Design, Evaluation of Drug Candidate and Molecular Docking Study of Some Novel quinazolinone based thiazolidine derivatives As Inhibitor of Human Dihydrofolate Reductase Enzyme

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ABSTRACT:

Objectives: One of the best targets for anticancer medication is human dihydrofolate reductase (hDHFR), as it is crucial to produce purines and pyrimidines. Moreover, it keeps the biological folate pools inside the cells. Due to certain similarities to folic acid, quinazolinone-based thiazolidine chemicals are more well-known and have offered appealing scaffolding for developing anticancer medicines. To assess the potential for various quinazolinyl thiazolidine scaffolds as inhibitors of the human dihydrofolate reductase enzyme, molecular docking and in-silico investigations were conducted in this work.

Methods: Ten compounds from the class of quinazolinones and the common medication methotrexate were included in the investigation. The PyRx suite was used to perform automated molecular docking of compounds based on thiazolidine quinazolinone with human DHFR. Molinspiration made predictions about the features of molecular descriptors.

Results: As shown by the findings of the molecular docking, all of the derivatives met Lipinski's rule of five and occupied the same cavity in the protein molecule as the synthetic medication methotrexate and the natural ligand folic acid. In comparison to methotrexate, all the chemical complex's binding energies have significantly lower values.

Conclusion: According to the molecular docking investigation, the chemicals may function as a possible substitute for hDHFR. The created pharmacophore may also be utilised to create and develop novel medications. This work provides strong evidence in favour of the hypothesis that these chemicals are potential human DHFR inhibitors.

Keywords: Quinazolinone based thiazolidines, Lipinski's rule, molecular docking, ADME, human DHFR inhibitors as anticancer agents.

INTRODUCTION:

Cancer is the second largest cause of mortality worldwide and is defined as abnormal cell proliferation. The creation of secure and selective drugs with a high therapeutic index is an essential topic of research because many of the currently employed therapeutic agents have a variety of adverse effects brought on by their non-selective action. A distinctive bioactive scaffold called the quinazolinone nucleus can be found in a number of important biologically important drugs [2–8]. As indicated by their usage as antibacterial, antimalarial, antifungal, and anticancer medicines, dihydrofolate reductase inhibitors represent a significant family of medications. The development of novel and selective human DHFR inhibitors by the medicinal chemistry community has resulted in a new generation of DHFR inhibitors as a result of advancements in our understanding of the biochemical underpinnings of the mechanisms underlying enzyme selectivity and antiproliferative effects. Tetrahydrofolate is formed when dihydrofolate is hydrogenated by the enzyme dihydrofolate reductase (DHFR) [9]. It is a crucial enzyme in the biosynthetic process that produces folate. A helpful DHFR inhibitor is trimethoprim [10]. Tyrosine tRNA ligase is a crucial aminoacyl tRNA ligase for the production of proteins [11].

The four isomeric forms of quinazoline-quinoxaline, cinnoline, and phthalazine-depend on

where the nitrogen atom is in the heterocyclic ring structure. Quinazoline is a fused heterocycle that contains nitrogen. [12] Quinazolinone (4(3H)-quinazolinone & 2(1H)-quinazolinone) is produced when the quinazoline ring becomes carbonyl linked. Among all the isomeric forms, quinazoline and quinazolinone are crucial nitrogen heterocycles for medicine because they have a variety of biological effects, such as antimicrobial, anticonvulsant, anti-cancer, anti-inflammatory, anti-diabetic, anti-tumor, anti-hypertension, anti-inflammatory, anti-cellular phosphorylation, anti-kinase, anti-tumor, and anti-tumor properties. [25] The quinazoline and quinazolinone moiety is found in a wide variety of synthetic and natural product-based medications that are used in clinical settings to treat a wide range of medical problems. [26]

It was exceedingly expensive, time-consuming, and probably less successful to find novel therapeutic medications using traditional approaches. Virtual screening is a sensible and simple method that is proposed to address the weaknesses of previous tactics. It is backed by the presentation of structural information.

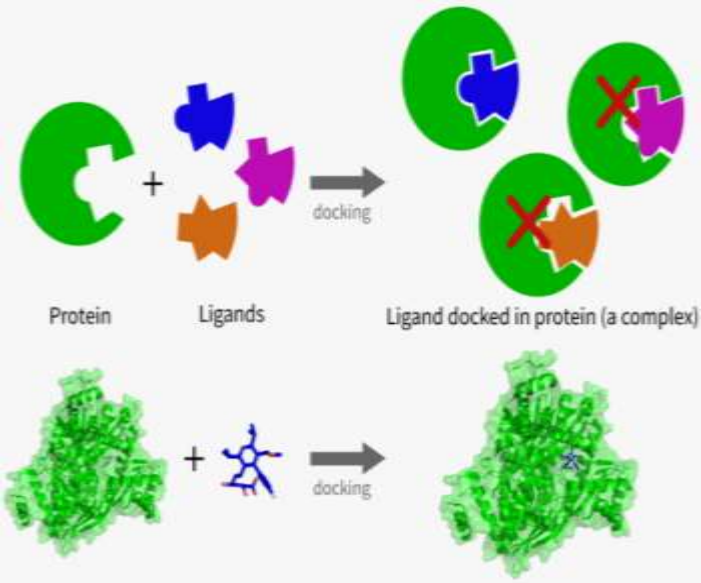


Fig.1: Computer-aided drug design

The classification of virtual screening methods as structure- and ligand-based drug design strategies is common. The structure-based drug strategy addresses molecular hooking up, whereas ligand-based methods explore quantitative structure activity relationship (QSAR), molecular docking, and pharmacophore modelling [27]. A chemical's interactions with a target molecule are determined through the molecular docking technique. It predicts the affinity of molecules for interacting to create a stable complex with the supermolecule by determining the preferred orientation of the least free energy [28]. The two key methods in molecular docking are, in most cases, Shape Complementarity and Simulation.

MATERIALS AND METHODS:

Software required:

A computer with the computational tools swiss dock, PyRx, and Biovia discovery studio visualizer tools (HP Pavilion AMD RyzenTM 5 Hexa Core 5500 APU @ 2.1GHz with turbo boost up to 4GHz Processor version 5500U and 16.00 GB RAM with 64-bit Windows-11 operating system) was used to conduct the molecular docking study.

Ligand and macromolecule preparation:

The free Chemsketch 2021 programme was used to design and optimise the chemical structures of the ligands used in this study. Molar data was stored before being converted to PDB format using Open Bable 2.3.2, which was required for PyRx software execution. The target enzyme was readyed by eliminating the native ligand and water molecules attached to it before starting the molecular docking technique. After that, hydrogen atoms were added to the investigation ligand, their rotatable bonds and torsions were allocated, and the files were stored as ligand pdbqt.

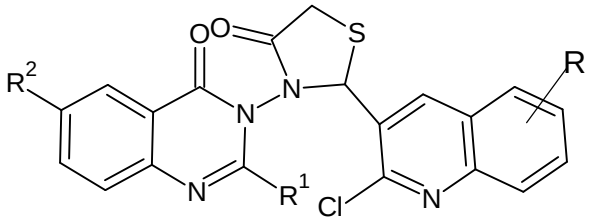


Fig.2: Quinazolinone based thiazolidine derivatives.

Table.1:R,R^1,R^2 Substitution quinazolinyl thiazolidine compound 4a-4j

Compound Code	R	R1	R2
Compound 4a	-H	CH_3	6-Br
Compound 4b	6-CH_3	CH_3	6-Br
Compound 4c	8-CH_3	CH_3	6-Br
Compound 4d	6-OCH_3	CH_3	6-Br
Compound 4e	8-OCH_3	CH_3	6-Br

Compound Code	R	R1	R2
Compound 4f	-H	Ph	6-Br
Compound 4g	6-CH_3	Ph	6-Br
Compound 4h	8-CH_3	Ph	6-Br
Compound 4i	6-OCH_3	Ph	6-Br
Compound 4j	8-OCH_3	Ph	6-Br

In silico ADME (Absorption, Distribution, Metabolism and Excretion Studies):

The pharmacokinetics of chemicals in an organism's body are described by ADME. It evaluates the risk involved in giving a patient or other creature a medicinal drug. These pharmacokinetic properties are identified in silico using Pre ADMET (https://preadmet.bmdrc.kr/), Swiss ADME (http://www.swissadme.ch/), and other internet resources. When Lipinski's rule of five is broken twice or more, the molecules become inactive. It takes a delicate balancing act between a number of chemical qualities and structural characteristics to determine whether a molecule is similar to medications already available on the market.

As a result, the bio-via discovery studio programme created the 10 distinct conformers (Fig. 2), and blind docking was carried out to determine if these molecules bind in the active site or anywhere in the target.

Preparation of Target Protein Systems for Docking

A requirement for conducting a successful study is the requirement of providing an accurate depiction of the protein structure. The following factors were considered as a result to ensure quality. The RCSB PDB website (https://www.rcsb.org/) was used to download the proteins for this study. The crystal structure of human DHFR, found at a resolution of 1.9A0 and attached to its inhibitor methotrexate, was utilised to display the PDB files using Discovery Studio (MTX). These enzymes' 3D coordinates were taken from the Protein Data Bank (PDB), and all water molecules that were part of the protein structure were eliminated. Using the CHRAMM force field, which is for the molecular weight. 20 to 120 Ao2 is the topological polar surface area. The unsaturation available in DS, hydrogen atoms were supplied to the target protein structures. After that, the hydrogen atoms were minimised using the smart minimizer protocol with a restriction on heavy atoms. In molecular docking experiments, the generated target protein structures were employed.

Molecular Docking Study Using Autodock 4.2 (PyRx)

The binding energies of the training set compounds along with the potential hits at the active site of the hDHFR enzyme were determined using Autodock 4.2 (PyRx). The scoring functions from several programmes (PyRx, Autodock 4.2, and Swiss dock) may be of great benefit in predicting favourable binding conformations because none of the scoring systems used in the currently available docking tools perform better for all macromolecular targets. Additionally, it calculates the torsional energy that results in the docked compound's binding. The high-resolution crystal structures of hDHFR (PDB ID: 1U72 for hDHFR) used to build the beginning protein were stored in the protein data bank. Using the Lamarckian genetic algorithm (LGA), potential hits and the training set compounds were docked in the "docking active site," which was defined by a grid centred on the complex structure's ligand. The settings were set at a population size of 150, a mutation rate of 0.02, and a crossover rate of 0.8. It made use of the standard grid spacing (0.375 A0). Up to 2.5 million energy evaluations and a maximum of 27000 generations were used in the simulations. Ten simulations were run for each simulation, resulting in ten docked conformations. The binding conformations between ligands and proteins were thought to be those with the lowest energy. The Discovery Studio Visualiser 2021 was used for all computational analyses and visualisations.

RESULTS AND DISCUSSION:

Absorption, distribution, metabolism, and excretion (ADME results):

According to the bioavailability score, the coloured zone is the ideal physicochemical area for oral bioavailability in the range of 0.16 to 0.55, taking into account the attributes of flexibility, lipophilicity, saturation, size, polarity, and solubility. The compound log P has a lipophilicity that can range from -0.7 to +5.0. Between 150 and 550 g/mol is the possible range fraction varies from 0.25 to 1.0, suggesting that the fraction of carbon atoms in the sp3 hybridization

should not be less than 0.25. The number of rotatable bonds should be between 0 and 9.

According to the physical characteristics, the compound is 4a. The weight of the molecules was 501.78 g/mol. The total number of heavy atoms is 30, and there are 20 of them that are aromatic. Carbon atoms made up 0.17 percent of the sp3 hybridization. Four rotatable bonds, five hydrogen bond acceptors, and one hydrogen bond donor made up the total number of bonds in the system. The topological polar surface area was determined to be 93.39 Ao2 and the molar refractivity to be 126.83.

Table.2: ADME analysis of designed quinazolinyl thiazolidine derivatives (4a-4j)

Physicochemical properties:						
Sl.no	**Molecules**	**4a**	**4b**	**4c**	**4d**	**4e**
1	Molecular weight (g/mol)	501.78	515.81	515.81	531.81	531.81
2	Num. heavy atoms	30	31	31	32	32
3	Num. atom. heavy atoms	20	20	20	20	20
4	Fraction Csp3	0.14	0.18	0.18	0.18	0.18
5	Num. rotatable bonds	2	2	2	3	3
6	Num. H-bond acceptors	4	4	4	5	5
7	Num. H-bond donors	0	0	0	0	0
8	Molar Refractivity	126.83	131.80	131.80	133.32	133.32
9	TPSA	93.39 Å²	93.39 Å²	93.39 Å²	102.62 Å²	102.62 Å²
Lipophilicity:						
Sl.no	**Molecules**	**4a**	**4b**	**4c**	**4d**	**4e**
1	Log $P_{o/w}$ (iLOGP)	3.47	3.74	3.64	3.81	3.58
2	Log $P_{o/w}$ (XLOGP3)	4.57	4.93	4.93	4.54	4.54
3	Log $P_{o/w}$ (WLOGP)	3.87	4.18	4.18	3.88	3.88
4	Log $P_{o/w}$ (MLOGP)	3.97	4.18	4.18	3.65	3.65
5	Log $P_{o/w}$ (SILICOS-IT)	4.25	4.77	4.77	4.31	4.31
6	Consensus Log $P_{o/w}$	4.03	4.36	4.34	4.04	3.99
Pharmacokinetics:						
Sl.no	**Molecules**	**4a**	**4b**	**4c**	**4d**	**4e**
1	GI absorption	High	High	High	High	High
2	BBB permeant	No	No	No	No	No
3	P-gp substrate	No	No	No	No	No
4	CYP1A2 inhibitor	Yes	No	No	No	No
5	CYP2C19 inhibitor	Yes	Yes	Yes	Yes	Yes
6	CYP2C9 inhibitor	Yes	Yes	Yes	Yes	Yes
7	CYP2D6 inhibitor	No	No	No	No	No
8	CYP3A4 inhibitor	No	No	No	No	No
9	Log K_p (skin permeation)	-6.12 cm/s	-5.95 cm/s	-5.95 cm/s	-6.32 cm/s	-6.32 cm/s
Drug likeness:						
Sl.no	**Molecules**	**4a**	**4b**	**4c**	**4d**	**4e**
1	Lipinski	No;2 violations: MW>500, MLOGP>4.15	No;2 violations: MW>500, MLOGP> 4.15	No; 2 violations: MW>500, MLOGP>4. 15	Yes; 1 violation: MW>500	Yes; 1 violation: MW>500
2	Ghose	No; 2 violations:	No; 2 violations:	No; 2 violations:	No; 2 violations:	No; 2 violations:

		MW>480, MR>130	MW>480, MR>130	MW>480, MR>130	MW>480, MR>130	MW>480, MR>130
3	Veber	Yes	Yes	Yes	Yes	Yes
4	Egan	Yes	Yes	Yes	Yes	Yes
5	Muegge	Yes	Yes	Yes	Yes	Yes
6	Bioavailability Score	0.16	0.17	0.17	0.55	0.55
Physicochemical properties:						
Sl.no	**Molecules**	**4f**	**4g**	**4h**	**4i**	**4j**
1	Molecular weight (g/mol)	563.85	577.88	577.88	593.88	593.88
2	Num. heavy atoms	35	36	36	37	37
3	Num. atom. heavy atoms	26	26	26	26	26
4	Fraction Csp3	0.08	0.11	0.11	0.11	0.11
5	Num. rotatable bonds	3	3	3	4	4
6	Num. H-bond acceptors	4	4	4	5	5
7	Num. H-bond donors	0	0	0	0	0
8	Molar Refractivity	147.30	152.27	152.27	153.79	153.79
9	TPSA	93.39 Å²	93.39 Å²	93.39 Å²	102.62 Å²	102.62 Å²
Lipophilicity:						
Sl.no	**Molecules**	**4f**	**4g**	**4h**	**4i**	**4j**
1	Log $P_{o/w}$ (iLOGP)	3.89	4.19	4.17	4.25	4.09
2	Log $P_{o/w}$ (XLOGP3)	6.23	6.59	6.59	6.20	6.20
3	Log $P_{o/w}$ (WLOGP)	5.23	5.54	5.54	5.24	5.24
4	Log $P_{o/w}$ (MLOGP)	4.78	4.98	4.98	4.45	4.45
5	Log $P_{o/w}$ (SILICOS-IT)	5.25	5.77	5.77	5.31	5.31
6	Consensus Log $P_{o/w}$	5.08	5.41	5.41	5.09	5.06
Pharmacokinetics:						
Sl.no	**Molecules**	**4f**	**4g**	**4h**	**4i**	**4j**
1	GI absorption	High	High	High	High	High
2	BBB permeant	No	No	No	No	No
3	P-gp substrate	No	No	No	No	No
4	CYP1A2 inhibitor	No	No	No	No	No
5	CYP2C19 inhibitor	Yes	Yes	Yes	Yes	Yes
6	CYP2C9 inhibitor	Yes	Yes	Yes	Yes	Yes
7	CYP2D6 inhibitor	No	No	No	No	No
8	CYP3A4 inhibitor	No	No	No	No	No
9	Log K_p (skin permeation)	-5.32 cm/	-5.15 cm/s	-5.15 cm/s	-5.52 cm/s	-5.52 cm/s
Drug likeness:						
Sl.no	**Molecules**	**4f**	**4g**	**4h**	**4i**	**4j**
1	Lipinski	No; 2 violations: MW>500, MLOGP>4.15	No; 2 violations: MW>500, MLOGP> 4.15	No; 2 violations: MW>500, MLOGP>4. 15	No; 2 violations: MW>500, MLOGP>4. 15	No; 2 violations: MW>500, MLOGP>4. 15
2	Ghose	No; 2 violations:	No; 2 violations:	No; 2 violations:	No; 2 violations:	No; 2 violations:

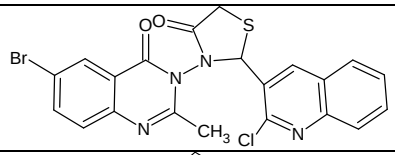
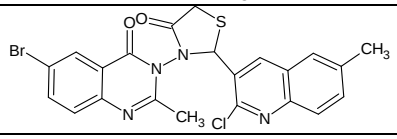
		MW>480, MR>130	MW>480, MR>130	MW>480, MR>130	MW>480, MR>130	MW>480, MR>130
3	Veber	Yes	Yes	Yes	Yes	Yes
4	Egan	Yes	Yes	Yes	Yes	Yes
5	Muegge	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5
6	Bioavailability Score	0.17	0.17	0.17	0.17	0.17

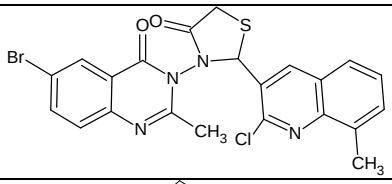
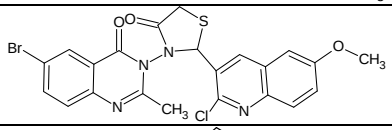
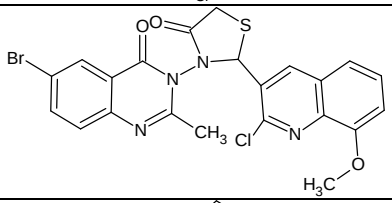
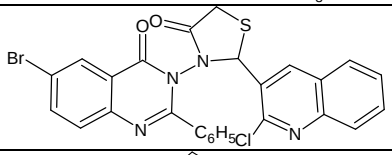
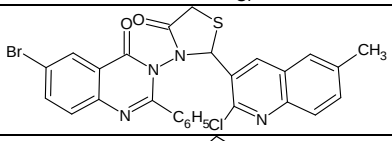
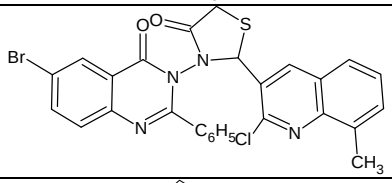
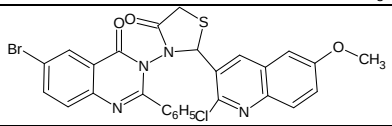
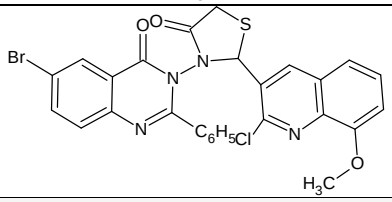
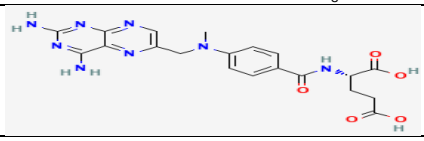
Molecular docking results:

development of anti-cancer drugs is the goal We learned about the derivatives responsible for the anti-cancer activity through an in silico docking analysis of 10 drugs. In the putative binding site of the crystal structure of the human DHFR (PDB ID: 1U72), which reveals a sizable space bounded by a membrane-binding domain that serves as an entry channel for the substrate to the active site, the obtained results showed that all the studied ligands have similar positions and orientations. Also, every small molecule's affinity can be thought of as a special instrument in the field of medication development. The affinity of organic compounds and the free energy of binding are correlated. It may also be the potential method by which derivatives showed their anti-cancer action as on this protein constituent is most appropriately docked. This relationship can help forecast and explain the activity of organic chemicals towards the specific target protein.

The method and crucial factor used to categorise which ligands are more likely to be effective and interact with a given receptor in a more significant way based on the projected free energy of binding, or docking score, which predicts the free energy of protein-ligand binding, Typically, between 25 and 30 percent of drug compounds tested in-silico prove to be powerful and efficient drug molecules for the researched receptor molecules. Based on the docking binding score, the 4a molecule demonstrated action that was somewhat comparable to the standard medicine methotrexate, which has a binding affinity score of -9.8 kcal/mol, and an excellent binding affinity score of -10.8 kcal/mol in compared to the other derivatives. The 4a molecule interacted with the same 1U72 protein, however typical methotrexate medications had superior therapeutic effect. The following amino acid residues have interacted with the 4n scaffolds: LYS55, GLY20, ASP21, PHE31, SER59, ILE60, GLY17, PRO61, ASN64, ARG70, LEU22, LEU67, PHE34, GLU30, ALA9, TRP24, VAL8, VAL115, GLY116, GLY117, TYR121, THR56, and ILE16. Several of the amino acid residues have reacted similarly to the common medication methotrexate (LEU22, GLU30, TYR33, VAL8, THR136, ALA9, TYR121, VAL115, ILE7, PHE34, THR56, SER59, ILE60, PRO61, LEU67, ASN64, ARG70, LYS68, GLN35, ARG32, and PHE31).

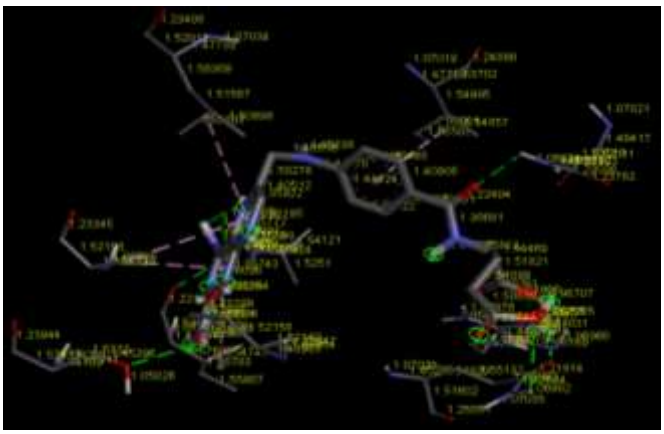
Table-3: Docking score of the designed quinazolinone based thiazolidine derivatives. (4a-4j)

Comp. Code	Ligand structure	Rmsd/ub	Rmsd/lb	Binding affinity Score (kcal/mol)
4a		0	0	-10.8
4b		0	0	-10.5

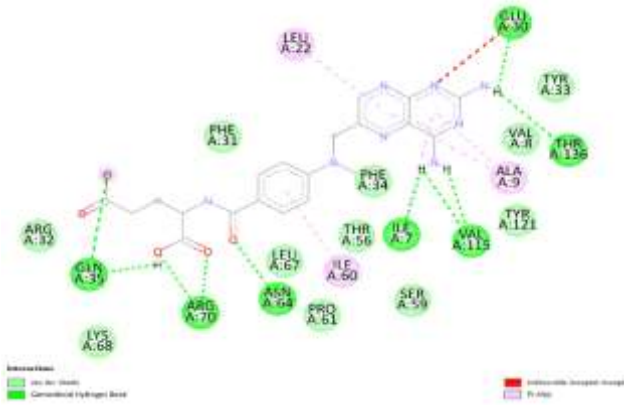
4c		0	0	-10.4
4d		0	0	-9.1
4e		0	0	-9.6
4f		0	0	-9.0
4g		0	0	-9.2
4h		0	0	-9.0
4i		0	0	-9.5
4j		0	0	-8.9
Methotrexate		0	0	-9.8

Docking parameters: Interacting Amino Acids with Distance in Å

Drug molecules will interact with amino acids during the docking simulation, which involves some energy expenditure. According to their energy and how closely they are coupled, hydrophobic amino acids can both activate and inhibit protein activity, which is why it is important to understand how they interact. In this study, the top medications methotrexate and compound 4a (LYS55, GLY20, ASP21, PHE31, SER59, ILE60, GLY17, PRO61, ASN64, ARG70, LEU22, LEU67, PHE34, GLU30, ALA9, TYR121, THR56, ILE16) came into contact with the greatest number of amino acids (LEU22, GLU30, TYR33, VAL8, THR136, ALA9, TYR121, VAL115, ILE7, PHE34, THR56, SER59, ILE60, PRO61, LEU67, ASN64, ARG70, LYS68, GLN35, ARG32, &PHE31)

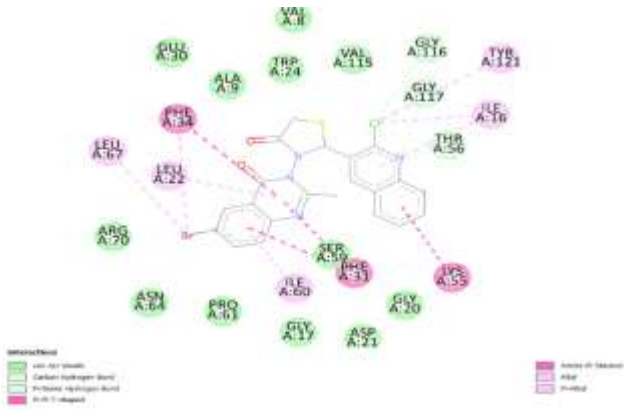


Methotrexate



Methotrexate

4a



4a

Figure-3: a) 3D and b) 2D interaction diagrams of predicted complexes of human DHFR with compound methotrexate (binding energy= -9.8 kcal/mol); c) 3D and d) 2D interaction diagrams of predicted complexes of human DHFR with compound 4a (binding energy= -10.8 kcal/mol)

CONCLUSION:

Ten different compounds that are derivatives of quinazolinyl thiazolidine were molecularly docked to act as human DHFR inhibitors. According to the results of the molecular docking experiments, all of the drugs interact favorably with the target receptor. The ligand has the highest binding energy of -10.8 kcal/mol and interacts with the receptor compound 4a's active site through interactions with amino acids (LYS55, GLY20, ASP21, PHE31, SER59, ILE60, GLY17, PRO61, ASN64, ARG70, LEU22, LEU67, PHE34, GLU30, ALA9, TRP24, VAL8, VAL115, GLY116, GLY (LEU22, GLU30, TYR33, VAL8, THR136, ALA9, TYR121, VAL115, ILE7, PHE34, THR56, SER59, ILE60, PRO61, LEU67, ASN64, ARG70, LYS68, GLN35, ARG32, & PHE31). Studies on molecular docking and ADME provide useful information for designing structural bases. These two approaches will significantly help pharmaceutical and medicinal chemist to design new anti-cancer agents.

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CONFLICT OF INTEREST:

The authors declare that no financial or commercial ties that might be viewed as creating a conflict of interest existed throughout the research.

AUTHOR CONTRIBUTION:

Nagaraj N Durgadasheemi and Shivanand N Kolageri both did a proper literature survey, collected data, design the work, wrote a portion of the paper, and provided maximum effort in the correction, both did proper design the manuscript. Shivanand N Kolageri Conceived and design the analysis. The final draft was checked by all the authors.

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