



Identification Of Saccharin-Based Anti-Platelet Candidates Computationally Targeting Human Platelet Gp-Vi Receptor As Its Surface Expression Is Enhanced On Platelets In Type-Ii Diabetics.

Mr. Omkar Dhakane, Mr. Akshay Fulsundar, Dr. Rahul Lokhande

Abstract: Increased collagen-mediated platelet activation is associated with diabetes and is a contributing factor to thrombo-ischemic consequences. The primary platelet collagen receptor has just recently been determined to be the platelet glycoprotein VI (GPVI). Diabetes is a major contributor to ischaemic stroke, retinopathy, and chronic renal failure due to accelerated atherosclerosis and diabetic microvascular disease. Collagen-induced platelet activation and aggregation are significantly influenced by platelet glycoprotein VI (GPVI). Additionally, diabetes lowers platelet nitric oxide synthase activity. Therefore, the development of antiplatelet therapies that specifically reduce atherothrombosis without interfering with bleeding control remained an unmet therapeutic demand. Numerous saccharin derivatives that have been shown to exhibit anti-cancer efficacy against isoforms of the human carbonic anhydrase enzyme were subjected to docking and ADMET experiments, after which their physical characteristics were assessed.

Keywords: Saccharine, Anti-platelet, GP-VI receptor, Type-II diabetes, Molecular docking, ADMET.

Introduction: Glycoproteins are essential macromolecules that are involved in a wide range of normal and aberrant physiological states. These essential protein-carbohydrate molecules are found in membranes, hormones, enzymes, and antibodies, among other forms. Glycoproteins have gained attention recently due to their biological significance, since they have been implicated directly or indirectly in diseases like diabetes mellitus. A study conducted in 2004 by Cabeza N. et al. come to the conclusion that diabetes is linked to increased collagen-mediated platelet activation, which is a major factor in thromboischemic consequences. In that study, 385 patients with type-II diabetes had their platelet collagen receptor glycoprotein VI (GPVI) closely examined.

Patients with diabetes had considerably higher surface expression of the platelet Fc receptor, which forms a functional complex with GPVI, than with those without the disease (P, significance value=0.02). The findings suggested that type II diabetes affected or modified the activity of the collagen receptor GPVI, which may be a major factor in atherothrombotic problems. According to the study's findings, GPVI inhibition could emerge as a promising pharmaceutical target for the management of high-risk diabetic patients. The primary pathophysiological process underlying ischemic stroke and myocardial infarction

was considered to be caused by the pathological activation of platelets upon interaction with subendothelial collagen at areas of atherosclerotic plaque erosion or rupture.

The formation of microthrombi, increased platelet-leucocyte aggregation, the release of strong vasoconstrictor and pro-inflammatory molecules, and subsequent impaired microcirculation within the infarcted myocardium are all ways that activated platelets cause ischaemia/reperfusion injury in addition to their important role in acute arterial thrombus formation. A range of antiplatelet medications are now on the market to prevent or treat arterial thrombosis: P2Y₁₂ receptor antagonists prevent the accumulation of platelet activation caused by ADP, cyclooxygenase-1 inhibitor ASA through irreversible blockade of TxA₂ production, and GPIIb-IIIa (integrin α IIb β 3) inhibitors prevent fibrinogen from binding to activated platelets, thereby preventing platelet aggregation.

In order to virtually control unnecessary platelet activation without changing hemostasis and running the danger of life-threatening bleeding complications and disorders, new and unconventional antiplatelet treatments are therefore crucial. This forces GPVI to become the main focus of innovative antithrombotic treatment techniques. This article discusses the potential of GPVI as a target for novel therapeutic strategies in thrombotic and inflammatory diseases based on recent scientific findings and ongoing clinical phase I and phase II trials. It also provides an overview of the dynamic evolution of the system by summarizing docking of potential repurposed ligands, their physical properties, pharmacokinetic and toxicity profiles, and molecular dynamics simulation of the ligand-receptor complex for a fixed period of time.

The benchmark for the docking studies was EXP3179, a metabolite of losartan. According to a 2006 study by Grothusen C. et al., EXP3179, independent of AT₁-Receptor Antagonism, inhibits collagen-dependent platelet activation through glycoprotein receptor-VI. EXP3179 was first identified as an active metabolite of Losartan (LOS), an angiotensin II type 1 (AT₁)-receptor antagonist that is produced when LOS is metabolized by the cytochrome-P450 pathway in the liver. Even if the basal processes did not stay clear, it was observed that EXP3179 was detectable in patients following LOS injection and prevented platelet activation. According to recent findings from other labs, EXP3179 functions as an activator of the peroxisome proliferator-activated receptor and stimulates endothelial nitric oxide synthase (eNOS).

Specifically, EXP3179, a metabolite of losartan that obstructs AT₁ receptors, functions as a selective GPVI inhibitor without the need for AT₁-receptor antagonistic effects. Working with saccharin derivatives, which are known to have anti-cancer properties, is the concept here. Target hunting for the supplied ligand, saccharin, and its docking to the GP-VI receptor produced a binding free energy value that was more negative than the standard used, EXP3179. This develops a theory that could lead to the discovery of saccharin and its derivatives as possible ligands for the antagonism of the human platelet GP-VI receptor (PDB ID: 2GI7).

Drug Discovery: In order to create new treatments, the process of drug discovery involves using computational, experimental, and clinical research. Although this procedure is time-consuming and expensive, it is currently the most widely used method for creating effective medications and therapies for a wide range of illnesses. The utilization of drug discovery is growing as a result of new technologies that enable theoretical and computational research. New medication development frequently starts with data from computational and theoretical investigations. These substances may not be able to be produced and examined in experimental research due to unconfirmed theoretical facts.

Scientists can thoroughly examine the structure and characteristics of both organic and inorganic compounds through a variety of computational investigations that occur during drug discovery, including molecular modeling, molecular docking, and MD simulations. In order to ascertain how a therapy can interact with various chemicals, receptors, and other conditions present in humans or other animals, scientists can delve into the understanding of predicting the affinity of molecules in biological and chemical systems by examining these features. For example, molecular dynamics is frequently employed in drug discovery to find structural voids that are crucial for figuring out binding affinity.

To determine if specific treatments should be synthesized and evaluated clinically or whether additional optimization is required for the design of novel, safer, and more effective medications, this data is then gathered and examined.

Molecular Dynamics: A computational study called molecular dynamic simulations forecasts how each atom in a molecule will move over time. Molecular dynamics is incredibly helpful for simulating the behaviour of chemical and biological settings since it can assess the movement of water, ions, tiny and macromolecules, or even complicated systems. Scientists can learn more about how molecules may interact with one another using this theoretical technique, particularly whether a molecule will leave or stay in a binding pocket. A chemical is generally considered to form a stable complex with the receptor and be energetically favourable if it stays in a binding pocket. However, the complex is unstable if the molecule escapes the binding region.

Low Mode MD:

- i. Low Mode MD is a conformational search technique that concentrates an MD trajectory along the low-mode vibrations by using implicit vibrational analysis.
- ii. Low Mode MD can be used to model ligands and solvents in the active sites, explore the flexibility of specific structural areas of macromolecules like protein loops, and model proteins of recognized families (like antibodies).
- iii. This has the effect of searching for minima along the valleys and troughs on potential energy surface. Low Mode MD is the default conformational search method in MOE because it has the best overall performance on a wide set of structures from small molecules to peptides, macrocycles, and protein loops.
- iv. Additionally, it can be applied to thorough conformational characterization of medium-sized compounds, including macrocycles and short peptides. Additionally, the technique permits the addition of limits and tethers to the system.

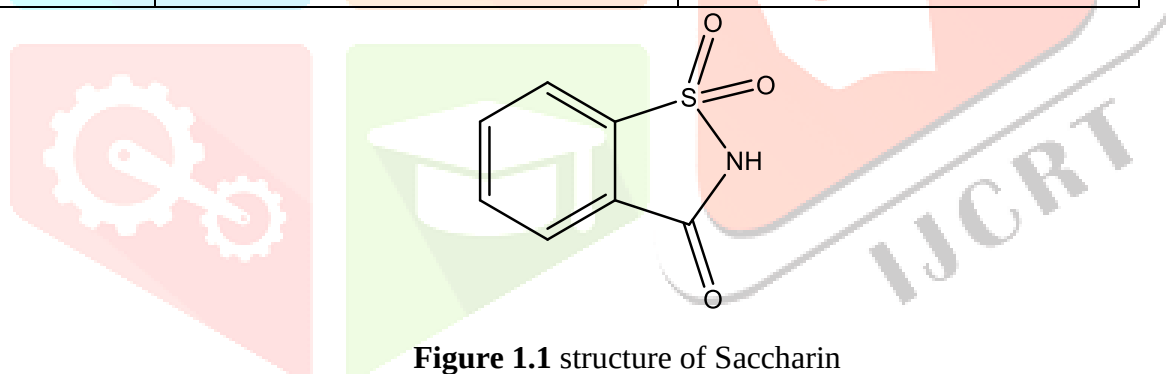
Protein Loop Sampling:

- i. Protein loops and other complex systems with many degrees of freedom, intricate nonbonded interactions, steric hindrance, and structural rigidity that prevent conformational switching can make conformational search extremely difficult.
- ii. For this purpose, classical MD/MC methods are typically quite sluggish since they generate structures with minimal conformational diversity by spending much of their time close to the equilibrium energy conformation.
- iii. Low Mode MD, on the other hand, can effectively explore the conformational space of a protein loop by emphasizing the low mode conformational changes, which are mostly on dihedral rotations.

SACCHARIN: Saccharin is a white, crystalline material that is either odourless or faintly fragrant. It is 500 times sweeter than sugar in diluted aqueous solution, with a sweet taste that can be detected at a dilution of 1:100,000. It also has a bitter, metallic aftertaste. Although it has a bitter or metallic aftertaste, particularly at high concentrations, it is roughly 300–400 times sweeter than sucrose. It is known chemically as 2,3-dihydro-3-oxobenzisulfonazole, or o-sulpha benzamide. It is a toluene sulphonamide derivative that exists as calcium, sodium, and acid saccharin. In solid form, saccharin and its salts are stable, but in solution, they exhibit strong hydrolytic thermal and photostability. It is an organic acid that is weak. This form is neutral.

Table 1.1 Physiochemical properties of Saccharin

Sr.No	Properties	Values
1	IUPAC name	2-benzothiazol-1,1,3-trione
2	Another name benzoic	Sulfimide
3	Appearance	White crystalline solid
4	Chemical formula	C ₇ H ₅ NO ₃ S
5	Molecular weight	183.18 g.mol ⁻¹
6	Density	0.828 g/cm ³
7	Melting point	228.8 to 229.7 °C
8	Solubility in water	3,448 g/L
9	Solubility in ethanol	32,258 g/L
10	Solubility in acetone	83,333 g/L
11	Solubility in glycerol	20 g/L
12	Acidity (pKa)	1.6
13	Molar refractivity	44.72
14	TPSA	71.62
15	Num. heavy atoms	12
16	Num. arom. heavy atoms	6
17	Num. H-bond acceptors	3
18	Num. H-bond donors	1
19	Uv (vis) Spectroscopy maximum	2673 nm

**Figure 1.1** structure of Saccharin

Therapeutic benefits of Saccharin

- An artificial sweetener, saccharin essentially has no nutritional value.
- Products including drinks, sweets, cookies, and medications are sweetened with saccharin.
- The use of saccharin to treat hypertension and hyperglycemia has been studied.
- Saccharin has high GI absorption. But don not cross BBB.
- It has no effect on P-glycoprotein substrate, cytochrome P450 1A2, 2C19, 2C9, 2D6, 3A4 inhibitors.
- Skin permeation (Log K_p = -6.77cm/s).

Methodology:

Ligand Preparation

- i. The molecules were sketched using *ChemDraw Professional 16.0*
- ii. Their .sdf format was saved. Using *OpenBabel GUI 2.4.1*, .sdf format of molecules were converted to their respective SMILES.
- iii. SMILES was pasted to the *Ligand Builder* to get the molecule imported to the MOE workstation.
- iv. Further, energy minimization was done followed by saving the molecules in .moe format.

Protein preparation

- i. The 3D X-ray crystal structure of human platelet Glycoprotein receptor (2GI7) obtained from The Protein Data Bank were imported into the *MOE 2015.10 i4w9*.
- ii. Using the feature *QuickPrep*, structure preparation, 3D protonation allowing ASN/GLN/HIS “Flips” was done.
- iii. Water molecules farther than 4.5Å from the receptor were deleted. Atoms farther than 8Å from the ligands were fixed.
- iv. The receptor was tethered to Strength: 10 and buffer 0.25. Lastly, the complex was refined to an RMS Gradient of 0.1 kcal/mol/Å.

Receptor Active Site Generation

- i. Applying the feature of Site Finder Computing, a list of probable active sites was ranked. As per the literature the active amino acid residues matched with the most suited active amino acid residues predicted by the software viz. 1:(LYS41 LEU42 SER43 ARG60 SER61 ALA63 GLY64 ARG65 ARG166 ASP167 PRO168 TYR169 LEU170) for human platelet Glycoprotein VI receptor (2GI7).

Docking into the Human Platelet Glycoprotein VI receptor binding sites

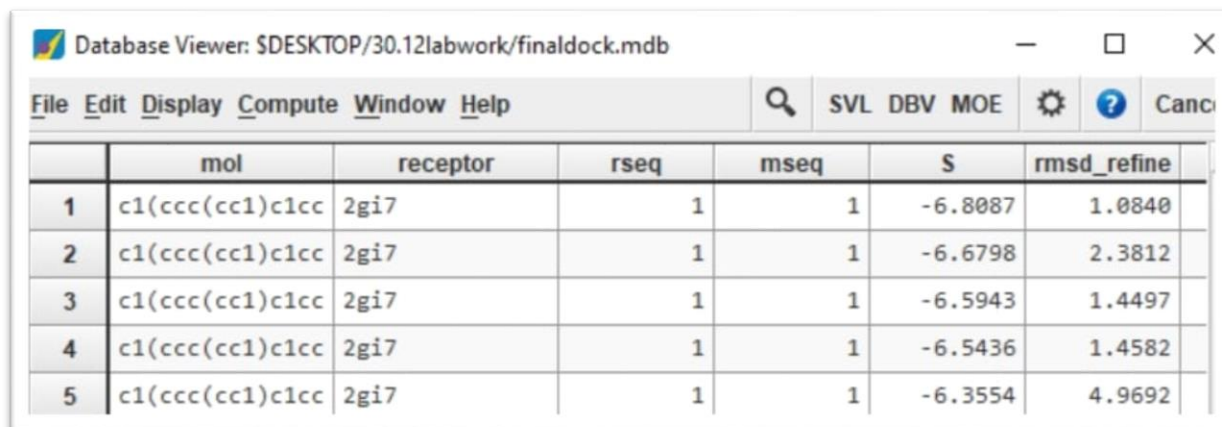
- i. Using Triangle Matcher as the placement method and the active amino acid residues as dummy atoms, the associated Score based on London dG produces 30 poses for a single molecule.
- ii. The top five poses that accounted for the top five binding affinities were determined by refinement to be induced fit and scoring based on GBVI/WSA dG.

Prediction of ADME and toxicity

- i. Nowadays, compared to the traditional medicinal chemistry strategy, high throughput drug discovery techniques have greatly improved the number of lead compounds in a shorter period of time; yet, many of these promising molecules frequently fail because of their inadequate ADMET properties.
- ii. The online pkCSM-pharmacokinetic Server, which forecasts the properties based on graph-based signatures, was used to determine the pharmacokinetic characteristics and toxicities of the compounds.

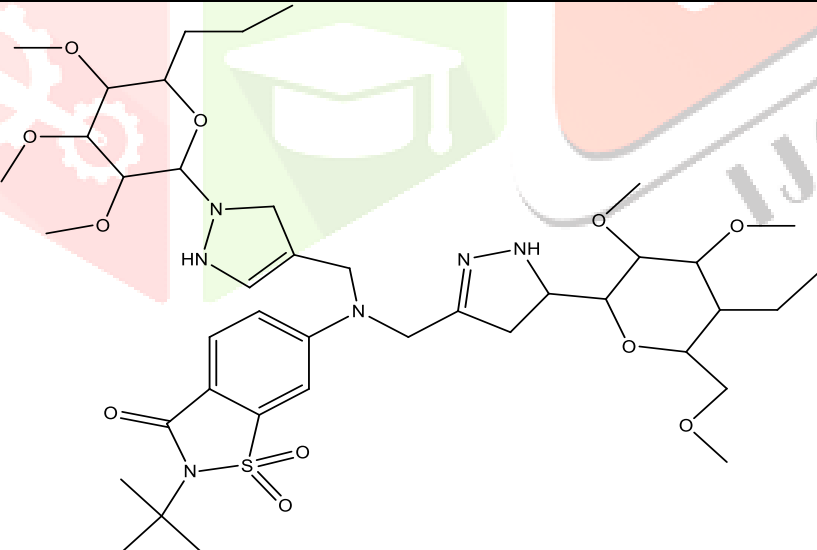
Results

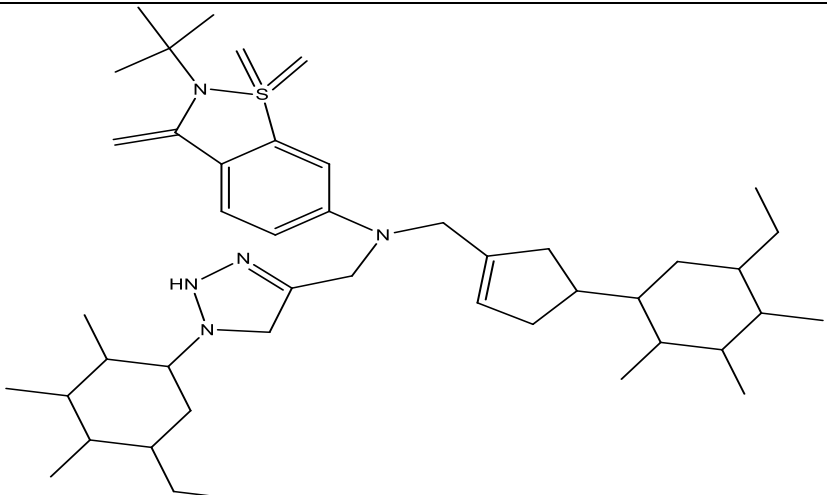
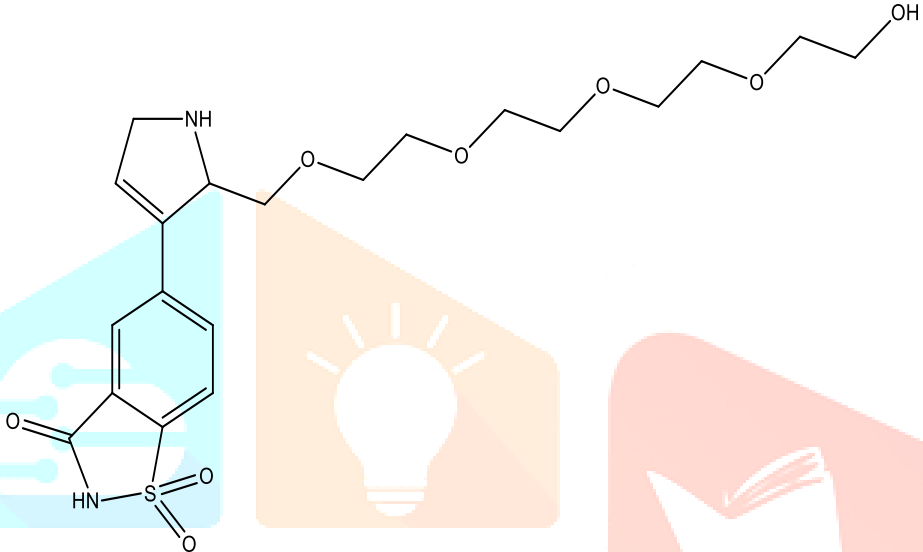
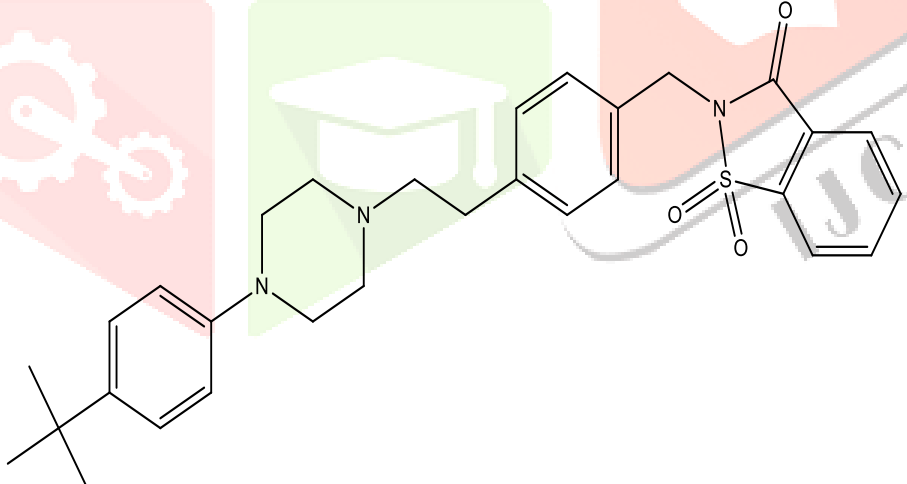
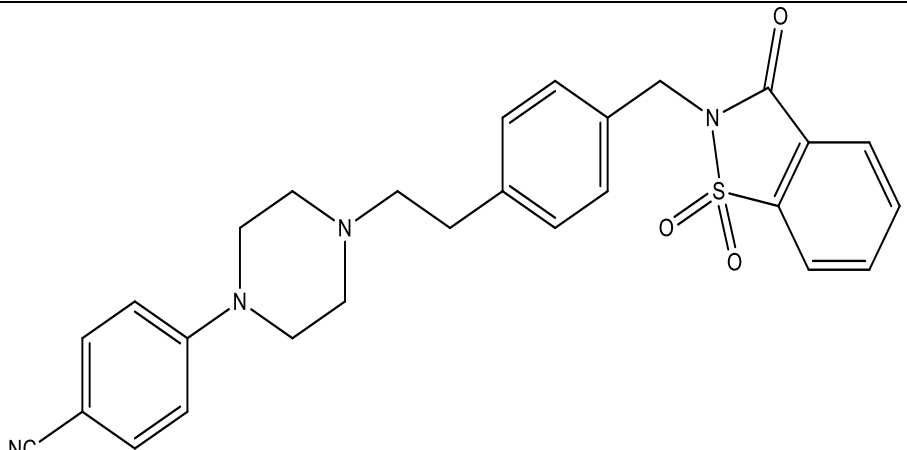
Fig 1.2 scores table for EXP3179 complexed with 2G17

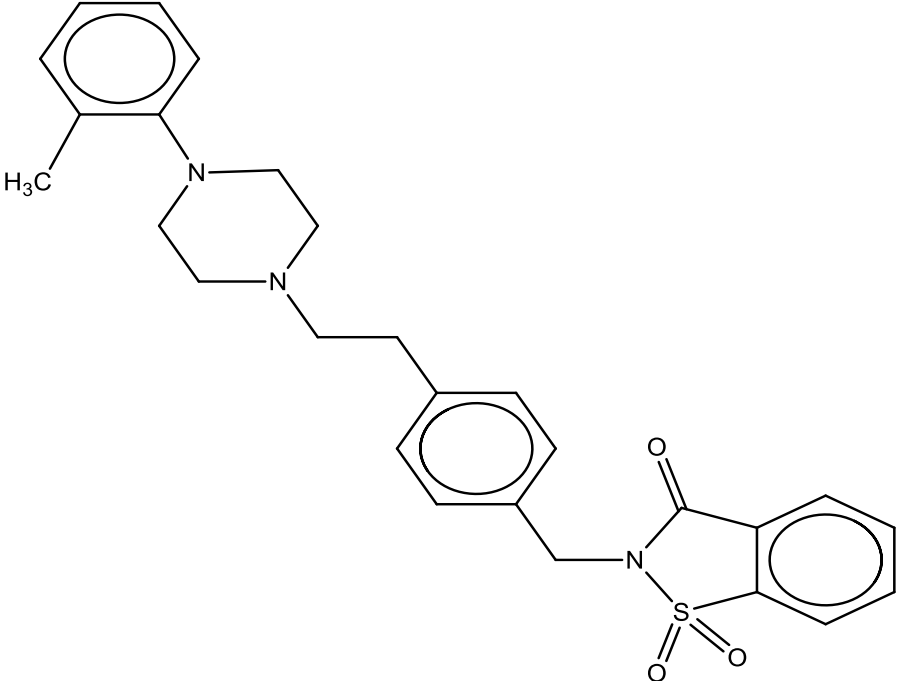
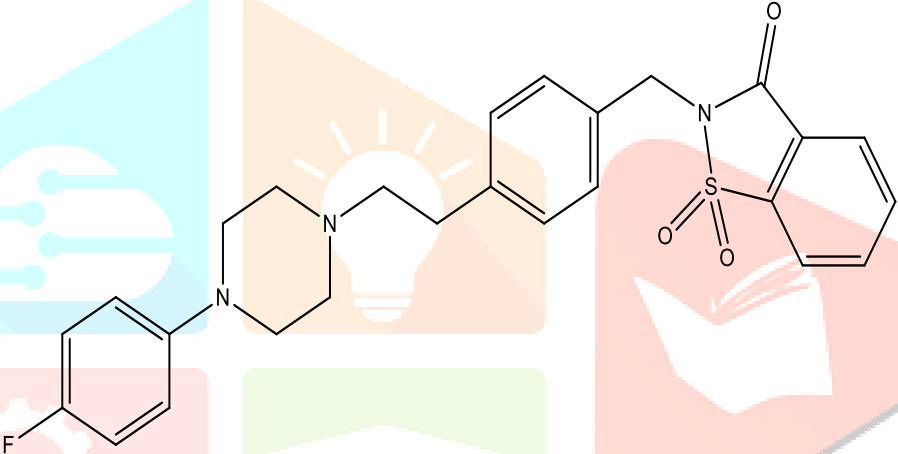
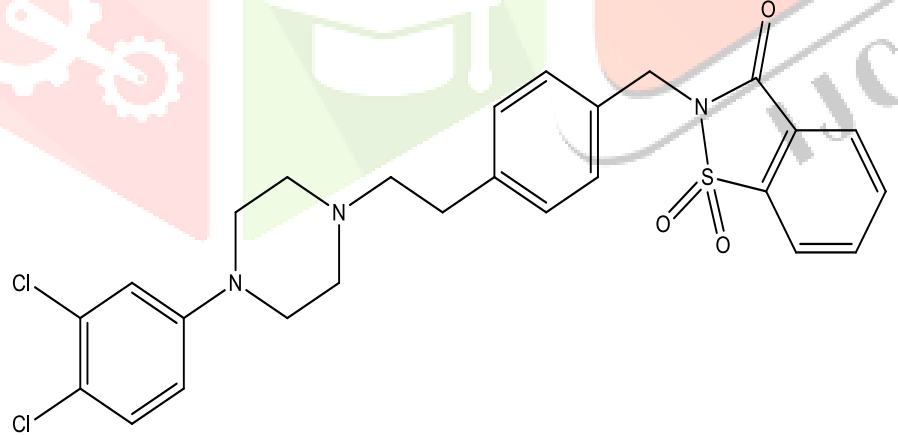
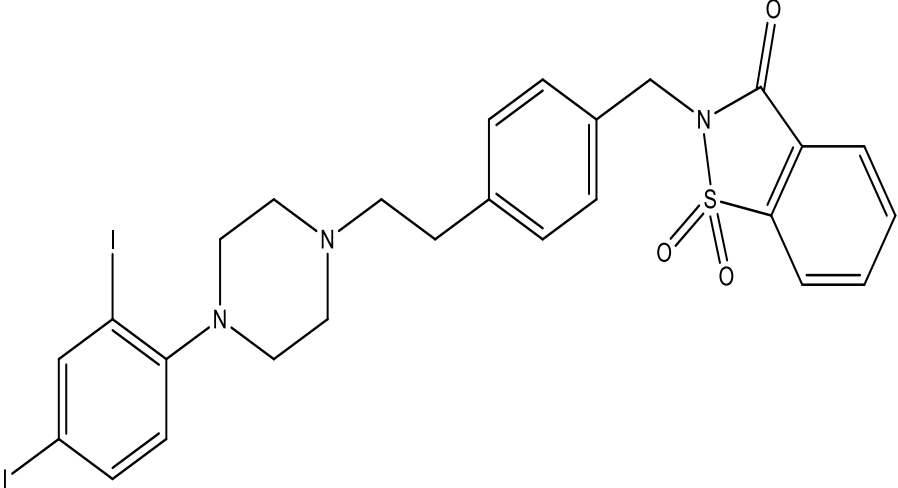


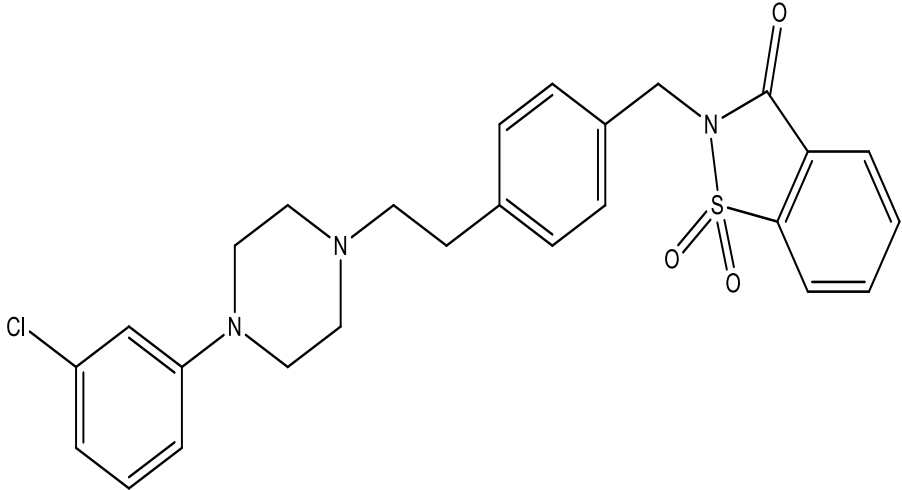
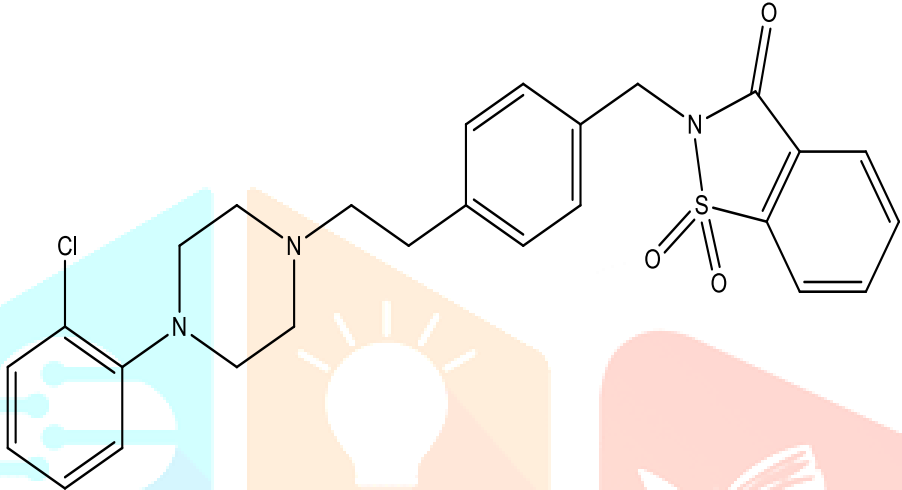
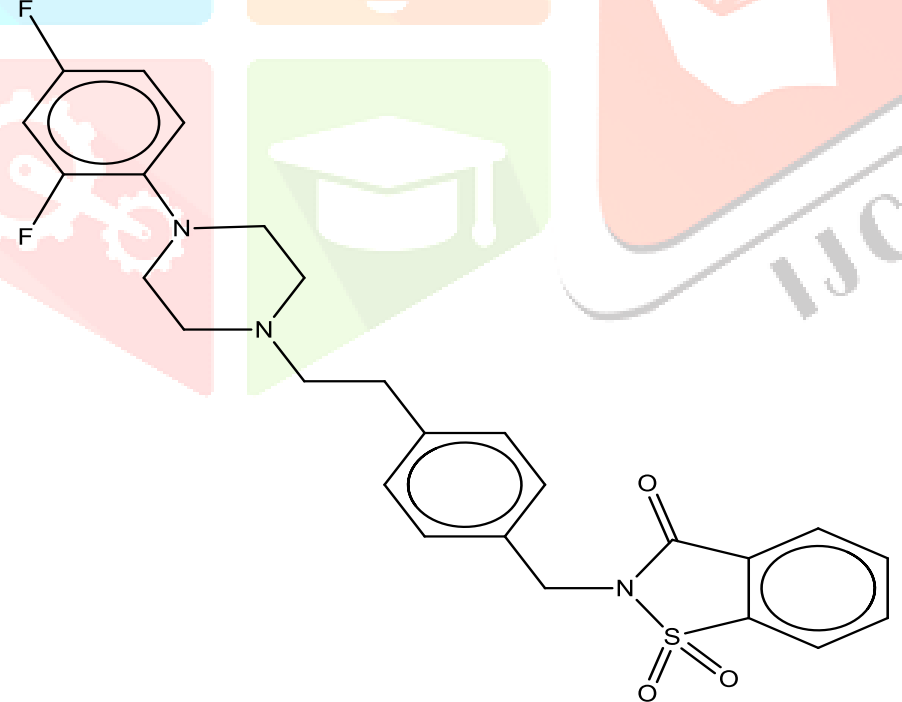
	mol	receptor	rseq	mseq	S	rmsd_refine
1	c1(ccc(cc1)c1cc	2gi7	1	1	-6.8087	1.0840
2	c1(ccc(cc1)c1cc	2gi7	1	1	-6.6798	2.3812
3	c1(ccc(cc1)c1cc	2gi7	1	1	-6.5943	1.4497
4	c1(ccc(cc1)c1cc	2gi7	1	1	-6.5436	1.4582
5	c1(ccc(cc1)c1cc	2gi7	1	1	-6.3554	4.9692

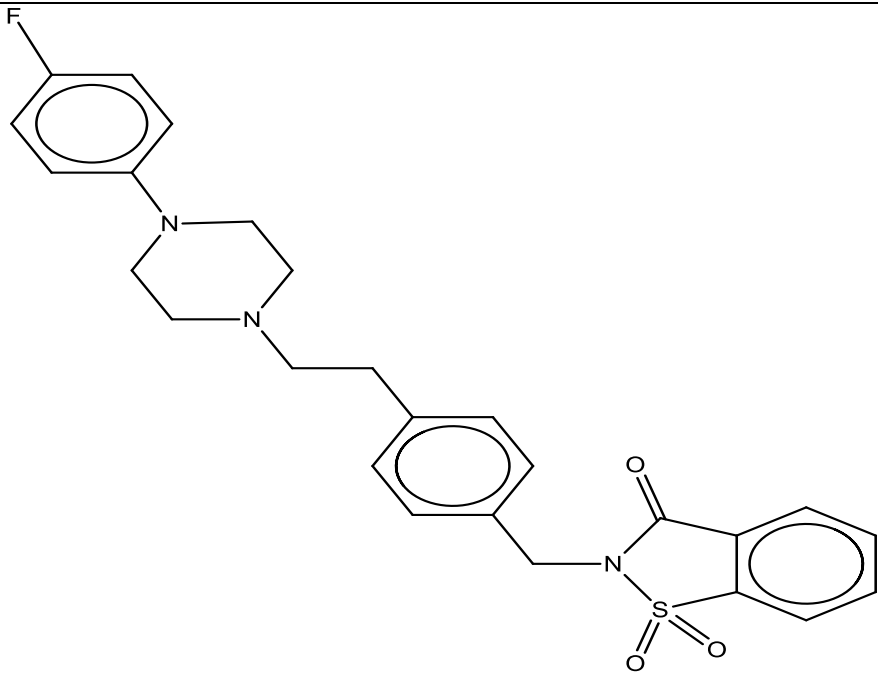
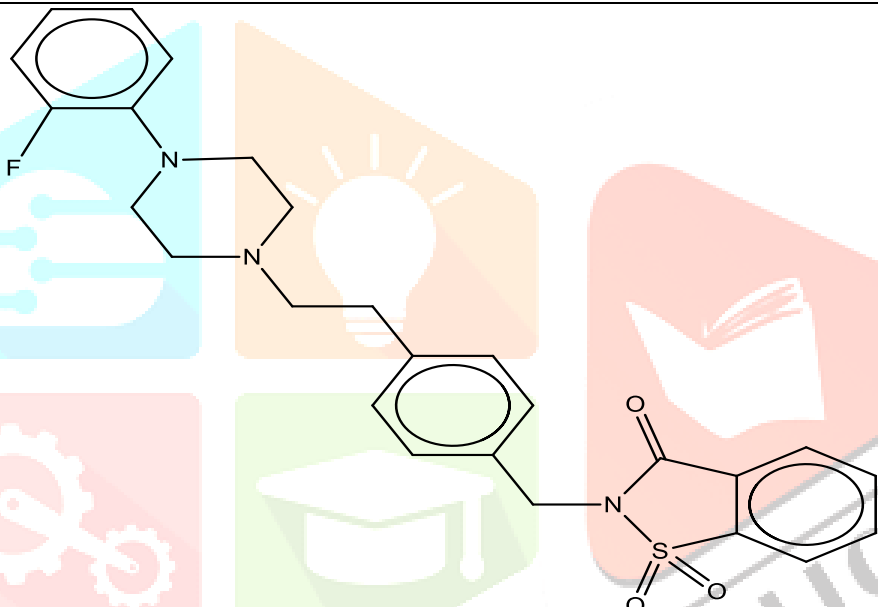
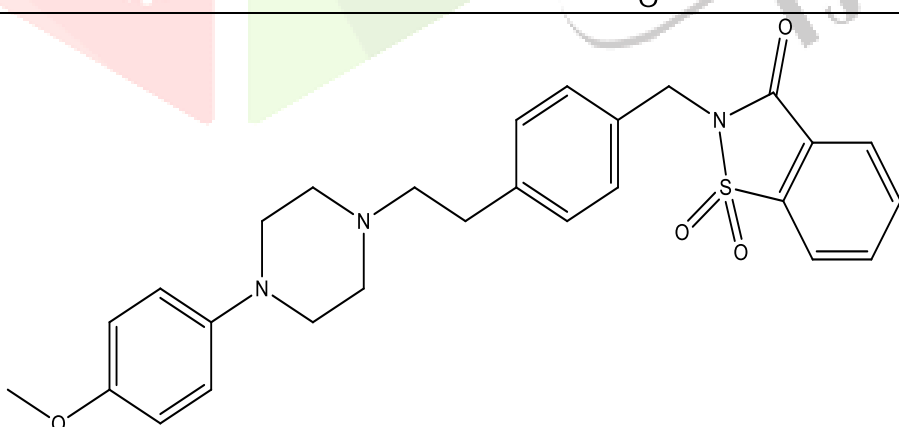
Table 1.2 Docking scores for the series of ligands interacting with target human platelet GP-VI receptor. Standard drug taken: EXP3179, an active metabolite of the angiotensin II type I (AT1) receptor antagonist Losartan (LOS). Docking it to the active site of platelet GP-VI receptor produced an S-score of -6.8087

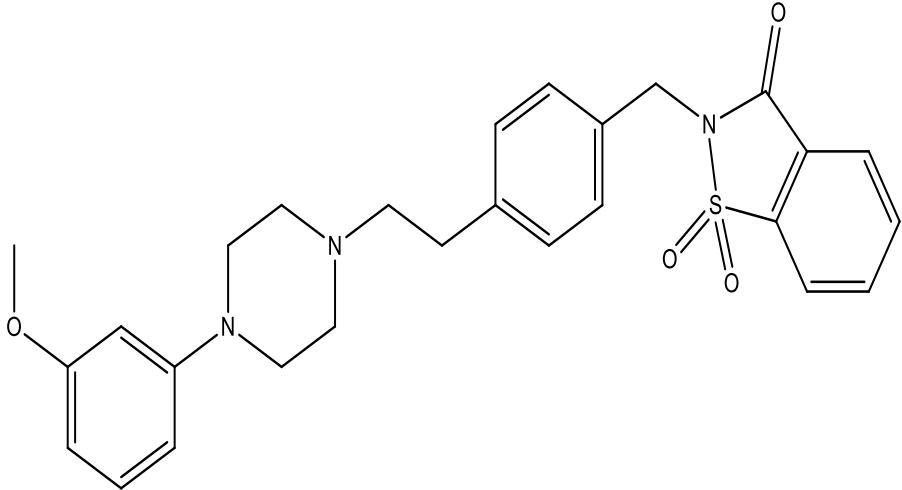
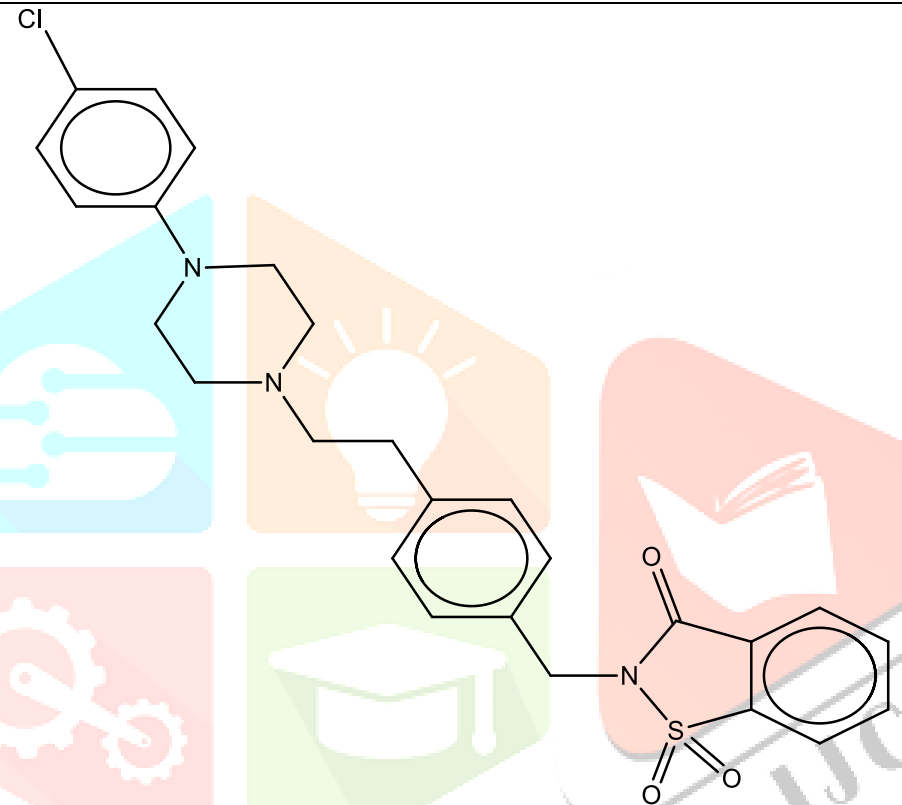
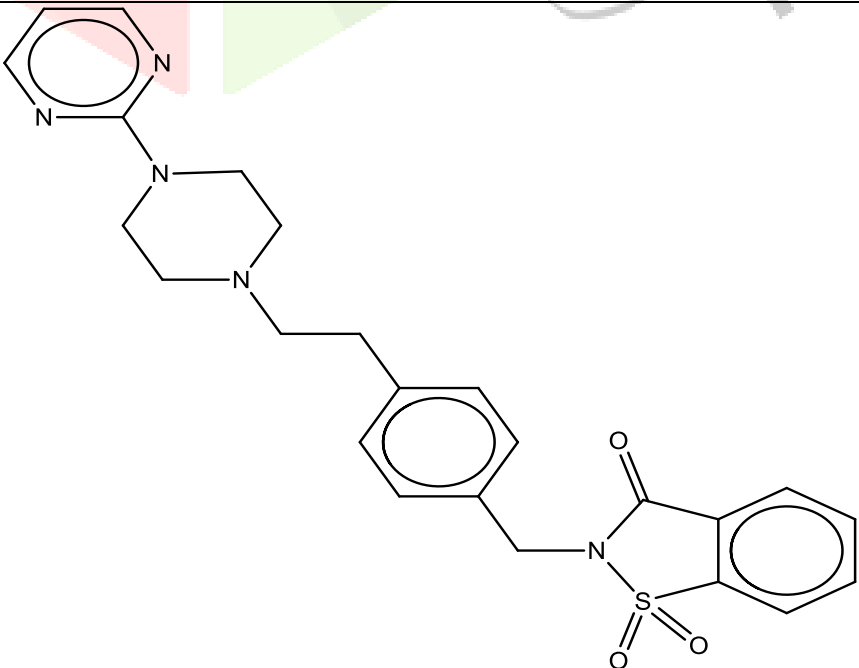
Sr.No	Compound	S-score (kcal/mol) for human platelet GP-VI
1		-9.4021

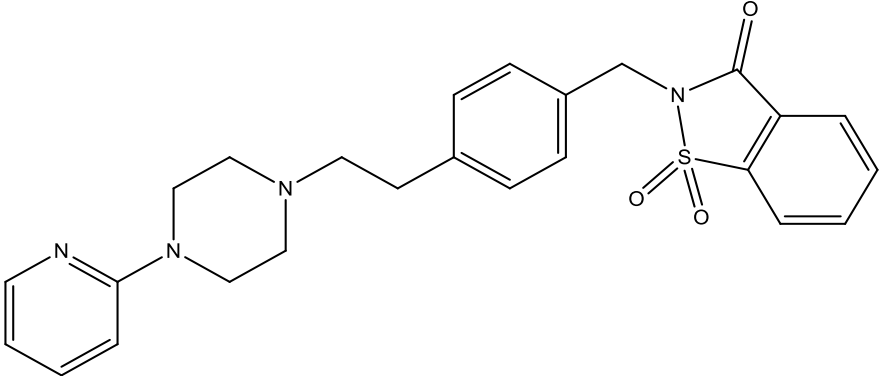
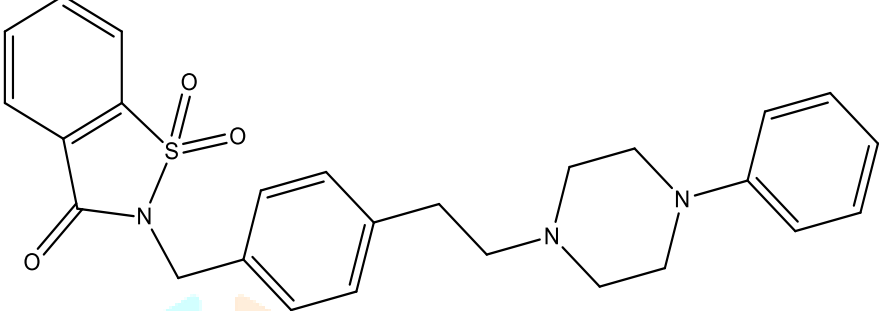
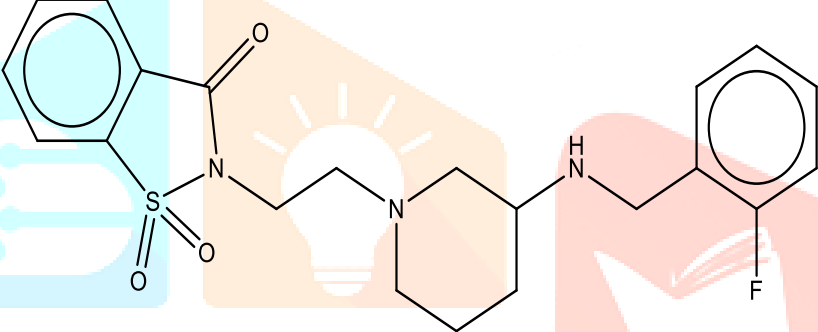
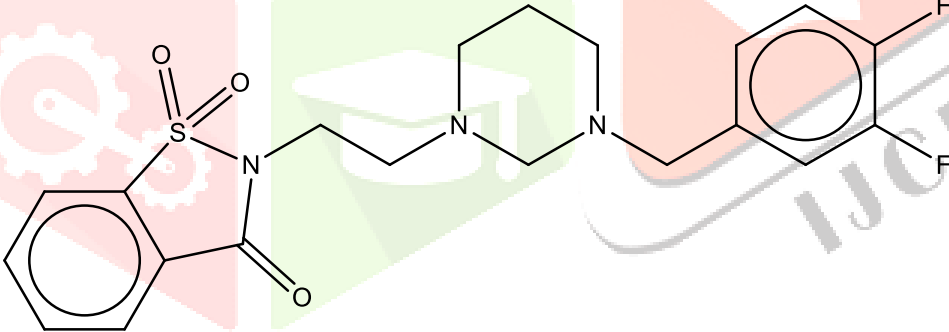
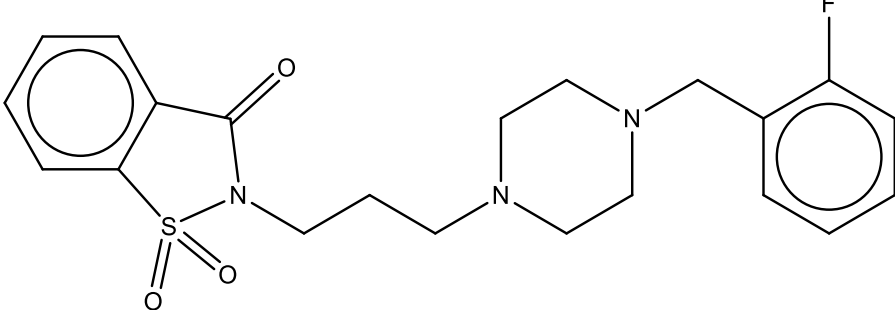
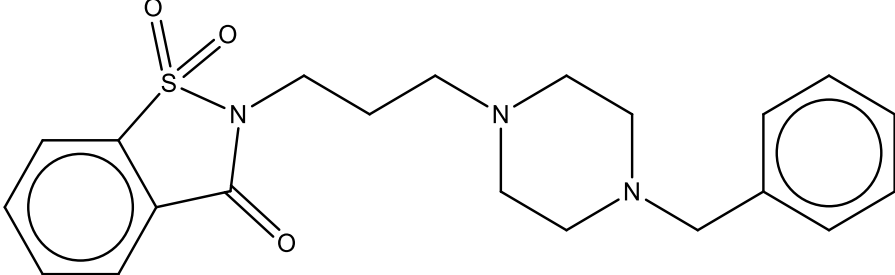
2		-8.6810
3		-7.1238
4		-6.9530
5		-6.9697

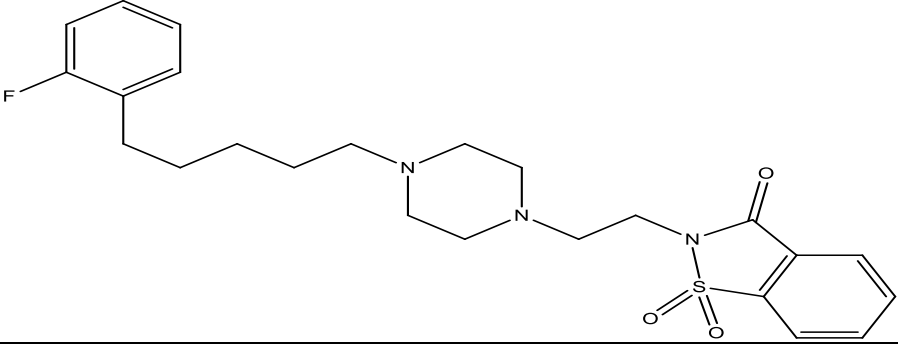
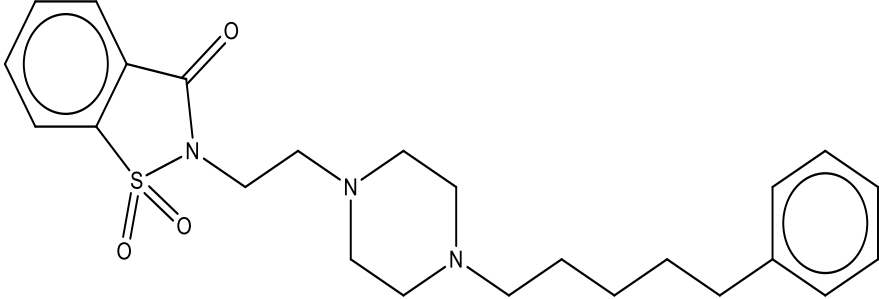
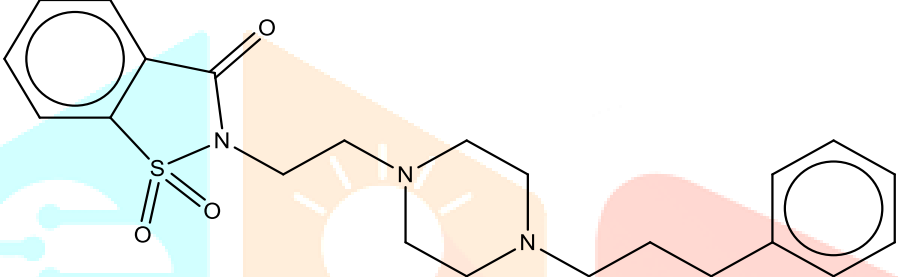
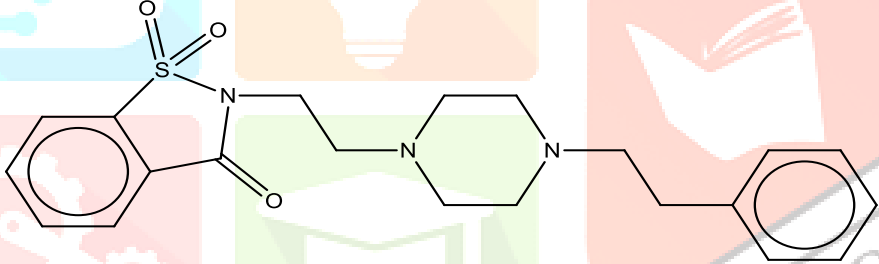
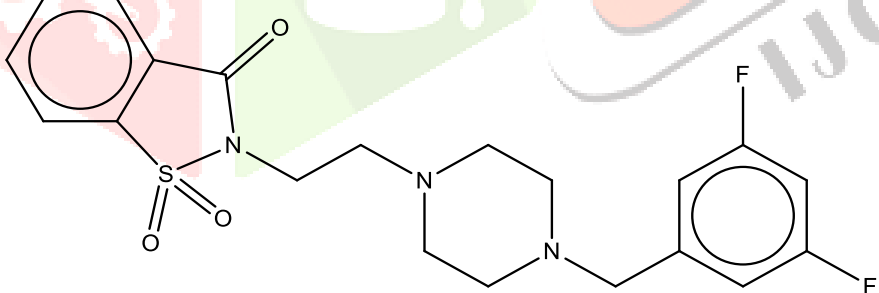
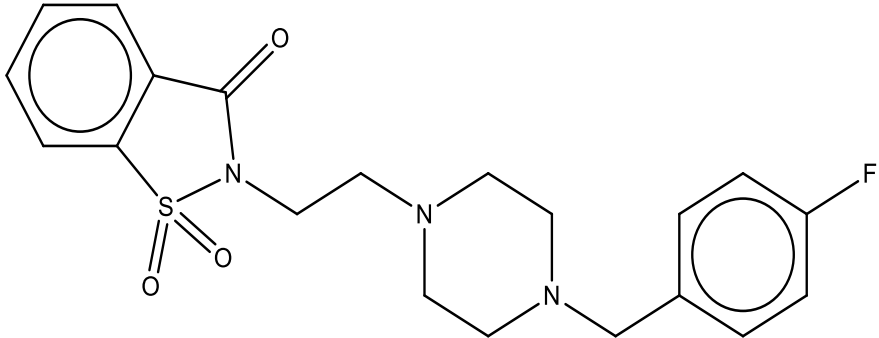
6		-6.6014
7		-7.1770
8		-6.9530
9		-6.4511

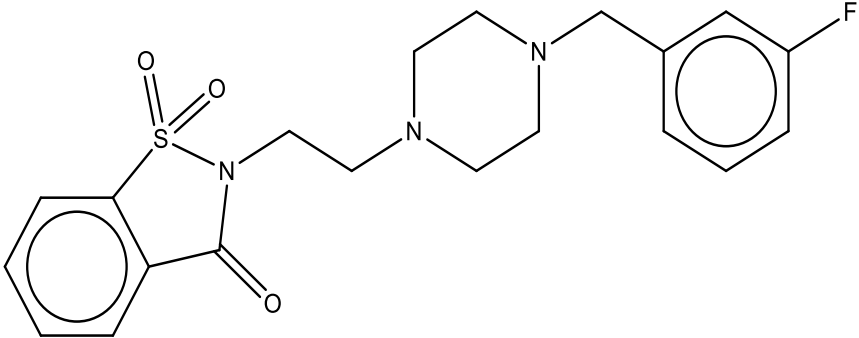
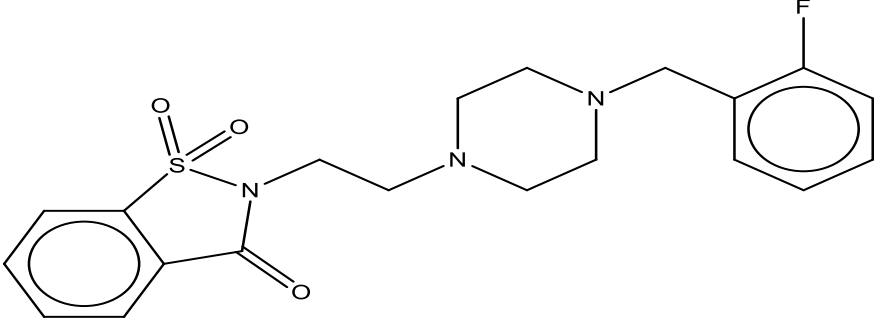
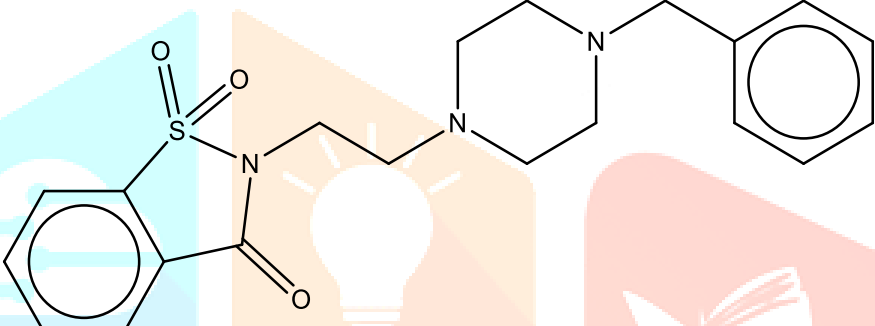
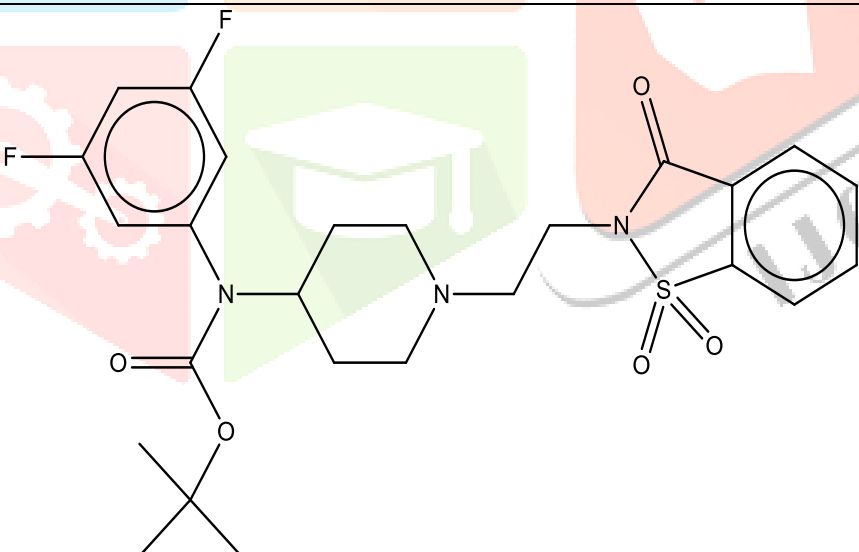
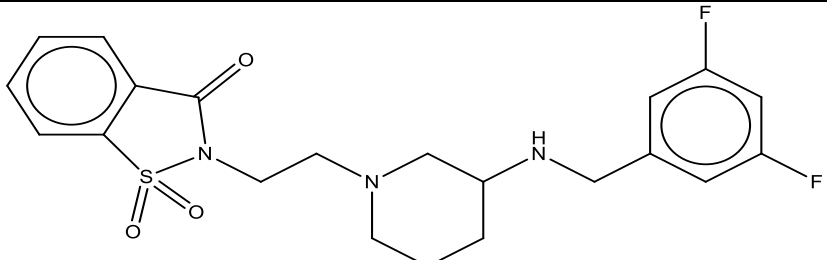
10		-7.0470
11		-6.8991
12		-6.5032

13		-6.4123
14		-6.1236
15		-7.0681

16		-6.9888
17		-6.2114
18		-6.2154

19		-7.0736
20		-6.8772
21		-6.2145
22		-6.9921
23		-6.1254
24		-6.1256

25		-6.9921
26		-6.9921
27		-6.0546
28		-6.0124
29		-6.1265
30		-5.1248

31		-6.0125
32		-6.1987
33		-6.2987
34		-5.1248
35		-6.0125

ADMET and physicochemical Properties

The ADMET and physicochemical properties of molecule with an appreciable S-score are listed below, table-wise.

Table 1.3. The predicted absorption profiles of ligand series targeting the human platelet GP-Vi by using pkCSM server

ABSORPTION					
Sr.No	Compounds	Properties			
		Caco2 permeability	Intestinal Absorption	Skin Permeability	P-glycoprotein I/II inhibitor
1	Mol 01	0.428	41.943	-2.735	No
2	Mol 02	-0.489	0	-2.735	No
3	Mol 03	0.910	66.891	-2.714	No
4	Mol 04	0.90	89.366	-2.733	No
5	Mol 05	1.127	92.802	-2.741	No
6	Mol 06	1.127	92.802	-2.741	Yes
7	Mol 07	0.921	90.911	-2.732	No
8	Mol 08	0.934	89.317	-2.731	No
9	Mol 09	0.911	91.018	-2.74	No
10	Mol 10	0.90	90.978	-2.733	No
11	Mol 11	0.948	90.978	-2.733	No
12	Mol 13	0.951	91.652	-2.738	No
13	Mol 14	0.917	91.652	-2.738	No
14	Mol 15	1.099	92.636	-2.736	No
15	Mol 16	1.099	92.636	-2.736	No
16	Mol 17	0.920	92.208	-2.734	No
17	Mol 19	1.51	94.491	-2.76	No
18	Mol 20	0.932	92.439	-2.735	No
19	Mol 21	0.90	91.467	-2.735	No
20	Mol 23	1.079	92.573	-2.748	No
21	Mol 24	1.082	93.331	-2.748	Yes
22	Mol 25	1.055	91.703	-2.724	Yes
23	Mol 26	1.062	92.805	-2.724	No
24	Mol 27	1.058	92.462	-2.722	Yes

Table 1.4. The predicted distribution profiles of ligand series targeting the human platelet GP-VI using pkCSM server.

Sr.no	Compounds	DISTRIBUTION			
		Properties			
		VDss (human)	Fraction unbound (human)	BBB Permeability	CNS Permeability
1	Mol 01	-0.401	0.225	-3.559	-4.554
2	Mol 02	-1.016	0.498	-1.883	-5.56
3	Mol 03	-0.785	0.591	-1.561	-3.476
4	Mol 04	0.428	0.013	0.298	-3.037
5	Mol 05	0.413	0.03	-0.527	-3.255
6	Mol 06	0.413	0.03	-0.527	-3.255
7	Mol 07	0.513	0.021	0.222	-3.057
8	Mol 08	0.497	0.011	0.223	-2.965
9	Mol 09	0.214	0.045	0.268	-2.261
10	Mol 10	0.5	0.023	0.223	-2.079
11	Mol 11	0.5	0.023	0.223	-2.079
12	Mol 13	0.339	0.035	0.231	-2.224
13	Mol 14	0.039	0.035	0.231	-2.224
14	Mol 15	0.384	0.041	-0.591	-3.358
15	Mol 16	0.384	0.041	-0.591	-3.358
16	Mol 17	0.524	0.026	0.251	-2.111
17	Mol 19	0.41	0.1	-0.706	-2.521
18	Mol 20	0.502	0.036	0.424	-2.194
19	Mol 21	0.615	0.228	-0.487	-2.65
20	Mol 23	1.047	0.213	0.515	-2.555
21	Mol 24	1.234	0.213	0.522	-2.516
22	Mol 25	1.013	0.132	0.373	-2.661
23	Mol 26	1.185	0.161	0.423	-2.61
24	Mol 27	1.119	0.131	0.381	-2.622

Table 1.5. The predicted metabolism profiles of ligand series targeting the human platelet GP-VI by using pkCSM server

Sr.no	Compounds	METABOLISM				
		Properties				
		CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
1	Mol 01	No	No	No	No	No
2	Mol 02	No	No	No	No	No
3	Mol 03	No	No	No	No	No
4	Mol 04	No	No	Yes	Yes	No
5	Mol 05	No	No	Yes	No	No
6	Mol 06	No	Yes	Yes	Yes	No
7	Mol 07	No	Yes	Yes	Yes	No
8	Mol 08	No	Yes	Yes	Yes	No
9	Mol 09	No	Yes	Yes	No	No
10	Mol 10	No	Yes	Yes	No	No
11	Mol 11	No	Yes	Yes	No	No
12	Mol 13	No	Yes	Yes	No	No
13	Mol 14	No	Yes	Yes	No	No
14	Mol 15	No	No	Yes	No	No
15	Mol 16	No	No	Yes	No	Yes

16	Mol 17	No	Yes	No	No	Yes
17	Mol 19	No	No	No	No	Yes
18	Mol 20	No	Yes	Yes	No	Yes
19	Mol 21	No	Yes	No	No	No
20	Mol 23	No	No	No	No	Yes
21	Mol 24	No	No	No	No	Yes
22	Mol 25	No	Yes	No	Yes	Yes
23	Mol 26	No	Yes	No	No	Yes
24	Mol 27	No	Yes	No	Yes	Yes

Table 1.6. The predicted excretion profiles of ligand series targeting the human platelet GP-VI by using pkCSM server

EXCRETION				
Sr. no	Compounds	Properties		
		Total clearance	Renal OCT2 substrate	
1	Mol 01	0.98	No	
2	Mol 02	0.667	No	
3	Mol 03	0.916	No	
4	Mol 04	0.414	No	
5	Mol 05	0.589	No	
6	Mol 06	0.511	No	
7	Mol 07	0.539	No	
8	Mol 08	0.583	No	
9	Mol 09	0.426	No	
10	Mol 10	0.539	No	
11	Mol 11	0.539	No	
12	Mol 13	0.494	No	
13	Mol 14	0.494	No	
14	Mol 15	0.588	No	
15	Mol 16	0.568	No	
16	Mol 17	0.572	No	
17	Mol 19	0.493	Yes	
18	Mol 20	0.569	No	
19	Mol 21	0.566	Yes	
20	Mol 23	0.446	Yes	
21	Mol 24	0.51	Yes	
22	Mol 25	0.602	Yes	
23	Mol 26	0.656	Yes	
24	Mol 27	0.681	Yes	

Table 1.7. The predicted toxicity profiles of ligand series targeting the human platelet GP-VI by using pkCSM server

TOXICITY								
Sr.no	Compounds	Properties						
		AMES Toxicity	Max.Tolerated Dose (human) Log(mg/kg/day)	hERG I/II inhibitor	Oral rat acute toxicity (LD50)	Oral rat chronic toxicity (LOAEL)	Hepatotoxicity	Skin sensitization
1	Mol 01	No	0.06	No	1.963	1.35	Yes	No
2	Mol 02	No	-0.794	No	2.509	4.231	No	No
3	Mol 03	No	0.563	No	1.984	1.675	No	No
4	Mol 04	No	0.211	Yes	2.776	1.402	Yes	No
5	Mol 05	No	0.109	Yes	2.656	1.231	No	No
6	Mol 06	No	0.109	Yes	2.656	1.231	Yes	No
7	Mol 07	No	0.23	Yes	2.706	1.692	Yes	No
8	Mol 08	No	0.237	Yes	2.755	1.5	No	No
9	Mol 09	No	0.213	Yes	2.662	1.569	Yes	No
10	Mol 10	No	0.228	Yes	2.701	1.503	No	No
11	Mol 11	No	0.228	Yes	2.701	1.503	yes	No
12	Mol 13	No	0.214	Yes	2.655	1.463	No	No
13	Mol 14	No	0.214	Yes	2.655	1.463	No	No
14	Mol 15	No	0.184	Yes	2.646	1.646	No	No
15	Mol 16	No	0.184	Yes	2.646	1.388	No	No
16	Mol 17	No	0.233	Yes	2.657	1.45	Yes	No
17	Mol 19	No	0.225	No	2.912	1.128	Yes	No
18	Mol 20	No	0.221	Yes	2.639	1.405	Yes	No
19	Mol 21	No	-0.153	No	2.918	1.177	Yes	No
20	Mol 23	No	-0.456	No	3.025	1.507	Yes	No
21	Mol 24	No	-0.426	No	3.044	1.525	Yes	No
22	Mol 25	No	-0.342	No	3.058	1.217	Yes	No
23	Mol 26	No	-0.329	No	2.996	1.257	Yes	No
24	Mol 27	No	-0.301	No	3.073	1.24	Yes	No

Table 1.8. The predicted physical properties of ligand series targeting the human platelet GP-VI by using pkCSM server and MOE

Sr.no	compounds	Molecular weight	#Rotatable bonds	#h-bond Donors	#h-bond Acceptors	Surface Area	TPSA	Log P	Water Solubility
1	Mol 01	856.997	17	2	20	345.583	211.410	-0.379	-3.67
2	Mol 02	744.781	9	10	20	292.109	299.410	-5.6118	-2.54
3	Mol 03	458.493	14	3	11	179.840	210.410	-0.8523	-3.304
4	Mol 04	529.584	6	0	5	213.517	60.930	4.4148	-5.162
5	Mol 05	486.597	6	0	6	205.413	84.720	3.26768	-4.676
6	Mol 06	486.597	6	0	6	205.413	60.930	3.26768	-4.676
7	Mol 07	540.483	6	0	5	208.523	60.930	4.1585	-5.016
8	Mol 08	530.477	6	0	5	215.262	60.930	4.7028	-5.226
9	Mol 09	497.567	6	0	5	202.986	60.930	3.6748	-4.954
10	Mol 10	496.032	6	0	5	204.959	60.930	4.0494	-4.965
11	Mol 11	496.032	6	0	5	204.959	60.930	4.0494	-4.965
12	Mol 13	479.577	6	0	5	198.821	60.930	3.5351	-4.807
13	Mol 14	479.577	6	0	5	198.821	60.930	3.5351	-4.807
14	Mol 15	491.613	7	0	6	206.134	70.16	3.4046	-4.868
15	Mol 16	491.613	7	0	6	206.134	70.16	3.4046	-4.868
16	Mol 17	475.614	6	0	5	201.020	60.930	3.70442	-4.796
17	Mol 19	462.575	6	0	6	193.875	73.82	2.791	-3.624
18	Mol 20	461.587	6	0	5	194.655	60.930	3.396	-4.667
19	Mol 21	417.506	6	1	5	169.919	60.930	2.2244	-2.75
20	Mol 23	417.506	6	0	5	170.129	60.930	2.1781	-2.986
21	Mol 24	399.516	6	0	5	165.963	60.930	2.039	-2.735
22	Mol 25	459.587	9	0	5	189.223	60.930	3.0008	-3.809
23	Mol 26	427.57	8	0	5	178.693	60.930	2.4716	-3.33
24	Mol 27	441.597	9	0	5	185.058	60.930	2.8617	-3.634

2GI7-Saccharin Derivatives Interaction Profile

Below are the interactions profile of Saccharin Derivatives with a good docking score and over-all properties:

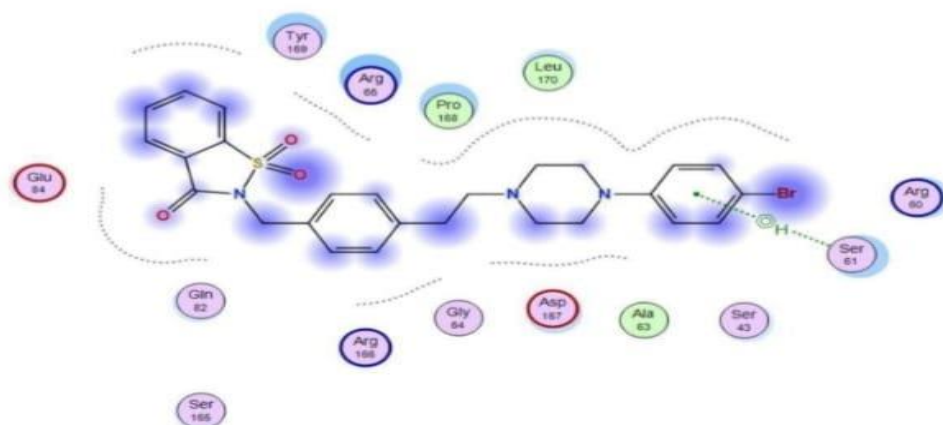


Figure1.2. Structure 7

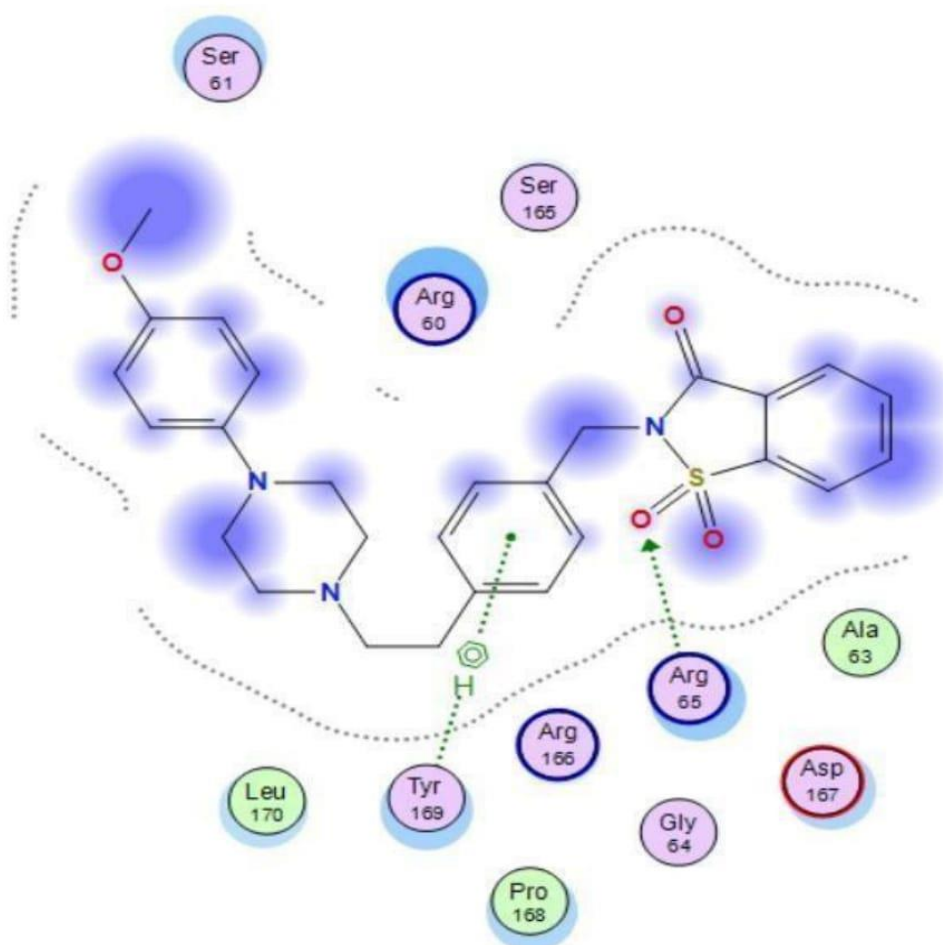


Figure 1.3. Structure 15

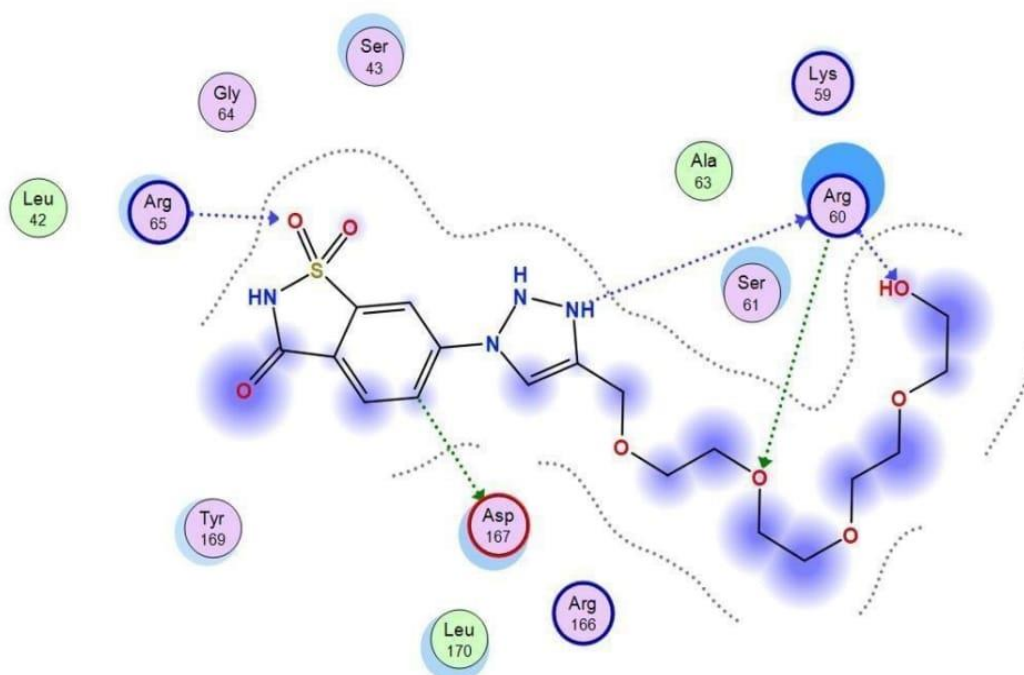


Figure 1.4. Structure 3

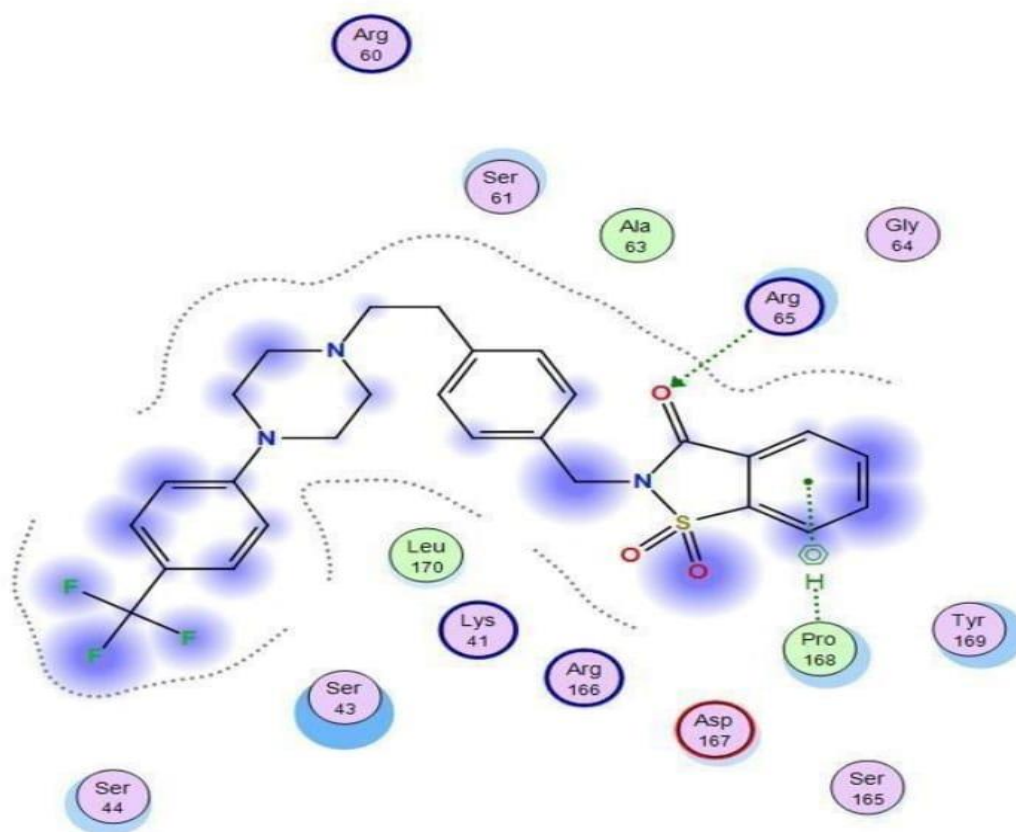


Figure 1.5. Structure 3

Conclusion:

The purpose of the proposed study was to use saccharin derivatives as potential ligands that selectively inhibit atherothrombosis and thereby lower the mortality rate from diabetic complications, thereby addressing the clinical need for developing antiplatelet strategies.

Numerous antiplatelet medications are now on the market to prevent or treat arterial thrombosis, including GPIIb-IIIa (integrin α Ib β 3) inhibitors that prevent fibrinogen from binding to activated platelets and thereby inhibiting platelet aggregation, cyclooxygenase-1 inhibitor ASA that prevents irreversible blockade of TxA₂ production, and P2Y₁₂ receptor antagonists that prevent the accumulation of platelet activation brought on by ADP. Even with ongoing improvements in antithrombotic therapy, acute myocardial infarction and ischemic stroke continue to rank among the leading causes of death and permanent disability in western nations, and current antiplatelet therapy is linked to an increased risk of bleeding because of bargained hemostasis. In order to virtually control unnecessary platelet activation without changing hemostasis and running the danger of life-threatening bleeding complications and disorders, new and unconventional antiplatelet treatments are therefore crucial. This forces GPVI to become the main focus of innovative antithrombotic treatment techniques.

Reference:

1. Cabeza N, Li Z, Schulz C, Kremmer E, Massberg S, Bußlmann A, Gawaz M: Surface Expression of Collagen Receptor Fc Receptor/Glycoprotein VI Is Enhanced on Platelets in Type 2 Diabetes and Mediates Release of CD40 Ligand and Activation of Endothelial Cells. DIABETES, VOL. 53, AUGUST 2004 2. O. Borst and M. Gawaz, Glycoprotein VI - novel target in antiplatelet medication, Pharmacology & Therapeutics, <https://doi.org/10.1016/j.pharmthera.2020.107630> 12.
3. Salmaso, V., & Moro, S. (2018). Bridging Molecular Docking to Molecular Dynamics in Exploring Ligand-Protein Recognition Process: An Overview. Frontiers in Pharmacology, 9, 923.
4. Maliwal D, Telvekar V, Pissurlenkar R.: Identification of Novel Potential Anti-Diabetic Candidates targeting Human Pancreatic alpha amylase and human alpha glycosidase: An exhaustive Structure Based Screening; Canadian Journal of Chemistry, December 2021, DOI:10.1139/cjc-2021-0238
5. Reynolds CH, Merz KM, Ringe D, eds. (2010). Drug Design: Structure- and Ligand- Based Approaches (1 ed.). Cambridge, UK: Cambridge University Press. ISBN 978- 0521887236.
6. Halushka PV, Rogers RC, Loadholt CB, Colwell JA: Platelet thromboxane synthesis in diabetes mellitus. J Lab Clin Med 97:87–96, 1981
7. Jump up to: a b Chemical Computing Group (November 7, 2022). "Molecular Operating Environment Products". chemcomp.com. Retrieved November 7, 2022.
8. "Molecular Simulation - an overview | ScienceDirect Topics". www.sciencedirect.com.
9. Meng, Xuan-Yu; Zhang, Hong-Xing; Mezei, Mihaly; Cui, Meng (2011-06- 01). "Molecular Docking: A powerful approach for structure-based drug discovery". Current Computer-Aided Drug Design. 7 (2): 146–157. doi:10.2174/157340911795677602. ISSN 1573- 4099. PMC 3151162. PMID 21534921.
10. Bartuzi, Damian; Kaczor, Agnieszka A.; Targowska-Duda, Katarzyna M.; Matosiuk, Dariusz (2017-02-22). "Recent Advances and Applications of Molecular Docking to G Protein-Coupled Receptors". Molecules. 22 (2): 340. doi:10.3390/molecules22020340. ISSN 1420- 3049. PMC 6155844. PMID 28241450.
11. Kastiris, Panagiotis L.; Bonvin, Alexandre M. J. J. (2013-02-06). "On the binding affinity of macromolecular interactions: daring to ask why proteins interact". Journal of the Royal Society Interface. 10 (79):20120835. doi:10.1098/rsif.2012.0835. PMC 3565702. PMID 23235262.
12. Pinzi, Luca; Rastelli, Giulio (2019-09-04). "Molecular Docking: Shifting Paradigms in Drug Discovery". International Journal of Molecular Sciences. 20 (18): 4331. doi:10.3390/ijms20184331. ISSN 1422-0067. PMC 6769923. PMID 31487867.

13. Bank, RCSB Protein Data. "RCSB PDB: Homepage". www.rcsb.org. Retrieved 2022- 11-08.
14. Smyth, M S; Martin, J H J (February 2000). "x Ray crystallography". Molecular Pathology. 53 (1):8–14. doi:10.1136/mp.53.1.8. ISSN 1366- 8714. PMC 1186895. PMID 10884915.
15. "X-Ray Crystallography - an overview | ScienceDirect Topics". www.sciencedirect.com.
16. 1 "X-ray Crystallography". Chemistry LibreTexts. 2013-10-02. Retrieved 2022-11-08.
17. List of softwares used in molecular docking - Molecular Docking". sites.google.com. Retrieved 2022-11-08. molecular
18. Pagadala, Nataraj S.; Syed, Khajamohiddin; Tuszynski, Jack (2017-01-16). "Software for docking: a review". Biophysical 102. doi:10.1007/s12551-016-0247-1. ISSN 1867- 2450. PMC 5425816. PMID 28510083. Reviews. 9 (2): 91–
19. "UniProt". www.uniprot.org. Retrieved 2022-11-08.
20. Hollingsworth, Scott A.; Dror, Ron O. (2018-09-19). "Molecular dynamics simulation for all". Neuron. 99 (6): 1129–1143. doi:10.1016/j.neuron.2018.08.011. ISSN 0896- 6273. PMC 6209097. PMID 30236283.
21. Jump up to:a b Hernández-Rodríguez, Maricarmen; Rosales-Hernández, Martha C.; Mendieta-Wejebe, Jessica E.; Martínez-Archundia, Marlet; Basurto, José Correa (2016). "Current Tools and Methods in Molecular Dynamics (MD) Simulations for Drug Design". Current Medicinal Chemistry. 23 (34): 3909–3924. doi:10.2174/0929867323666160530144742. ISSN 1875- 533X. PMID 27237821.
22. "Molecular Dynamics - an overview | ScienceDirect Topics". www.sciencedirect.com.
23. Zhou, Shu-Feng; Zhong, Wei-Zhu (2017-02-13). "Drug Design and Discovery: Principles and Applications". Molecules. 22 (2): 279. doi:10.3390/molecules22020279. ISSN 1420- 3049. PMC 6155886. PMID 28208821.
24. "Drug Development - an overview | ScienceDirect Topics". www.sciencedirect.com.
25. Jumper, John; Evans, Richard; Pritzel, Alexander; Green, Tim; Figurnov, Michael; Ronneberger, Olaf; Tunyasuvunakool, Kathryn; Bates, Russ; Židek, Augustin; Potapenko, Anna; Bridgland, Alex; Meyer, Clemens; Kohl, Simon A. A.; Ballard, Andrew J.; Cowie, Andrew (August 2021). "Highly accurate protein structure prediction with AlphaFold". Nature. 596 (7873): 583– 589. Bibcode:2021Natur.596..583J. doi:10.1038/s41586-021-03819-2. ISSN 1476- 4687. PMC 8371605. PMID 34265844.