



Molecular Docking Simulation, Pharmacokinetic and Drug-Likeness Properties Prediction of Some Flavanoid Derivatives as Anti Cholerae Agents

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ABSTRACT

Cholerae is a bacterial disease featured by dehydration and severe diarrhea. It is caused by alimentary infection with *vibrio cholerae*. Due to the wide applicability of plants derivatives in medicinal and pharmaceutical chemistry, a new series of flavonoid compounds were used in this work. In this research, molecular docking studies was carried out on flavonoid derivatives as anti-cholera agents against *V. Cholerae* target (thymine kinase) with the pdb ID: 4BEQ. The drug-likeness and pharmacokinetic properties of the investigated molecules were also studied. The virtual docking stimulation carried out on the anti-cholera agents has explored their theoretical binding affinities with the active sites of the *V. Cholerae* target (thymine kinase). Compound F1, F2, F3, F7 and F8 were selected and discussed out of 13 flavonoid derivatives. Compound F1 has the highest binding affinity of -8.4 Kcal/mol out of the 13 flavonoid derivative investigated. It formed 2 conventional hydrogen bond interactions with LYS125 (2.67 Å) and GLU126 (2.39 Å) amino acid residues. It also formed other interaction with LYS125 and amino acid residue, respectively. The drug-likeness of the studied compounds showed a good response to the Lipinski's rule of five by not violating the filtering criterion thereby confirming its drug-likeness property and oral bioavailability, respectively.

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INTRODUCTION

Cholerae is an infectious disease that causes severe watery diarrhea, which can lead to dehydration and even death if untreated. It is caused by eating food or drinking water contaminated with a bacterium called *Vibrio cholerae* (Ayenigbara *et al.*, 2019).

Cholerae is a bacterial disease usually spread through contaminated water. Cholera causes severe diarrhea and dehydration. Left untreated, cholera can be fatal within hours (Baker-Austin *et al.*, 2018).

In most cases, infection causes only mild diarrhea or no symptoms at all. In 5-10% of cases, however, patients develop very severe watery diarrhea and vomiting from 6 hours to 5 days after exposure to the bacterium. In these cases, the

loss of large amounts of fluids can rapidly leads to severe dehydration. In the absence of adequate treatment, death can occur within hours (Moore *et al.*, 2017).

The concept of computational chemistry like computer-aided drug design (CADD) might save the time of discovering or designing new compounds with better potency, and also reduce the cost of synthesis. Virtual docking simulation is very important when carrying out a structure-based drug design (SBDD). Molecular docking simulation predicts the binding affinities an orientation when two molecules bind with each other to form a stable complex (Ibrahim *et al.*, 2020a).

Drug-likeness properties give the conditions or criteria for drug potency of a



particular chemical compound which include the use of filtering criteria like lipinski's rule of five to predict the drug-likeness of a small molecule, which states that if any chemical violates more than two of these criteria (Molecular weight \leq 500g/mol, Number of hydrogen bond donor \leq 5, Number of hydrogen bond acceptors \leq 10, and calculated logP \leq 5 the molecule is said to be impermeable or badly absorbed) (Lei *et al.*, 2019). The Absorption, Distribution, Metabolism Excretion and Toxicity (ADMET) properties also known as pharmacokinetic properties describe the fate of a small molecule (ligand) in the body of a living organism (Chandrasekaran *et al.*, 2018).

The aim of this work is to carry out molecular docking virtual screening on flavonoid derivatives as anti-cholera agents with the prediction of their drug-likeness and pharmacokinetic properties.

MATERIALS AND METHODS

Table 1: The flavonoid derivatives

S/N	Molecular formula
F1	C ₁₂ H ₂₀ O ₂
F2	C ₁₄ H ₂₃ O ₄
F3	C ₁₆ H ₂₀ O
F4	C ₁₈ H ₁₂ O ₅
F5	C ₆ H ₂₄ O ₅
F6	C ₂₀ H ₁₅ O ₉
F7	C ₂₁ H ₁₃ O ₃
F8	C ₁₄ H ₂₀ O ₆
F9	C ₅ H ₁₉ O ₇
F10	C ₅ H ₂₀ O ₅
F11	C ₁₆ H ₂₄ O ₇
F12	C ₁₂ H ₂₂ O ₃
F13	C ₁₄ H ₂₀ O

Molecular Structure Drawing, Optimum Structure Optimization and Preparation

The structures of the dataset were drawn using chemdraw 12.0 software. After drawing the 2D structures of the dataset, they were automatically converted to 3D by Spartan 14 software before energy minimization. The energy minimization was carried out before finding the most optimum conformation of the dataset using the Spartan 14 software. The most optimum conformation of all the dataset was determined at B3LYP/6-31G* level of theory using Density

Materials

A logiq model M76T computer system, with the following specifications: Genuine Intel(R) CPU 585 @ 2.16GHz, 2.16 GHz, 4.00GB (RAM) with a system type of 64-bit operating system, x64-based processor and a computer name of Desktop-Stall13 was used to explore the nature of interactions between the active site of receptor target (Salmonella typhi) and the ligand (drug) with the help of Pyrex virtual screening software, chimera, and discovery studio (Ibrahim *et al.*, 2019).

Molecular Docking Simulation Method

Collection of Dataset

The dataset which comprises thirteen (13) set of flavonoid derivatives were selected from the literature. Table 1 present the molecular formula for all the dataset used in this research.

Functional theory (DFT) method. Dataset/ligands were prepared from the optimum conformations of the investigated compounds and saved in pdb file format using Spartan'14 for the docking analysis (Ibrahim *et al.*, 2020b).

Target Receptor Preparation

The 3D crystal structure of the DNA thymine kinase receptor with pdb ID: 4BEQ was downloaded from the protein data bank. Discovery studio visualizer was used for the preparation of the enzyme for the docking analysis. In the



preparation process, polar hydrogen was added, Water molecule was removed but no co-crystallized ligand was found on the structure of the receptor and saved in pdb file (Ibrahim *et al.*, 2020c).

Molecular Docking Simulation

The docking of the ligands to the active site of DNA thymine kinase receptor was achieved with the help of Pyrex software using Auto dock vina by following successful docking protocols (Abdullahi *et al.*, 2020).

Recoupling of Docked Ligand, Receptor and Visualization of Complex Interaction

Re-formation of the complexes (ligand-receptor) for further investigation was achieved utilizing chimera software. For a successful reformation of the complexes right protocols were strictly followed. Discovery studio visualizer was used to investigate the interaction of the complexes. The 2D and the 3D structures of the interactions were saved using snipping tool (Ibrahim *et al.*, 2020d).

Drug-likeness and Pharmacokinetic Study

The pharmacokinetics properties or the ADMET properties and the drug likeness

predictions were determined using SwissADME (<http://www.swissadme.ch/index.php>) and pkCSM ([http:// structure.bioc.cam.ac.uk/pkCSM](http://structure.bioc.cam.ac.uk/pkCSM)) free web tools used in evaluating ADMET properties and drug-likeness of small molecules (Daina *et al.*, 2017).

RESULTS AND DISCUSSIONS

Molecular Docking Simulation of the Flavonoid Derivatives

The binding mode of Flavonoid derivatives in the active site of DNA thymine kinase receptor was explored via molecular docking. Table 2 shows the binding affinities and mode of interaction of five the most potent Flavonoid anti-cholera agents. The binding affinities of the studied molecules range from -8.4 Kcal/mol to -5.1 kcal/mol, respectively. From Table 2, molecule F1 was identified to have the highest binding affinity of -8.4 kcal/mol among other selected compounds followed by molecule F2 with a binding affinity of -8.1 kcal/mol, then molecule F3 with a binding affinity of -7.5 Kcal/mol, then molecule F7 with a binding affinity of -7.3 kcal/mol and molecule F8 having a binding affinity of -7.0 kcal/mol, respectively.

Table 2: Binding affinities and mode of interactions of the best five (5) selected ligands

Entry	Binding affinity (Kcal/mol)	Hydrogen bond interactions	Carbon hydrogen bond interactions	Hydrophobic interactions	Electrostatic interactions
F1	-8.4	LYS124 (2.67Å) and GLU126 (1.13Å)	LYS 125 LYS 125	LYS 125	TRP 88
F2	-8.1	LYS125 (2.15Å) and GLU126 (1.13Å)	ARG216 VAL102 LYS125	ILE13	LYS 222
F3	-7.5	GLN56 (2.21 Å) GLN61 (1.13Å)	TRP88	TRP88	
F7	-7.3	ASP70 (2.23Å) ARG73 (2.05Å)	ILE74	ARG73	LYS124
F8	-7.0	ARG13 (2.27Å), LYS140 (2.85Å) and ARG23 (2.43 Å)	TRY12	TRY12, TRY12 and TRP88	VAL127

Compound F1 with the highest binding affinity of -8.4 kcal/mol formed a conventional hydrogen bond with LYS124 (2.67Å) and GLU126 (1.13Å) amino acid residue in the binding pose of

the receptor. It also formed two carbon hydrogen bond with LYS125 amino acid residue in the binding pose of the receptor. Furthermore, it also formed hydrophobic and electrostatic interactions

with LYS 125 and TRP88 amino acid residue residues in the binding pose of the receptor. Its high binding energy may be as a result of the

interactions with the amino acid residues. Figure 1 shows the 2D structure of molecule F1 in complex with DNA thymine kinase receptor.

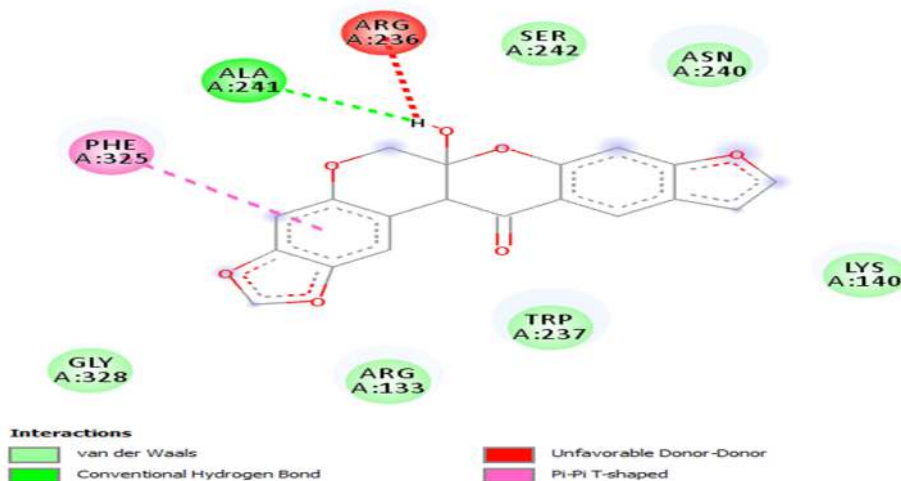


Figure 1: 2D structure of molecule F1 in complex with DNA thymine kinase receptor.

The second ligand with a higher binding affinity of -8.1 Kcal/mol was molecule F2. It formed a conventional hydrogen bond with LYS125 (2.15 Å) and GLU126 (1.13Å), a carbon hydrogen bond with ARG216, VAL102, LYS125 amino acid residues, respectively. A hydrophobic interaction was also observed with ILE13 amino acid residue in the binding pose of the receptor. Not the

mentioned interactions were only observed in the binding pose of the receptor but also electrostatic interaction was also observed with LYS22 amino acid residue respectively. Figure 2 shows the 2D structure of molecule F2 in complex with DNA thymine kinase receptor.

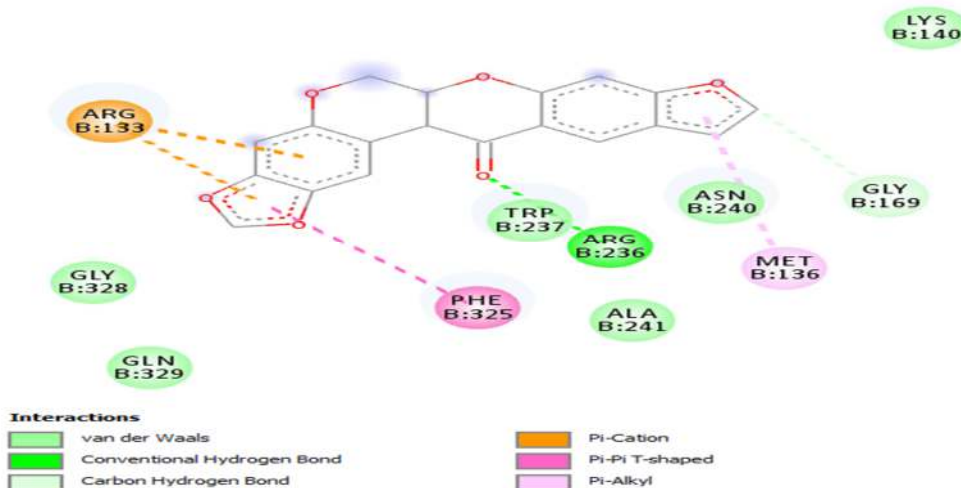


Figure 2: 2D structure of molecule F2 in complex with DNA gyrase B receptor

Molecule F3 is the third in terms of binding affinity (-7.5kcal/mol) which formed a conventional hydrogen bond interaction with GLN56 (2.21 Å), GLN61 (1.13Å) amino acid residues, respectively. A carbon hydrogen bond and hydrophobic interactions were also observed

with TRP88 amino acid residue in the binding pose of the receptor. Figure 3 shows the 2D structure of molecule F3 in complex with thymine kinase receptor.

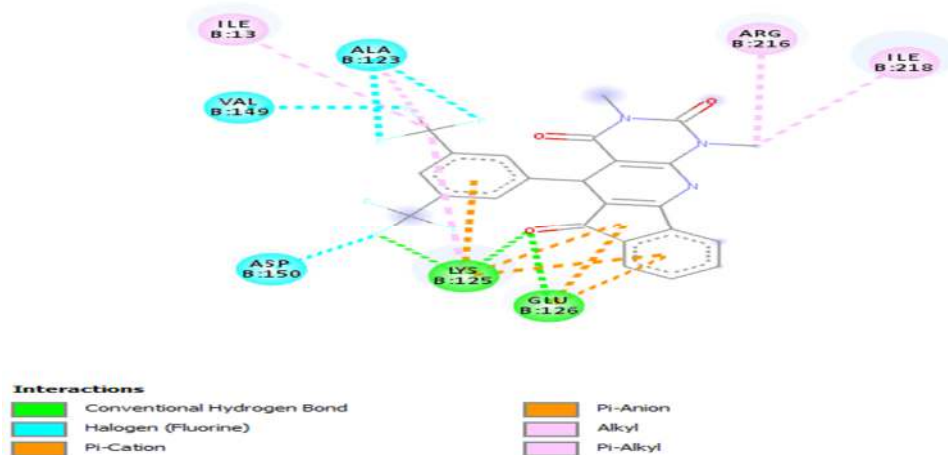


Figure 3: 2D structure of molecule F3 in complex with DNA thymine kinase receptor

Molecule F7 with a binding affinity of -7.3kcal/mol formed a conventional hydrogen bond interaction with ASP70 (2.36Å) and ARG73 (2.05Å) amino acid residues, respectively. Carbon hydrogen bonds were also formed with ILE74 and ILE74 amino acid residues, respectively. Molecules F7 formed hydrophobic interactions

with ILE74 residue as well as electrostatic interaction with ARG73 amino acid residue, respectively. Figure 4 shows the 2D structure of molecule F7 in complex with DNA thymine kinase receptor.

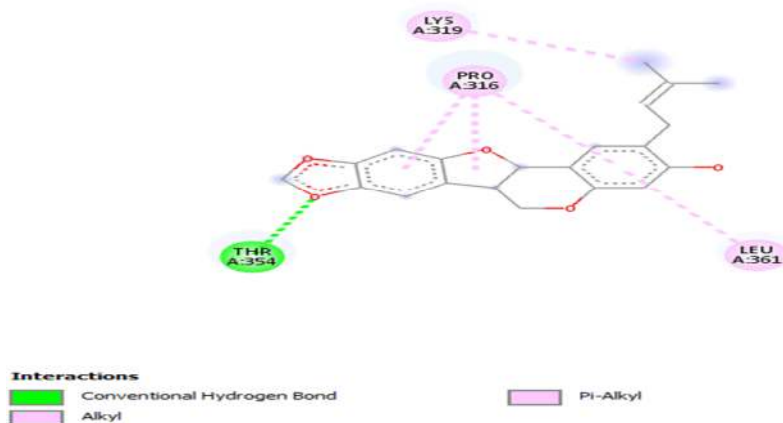


Figure 4: 2D and 3D structure of molecule F7 in complex with DNA thymine kinase receptor

Molecule F8 with - 7.0 kcal/mol binding affinity formed a conventional hydrogen bond interaction with ARG133 (2.27Å), LYS140 (2.33Å) and ARG236 (2.43Å) amino acid residue respectively. A carbon hydrogen bond was observed with TRY12 amino acid in the binding pose of the receptor. Hydrophobic interactions

with TRY12, TRY12 and TRP88 with amino acid residues were observed. Also electrostatic interaction was observed with VAL127 amino acid residue. Figure 5 shows the 2D structure of molecule F8 in complex with DNA thymine kinase receptor.

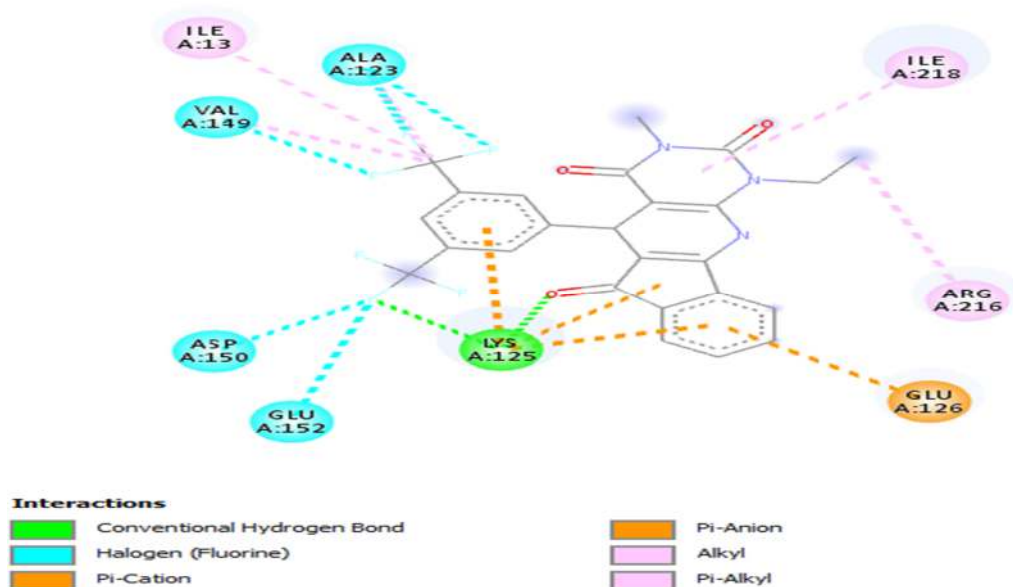


Figure 5: 2D structure of molecule F8 in complex with DNA thymine kinase receptor

Drug- likeness properties of the Flavonoid Derivatives

The drug-likeness of the flavonoid derivatives was predicted following the Lipinski's rule of five (Table 3). All the selected flavonoid derivatives violated neither of the Lipinski rule of five except molecule F3 which have one (1) violation (WLOG P was >5) respectively. Their Molecular Weight was <500, the number of hydrogen bond donors and acceptors for all were

less than 5 and 10, respectively. Since none of the molecules violated more than one of Lipinski's rule of five, in that regard the compounds are predicted to be drug-like in nature, orally bioavailable and active. The Bioavailability Radar gives an overview of the drug-likeness of a molecule (Figure 6). The region painted pink indicates the range for each properties. The bioavailability radar of all the reported compounds is shown in Figure 6.

Table 3: Drug-likeness of the flavonoid derivatives

S/N	M. F	M. W (g/mol)	WLOGP	H. Bond donors	H. Bond acceptors	Lipinski violation
F1	C ₁₂ H ₂₀ O ₂	326.20	5.66	0	4	0
F2	C ₁₄ H ₂₃ O ₄	322.31	4.74	0	5	0
F3	C ₁₆ H ₂₀ O	412.60	8.44	0	4	1
F7	C ₂₁ H ₁₃ O ₃	328.31	4.42	0	5	0
F8	C ₁₄ H ₂₀ O ₆	336.30	4.47	1	5	0

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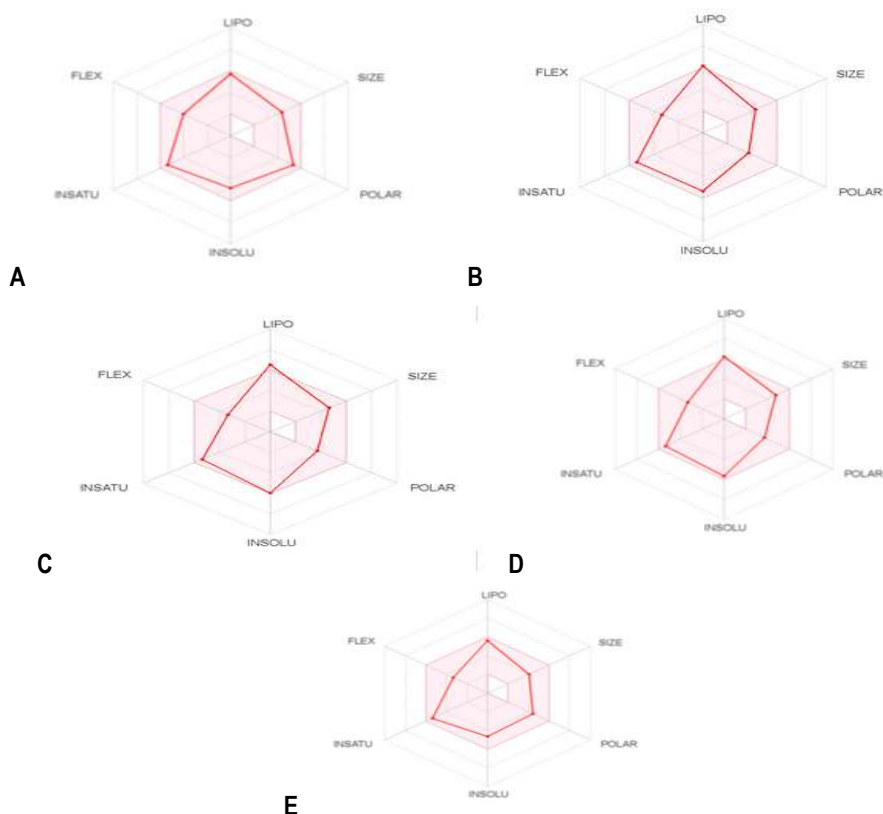


Figure 6: The Bioavailability Radar of (A) molecule F1, (B) molecule F2, (C) molecule F3, (D) molecule F7 and (E) molecule F8

The Pharmacokinetics Properties of the Flavonoid Derivatives

The pharmacokinetics properties predicted for the five selected compounds are presented in Table 4. The intestinal absorption values for these compounds were all above 90% but less than 100%. Their intestinal absorption values have passed the threshold value of 30%, which clearly shows that these flavonoid derivatives have high human intestinal absorption properties. The BBB permeability (log BB) values for some of the selected ligands were < -1 , which signifies those compounds are poorly distributed through the brain. The CNS permeability (log PS) values of some were > -2 which are considered to penetrate the central nervous system. The compound (F1) with the highest binding affinity

was found to be both possess substrate and inhibitors of CYP3A4, there by affirming their metabolic properties. In addition to that, the total clearance for the drug molecule in body was within the permissive limits. With respect to the predicted parameters the compounds are said to have high absorption value, low toxicity level and good permeability to the cell membrane. All the flavonoid derivatives were predicted to have good pharmacokinetic profiles.

The Boiled-egg plot between WLOGP and TPSA to predict gastrointestinal absorption and brain penetration of the selected molecule was shown in (Figure 7). It can be seen that none of the molecule possess the BBB permeant but are within the GI absorption region.

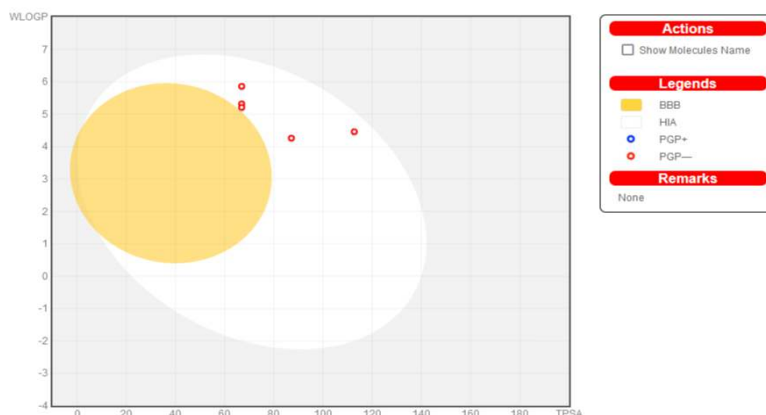


Figure 7: The boiled egg plot of flavonoid derivative

Table 4: The ADMET properties of the five selected Flavonoid derivatives with the highest binding affinity

S/N	Absorption Intestinal absorption	Distribution Permeability		Metabolism						Excretion Total Clearance	Toxicity AMES toxicity	
		BBB Log BB	CNS Log PS	CYP								
				Substrate		Inhibitors						
				2D6	3A4	1A2	2C19	2C9	2D6	3A4		
F1	93.348	-0.707	-2.723	No	Yes	Yes	Yes	Yes	No	Yes	0.217	No
F2	94.298	-0.679	-2.713	No	Yes	Yes	Yes	Yes	No	Yes	-0.169	No
F3	90.939	-0.857	-2.747	No	Yes	Yes	Yes	Yes	No	Yes	0.332	No
F7	90.341	-0.685	-2.889	No	Yes	Yes	Yes	Yes	No	Yes	-0.054	No
F8	93.484	-0.831	-2.996	No	Yes	Yes	Yes	Yes	No	Yes	-0.063	No

BBB=Blood brain barrier, CNS=Central nervous system, CYP=Cytochrome

CONCLUSION

The molecular docking results of the studied compounds in the active site of DNA thymine kinase (receptor) showed that compound F1 had the highest binding affinity of -8.4 Kcal/mol among the other investigated ligands. The drug-likeness and the pharmacokinetic of the compounds which predicted via SwissADME and pkCSM free web tools were found to be pharmacologically active, non-toxic, orally bioavailable and permeable. None of these molecules violate more than one of the Lipinski's rule of five which is the minimum criteria for drug-likeness of a small molecule.

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