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Molecular Docking Analysis Of P2x Receptor Antagonists: Insights Into Neurological Pain Modulation

Manisha Rauthan[1], Krishana Kumar Sharma[2]
[1]Research Scholar, Department of Pharmacology, Teerthankar Mahaveer College of Pharmacy, Teerthankar Mahaveer University, Moradabad, Uttar Pradesh, India.
[2]Professor, Department of Pharmacology, Teerthankar Mahaveer College of Pharmacy, Teerthankar Mahaveer University, Moradabad, Uttar Pradesh, India.

Abstract:
Background: *Because of its complex etiology and persistence independent of traditional therapy, deafferentation pain is regarded as among an utmost difficult type of persistent pain. Transmission of pain signals across central and peripheral nerve systems depends critically on P2X receptors, a type of Ion channels activated by ATP. The increasing attention on these receptors has underlined their possible therapeutic target value. Particularly P2X receptor antagonists provide interesting means to interfere with the nociceptive channels causing neuropathic pain.*
Aim: *This work investigates how antagonists interact with P2X receptor subtypes using molecular docking techniques. Investigating structural dynamics and interaction processes at the molecular level is meant to help to produce more selective and strong medicinal medicines.*
Docking studies found notable binding interactions between certain antagonists and important residues within P2X3 and P2X7 receptors. Mostly in the ATP-binding pockets, these interactions produced structural changes that reduce receptor activity. Notably, P2X7 antagonists revealed high binding affinities, underlining their analgesic potential.
Conclusion: *Overall, results of the docking simulations confirm the possibility of P2X receptor antagonists in neuropathic pain treatment. The structural insights revealed from this study open the path for the creation of next-generation antagonists with better effectiveness and specificity.*
Keywords: *Molecular docking, P2X receptors, Antagonist, Neurological Pain, Neuropathic pain, Pain modulation*

1. INTRODUCTION:

Pain is an essential physiological warning sign that indicates the body to impending harm or tissue damage. Although generally protective, pain in certain pathological situations becomes chronic and disabling, enormously affecting a person's quality of life. Among various chronic pain syndromes, neuropathic pain—due to injury or dysfunction in the nerve system—is a specific challenge because of its resistance to conventional analgesics. (1- 3) Neuropathic pain is typically associated with diseases like diabetic neuropathy, multiple sclerosis, and post-herpetic neuralgia. Conventional medications such as NSAIDs and opioids are often ineffective in providing relief in these situations, as they act against the nociceptive pain mechanisms and not against the dysfunctional neural pathways seen in neuropathy.

Latest research in the fields of molecular neurobiology and pharmacology has unveiled the vital role played by purinergic signaling, particularly through P2X receptors, in pain control. P2X receptors are ATP-gated ion medium (Burnstock's in 2008) which become activated in response cytosolic ATP, a substance produced due to cell damage or stress. Upon activation, they increase the drift of divalent like Na^+, K^+, and Ca^{2+}, thereby promoting neuronal excitement and pain transmission. (5-7)

P2X receptor brood comprise of seven known subtypes—P2X1 to P2X7 (4) each with separate functional roles and tissue distribution. Of these, P2X3, P2X4, and P2X7 enteroceptor had been most closely incriminate due to chronic and neurogenic agony mechanisms. These subtypes are compelling candidates for the development of new analgesics that more precisely and effectively modulate purinergic transmission. (8-10) Knowledge of the molecular basis of how antagonists act on these receptors is important in the development of therapeutic methods. Targeted blockage of these ion channels could modify maladaptive neural plasticity and neuroinflammatory responses, thereby reducing chronic pain sensations. This study tackles these prospects through a thorough molecular docking study of selective P2X receptor antagonists. (11-12)

1.1 Signaling Purinergic and P2X Receptors:

Purinergic signaling is a fundamental mechanism that regulates a broad variety of anatomical procedure like inflammation, neurotransmission, and immunological reactions. It is primarily regulated by cytosolic nucleotides like adenosine triphosphate. The P2X receptor family is especially significant among purinergic receptors owing to their involvement in nociceptive transmission and fast synaptic transmission. (13-15) Trimeric peptide - barricaded ion medium termed P2X receptors are operated upon attaching with adenosine triphosphate. Depolarization and subsequent signaling cascades are induced by such activation, allowing cations—majority being sodium (Na^+), potassium (K^+), and calcium (Ca^{2+})—to penetrate the cell. (16) With receptors with unique roles in pain sensation and immunological stimulation, all of the seven identified P2X subtypes (P2X1 to P2X7) possess a unique expression profile and functional characterization.**P2X3, P2X4, and P2X7** receptors have become main contributor in physiology of pain: (17)

1.1.1 P2X3 Receptor:

Sensory neurons, especially those in the rear root ganglia (DRG), are the main source of utterance for the P2X3 receptor. Neuronal agitation and the transferal of pain signals result from its initiation by ATP produced from damaged or provocative tissue. These receptors, which are very sympathetic to extracellular ATP, are associated with a number of pain dysfunction, including: visceral pain, migraine, and cancer-related pain. They are an ideal target for the formation of new palliative due to their unique utterance in nociceptive pathways. (18-20)

1.1.2 P2X4 Receptor:

The mean nervous system's microglial cells are the prime location for P2X4 receptors. When activated, they set forth microglial response that include the production of chemokines and pro- inflammatory cytokines, which assist to continue neuropathic pain and central mean sensitization. It has been shown that P2X4 receptor activation change the spinal cord over time, enhancing pain perception. They are a primary target for treatments meant to reduce sever pain because of their crucial engagement in neuroinflammation. (21-24)

1.1.3 P2X7 Receptor:

The P2X7 receptor, which is broadly demonstrate in neurons, neuroglial cells, and immune cells, is important for both immune activation and chronic inflammation. It has a leading contribution in the generation of inflammatory mediators such as interleukin-1β [IL-1β] (25), which contribute to neuroinflammatory cascades and escalate pain signals. The P2X7 receptor is an especially appealing option for targeted pharmaceutical intervention in chronic and treatment-resistant pain syndromes due to its capability to cause cell death, cytokine releases, and protracted inflammatory signaling. (26-27)

1.2 The Prospective Use of P2X Receptor Antagonists in Medications:

P2X receptors play a key role in both neuroinflammation and the transmission of pain, therefore using antagonists to specifically block their activity has emerged as a promising pain management strategy. By blocking ATP from binding to the receptor, these antagonists inhibit ion channel activity and disrupt downstream nociceptive signals. The pharmacological efficacy and subtype selectivity of several P2X receptor antagonists, such as Suramin, A-317491, and TNP-ATP, have been identified and investigated. These medications have different affinities for different receptor subtypes to reduce side effects and increase therapeutic efficacy. The goal is to develop antagonists that can precisely target aberrant pain circuits without interfering with normal physiological functions. The structural similarities among receptor subtypes make it more difficult to create highly selective molecules. When P2X receptors are widely distributed throughout the subject body, off-target effects are more likely to occur. Complex receptor-ligand dynamics require a deeper understanding of molecular interactions in order to improve specificity and efficacy. To overcome these challenges, molecular docking has shown to be a very helpful computational technique. Atomic-level simulation of receptor-antagonist interactions permits researchers to predict binding affinities, identify crucial binding residues, and enhance chemical structures for enhanced performance. Lastly, the development of highly selective P2X receptor antagonists, guided by extensive in vitro and in silico research, could fundamentally change the treatment of chronic pain, especially for conditions that don't improve with traditional analgesics. (28)

3. RESULT AND DISCUSSION:

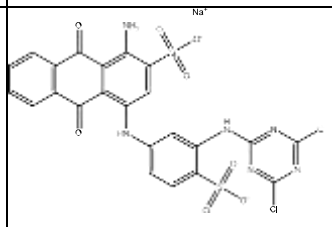
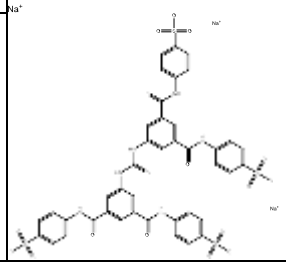
3.1 Docking Studies:

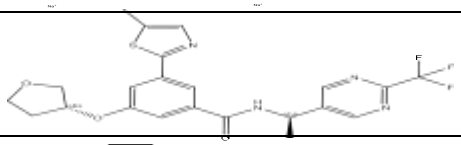
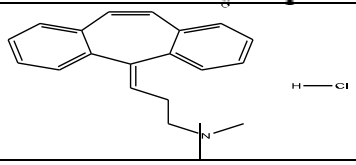
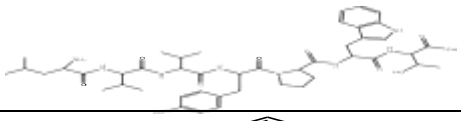
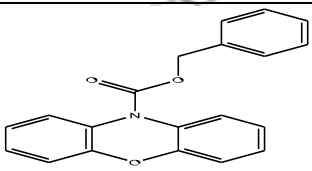
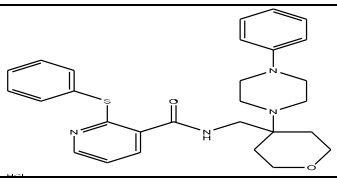
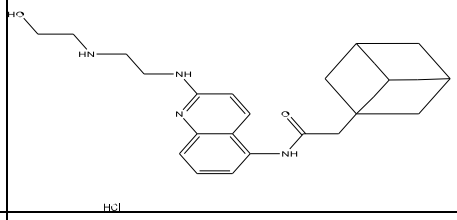
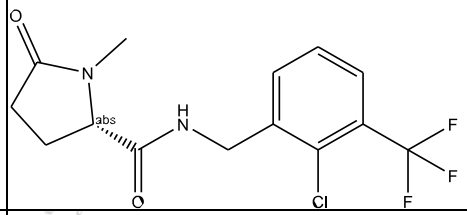
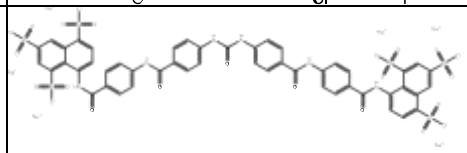
High-precision predictions of ligand binding locations and affinities inside the P2X receptor binding sites were made possible by the use of the GLIDE module of the Schrödinger Suite for molecular docking studies. Discovery Studio was used to show ligand–protein interactions in both 2D and 3D formats in order to better comprehend each molecule's orientation, interacting residues, and spatial fit inside the receptor binding pocket. LigPrep was first used to build all ligand structures, transforming basic 2D structures into optimal 3D models and producing ionization, tautomeric, and stereo isomeric versions as required. During minimization, the OPLS_2005 force field was used to guarantee conformations that were physiologically significant. The Protein Preparation Wizard were used to construct the protein targets that corresponded to each receptor subtype, which were retrieved from the RCSB PDB database (particular PDB IDs were utilized as per Table 2). Water molecules and heteroatoms—aside from those engaged in ligand interactions—were eliminated. Prior to docking, side chains that were lacking were fixed and hydrogen bonds were optimized. Standard precision (SP) docking was used to place each ligand into its corresponding receptor. The tables below provide each ligand-receptor complex's final docking scores and interaction energies.

3.2 Ligand Interaction Insights:

PSB-1011 sodium's complex sulfonated structure with sodium ions suggests strong hydrophilic interactions. Despite its low docking score, which indicates moderate binding, its solubility profile makes it a promising candidate for additional investigation on aquatic systems. NF 110 had the best docking score, indicating a strong binding affinity. The large molecular structure and sulfonated groups within the receptor pocket likely promote strong hydrogen bonding and electrostatic interactions. Eliapixant's fluorinated structure, which may enhance membrane permeability, and its relatively low docking score make it a promising oral drug candidate. A common muscle relaxant, cyclobenzaprine hydrochloride, surprisingly demonstrated strong binding. This may indicate neuromodulatory effects related to P2X interaction that require more investigation. The small molecule PSB-12054 demonstrated good synthetic feasibility and binding affinity, making it a viable scaffold for further derivatives; Consistent interaction scores between JNJ-47965567 and AZ10606120 suggested that they were stable mid-sized compounds appropriate for pharmaceutical development; Spinorphin, a peptide-based molecule, may function via peptide recognition or allosteric processes, despite showing lesser binding. Because of the fluorine atoms that enhanced lipophilicity and receptor fit, GSK-1482160 demonstrated a strong potential for selectivity despite its lower size. With the highest molecular weight and the most negative docking score, NF 279 has the potential for broad-spectrum interactions but also higher entropic costs.

Table No. 1: Detailed of ligand:

S. No.	Structure	Name & Pubchem id	Molecular Formula	Molecula r weight
1.		PSB-1011 sodium, (78253)	C23H12Cl2N6N a2O8S2	681.4 g/mol
2.		NF 110, (16066783)	C41H28N6Na4 O17S4	1096.9 g/mol

3.		Eliapixant, (121397587)	C22H21F3N4O3 S	478.5 g/mol
4.		Cyclobenzaprine Hydrochloride, (22576)	C20H22ClN	311.8 g/mol
5.		Spinorphin, (3081832)	C45H64N8O10	877.0 g/mol
6.		psb-12054, (60168729)	C20H15NO3	317.3 g/mol
7.		JNJ- 47965567, (66553218)	C28H32N4O2S	488.6 g/mol
8.		AZ1060612 0, (10310632)	C25H34N4O2	422.6 g/mol
9.		GSK-1482160, (23649427)	C14H14ClF3N2O2	334.72 g/mol
10.		NF 279, (5311315)	C49H30N6Na6O23S6	1401.1 g/mol

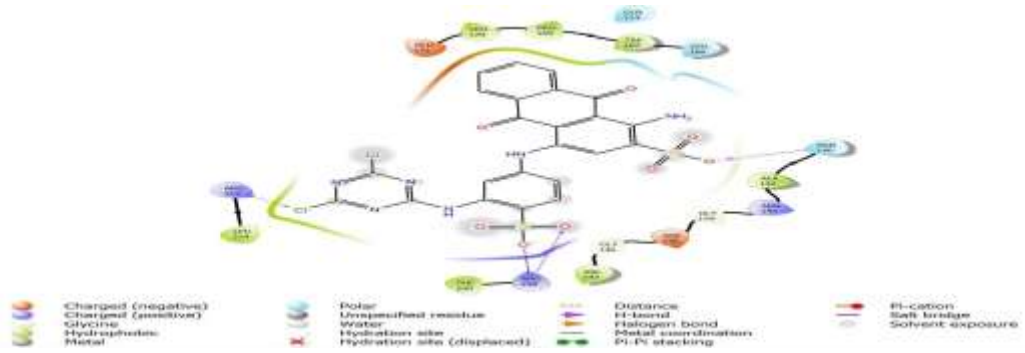


Figure – 1

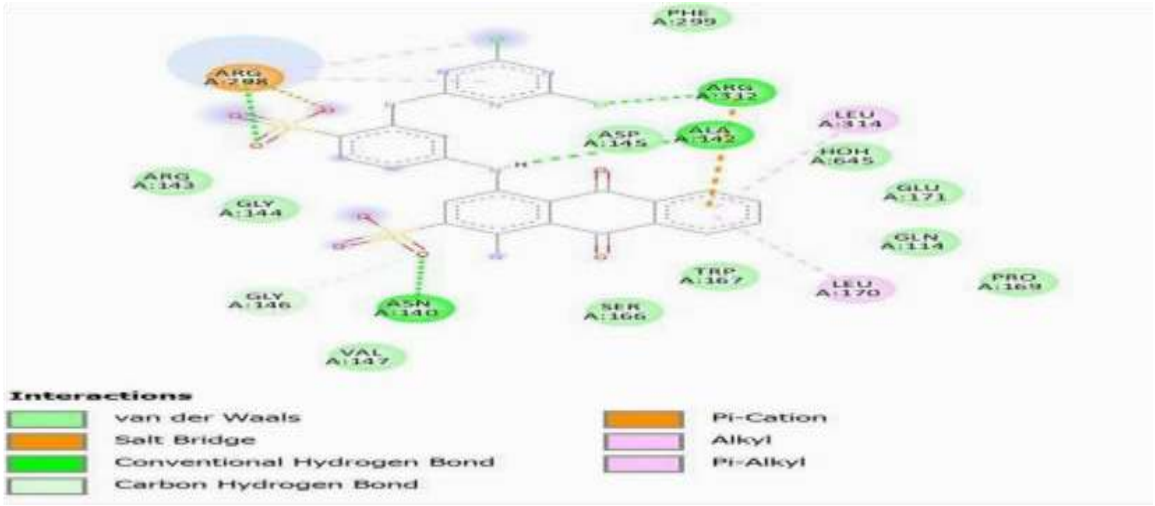


Figure – 2

2d Interaction of PSB-1011 sodium, (78253) on the protein 4DW1

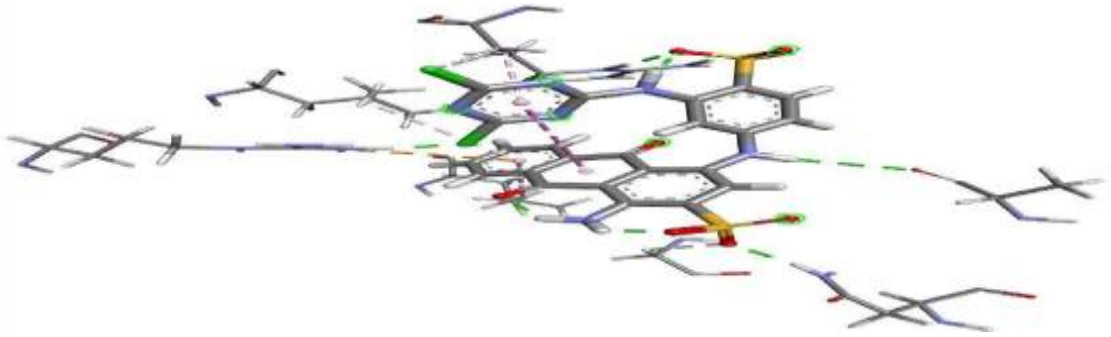


Figure – 3

3d Interaction of PSB-1011 sodium, (78253) on the protein 4DW1

S.NO	Docking Score	Energy
1	-4.313	62.337

Figure – 4

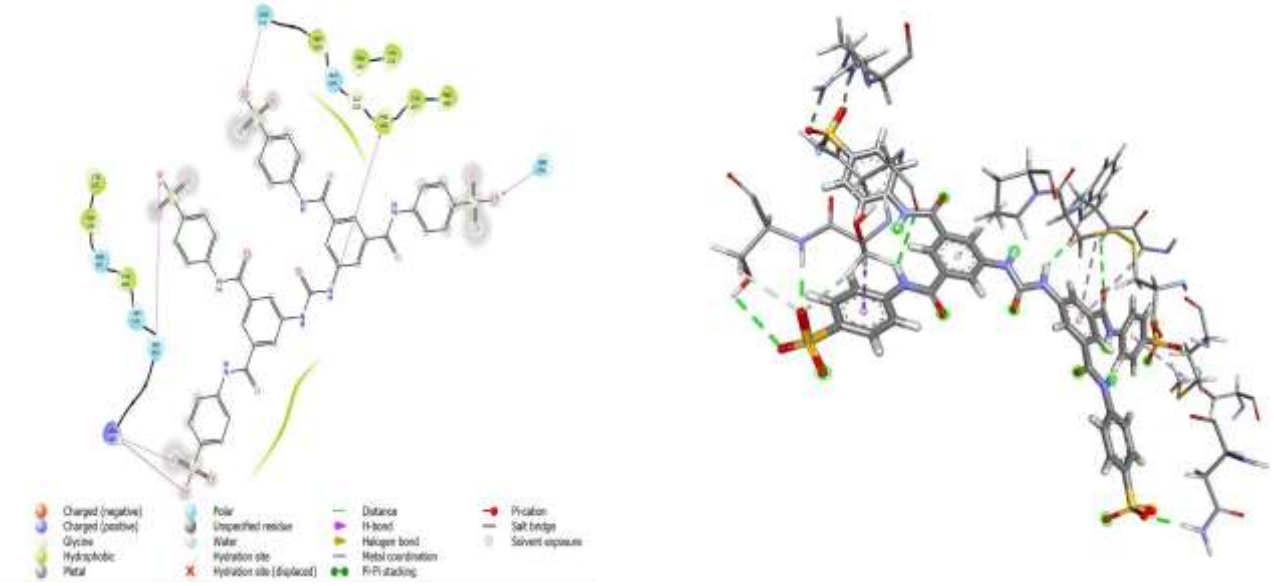


Figure – 5

2d Interaction of NF 110, (16066783) on the protein 5SVJ.

3d NF 110, (16066783) on the protein 5SVJ

S.NO	Docking Score	Energy
1	-7.739	102.118

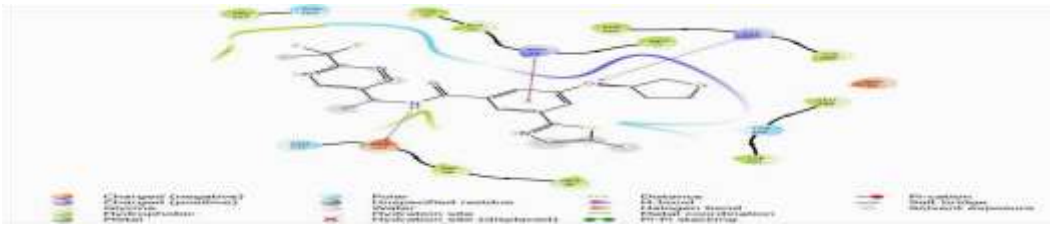


Figure: 6

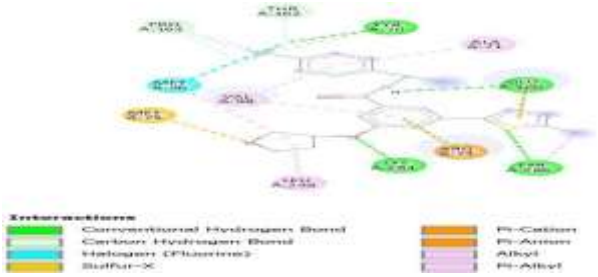


Figure: 7

2d Interaction of Eliapixant, (121397587)) on the protein 5SV

Figure – 8

3d Interaction of Eliapixant, (121397587)) on the protein 5SVJ

S.NO	Docking Score	Energy
1	-4.009	31.7

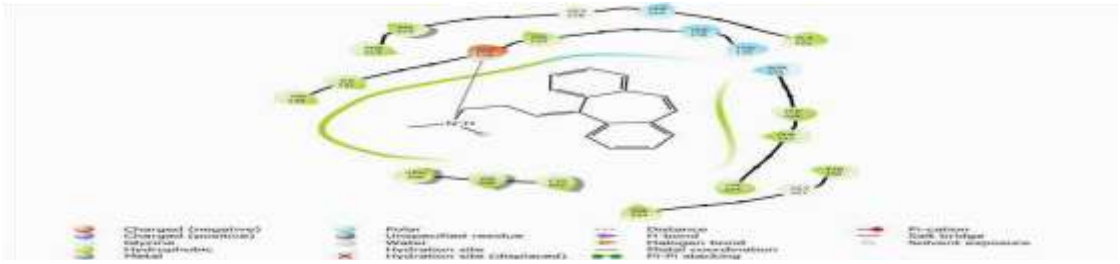


Figure - 9

2d Interaction of Cyclobenzaprine Hydrochloride, (22576) on the protein 6BQG

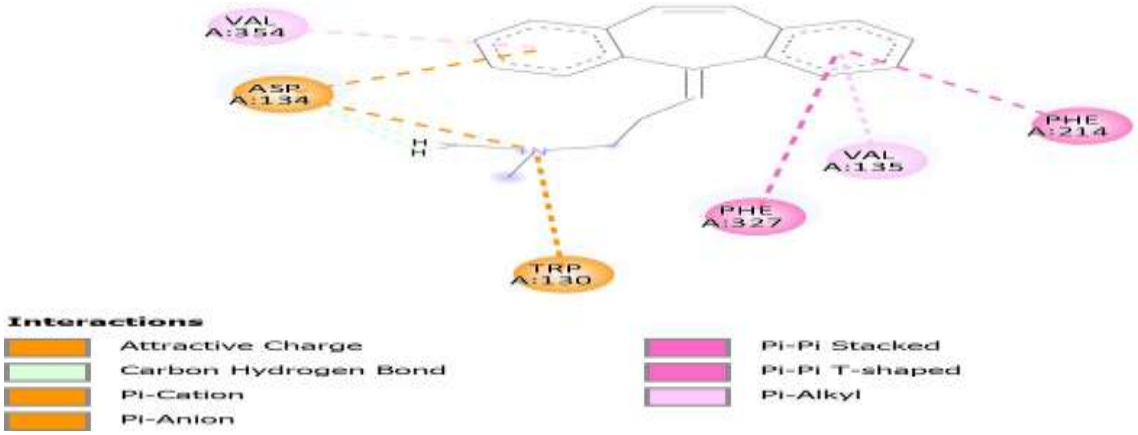


Figure – 10

2d Interaction of Cyclobenzaprine Hydrochloride, (22576) on the protein 6BQG

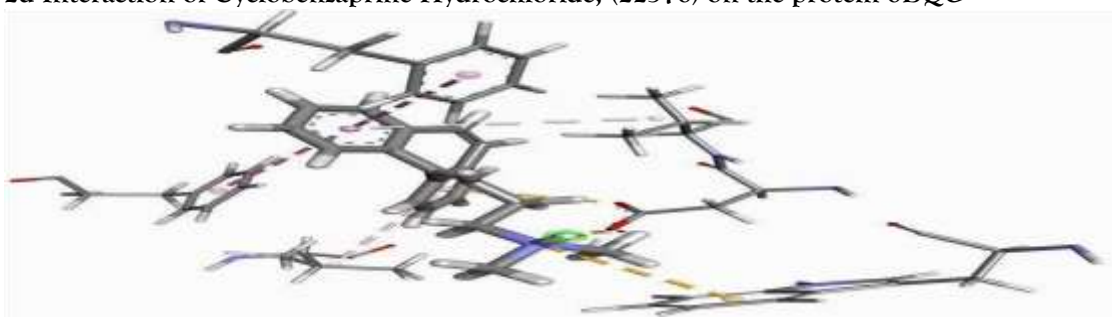


Figure – 11

3d Interaction of Cyclobenzaprine Hydrochloride, (22576) on the protein 6 BQG

S.NO	Docking Score	Energy
1	-7.258	31.047

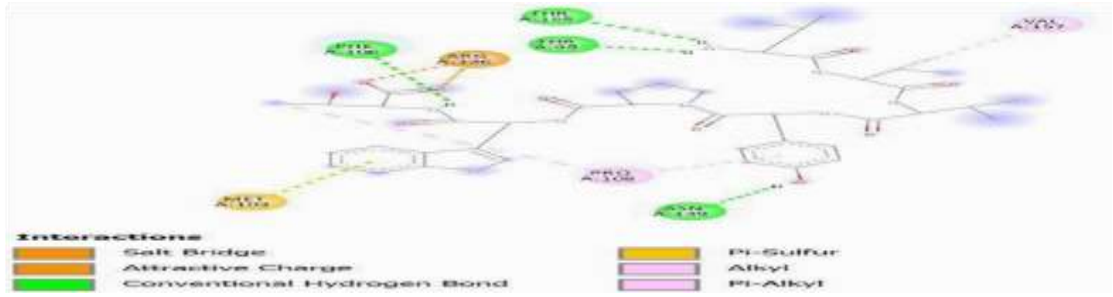


Figure – 11

2d Interaction of Spinorphin, (3081832) on the protein 5SVJ

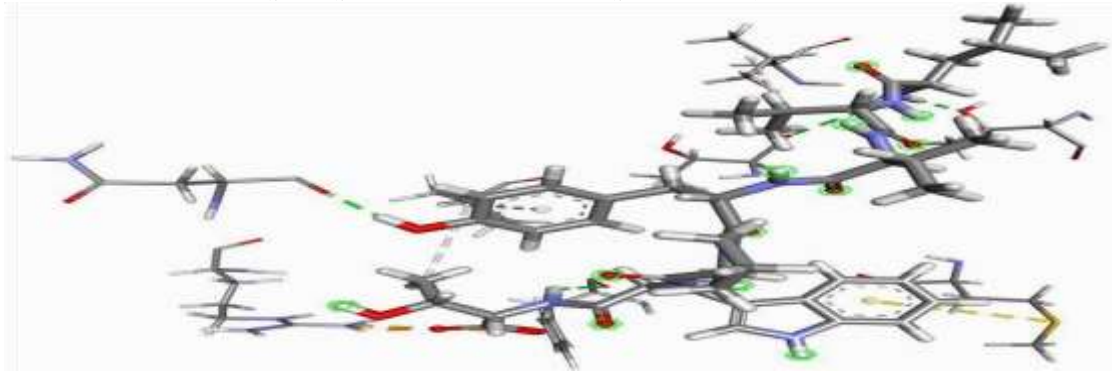


Figure – 12

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3d Interaction of Spinorphin, (3081832) on the protein 5 SVJ

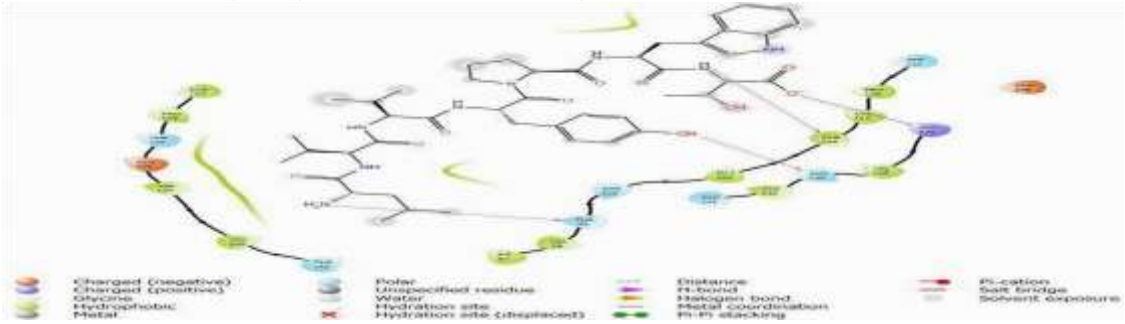

Figure – 13

2d Interaction of Spinorphin, (3081832) on the protein 5SVJ

S.NO	Docking Score	Energy
1	-4.328	12.469

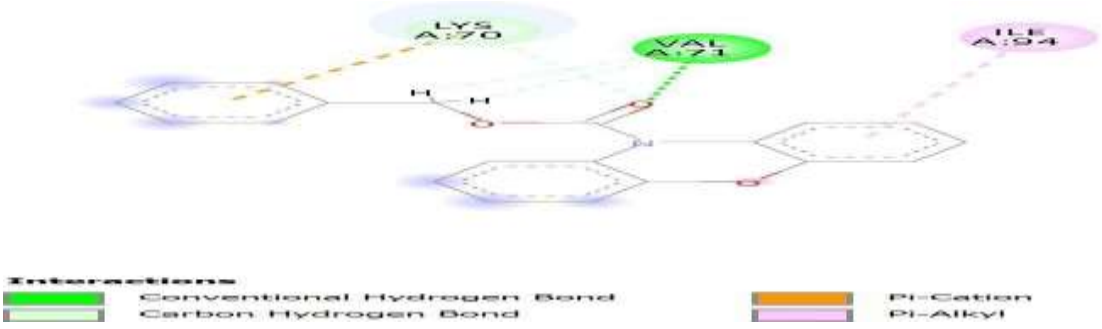

Figure 14

2d Interaction of psb-12054, (60168729) on the protein 3 H9V

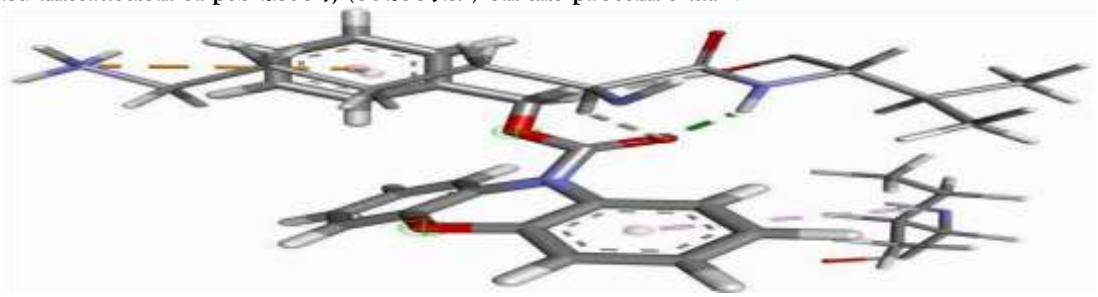

Figure – 15

3d Interaction of psb-12054, (60168729) on the protein 3H9V

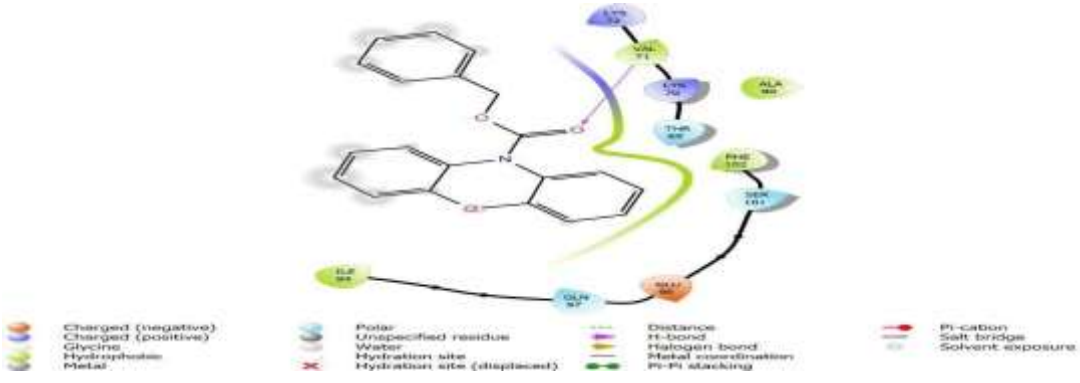

Figure – 16

S.NO	Docking Score	Energy
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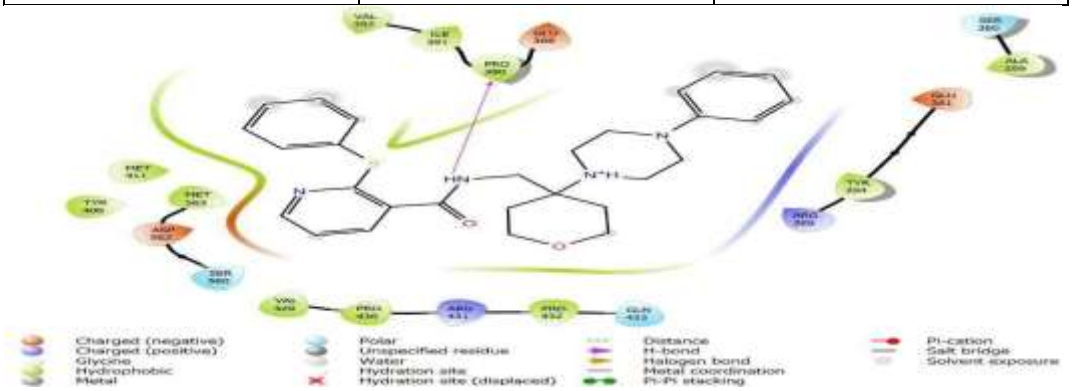

Figure – 17
2d Interaction of JNJ-47965567, (66553218) on the protein 6U9V

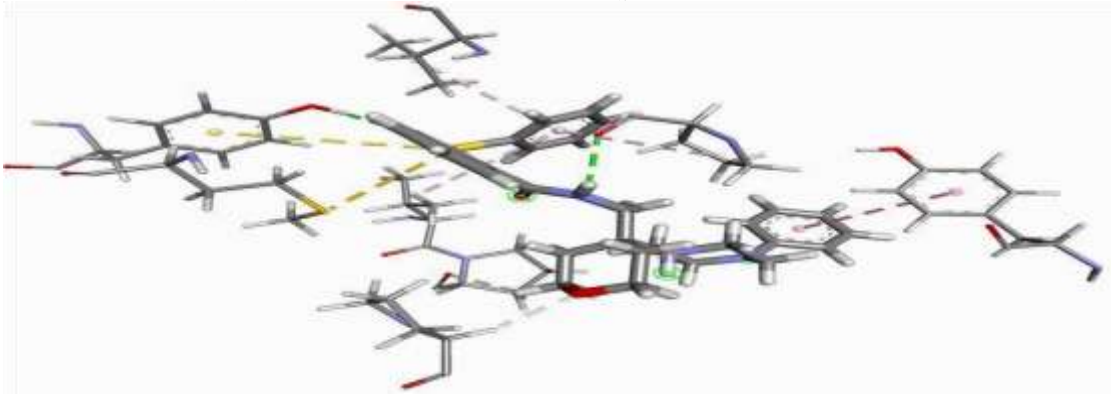

Figure - 18
3d Interaction of JNJ-47965567, (66553218) on the protein 6 U9V

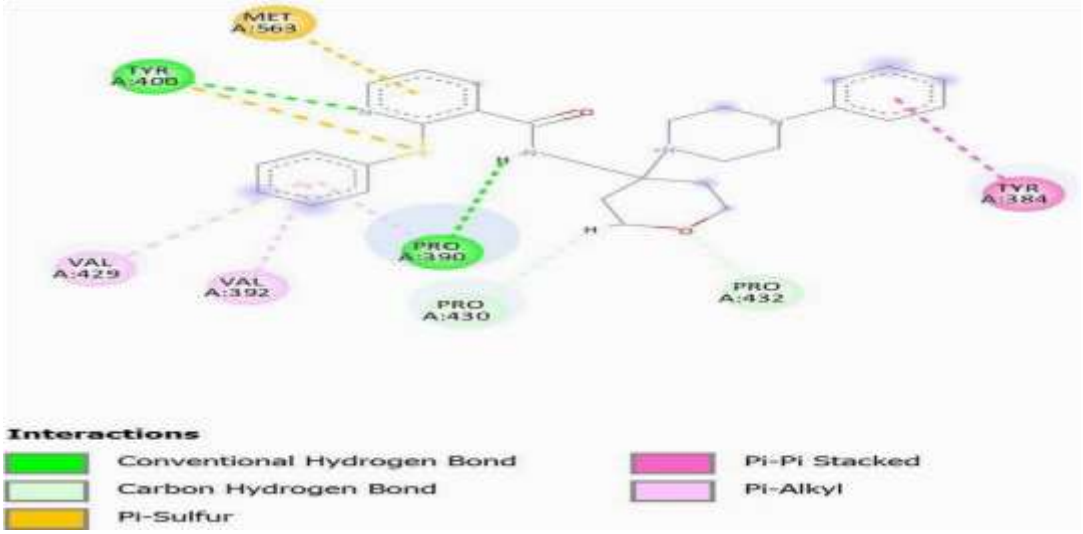

Figure – 19
2d Interaction of JNJ-47965567, (66553218) on the protein 6U9V

S.NO	Docking Score	Energy
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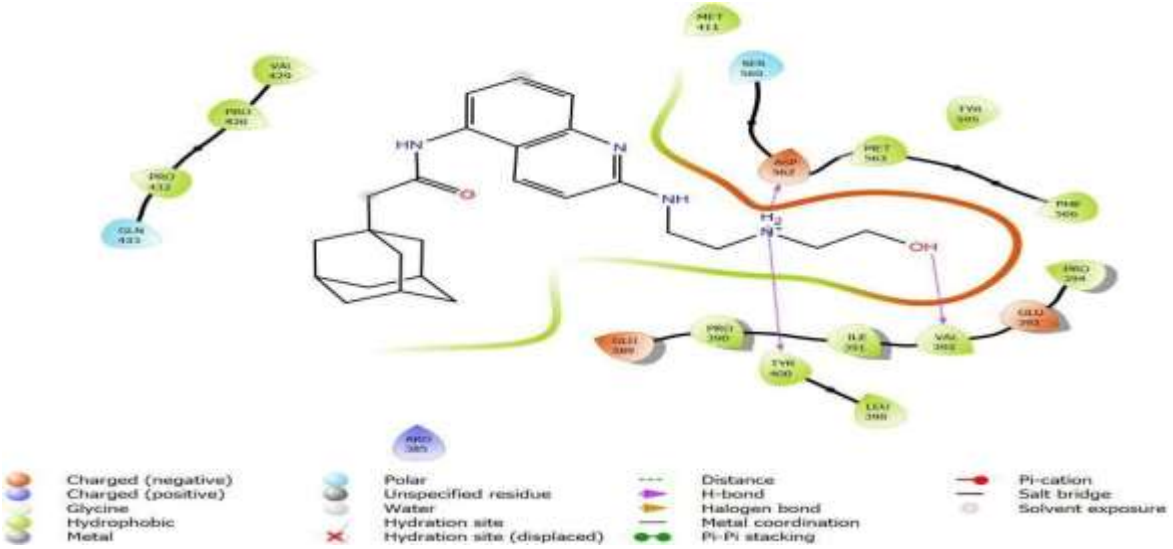

Figure – 20

2d Interaction of AZ10606120, (10310632) on the protein 6 U9V

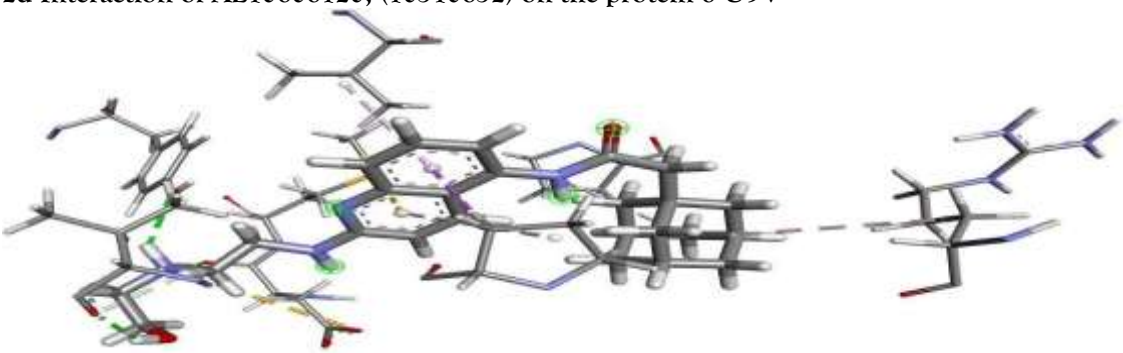

Figure – 21

3d Interaction of AZ10606120, (10310632) on the protein 6U9V

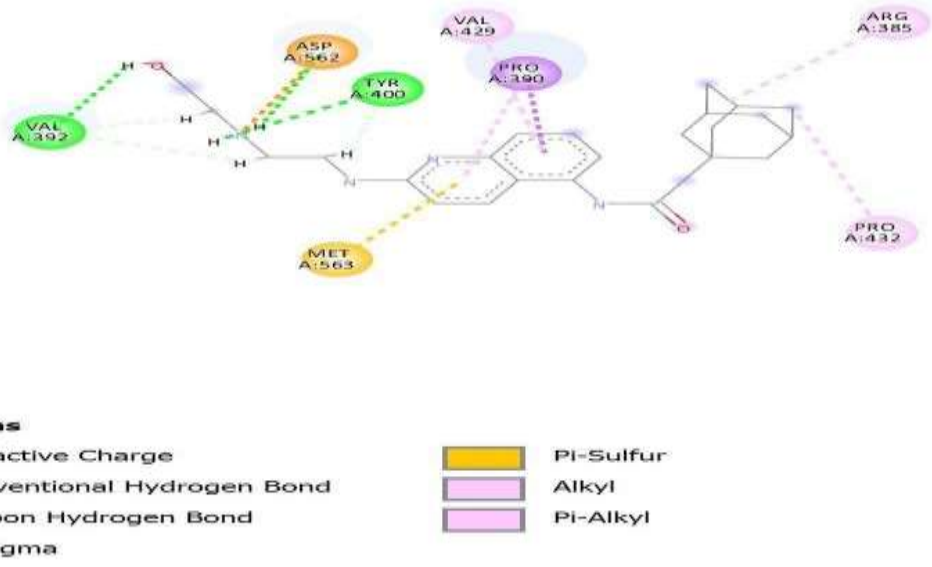

Figure – 22

2d Interaction of AZ10606120, (10310632) on the protein 6U9V

S.NO	Docking Score	Energy
1	-5.177	51.788

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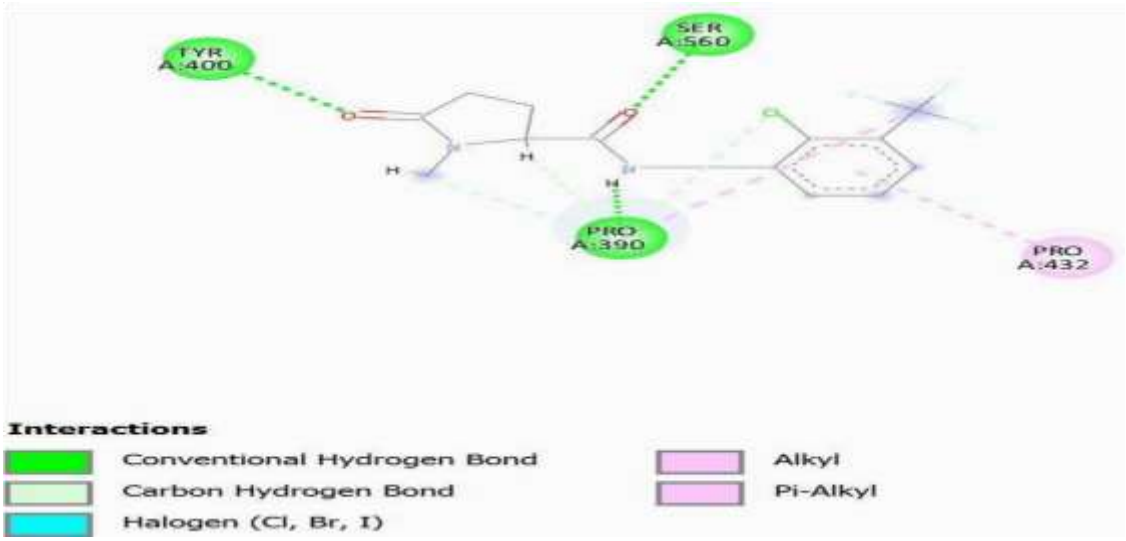


Figure – 23

2d Interaction of GSK-1482160,(23649427) on the protein 6U9V

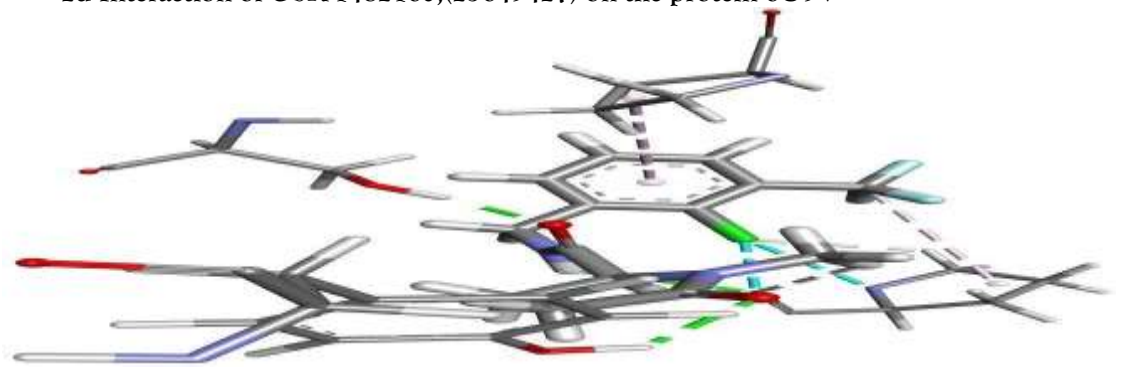


Figure – 24

3d Interaction of GSK-1482160,(23649427) on the protein 6 U9V

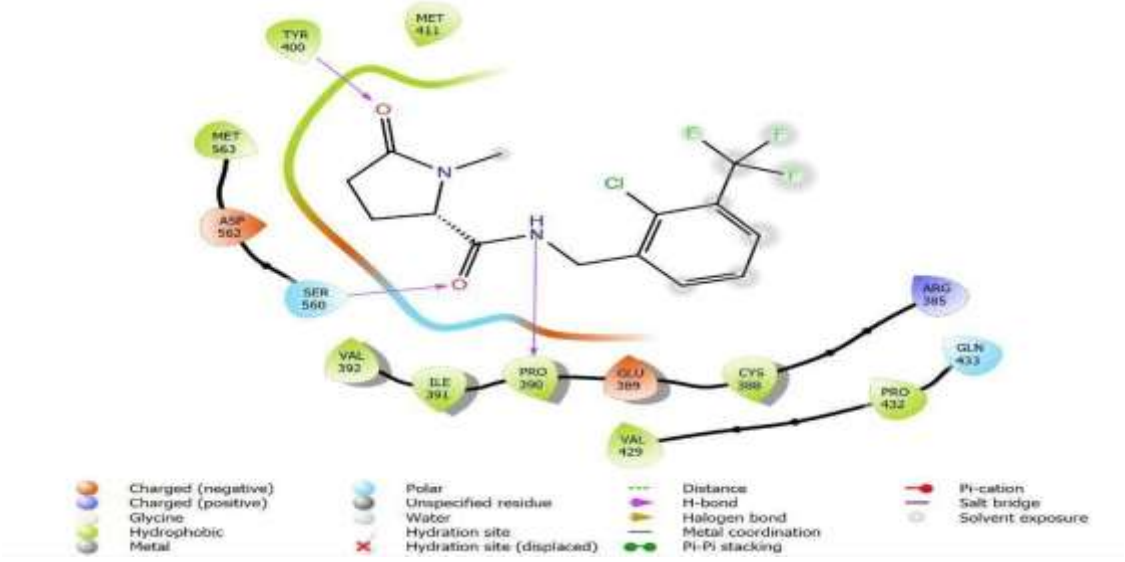


Figure – 25

2d Interaction of GSK-1482160, (23649427) on the protein 6U9V

S.NO	Docking Score	Energy
1	-4.917	20.742

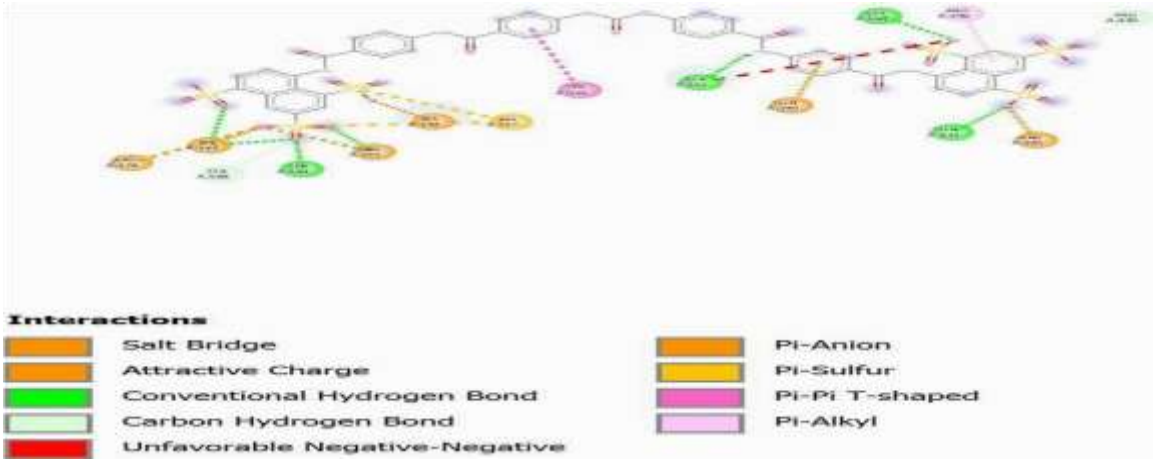


Figure – 26

2d Interaction of NF 279, (5311315) on the protein 6 U9V

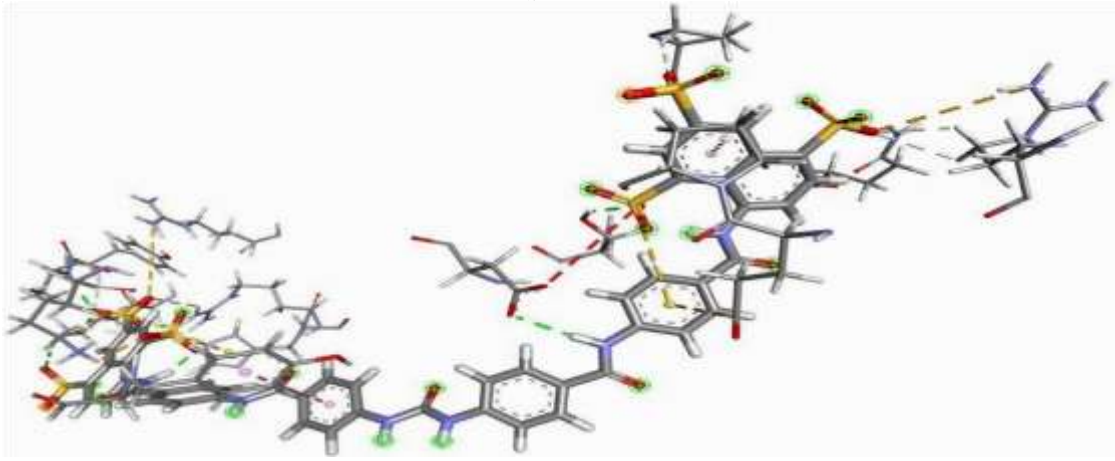


Figure – 27

3d Interaction of NF 279, (5311315) on the protein 6U9V

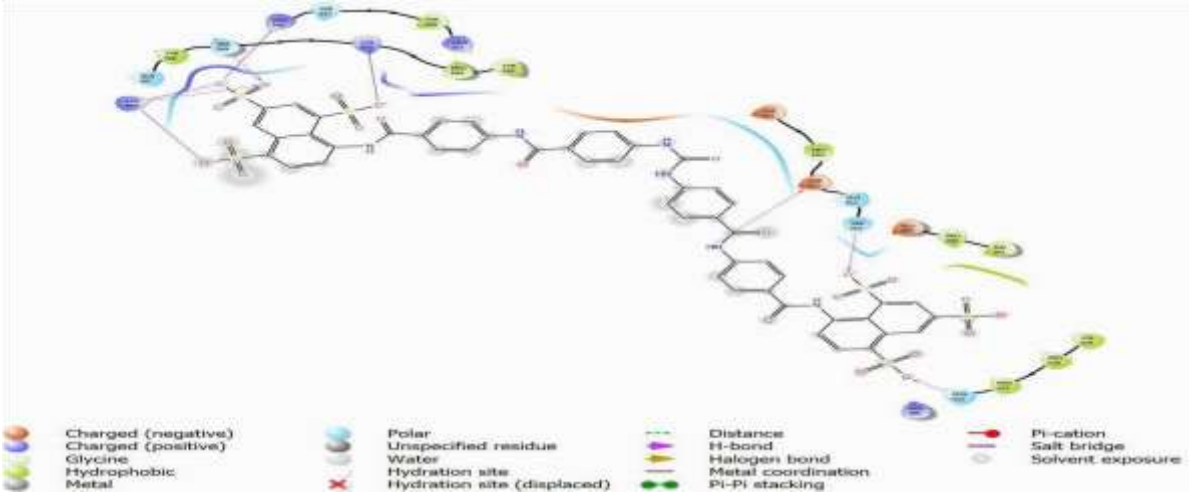
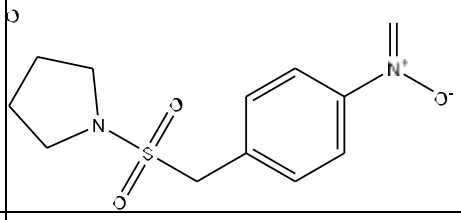
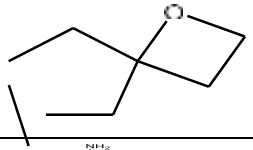
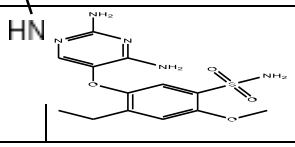
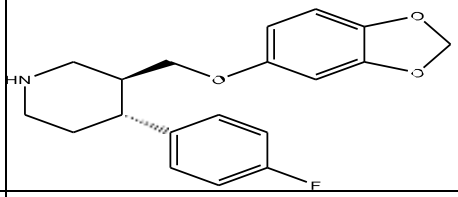
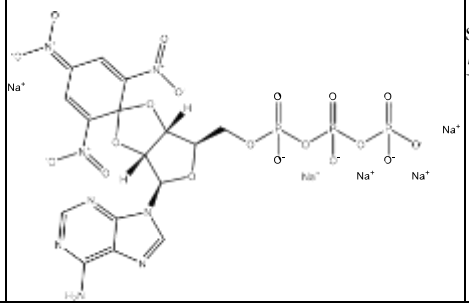


Figure - 28

2d Interaction of NF 279, (5311315) on the protein 6 U9V

S.NO	Docking Score	Energy
1	-7.353	160.708

Table No. 2 Detail of ligand:

S. No.	Structure	Name & Pubchem id	Molecular Formula	Molecular weight
1.		1-((4-Nitrobenzyl) sulfonyl)pyrrolidine, 12099957	C11H14N2O4S	270.31 g/mol
2.		1-Oxa-6-azaspiro[3.4] octane, 54759147	C6H11NO	113.16 g/mol
3.		Gefapixant, 24764487	C14H19N5O4S	353.40 g/mol
4.		Paroxetine, 43815	C19H20FNO3	329.4 g/mol
5.		Tnp-ATP sodium, 53321667	C16H12N8Na5O19P3	828.2 g/mol

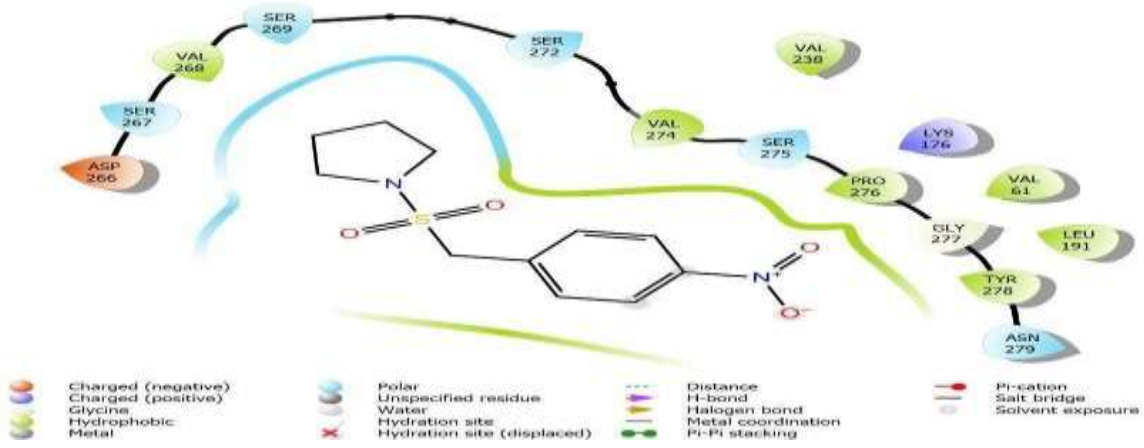


Figure – 29
2d Interaction of 1-((4-Nitrobenzyl) sulfonyl) pyrrolidine, 12099957 on the protein 5YVE

Figure – 30
2d Interaction of 1-((4-Nitrobenzyl) sulfonyl) pyrrolidine, 12099957 on the protein 5 YVE

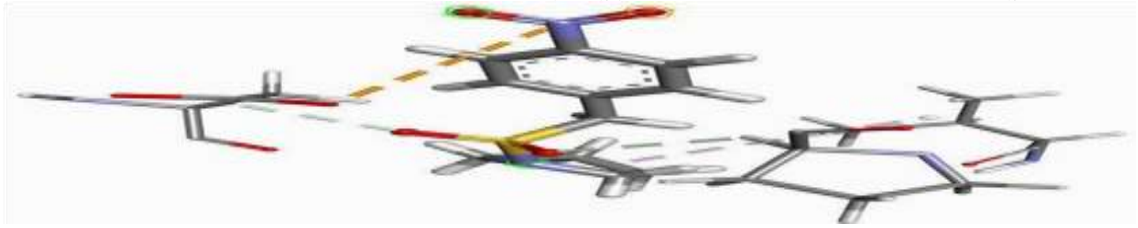


Figure – 31
3d Interaction of 1-((4-Nitrobenzyl) sulfonyl) pyrrolidine, 12099957 on the protein 5YVE

S.NO	Docking Score	Energy
1	-3.811	16.79

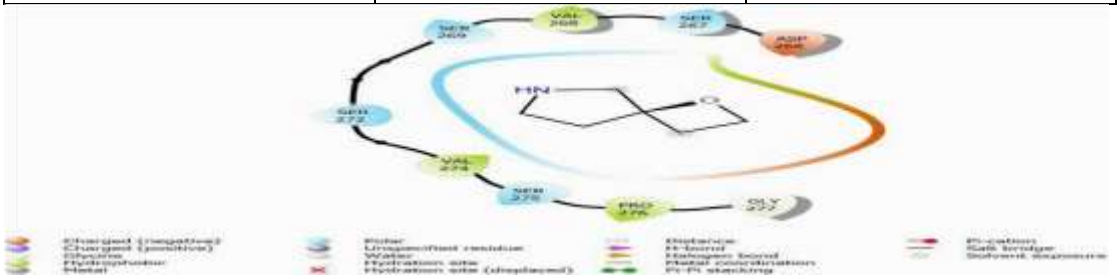


Figure – 32
2d Interaction of 1-Oxa-6-azaspiro[3.4]octane, 5470147on the protein 5 YVE

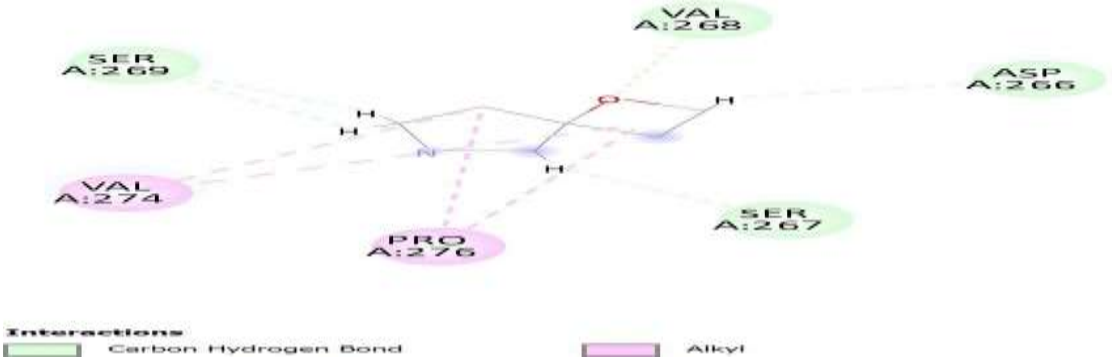


Figure – 33
2d Interaction of 1-Oxa-6-azaspiro[3.4]octane, 54759147on the protein 5YVE

Figure - 34

3d Interaction of 1-Oxa-6-azaspiro[3.4]octane, 54759147on the protein 5YVE

S.NO	Docking Score	Energy
1	-4.917	27.95

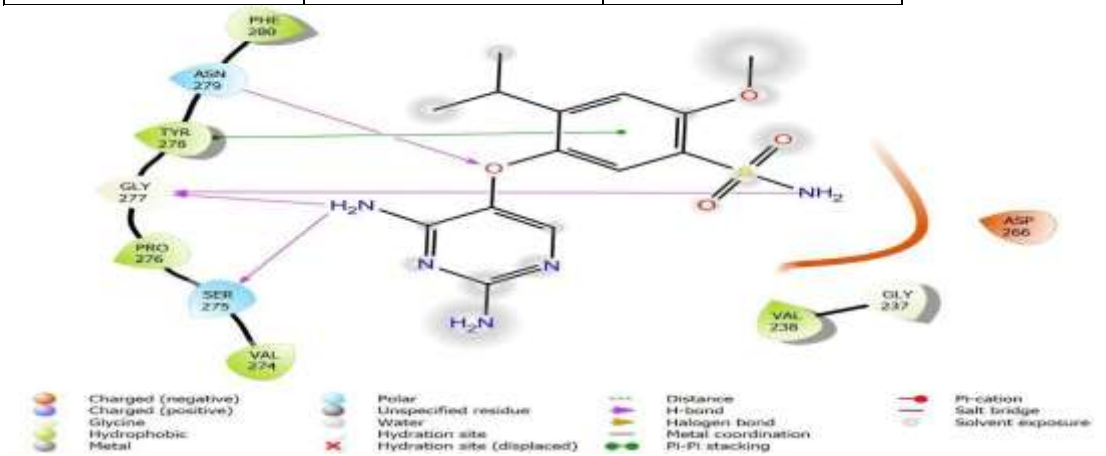


Figure – 35

2d Interaction of Gefapixant, 24764487 on the protein 5YVE

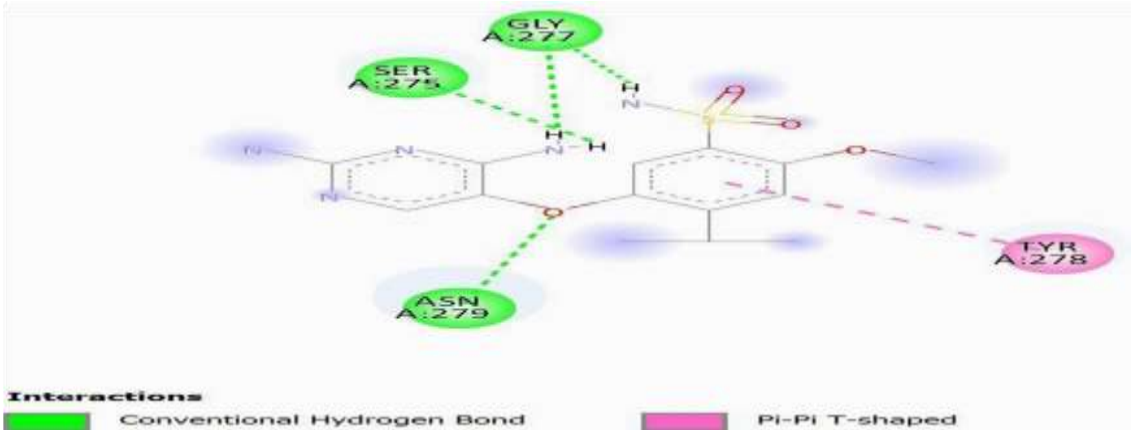


Figure – 36

2d Interaction of Gefapixant, 24764487 on the protein 5 YVE

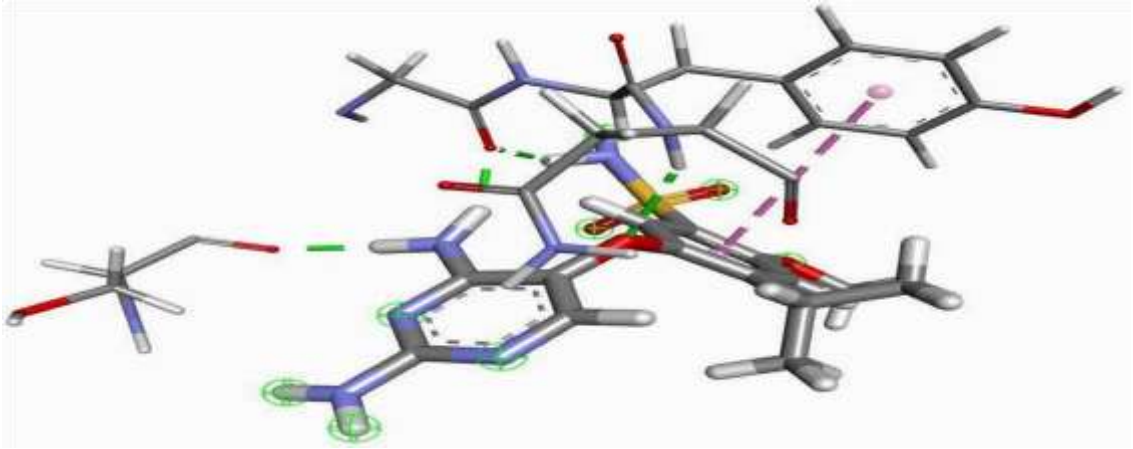


Figure – 37

3d Interaction of Gefapixant, 24764487 on the protein 5YVE

S.NO	Docking Score	Energy
1	-4.092	13.559

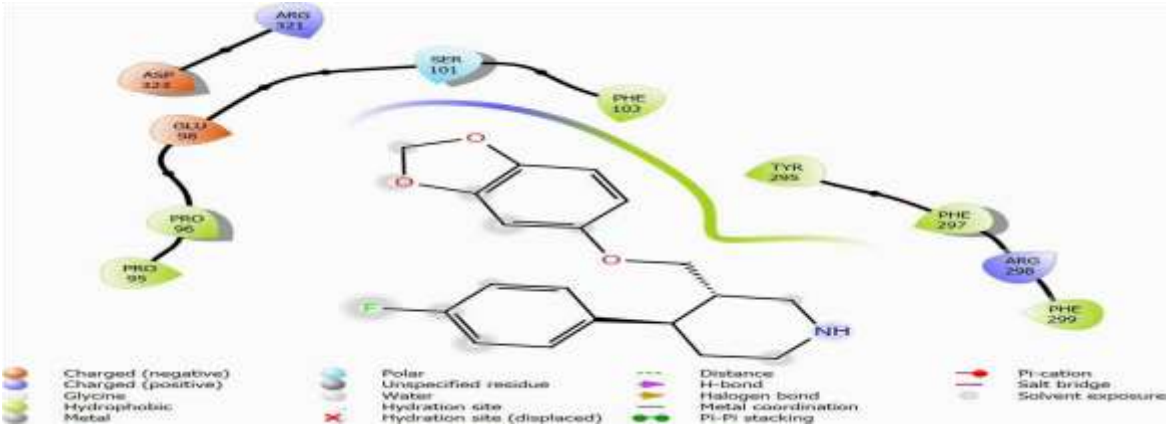


Figure – 38
2d Interaction of Paroxetine, 43815 on the protein 2H9V

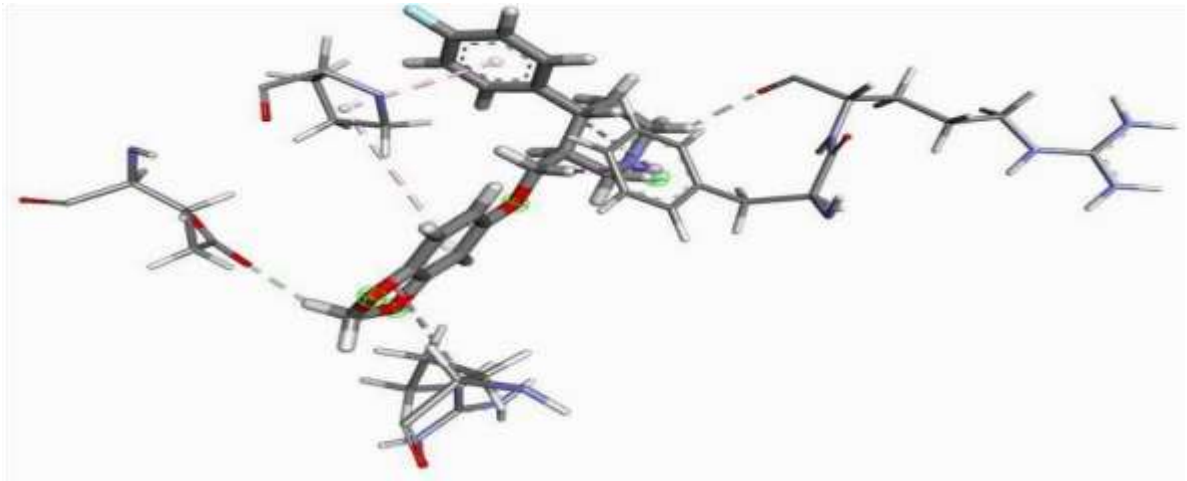


Figure – 39

3d Interaction of Paroxetine, 43815 on the protein 2 H9V

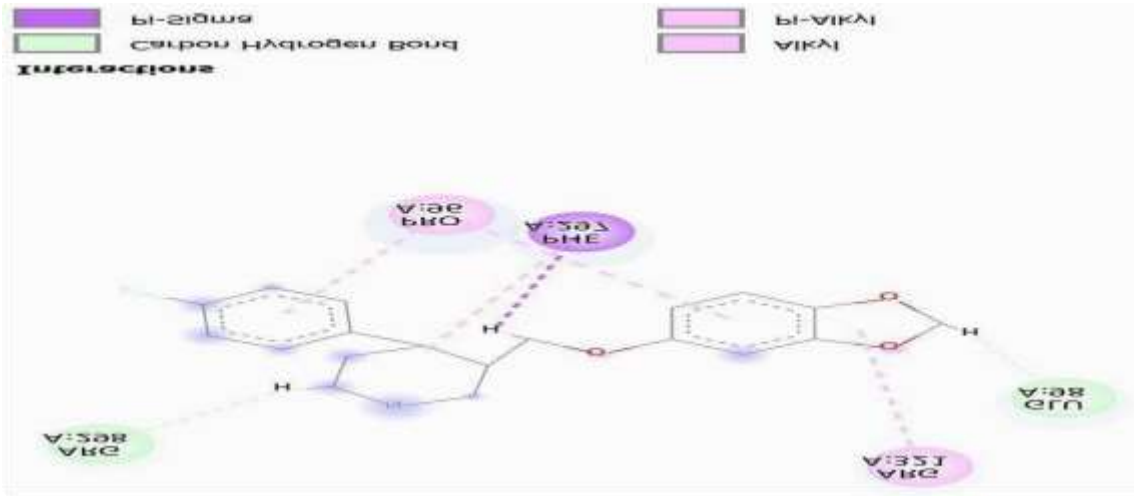


Figure – 40
2d Interaction of Paroxetine, 43815 on the protein 2H9V

S.NO	Docking Score	Energy
1	-3.614	38.35

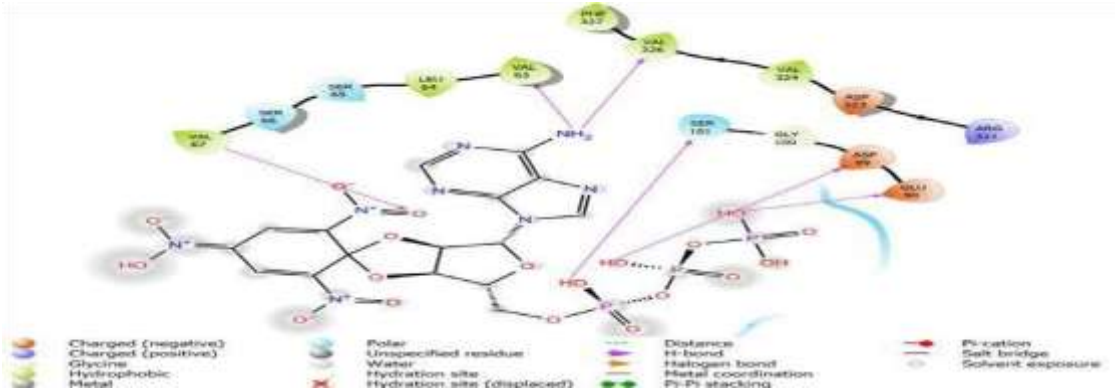


Figure – 41

2d Interaction of Tnp-ATP sodium, 53321667 on the protein 2H9V

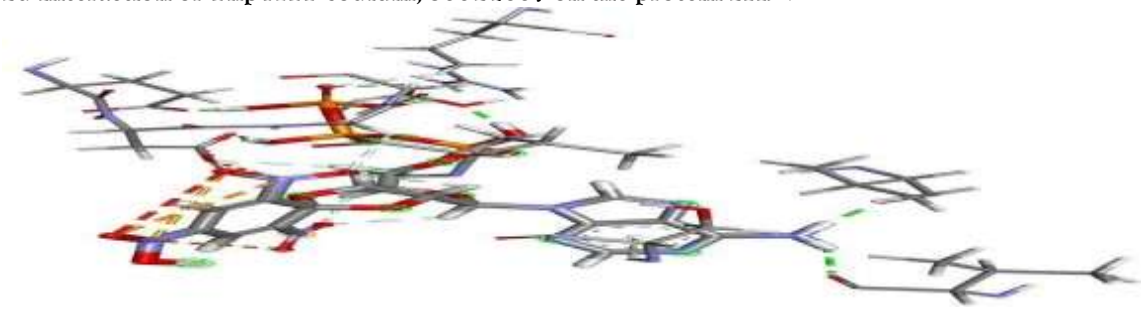


Figure – 42

3d Interaction of Tnp-ATP sodium, 53321667 on the protein 2H9V

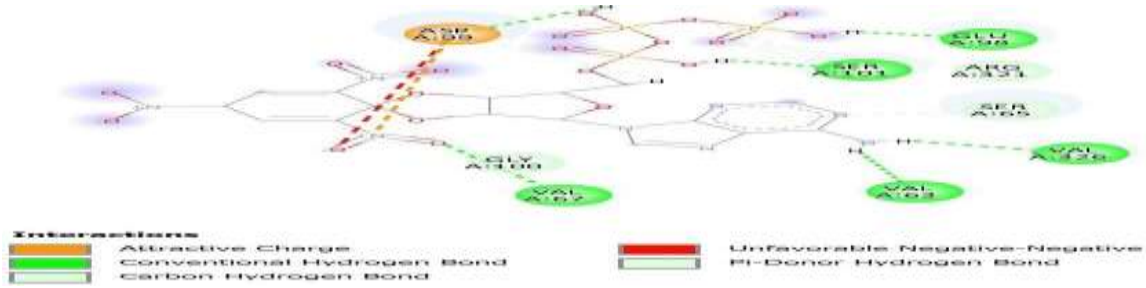


Figure - 43

2d Interaction of Tnp-ATP sodium, 53321667 on the protein 2H9V

S.NO	Docking Score	Energy
1	-6.879	25.515

4. DISCUSSION:

Several antagonists have the intriguing potential to interact with P2X receptor subtypes linked to neuropathic pain, according to the molecular docking analysis carried out in this work. NF 110 had the best docking score (-7.739) among the compounds under investigation, suggesting a high binding affinity for the receptor binding site. The presence of many sulfonate groups inside the receptor's ATP-binding domain, which promote hydrogen bonding and electrostatic interactions, is responsible for this interaction. Strong binding properties like this point to its potential as a lead chemical for more research. Similarly, NF 279 had the greatest interaction energy and a significant docking score of -7.353, indicating a complicated yet persistent interaction. Its huge molecular size and polyanionic nature may help it attach firmly in the receptor pocket, but they may also cause issues with membrane permeability and bioavailability. AZ10606120 and cyclobenzaprine hydrochloride both demonstrated excellent docking capabilities, demonstrating their compatibility with P2X receptor binding sites that may be used to create centrally acting analgesics.

Docking scores for GSK-1482160 and JNJ-47965567 were around -4.9 and -4.4, respectively, indicating stable interactions with the receptor. These ligands may have advantageous pharmacokinetics and be appropriate for oral delivery because of their balanced lipophilic- hydrophilic profiles and modest molecular weight. Their structural frameworks may serve as reference scaffolds for synthetic derivatives that are less harmful and more effective in the future. A peptide-based compound called spinorphin has relatively low docking scores, indicating a decreased binding affinity. Direct competitive inhibition, however, could not be the only factor contributing to its biological significance. Spinorphin and other peptide antagonists may work via non-classical or allosteric processes, which might indirectly modulate receptor activity. To determine its precise mechanism of action, further experimental research is necessary.Additionally, significant binding interactions between Eliapixant and PSB-12054 were found by docking. These compounds have advantageous structural characteristics, such fluorination and sulfonamide moieties, which improve receptor binding and pharmacological activities, even if their scores weren't the best. Particularly, eliapixant is a clinically developed drug, and its mediocre docking simulation results imply that extra pharmacodynamic and pharmacokinetic elements that are not entirely represented in silico may enhance in vivo action. The robustness of docking procedure were further verified by secondary ligand docking data, which included substances such as 1-Oxa-6-azaspiro [3.4] octane, TNP-ATP, or Gefapixant. Because its structural resemblance to ATP, TNP-ATP demonstrated a high affinity; nevertheless, stability and bioavailability issues restrict its use as a medicinal agent. on the other hand, gefapixant showed a low interconnection energy and stabilized docking score, indicating that it should continue to be evaluated in clinical settings. All things considered, the docking findings show that ligand structures with polyanionic groups, ideal donors and acceptors of hydrogen bonds, and moderate lipophilicity greatly aid in efficient receptor binding. The information high point the significance of supplementary between receptors and ligands as well as the probability of rationally designing P2X receptor antagonists that are more selective. These results provide a constructional foundation for creation of novel curative molecules for the reception of neuropathic and chronic pain, as well as opening the door for further preclinical vindication.

Table 4.1. Docking score of selected antagonist for P2X receptor Subtypes:

Antagonist	Docking Score	Energy
PSB-1011 sodium, (78253)	-4.313	62.337
NF 110, (16066783)	-7.739	102.118
Eliapixant, (121397587)	-4.009	31.7
Cyclobenzaprine Hydrochloride, (22576)	-7.258	31.047
Spinorphin, (3081832)	-4.328	12.469
psb-12054, (60168729)	-4.644	52.785
JNJ-47965567, (66553218)	-4.429	66.944
AZ10606120, (10310632)	-5.177	51.788
GSK-1482160, (23649427)	-4.917	20.742
NF 279, (5311315)	-7.353	160.708

Table.4.2 Ligand Bind Structure:

Antagonist	Docking Score	Energy

1-((4-Nitrobenzyl)sulfonyl)pyrrolidine, 12099957	-3.811	16.79
1-Oxa-6-azaspiro[3.4]octane, 54759147	-4.917	27.95
Gefapixant, 24764487	-4.092	13.559
Paroxetine, 43815	-3.614	38.35
Tnp-ATP sodium, 53321667	-6.879	25.515

5. CONCLUSION:

By the help of a molecular docking technique to assessed the binding affinity and interconnection patterns of P2X receptor antagonists, the recent work high point the therapeutic value of these drugs in the setting of neuropathic pain. Certain ligands, in particular NF 110, NF 279, and Cyclobenzaprine HCl, shown substantial binding affinities with the ATP-binding domains of P2X3, P2X4, and P2X7 receptor subtypes, according to thorough in silico study. These discoveries suggest that they may be effectual in modifying purinergic signaling pathways linked to tenacious pain. According to the interconnection patterns seen, constructional elements including heterocyclic scaffolds, aromatic rings, and sulfonate groups have a important or crucial role in receptor firmness and affinity. Moreover, substances such as AZ10606120 and Gefapixant had excellent pharmacokinetic characteristics and satblize docking scores, indicating their capability as scaffolds for further constructional optimization and therapeutic development. The finding also confirmed that complex or peptide-based compounds may nonetheless have special uses, maybe via indirect or allosteric regulation of receptor initiation, even if they sometimes have lower docking scores. The consequences give a logical foundation for evolution of antagonists specific to subtypes and offer important insights into the structure-activity correlations driving P2X receptor inhibition. To confirm these computer predictions and evaluate the drugs' safety, bioavailability, and therapeutic effectiveness, further research combining in-vitro tests and in-vivo models is important. All things considered, this study highlights the potential of molecular docking methods to speed up the development of new analgesics for neuropathic pain and encourages further investigation of P2X receptors as promising therapeutic target.

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