Original Article: *In Silico* Molecular Docking Againstc-KIT Tyrosine Kinase and ADME Studies of 4-Thiazolidinone Derivatives

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ABSTRACT

Nowadays, the molecular docking approach is used to model the interaction between a small molecule and a protein at the atomic level, which allow us to characterize the behaviour of small molecules in the binding site of target proteins and to elucidate fundamental biochemical processes, C-KIT, a receptor tyrosine kinase, is involved in intracellular signalling, and the mutated form of C-KIT plays a crucial role in the occurrence of some cancers. In this research, we designed novel thiazolidine-4-one derivatives of 3-ethyl-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one with various benzilidine groups attached to the five-membered imino-thiazolidinone ring and studied molecular docking against C-KIT Tyrosine kinase target protein (1T46). The docking studies of these compounds showed the good interaction of the synthesized molecules with the 1T46 target protein. The ADME studies of these molecules have also been studied to identify which of the synthesized molecules have the potential to cross the Human Intestinal lining (HIA) and the BBB barrier. Out of the 18 molecules studied, 12 derivatives exhibited the good potential to be absorbed by the intestine out of which only one molecule was able to indicate the potential to cross the BBB barrier. There were 5 molecules that could not cross both barriers. These studies could reveal which functionalities present attached to the thiazolidine-4-one could assist in human intestinal absorption and the crossing of the BBB barrier.

Introduction

Computational docking methods are used to screen various possible compounds, searching for new compounds with specific binding properties, or testing a range of modifications of an existing compound. Due to the rapid rise in the amount of molecular biological data available, the computer-aided analysis of molecular interactions becomes more realistic in addition to which as of now the computer

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prediction of the interaction between proteins and small molecules has advanced to the point that it allows accurate prediction of bound conformations and affinity.

Likewise, the binding of small molecule majorly organic compounds which are ligands to large protein targets is significant to both understanding biological processes and designing drugs [1]. As many proteins regulate biological functions by interacting with small molecules, these receptor proteins are often the prime targets for therapeutic agents. Therefore, a detailed understanding of interactions between small molecules and proteins may form the basis for a rational drug-design strategy which is attractive in drug development concept due to two reasons: it may facilitate the development of more selective therapeutic agents with fewer undesirable side effects and will offer some hopes for reduction of the enormous costs and time required in traditional random screening protocols for drug discovery. Hence, by assuming the receptor structure is available in the PDB database, a major challenge in lead discovery and optimization is to predict both ligand orientation as well as binding affinity which could often be referred to as "molecular docking" [2,3].

Molecular docking has become an increasingly important tool for drug discovery and is the most widely employed technique whose goal is to predict the position and orientation of a ligand (a small molecule) when it is bound to a protein receptor or enzyme. The completion of the human genome project has resulted in broadening the scope of new therapeutic targets in drug design and discovery. Accordingly, the advancement in strategies such as excessive high-throughput protein purification, crystallography, and nuclear magnetic resonance (NMR) spectroscopy has been providing structural information of protein–ligand and protein complexes. This leads to the advancement which resulted in the development of computer-aided drug design, also known as molecular docking [4-5]. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design which tries to predict the structure of the intermolecular complex formed between two or more constituent molecules, further trying to predict the position and orientation of a ligand when it is bound to a protein to know the predominant binding modes of a ligand with a protein of known three-dimensional structure. Simply this can be mentioned that docking is a method that predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Usually, these binding partners are biological macromolecules (e.g., protein, DNA/RNA, and peptide) or small molecules (e.g., endogenous ligands and drugs) and their preparations for the docking is just as important as the docking itself [6,7]. The computational approaches are currently being used for screening large databases of compounds to identify potential lead drug molecules. Hence, it can be mentioned that its main application lies in structure-based virtual screening for the identification of new active compounds towards a particular target protein [8]. It can also be stated that for a selected set of structures of a protein and a ligand, the ultimate goal of all docking methods is to predict the structure of the resulting complex and the biological activity of a given ligand.

In this study, molecular docking is performed between receptor i.e. protein molecule and ligand i.e. the novel thiazolidin-4-one derivatives which were already synthesized by the authors. They are the novel thiazolidine-4-one derivatives of 3-ethyl-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-onewhich belong to an important group of heterocyclic compounds containing sulphur, nitrogen, and carbonyl group in the 4^{th} position in a five-member ring [9,10]. They are an important class of bioactive molecules with diverse biological activities, so it is often called "wonder nucleus". Furthermore, thiazolidinone gives out various derivatives which attracted great attention due to the diversity of their biological effects [11] such as antidiarrheal [12], antimicrobial [13], antidiabetic [14,15], antiarrhythmic activity[16], anticancer [17-26], anti-HIV [27], Ca^{2+} channel blocker [28], cardioprotective

[29], anti-ischemic [30], cyclooxygenasesinhibitory [31], and anti-platelet activating factor [32].

C-KIT, a receptor tyrosine kinase, is intricate in intracellular signalling, and the mutated form of C-KIT has important role in existence of some cancers. The role of C-KIT has directed to the thought that inhibiting c-Kit kinase activity can be a goal for cancer therapy [33]. The encouraging results of inhibition of c-Kit for treatment of cancers have been detected in some cancers like gastrointestinal stromal tumour, acute myeloid leukemia, melanoma, and other tumours, and these results have stimulated attempts toward improvement of using c-Kit as a capable target for cancer therapy [34]. The main procedure of handling the cancers is chemotherapy, in which anti-tumour compounds are administered to patients. This treatment is thought to be effective, particularly in the early stages of the disease, but it does not permanently cure the patient or totally extinguish cancer. Many factors are associated to the treatment catastrophe, among which we can remark the stage of the disease, the battle of tumour cells to the drugs, and the side effects of the action as the drugs used kill both the cancer cells and the normal cells, often becoming resistant to treatment [35]. It is therefore important to develop effective anti-cancer therapeutic agents with well-defined pharmacokinetic properties.

Therefore, concerning the potentiality of thiazolidinone compounds and CKIT as potential target for cancer theory, we decided to conduct molecular docking against C-KIT Tyrosine kinase target protein (1T46) of the novel thiazolidine-4-one derivatives of 3-ethyl-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-onewithvarious benzilidine groups attached to the five-membered imino-thiazolidinone ring.

Experimental

Docking studies

In this study, the affinity and binding modes of the examined molecules against the target protein were determined. First, the water molecules were removed from the crystal structures of target proteins, retaining only main-chain amino acids which are essential for binding. The co-crystallized ligands were used as the reference ligands to predict the binding pockets (Figure 1) and later ligand was removed. Then, the polar hydrogen atoms were added to protein structures to protonate them. The structures of the examined compounds were drawn by using ChemDraw Ultra 7.0 and BIOVIA Discovery Studio Visualizer 2021 which were later saved by using PDB formats. Next, the saved files were opened by using MGL AutoDock Tools software where the protein preparation was done and selected as macromolecule then saved in PDBQT format. The configuration file was created which contained receptor name, ligand name, output file name, X, Y, and Z coordinates of the grid box, and also the size X, Y, and Z of the grid box. Then, the ligand was prepared and any rotatable bonds if available were added. Thereafter, the Command Prompt was opened and AutoDock Vina software was used for running the docking process for each target receptor by ligand by entering necessary codes or commands. In each case, 9 docked structural poses, affinity, and RMSD data were generated by using the algorithm. The output from the Vina split software was further analysed and visualized by using BIOVIA Discovery Studio Visualizer 2021.

Figure 1 depicts the structure of the protein **1T46** on which molecular docking of all 18 earlier synthesized compounds have been performed.

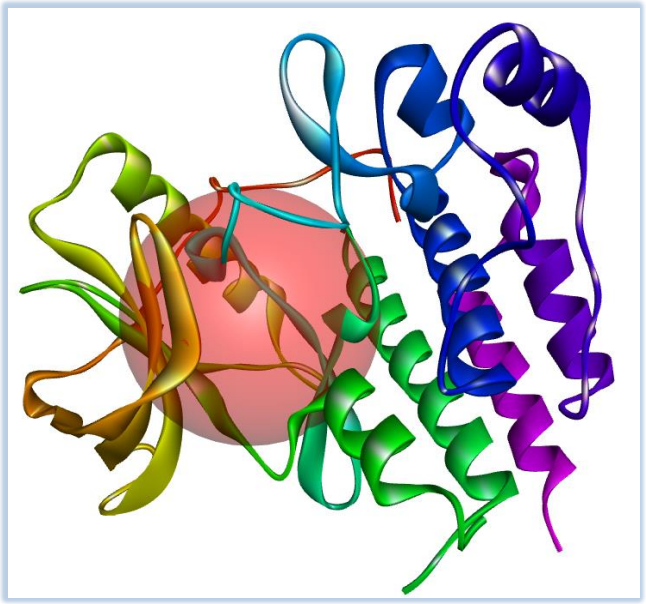


Figure 1. Proteins used for molecular docking - 1T46, C-KIT Tyrosine Kinase target prote0in

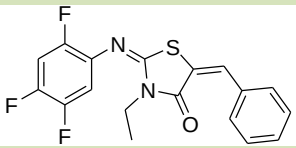
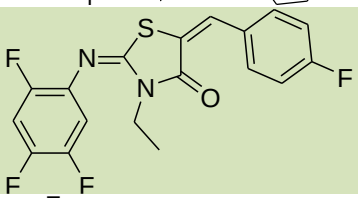
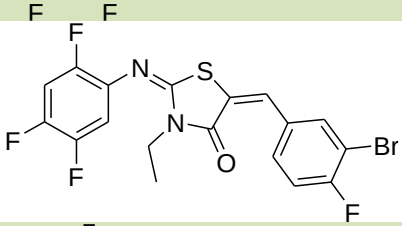
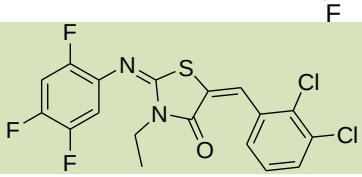
ADME study

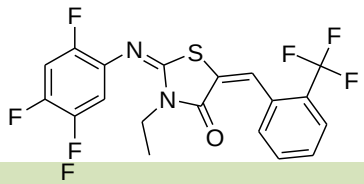
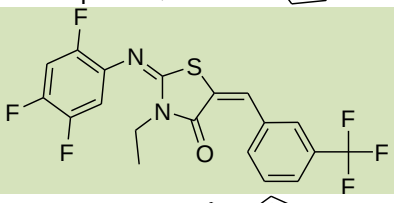
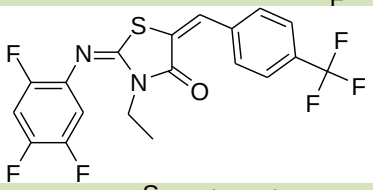
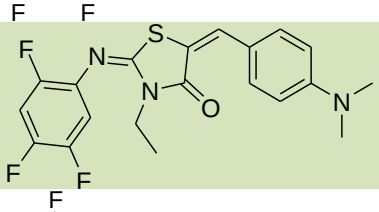
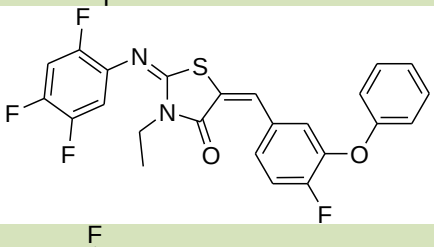
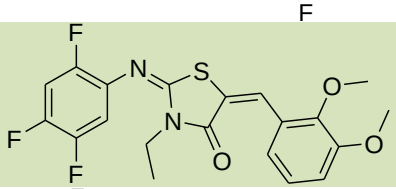
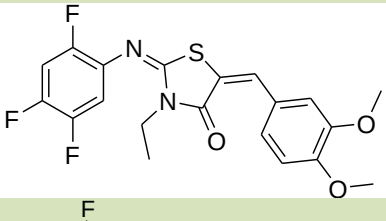
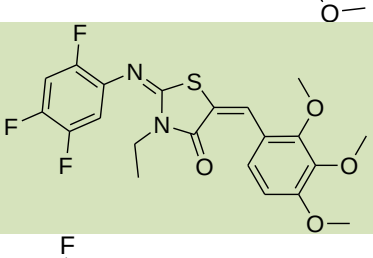
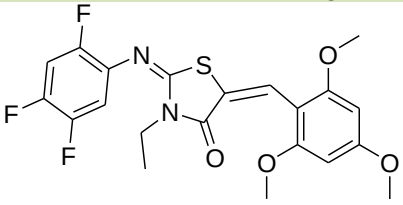
ADME study had been performed by using the Swiss ADME site (SwissADME). Primarily the structures were created with the help of ChemDraw Ultra 7.0 software and later uploaded on the Swiss ADME website to generate Smiles. These Smiles were used to generate ADME analysis data.

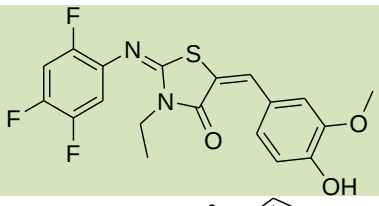
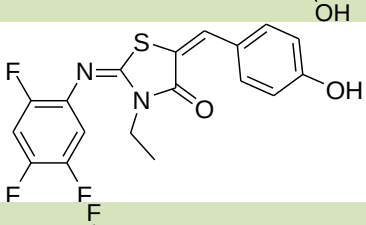
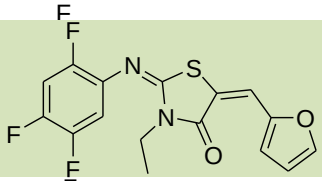
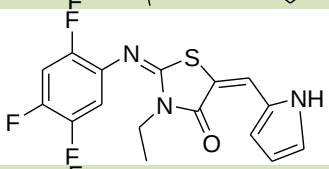
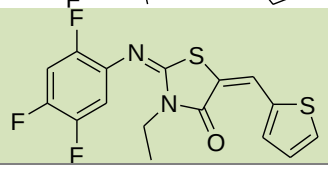
Results and Discussion

Molecular docking

Table 1. Molecules and their characteristics

Molecule No.	Name	Structure	Affinity (kcal/mol)
1	5-Benzylidene-3-ethyl-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one		-10.0
2	3-Ethyl-5-(4-fluoro-benzylidene)-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one		-9.7
3	5-(3-Bromo-4-fluoro-benzylidene)-3-ethyl-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one		-7.2
4	5-(2,3-Dichloro-benzylidene)-3-ethyl-2- (2,4,5-trifluoro-phenylimino)-thiazolidin-4-one		-10.2

5	3-Ethyl-5-(2-trifluoromethyl-benzylidene)-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one		-9.4
6	3-Ethyl-5-(3-trifluoromethyl-benzylidene)-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one		-9.0
7	3-Ethyl-5-(4-trifluoromethyl-benzylidene)-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one		-11.1
8	5-(4-Dimethylamino-benzylidene)-3-ethyl-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one		-7.6
9	3-Ethyl-5-(4-fluoro-3-phenoxy-benzylidene)-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one		-7.8
10	**5-(2,3-**Dimethoxy-benzylidene)-**3-**ethyl-**2-(2,4,5-**trifluoro-phenylimino)-thiazolidin-**4-**one		-9.5
11	**5-(3,4-**Dimethoxy-benzylidene)-**3-**ethyl-**2-(2,4,5-**trifluoro-phenylimino)-thiazolidin-**4-**one		-9.4
12	3-Ethyl-2-(2,4,5-trifluoro-phenylimino)-5-(2,3,4-trimethoxy-benzylidene)-thiazolidin-4-one		-7.1
13	3-Ethyl-2-(2,4,5-trifluoro-phenylimino)-5-(2,4,6-trimethoxy-benzylidene)-thiazolidin-4-one		-6.6

14	3-Ethyl-5-(4-hydroxy-3-methoxy-benzylidene)-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one		-9.5
15	3-Ethyl-5-(4-hydroxy-benzylidene)-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one		-9.5
16	**3-**Ethyl-**5-**furan-**2-**ylmethylene-**2-(2,4,5-**trifluoro-phenylimino)-thiazolidin-**4-**one		-9.5
17	**3-**Ethyl-**5-(1**H-pyrrol-**2-**ylmethylene)-**2-(2,4,5-**trifluoro-phenylimino)-thiazolidin-**4-**one		-9.1
18	**3-**Ethyl-**5-**thiophen-**2-**ylmethylene-**2-(2,4,5-**trifluoro-phenylimino)-thiazolidin-**4-**one		-9.2

➢ 3-Ethyl-5-(4-trifluoromethyl-benzylidene)-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one docking results against **1T46**

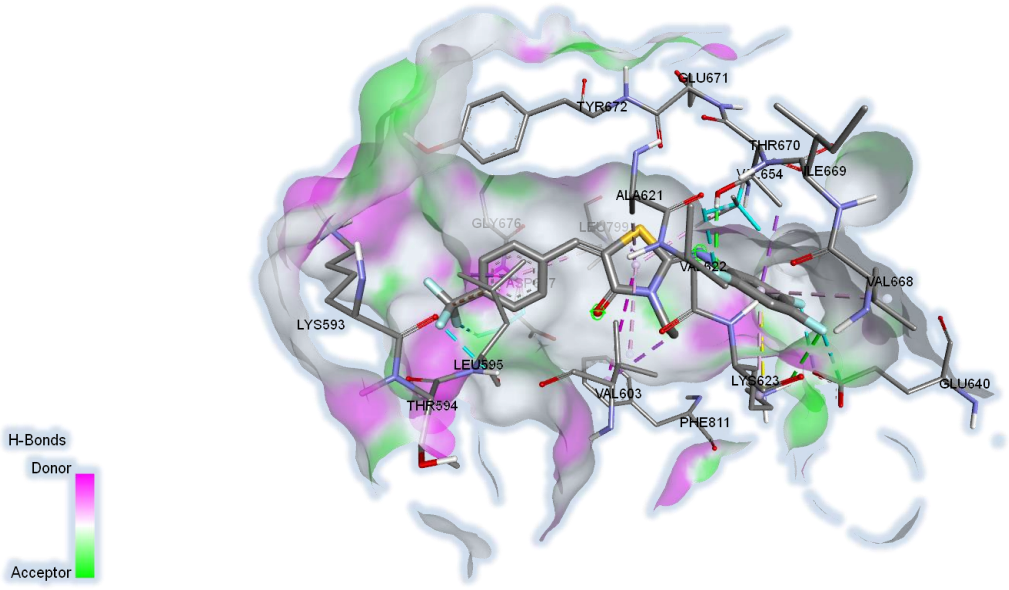


Figure 2. Molecular docking 3D interaction output of 3-Ethyl-5-(4-trifluoromethyl-benzylidene)-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one, **7** against 1T46

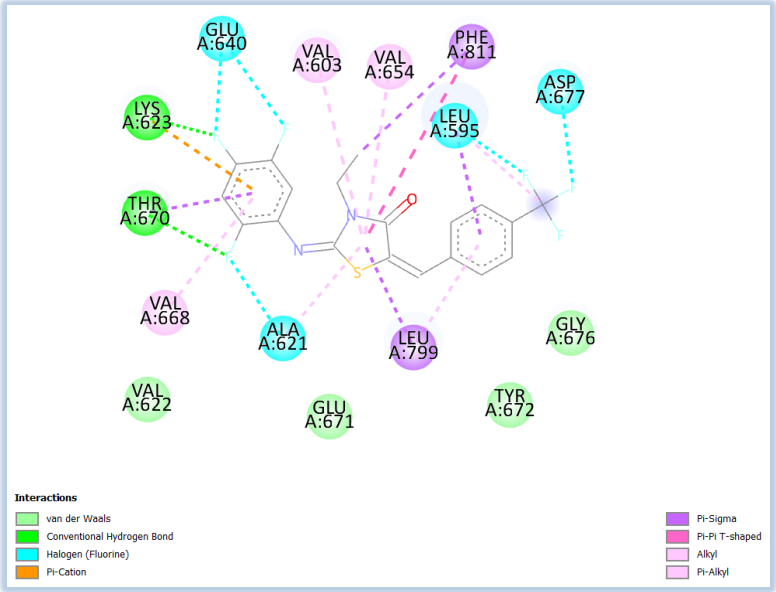


Figure 3. Molecular docking 2D interaction output of 3-Ethyl-5-(4-trifluoromethyl-benzylidene)-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one, 7 against 1T46

To visualize the interactions their 2D diagram and 3D interactions (color of bond interaction is justified in the table) of H-bonds, i.e. donor and acceptor are shown.

Table 2. Total Number of Favourable Interactions: 20

Sr. No.	NAME	COLOUR	DISTANCE	CATEGORY	TYPES OF BONDS	FROM	BONDS	TO	BONDS
1	A:LYS623:HZ3 - :UNK0:F24		2.81639	Hydrogen Bond;Halogen	Conventional Hydrogen Bond;Halogen (Fluorine)	A:LYS623:HZ3	H-Donor;Halogen Acceptor	:UNK0:F24	H-Acceptor;Halogen
2	A:THR670:HG1 - :UNK0:F23		2.56331	Hydrogen Bond;Halogen	Conventional Hydrogen Bond;Halogen (Fluorine)	A:THR670:HG1	H-Donor;Halogen Acceptor	:UNK0:F23	H-Acceptor;Halogen
3	A:LEU595:O - :UNK0:F27		3.2834	Halogen	Halogen (Fluorine)	A:LEU595:O	Halogen Acceptor	:UNK0:F27	Halogen
4	A:ALA621:O - :UNK0:F23		3.61139	Halogen	Halogen (Fluorine)	A:ALA621:O	Halogen Acceptor	:UNK0:F23	Halogen
5	A:GLU640:CD - :UNK0:F24		3.06836	Halogen	Halogen (Fluorine)	A:GLU640:CD	Halogen Acceptor	:UNK0:F24	Halogen
6	A:GLU640:OE1 - :UNK0:F25		2.9049	Halogen	Halogen (Fluorine)	A:GLU640:OE1	Halogen Acceptor	:UNK0:F25	Halogen
7	A:ASP677:OD2:		3.11815	Halogen	Halogen (Fluorine)	A:ASP677:OD2:	Halogen Accepto	:UNK0:F	Halogen

	B -:UNK0:F28					B	r	28	
8	A:LYS623:NZ -:UNK0	4.24359	Electrostatic	Pi-Cation	A:LYS623:NZ	Positive	:UNK0	Pi-Orbitals	
9	A:LEU595:CD2 - :UNK0	3.7209	Hydrophobic	Pi-Sigma	A:LEU595:CD2	C-H	:UNK0	Pi-Orbitals	
10	A:THR670:CG2 - :UNK0	3.43386	Hydrophobic	Pi-Sigma	A:THR670:CG2	C-H	:UNK0	Pi-Orbitals	
11	A:LEU799:CD1 - :UNK0	3.4092	Hydrophobic	Pi-Sigma	A:LEU799:CD1	C-H	:UNK0	Pi-Orbitals	
12	:UNK0:C14 - A:PHE811	3.74416	Hydrophobic	Pi-Sigma	:UNK0:C14	C-H	A:PHE811	Pi-Orbitals	
13	:UNK0 - A:PHE811	5.76464	Hydrophobic	Pi-Pi T-shaped	:UNK0	Pi-Orbitals	A:PHE811	Pi-Orbitals	
14	:UNK0:C26 - A:LEU595	4.64106	Hydrophobic	Alkyl	:UNK0:C26	Alkyl	A:LEU595	Alkyl	
15	:UNK0 - A:LYS623	4.58266	Hydrophobic	Pi-Alkyl	:UNK0	Pi-Orbitals	A:LYS623	Alkyl	
16	:UNK0 - A:VAL668	5.40553	Hydrophobic	Pi-Alkyl	:UNK0	Pi-Orbitals	A:VAL668	Alkyl	
17	:UNK0 - A:VAL603	4.69753	Hydrophobic	Pi-Alkyl	:UNK0	Pi-Orbitals	A:VAL603	Alkyl	
18	:UNK0 - A:ALA621	3.90841	Hydrophobic	Pi-Alkyl	:UNK0	Pi-Orbitals	A:ALA621	Alkyl	
19	:UNK0 - A:VAL654	5.47997	Hydrophobic	Pi-Alkyl	:UNK0	Pi-Orbitals	A:VAL654	Alkyl	
20	:UNK0 - A:LEU799	5.48695	Hydrophobic	Pi-Alkyl	:UNK0	Pi-Orbitals	A:LEU799	Alkyl	

The structure of 3-Ethyl-5-(4-trifluoromethyl-benzylidene)-2-(2, 4, 5-trifluoro-phenylimino)-thiazolidin-4-one as a ligand has been subjected to molecular docking with a protein molecule that would act as a receptor. Docking results observed 9 poses out of which pose having the lowest affinity (kcal/mol) was selected as the best docking pose and was considered for the ligand interaction. Here, 20 favorable interactions were observed where the ligand has bonded at the chosen pocket site in the selected pose. The given table demonstrates the information about the bonds between the ligand and amino acids which contains bond distance, types of bonds, from where the bond is forming and their types. The ligand formed two hydrogen bonds [conventional hydrogen bond with fluorine], five halogen bonds [with fluorine], one electrostaticbond [pi-cation] and twelve hydrophobic interactions [pi-sigma,pi-pi T-shaped, alkyl and pi-alkyl].

ADME study

The results of ADME studies of the 18 compounds have been depicted (Figure 4). Molecules with the absorption potential through the intestine appear in the white portion, while the absorbed molecules with

the potential to cross the BBB barrier appear in the yellow portion. The study shows that molecules **1, 2, 8, 10, 11, 12, 13, 14, 15, 16, 17**, and **18** are capable of being absorbed through the human intestine (HIA). Out of these 12 molecules only molecule **1** is observed to be capable of crossing the BBB barrier. This molecule demonstrates the good permeability potential across the BBB and has no substituents on the phenyl ring attached to the thiazolidin-4-one ring. Likewise, this molecule is demonstrated to follow all five rules of Lipinski's Rule, with no violations of any rule.

Molecule **8** indicates the good potential to be able to cross the BBB barrier, due to the presence of two methyl groups attached to the amine's nitrogen. The presence of heterocycles furan and pyrrole (as in molecules **16** and **17**) are close to the potential molecules that could cross the BBB barrier, while the thiophene presence (as in molecule **18**) decreases its potential to do so, probably due to larger size of sulphur, as compared with oxygen and nitrogen. The molecules **10, 11, 12, 13, 14**, and **15** having methoxy and hydroxyl groups are the good candidates that could be absorbed by the intestine.

Molecules **5, 6**, and **7** possessing $-CF_3$ functionalities, and molecule **9** possessing phenoxy group and fluoro groupson the phenyl ring attached to the thiazolidin-4-one ring, show no potential for absorption through the intestinal lining. The presence of halogen atoms –Br and –Cl is indicated to hamper its potential for intestinal absorption, as observed in molecules **3** and **4**. However, if only the –F group is present on the ring, the intestinal absorption improves and demonstrates more potential to cross the BBB barrier, as observed in the case of molecule **2**.

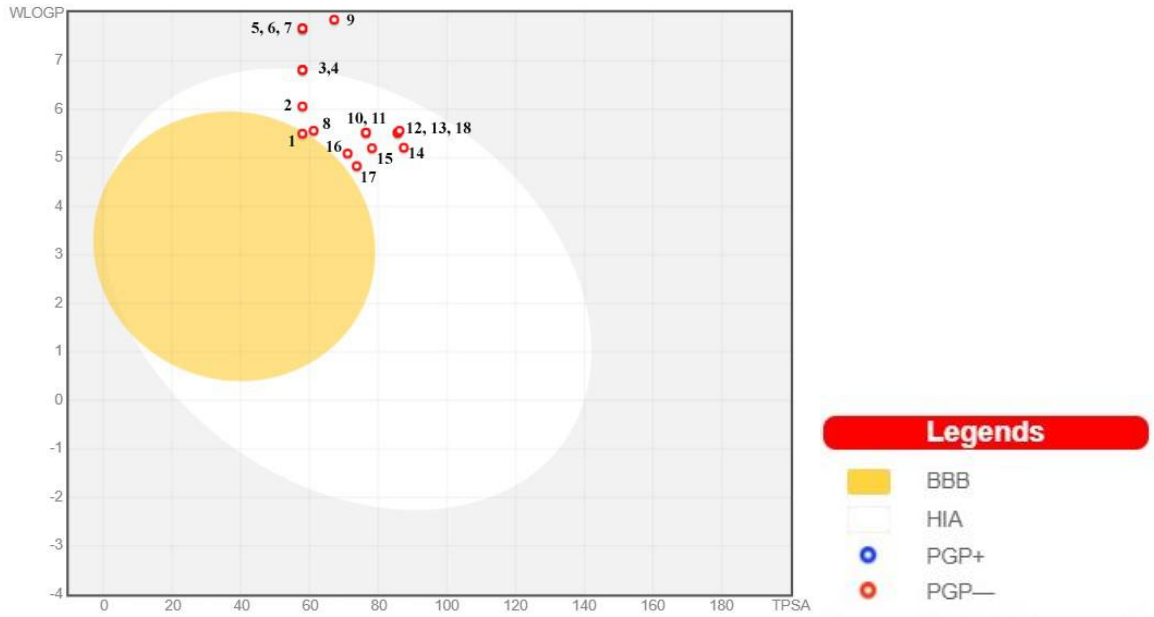


Figure 4. ADME Boiled egg Diagram

Table 3. Physicochemical Properties

Molecule No.	Physicochemical Properties					
	Formula	MW	Number of H-bond acceptors	Number of H-bond donors	MR	TPSA
Molecule 1	$C_{18}H_{13}F_3N_2OS$	362.37	5	0	96.85	57.97
Molecule 2	$C_{18}H_{12}F_4N_2OS$	380.36	6	0	96.81	57.97
Molecule 3	$C_{18}H_{11}BrF_4N_2OS$	459.26	6	0	104.51	57.97
Molecule 4	$C_{18}H_{11}Cl_2F_3N_2OS$	431.26	5	0	106.87	57.97
Molecule 5	$C_{19}H_{12}F_6N_2OS$	430.37	8	0	101.86	57.97
Molecule 6	$C_{19}H_{12}F_6N_2OS$	430.37	8	0	101.86	57.97
Molecule 7	$C_{19}H_{12}F_6N_2OS$	430.37	8	0	101.86	57.97
Molecule 8	$C_{20}H_{18}F_3N_3OS$	405.44	5	0	111.06	61.21
Molecule 9	$C_{24}H_{16}F_4N_2O_2S$	472.45	7	0	123.33	67.2
Molecule 10	$C_{20}H_{17}F_3N_2O_3S$	422.42	7	0	109.84	76.43
Molecule 11	$C_{20}H_{17}F_3N_2O_3S$	422.42	7	0	109.84	76.43
Molecule 12	$C_{21}H_{19}F_3N_2O_4S$	452.45	8	0	116.33	85.66
Molecule 13	$C_{21}H_{19}F_3N_2O_4S$	452.45	8	0	116.33	85.66
Molecule 14	$C_{19}H_{15}F_3N_2O_3S$	408.39	7	1	105.37	87.43
Molecule 15	$C_{18}H_{13}F_3N_2O_2S$	378.37	6	1	98.88	78.2
Molecule 16	$C_{16}H_{11}F_3N_2O_2S$	352.33	6	0	89.12	71.11
Molecule 17	$C_{16}H_{12}F_3N_3OS$	351.35	5	1	91.2	73.76
Molecule 18	$C_{16}H_{11}F_3N_2OS_2$	368.4	5	0	94.73	86.21

Table 4. Lipophilicity

Molecule No.	Lipophilicity					
	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P	Consensus Log P
Molecule 1	3.45	4.88	5.5	4.12	5.5	4.69
Molecule 2	3.67	4.98	6.06	4.51	5.92	5.03
Molecule 3	3.84	5.68	6.82	5.11	6.6	5.61
Molecule 4	3.87	6.14	6.81	5.11	6.79	5.74
Molecule 5	3.72	5.77	7.67	4.95	6.58	5.74
Molecule 6	3.7	5.77	7.67	4.95	6.58	5.73
Molecule 7	3.73	5.77	7.67	4.95	6.58	5.74
Molecule 8	3.73	5.01	5.56	4.39	5.18	4.78
Molecule 9	4.41	6.51	7.85	5.25	7.04	6.21
Molecule 10	3.97	4.83	5.52	3.83	5.63	4.76
Molecule 11	3.76	4.83	5.52	3.83	5.63	4.71

Molecule 12	4.08	4.8	5.52	3.5	5.71	4.72
Molecule 13	4.39	4.8	5.52	3.5	5.71	4.79
Molecule 14	3.62	4.5	5.21	3.61	5.09	4.41
Molecule 15	3.07	4.53	5.2	3.54	5.02	4.27
Molecule 16	3.31	3.98	5.09	2.85	4.89	4.02
Molecule 17	3.09	3.71	4.83	2.85	5.02	3.9
Molecule 18	3.43	4.6	5.56	3.7	6.13	4.69

Table 5. Water Solubility

	Water Solubility											
Molecule No.	**ESOL Log S**	**ESOL Solubility (mg/ml)**	**ESOL Solubility (mol/l)**	**ESOL Class**	**Ali Log S**	**Solubility (mg/ml)**	**Solubility (mol/l)**	**Class**	**Silicos-IT LogSw**	**Silicos-IT Solubility (mg/ml)**	**Silicos-IT Solubility (mol/l)**	**Silicos-IT class**
Molecule 1	-5.32	1.74E-03	4.81E-06	Moderately soluble	-5.83	5.33E-04	1.47E-06	Moderately soluble	-6.72	6.83E-05	1.88E-07	Poorly soluble
Molecule 2	-5.48	1.26E-03	3.32E-06	Moderately soluble	-5.94	4.40E-04	1.16E-06	Moderately soluble	-6.99	3.88E-05	1.02E-07	Poorly soluble
Molecule 3	-6.4	1.84E-04	4.01E-07	Poorly soluble	-6.66	9.99E-05	2.17E-07	Poorly soluble	-7.77	7.78E-06	1.69E-08	Poorly soluble
Molecule 4	-6.51	1.32E-04	3.07E-07	Poorly soluble	-7.14	3.12E-05	7.24E-08	Poorly soluble	-7.9	5.44E-06	1.26E-08	Poorly soluble
Molecule 5	-6.19	2.81E-04	6.52E-07	Poorly soluble	-6.76	7.55E-05	1.75E-07	Poorly soluble	-7.55	1.20E-05	2.79E-08	Poorly soluble
Molecule 6	-6.19	2.81E-04	6.52E-07	Poorly soluble	-6.76	7.55E-05	1.75E-07	Poorly soluble	-7.55	1.20E-05	2.79E-08	Poorly soluble
Molecule 7	-6.19	2.81E-04	6.52E-07	Poorly soluble	-6.76	7.55E-05	1.75E-07	Poorly soluble	-7.55	1.20E-05	2.79E-08	Poorly soluble
Molecule 8	-5.56	1.11E-03	2.73E-06	Moderately soluble	-6.04	3.74E-04	9.22E-07	Poorly soluble	-6.8	6.40E-05	1.58E-07	Poorly soluble
Molecule 9	-6.94	5.37E-05	1.14E-07	Poorly soluble	-7.72	9.05E-06	1.92E-08	Poorly soluble	-9.16	3.25E-07	6.89E-10	Poorly soluble
Molecule 10	-5.48	1.40E-03	3.33E-06	Moderately soluble	-6.17	2.87E-04	6.79E-07	Poorly soluble	-6.93	4.95E-05	1.17E-07	Poorly soluble
Molecule 11	-5.48	1.40E-03	3.33E-06	Moderately soluble	-6.17	2.87E-04	6.79E-07	Poorly soluble	-6.93	4.95E-05	1.17E-07	Poorly soluble
Molecule 12	-5.56	1.25E-03	2.76E-06	Moderately soluble	-6.33	2.11E-04	4.67E-07	Poorly soluble	-7.03	4.22E-05	9.33E-08	Poorly soluble
Molecule 13	-5.56	1.25E-03	2.76E-06	Moderately soluble	-6.33	2.11E-04	4.67E-07	Poorly soluble	-7.03	4.22E-05	9.33E-08	Poorly soluble
Molecule 14	-5.2	2.24E-03	5.49E-06	Moderately	-6.0	3.58E-04	8.77E-07	Poorly soluble	-6.24	2.34E-04	5.74E-07	Poorly soluble

	6			soluble	6							
Molecule 15	-5.18	2.48E-03	6.56E-06	Moderately soluble	-5.89	4.83E-04	1.28E-06	Moderately soluble	-6.14	2.75E-04	7.28E-07	Poorly soluble
Molecule 16	-4.67	7.48E-03	2.12E-05	Moderately soluble	-5.17	2.36E-03	6.69E-06	Moderately soluble	-5.95	3.99E-04	1.13E-06	Moderately soluble
Molecule 17	-4.5	1.12E-02	3.19E-05	Moderately soluble	-4.95	3.94E-03	1.12E-05	Moderately soluble	-5.94	4.00E-04	1.14E-06	Moderately soluble
Molecule 18	-5.16	2.53E-03	6.87E-06	Moderately soluble	-6.14	2.70E-04	7.33E-07	Poorly soluble	-5.99	3.77E-04	1.02E-06	Moderately soluble

Table 6. Pharmacokinetics

Molecule No.	Pharmacokinetics								
	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)
Molecule 1	High	Yes	No	Yes	Yes	Yes	No	No	-5.05
Molecule 2	High	No	No	No	Yes	Yes	No	No	-5.08
Molecule 3	High	No	No	No	Yes	Yes	No	No	-5.07
Molecule 4	High	No	No	No	Yes	Yes	No	No	-4.57
Molecule 5	Low	No	No	No	Yes	Yes	No	No	-4.83
Molecule 6	Low	No	No	No	Yes	Yes	No	No	-4.83
Molecule 7	Low	No	No	No	Yes	Yes	No	No	-4.83
Molecule 8	High	No	No	No	Yes	Yes	No	No	-5.22
Molecule 9	Low	No	No	No	Yes	Yes	No	No	-4.56
Molecule 10	High	No	No	No	Yes	Yes	No	No	-5.45
Molecule 11	High	No	No	No	Yes	Yes	No	No	-5.45
Molecule 12	High	No	No	No	Yes	Yes	No	No	-5.65
Molecule 13	High	No	No	No	Yes	Yes	No	No	-5.65
Molecule 14	High	No	No	No	Yes	Yes	No	No	-5.6
Molecule 15	High	No	No	No	Yes	Yes	No	Yes	-5.39
Molecule 16	High	No	No	Yes	Yes	Yes	No	Yes	-5.62
Molecule 17	High	No	No	Yes	Yes	Yes	No	Yes	-5.81
Molecule 18	High	No	No	Yes	Yes	Yes	No	No	-5.28

Table 7. Druglikeness

Molecule No.	Druglikeness					
	Lipinski Violations	Ghose Violations	Veber Violations	Egan Violations	Muegge Violations	Bioavailability Score
Molecule 1	0	0	0	0	0	0.55
Molecule 2	1	1	0	1	0	0.55
Molecule 3	1	1	0	1	1	0.55
Molecule 4	1	1	0	1	1	0.55
Molecule 5	1	1	0	1	1	0.55
Molecule 6	1	1	0	1	1	0.55
Molecule 7	1	1	0	1	1	0.55
Molecule 8	1	0	0	0	1	0.55
Molecule 9	1	1	0	1	1	0.55
Molecule 10	0	0	0	0	0	0.55
Molecule 11	0	0	0	0	0	0.55
Molecule 12	0	0	0	0	0	0.55
Molecule 13	0	0	0	0	0	0.55
Molecule 14	0	0	0	0	0	0.55
Molecule 15	0	0	0	0	0	0.55
Molecule 16	0	0	0	0	0	0.55
Molecule 17	0	0	0	0	0	0.55
Molecule 18	0	0	0	0	0	0.55

Table 8. Medicinal Chemistry

Molecule No.	Medicinal Chemistry			
	PAINS Alerts	Brenk Alerts	Leadlikeness Violations	Synthetic Accessibility
Molecule 1	0	3	2	3.7
Molecule 2	0	3	2	3.7
Molecule 3	0	3	2	3.72
Molecule 4	0	3	2	3.73
Molecule 5	0	3	2	3.83
Molecule 6	0	3	2	3.8
Molecule 7	0	3	2	3.8
Molecule 8	1	3	2	3.93
Molecule 9	0	3	2	4.03
Molecule 10	0	3	2	3.93
Molecule 11	0	3	2	3.87
Molecule 12	0	3	2	4.08
Molecule 13	0	3	2	4.07
Molecule 14	0	3	2	3.77
Molecule 15	0	3	2	3.67
Molecule 16	0	3	2	3.68
Molecule 17	0	3	2	3.71
Molecule 18	0	3	2	3.67

Conclusion

The synthesized thiazolidin-4-one derivatives have revealed the good interactions with the C-KIT Tyrosine Kinase (1T46) target protein, which indicates the good anti-viral potential of the molecules. The ADME studies show that groups like fluoro, hydroxyl, methyl, and methoxy demonstrate the good human intestinal absorption, which is not the case if chloro, bromo, and trifluoromethyl groups are attached to the heterocyclic ring. The *in-silico* methods can illustrate which functional groups in the molecules could aid in absorption in the body. This could give a proper direction to the synthetic organic chemist for synthesizing bio-active derivatives of thiazolidin-4-one.

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