancer potential of 2,4-disubstituted furan derivatives through molecular docking against protein 7UR3 using SwissDock and AutoDock software, along with ADME parameter analysis to identify drug-like candidates. **Methods**: A set of 2,4-disubstituted furan derivatives was designed and energy-minimized. The crystal structure of protein 7UR3 was retrieved from the RCSB Protein Data Bank, prepared by removal of non-essential water molecules, addition of polar hydrogens, and charge assignment. Docking was performed using SwissDock and AutoDock 4.2 (Lamarckian Genetic Algorithm) targeting the active site residues. Pharmacokinetic profiling, including Lipinski's rule of five, logP, gastrointestinal absorption, P-gp substrate prediction, and cytochrome P450 inhibition, was assessed using SwissADME. **Results**: Compounds 1, 3, 15, 16, and 17 showed higher binding affinity towards 7UR3 compared to other tested derivatives, with favorable docking scores in both SwissDock and AutoDock. These compounds exhibited stable interactions, including hydrogen bonding and hydrophobic contacts with key active site residues. ADME profiling revealed compliance with Lipinski's rule, high predicted gastrointestinal absorption, and absence of major CYP inhibition liabilities. **Conclusion:** In-silico molecular docking

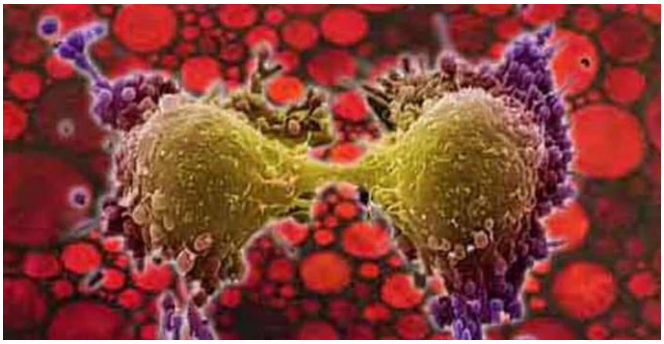
combined with ADME analysis suggests that compounds 1, 3, 15, 16, and 17 are promising 7UR3 binders with favorable pharmacokinetic properties, warranting further synthesis and biological evaluation for anticancer activity.

KEYWORDS: 2,4-disubstituted furan, molecular docking, SwissDock, AutoDock, ADME, anticancer activity, 7UR3.

INTRODUCTION

CANCER

- Cancer is a complex and multifactorial disease that involves the uncontrolled proliferation and spread of abnormal cells within the body.
- Due to the limitations and adverse effects associated with conventional cancer therapies such as chemotherapy and radiotherapy, the search for novel agents with potent anticancer activity has become a major field of research.
- Anticancer agents are compounds that can inhibit the growth of cancer cells, induce apoptosis (programmed cell death), or interfere with the mechanisms responsible for tumor progression and metastasis.
- Many naturally occurring phytochemicals have gained attention for their potential anticancer effects, as they often exhibit high efficacy with reduced toxicity compared to synthetic agents.
- These compounds can exert their anticancer activity via multiple mechanisms, including modulation of signaling pathways, inhibition of angiogenesis, generation of reactive oxygen species (ROS), and regulation of cell cycle checkpoints.
- In recent years, a significant number of in vitro and in vivo studies have been performed to evaluate the anticancer potential of medicinal plants and their bioactive constituents.
- The promising activity of these compounds highlights the importance of natural products as a valuable source for the development of new anticancer drugs.



TYPES

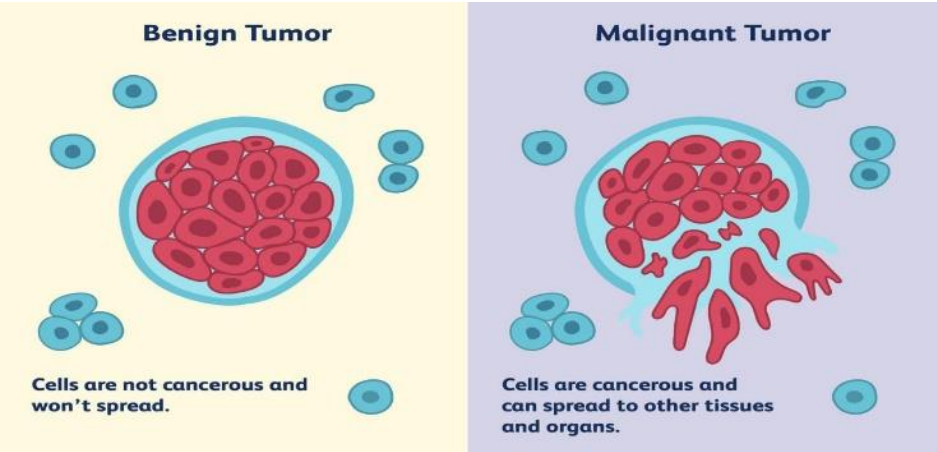
1. BENIGN TUMOR

- A benign tumor such as a common skin wart, remains confined to its original location, neither invading surrounding normal tissue nor spreading to distant body sites.
- Whereas benign tumors can usually we removed surgically.

2. MALIGNANT TUMOR

- A malignant tumor, however, is capable of both invading surrounding normal tissue and spreading throughout the body via the circulatory or lymphatic system (metastasis).
- Only malignant tumors are properly referred to as cancers, and it is the ability to invade and metastasize that makes cancer so dangerous.
- The spread of malignant tumors to distant body sites frequently makes them resistant to such localized treatment.
- Most cancers fall into one of the main groups:

a. Carcinomas
b. Sarcomas
c. Leukemias and lymphomas



A. CARCINOMAS

Carcinomas, which include approximately 90% of human cancer are malignancies of epithelial cells.

B. SARCOMAS

Sarcomas, which are rare in humans, are solid tumors of connective tissues, such as muscle, bone, cartilage and fibrous tissue.

C. LEUKEMIAS AND LYMPHOMAS

Leukemias and lymphomas, which account for approximately 8% of human's malignancies, arise from the blood-forming cells and from cells of the immune system, respectively.

MECHANISMS OF ACTION

2,4-Disubstituted furan binds to the protein 7URS (such as PKM2), where it inhibits its enzymatic and allosteric activity. By interfering with PKM2, it disrupts cancer cell metabolism, particularly glycolysis, which leads to a reduction in ATP production and the induction of metabolic stress. This disturbance in the metabolic pathways triggers apoptosis and/or causes cell cycle arrest, ultimately suppressing tumour cell proliferation and resulting in a notable anticancer effect.

CAUSES OF CANCER

- Tobacco
- Diet
- Genetics
- Lack of exercise
- Alcohol
- Radiation
- Air pollution
- Infection
- Household chemicals
- Age

SYMPTOMS

- Cough
- Unexplained bruising
- Pain in bone, joints or abdomen
- Frequent infection
- Tiredness
- Unexplained fever
- Unexplained rash
- Unexplained weight loss
- Shortness of breath

- Paleness
- Drenching night sweats
- Lumps or swelling

MANAGEMENT AND TREATMENT

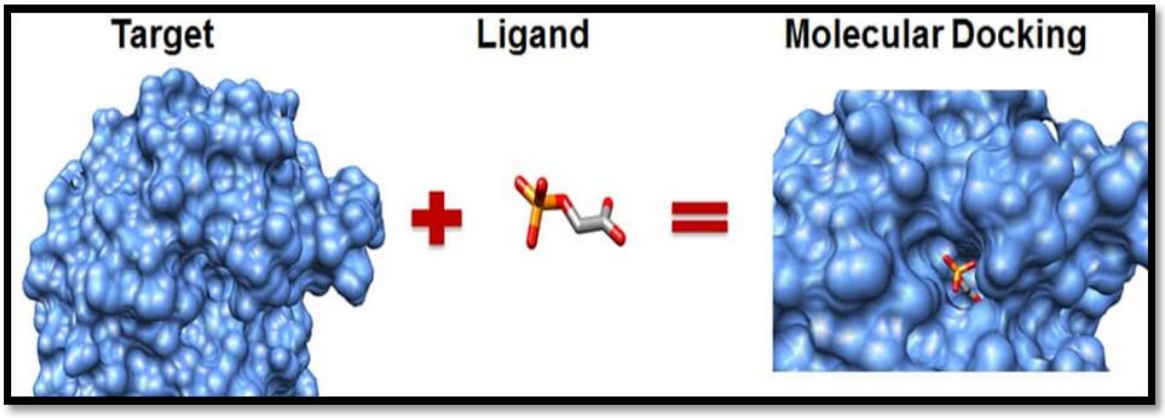
1. **Surgery:** Can remove cancerous tumors that haven't spread.
2. **Chemotherapy**: Destroys cancer cells with powerful drugs in pill form or intravenously (through a needle into a vein).
3. **Radiation therapy**: kills cancer cells with high dosages of radiation.
4. **Immunotherapy**: Engages your immune system to fight the disease.
5. **Targeted therapy**: Targets the genetic mutation (changes) that turn healthy cells into cancer cell.
6. **Hormone therapy**: Blocks cancer-causing hormones.
7. **Hormone therapy**: Replaces damaged blood stem cells with healthy ones.

MOLECULAR DOCKING

Molecular Docking is a method which involves orientation and best attempt to find a matching between two molecules it involves binding of one ligand to the active site of protein receptor to form a complex.

It relies on various algorithms and scoring functions to evaluate the binding modes and affinity, making it an essential tool in pharmacology, biochemistry and structural biology.

For example, Protein-ligand docking, more recently, docking is also applied to predict the binding mode between two macromolecules, for instance protein-protein docking.



TYPES OF MOLECULAR DOCKING

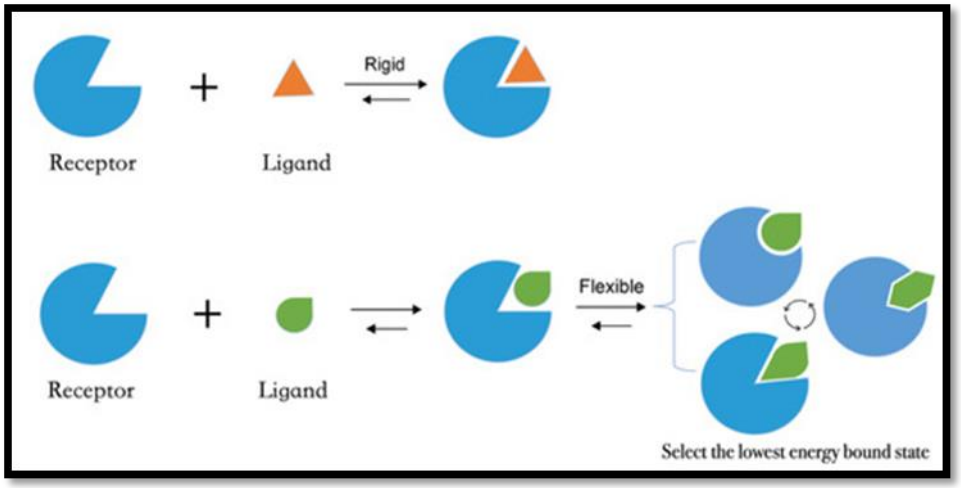
There are two distinctive forms of molecular docking,

1. RIGID DOCKING

Assuming the compounds are inflexible, we are seeking a rearrangement of one of the compounds in three-dimensional space that results in the best match to the other compounds in parameters of a scoring system. The ligand's conformation can be formed with or without receptor binding activity.

2. FIXED DOCKING

In conjunction with transformation, we evaluate molecular flexibility to identify confirmations for the receptor and ligand molecules as they exist in the complex.



MATERIALS AND METHODS

❖ FOR SWISSDOCK

1. Preparation of Target (Protein)

Download the 3D structure of the protein from the Protein Data Bank (PDB). Remove water molecules and any co-crystallized ligands not involved in docking. Add hydrogen atoms and optimize geometry. Save the prepared protein as a PDB file.

2. Preparation of Ligand

Draw or retrieve ligand structure (e.g., from PubChem). Optimize its geometry using molecular mechanics. Save the ligand as MOL2 format.

3. Access SwissDock

Choose between blind docking (entire protein surface) or targeted docking (specific binding site).

4. Upload & Set Parameters

Upload the protein (PDB) and ligand (MOL2). Choose docking type, scoring function, and optional parameters.

5. Docking Analysis

The ADME properties of selected lead molecules were calculated using the ADME and molecular properties module of the SWISSADME. The molinspiration tool in the SWISSADME is used to predict the "drug-likeness" features of various compounds from antiulcer activity. The physicochemical properties include formula, molecular weight, No. heavy atoms, No. aromatic heavy atoms, fraction Csp3, No. rotatable bonds. No. H-bond acceptors, No. H-bond donors, molar refractivity, TPSA [topological polar surface area]. The lipophilicity includes iLOGP, XLOGP3, WLOGP, MLOGP, Silicos-IT Log P, consensus LogP. The predicted water solubility compounds includes ESOL log S, ESOL solubility [mg/ml], ESOL solubility[mol/l], ESOL class, Ali log S, Ali solubility[mg/ml], Ali solubility[mol/l], Ali class, Silicos-IT log S, Silicos-IT solubility[mg/ml], Silicos-IT solubility [mol/l], Silicos-IT class.

The pharmacokinetics compounds include GI absorption, BBB permeant, Pgp substrate, CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, CYP3A4 inhibitor, Log Kp (skin permeation). The predicted drug-likeness compounds include Lipinski, Ghose, Veber, Egan, Muegge, bioavailability, PAINS, Brenk, Lead-likeness, Synthetic accessibility.

❖ **FOR AUTODOCK**

1. Preparation of Coordinate Files

Prepare the receptor and ligand structures with AutoDock Tools (ADT). Add polar hydrogens and assign appropriate charges. Convert files into PDBQT format that contains torsional flexibility and atomic partial charges.

2. Grid Map Calculation

Use AutoGrid to precalculate atomic affinity maps for different atom types on the receptor. Define the grid box around the binding site using ADT.

3. Docking Setup

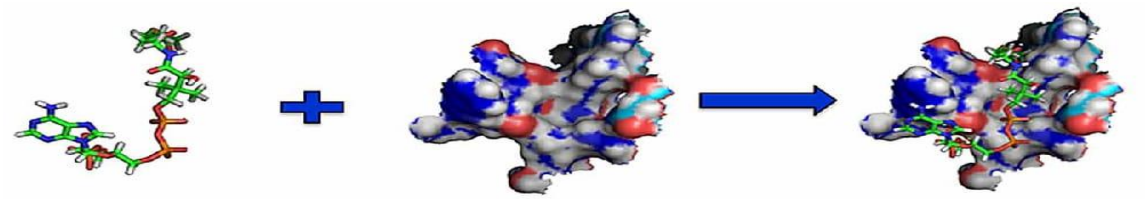
Prepare a docking parameter file (DPF) that controls the docking run, including search algorithms (e.g., Lamarckian Genetic Algorithm), number of runs, and flexible torsions.

4. Running AutoDock

Execute docking runs using AutoDock with the prepared DPF file. AutoDock explores different ligand conformations in the receptor binding site generating multiple docking poses.

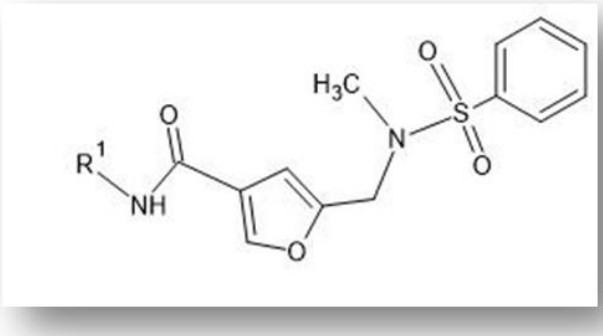
5. Result Analysis

Analyze output docking log files (.dlg) with AutoDockTools for binding energy and clustering of poses. Visualize docked conformations and assess ligand-receptor interactions. Docked conformations were evaluated based on binding energy (kcal/mol). The lowest-energy conformations were selected and analyzed using Mologromolecular viewer to study molecular interactions and hydrogen bonding patterns.



2,4- DISUBSTITUTED FURAN

2, 4- Disubstituted furan derivatives are organic compounds, characterized by a furan ring with two substituents at 2nd and 4th position**.**



COMMON STRUCTURE

It consists of,

- 5-membered heterocyclic aromatic ring
- 4- carbon atoms
- oxygen
- 2 different substituents attached to carbon atoms at 2nd and 4th position

RESULTS AND DISCUSSION

Table 1: List of IUPAC Name of 2,4-Disubstituted furan compounds.

S.No.	COMPDS No.	IUPAC NAME
1.	C1	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (3,5-dimethoxy-phenyl)-amide
2.	C2	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid(2,4,6-trifluoro-phenyl)-amide
3.	C3	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid(2-methoxy-phenyl)-amide
4.	C4	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid(2-methyl-4-nitro-phenyl)-amide
5.	C5	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid-2-chloro-benzylamide
6.	C6	4-{5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carbonyl}-piperazine-1-carboxylic acid ter-butylester
7.	C7	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid cyclopropyl-amide
8.	C8	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid(2-chloro-phenyl)-amide
9.	C9	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid(2-methyoxy-5-chloro-phenyl)-amide
10.	C10	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid(2,3-dimethoxy-phenyl)- amide
11.	C11	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid(4-methoxy-phenyl)-amide
12.	C12	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid(3-

		methoxy-phenyl)-amide
13.	C13	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid(2,5-dimethoxy-phenyl)-amide
14.	C14	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid(3,4,5-trimethoxy-phenyl)-amide
15.	C15	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid(4-hydroxy-phenyl)-amide
16.	C16	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid(2,6-dimethoxy-phenyl)-amide
17.	C17	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid(2-chloro-5-methoxy-phenyl)-amide
18.	C18	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid(2-chloro-4-hydroxy-phenyl)-amide
19.	C19	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid(2-hydroxy-4-fluoro-phenyl)-amide
20.	C20	5-[(Benzenesulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid phenylamide

The ADME Study Report of the Compounds of 2,4-Disubstituted furan

Captured various compounds were then subjected to ADME testing using SWISSADME software. The forecasted ADME property of various compound based on their structure, functional groups and molecular properties such as Mol/M.W (Molecular weight), BBB permeant (Blood-Brain Barrier parameter of compounds), GI (Gastrointestinal absorption), H-bond acceptors, H-bond donors, Violation and MLogP (Moriguchi octanol-water partition coefficient). Few compounds transgressed drug-likeness tests were removed as those compounds have poor ability to cross the biological membrane. The ADME report are mentioned under the following table.

TABLE 2: ADME Study report

+

Compound Number	M.W g/mol	BBB	GI Absorption	H-bond Acceptor	H-bond Donor	Violation	MLogP
1	445.49	No	Low	7	2	0	0.09
2	439.41	No	Low	8	2	0	2.09
3	415.46	No	High	6	2	0	0.65
4	415.46	No	High	6	2	0	0.65
5	433.91	No	High	5	2	0	1.39
6	405.51	No	High	6	2	0	0.85
7	349.40	No	High	6	2	0	0.09
8	419.88	No	High	5	2	0	1.44
9	449.91	No	High	6	2	0	1.14
10	445.46	No	Low	6	2	0	0.65
11	415.46	No	High	6	2	0	0.65
12	415.46	No	High	6	2	0	0.65

13	445.49	No	High	7	2	0	0.36
14	475.51	No	Low	8	2	0	0.08
15	401.44	No	Low	6	3	0	0.42
16	445.49	No	Low	7	2	0	0.36
17	449.91	No	Low	6	2	0	1.22
18	435.88	No	Low	6	3	0	0.92
19	419.43	No	Low	7	3	0	0.80
20	385.44	No	Low	5	2	0	0.94
Limit	≤500	No	Low	≤10	≤5	0	≤4.15

The molecular docking score of 2,4-Disubstituted Furan

The docking studies of the ligand to protein active sites were done by the modern molecular docking programmed SWISSDOCK old version to determine compounds binding affinity. In silico approach between selected ligands and Protein Data Bank: 1PWM of the diabetic disease. The good drug-likeness properties containing the ligand's docking score, yield [%].

TABLE 3: Docking score of SWISSDOCK.

S.NO	COMPOUND NO.	DOCKING SCORE (Kcal/Mol)
1	C10	-10.034
2	C13	-9.9580
3	C16	-9.8769
4	C14	-9.8404
5	C9	-9.8241
6	C2	-9.7652
7	C18	-9.6753
8	C17	-9.6741
9	C5	-9.5804
10	C12	-9.5636
11	C8	-9.4821
12	C1	-9.4638
13	C4	-9.311
14	C3	-9.2737
15	C11	-9.2428
16	C19	-9.1909
17	C6	-9.0085
18	C15	-9.0024
19	C20	-8.8229
20	C7	-8.6980
21	Pexidartinib	-6.958

TABLE 3: Docking score of AUTODOCK.

S.NO.	COMPOUND NO.	DOCKING SCORE (Kcal/Mol)
1	C1	-10.60

2	C3	-10.14
3	C14	-9.41
4	C15	-9.41
5	C17	-9.03
6	Pexidartinib	-11.07

The above 20 compounds of 2, 4-Disubstituted furan derivatives were selected for the anti-Cancer activity. Molecular docking studies was conducted using SwissDock and AutoDock, to evaluate the binding affinity of furan derivatives. In SwissDock, all the 20 compounds exhibited the docking score of more than -8kcal/mol and in AutoDock, only 5 compounds C1, C3, C14, C15, C17 exhibited the docking score of more than -8kcal/mol. In these top hit compounds, C1 having more docking score of -10.60kcal/ mol in AutoDock when compared to the standard drug Pexidartinib (-11.07kcal/mol). Moreover, they are having less than 500Daltons as molecular weight. So, it can easily be transported when compared to other heavy molecular weight molecules. The BBB activity is inactive (NO), so, it does not cause any side effects in CNS. The MLogP of Compounds value is less than 4.15. So, it easily crosses the cell membranes. From the above discussion, we suggested Compound 1, 3, 14, 15, 17 had more effectiveness against the Cancer activity.

FOR SWISSDOCK

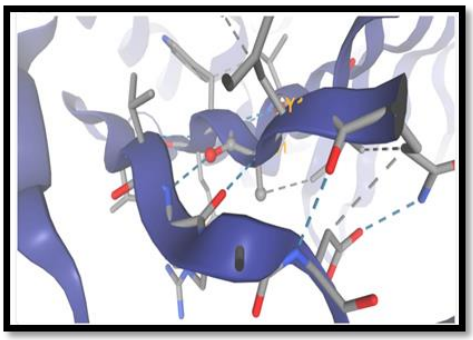


FIG. 1: C10

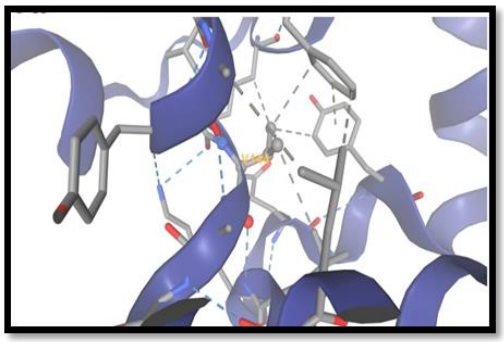


FIG. 2:C3

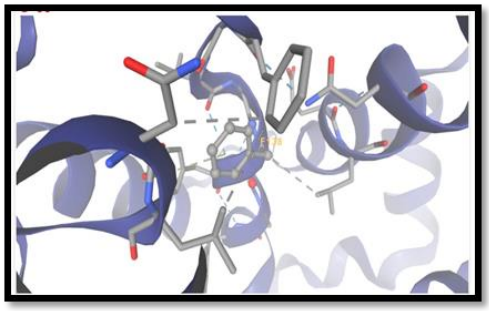


FIG. 3: C14

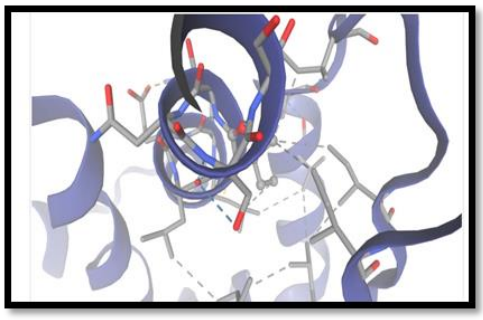


FIG. 4: C16

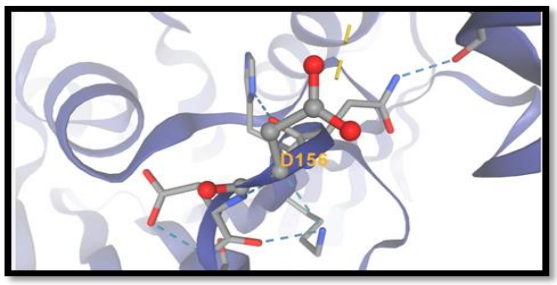


FIG. 5: C19

FOR AUTODOCK

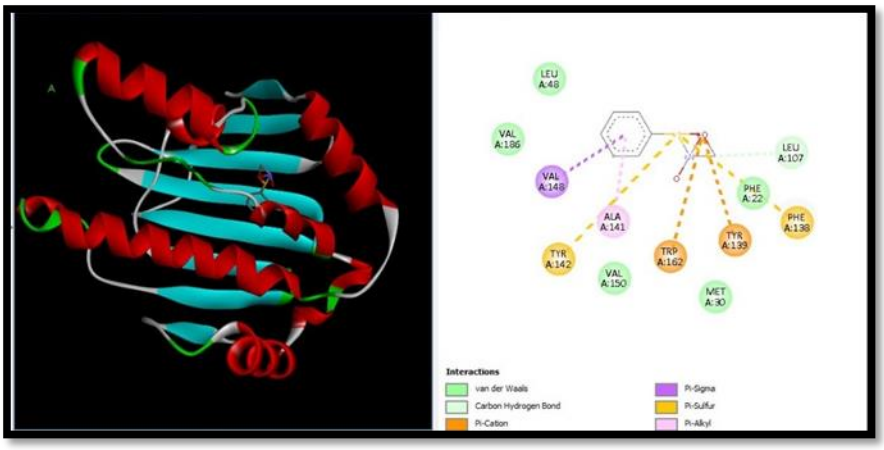


FIG. 6: C1

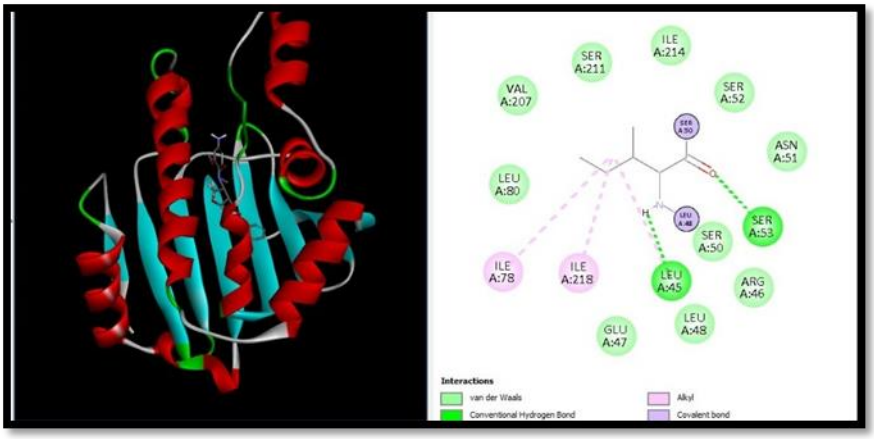


FIG. 7: C3

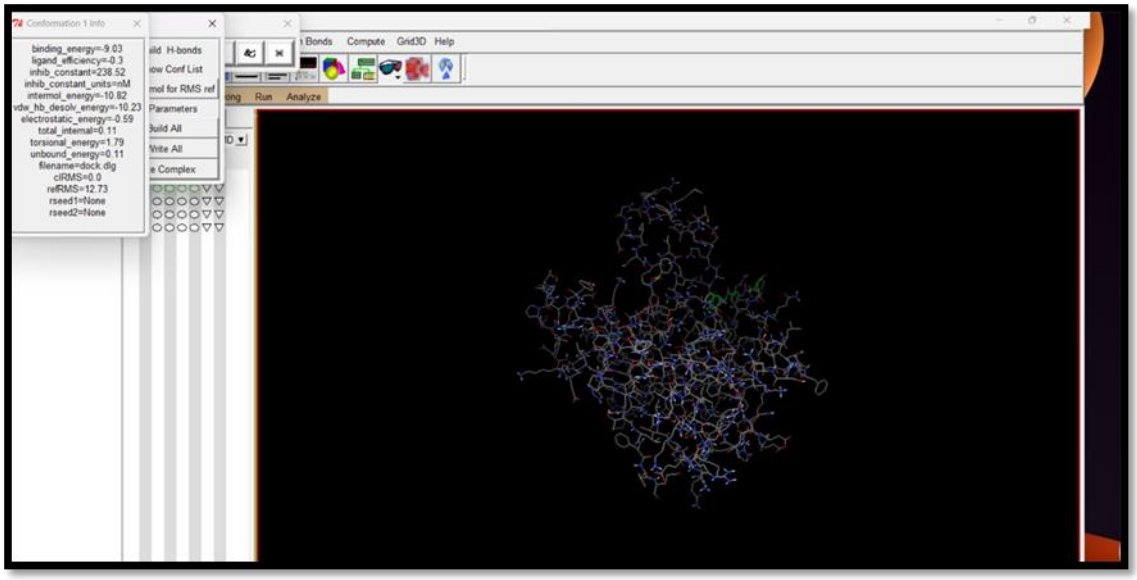


FIG. 8: C17

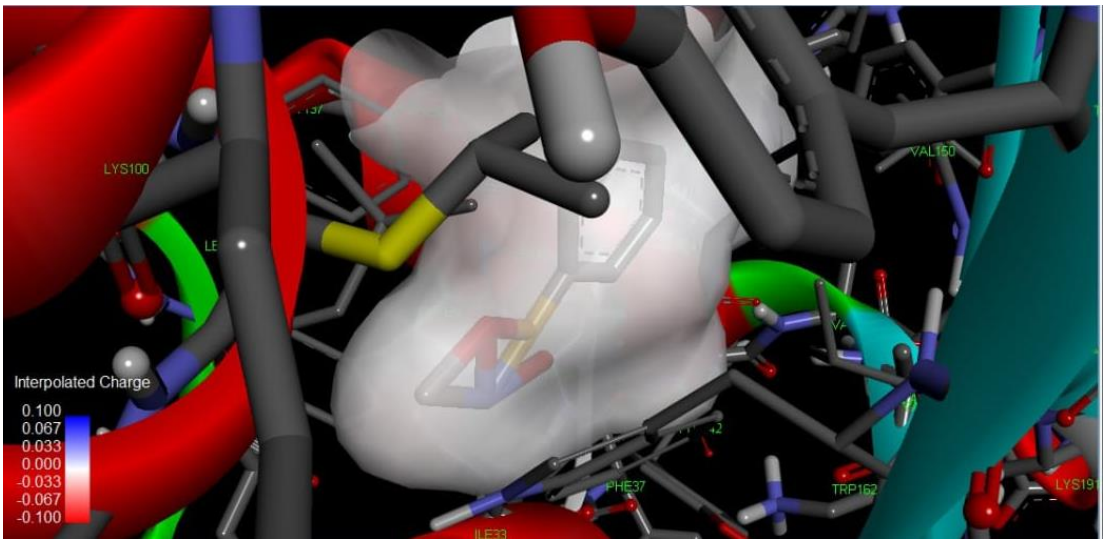


Fig. 9: C1-Interpolated Charge Surface of the Receptor Binding Site.

(Ligand-Bound Complex)

CONCLUSION

The molecular docking results of 2,4-disubstituted furan derivatives against the anticancer protein 7UR3 have demonstrated promising binding affinity in both SwissDock and AutoDock studies. All compounds docked using SwissDock showed docking scores greater than 8, indicating strong and energetically favorable interactions with the active site of 7UR3. Similarly, specific compounds in AutoDock (notably C1, C3, C15, C16 and C17) also exhibited docking scores above 8, confirming their high binding affinity and potential as lead candidates.In comparison to the standard drug, these selected derivatives exhibited superior

binding profiles and stronger interactions, suggesting that they may possess enhanced inhibitory potential.

Furthermore, the ADME profiling of these ligands revealed acceptable pharmacokinetic characteristics, including good drug-likeness and favorable absorption and distribution behavior, supporting their potential for further optimization and development as anticancer agents. Overall, the combination of high docking scores and promising ADME properties suggests that 2,4-disubstituted furan analogues, particularly compounds C1, C3, C15, C16 and C17, could serve as effective inhibitors of protein 7UR3 and warrant further in-vitro and in-vivo validation.

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