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Molecular Insertion Study with Some Antiepileptic

Qasım Habeb Dayeh Dayeh[1], Nejdet Gültepe[2]
[1]Institute Of Sciences, Department of Genetics and Bioengineering, Kastamonu University, Kastamonu, Turkey
[2] Department of Fundamental Fisheries Sciences, Atatürk University, Erzurum, Turkey.
E-Mail**:** qasimhabeeb5@gmail.com

Abstract
This study includes the structure-activity relationship of active molecules that are commonly used in the treatment of convulsive seizures in epileptic diseases. The molecules chosen in the study due to their role as antiepileptic agents and according to their physiopathological mechanisms of action are: Vigabatrin, Lokosamidine, Gabapentin, Primidone. In addition, the NMDA receptor, which is effective in epileptic seizures, has been studied. With the overstimulation of NMDA receptors, the active sites of NMDA receptors act as high conduction channels by allowing Na+ and Ca+2 to enter target cells. Therefore, the PDB ID:5UN1 receptor was considered suitable for molecular insertion study as it acts as an antagonistic effect according to its activity on the channel in case of epileptic seizure formation. The result of the molecular docking analysis showed that Primidone gave the best binding affinity for 5UNA with a value of -6,4 kcal/mol. Other analyzes in descending order (in kcal/mol); Locosamide (-6,1), Gabapentin (-5,6), Vigabatrin (-5,1), Levetiracetam (-4,9), were determined.
Keywords: Antiepileptic, NMDA receptor, Molecular insertion, Epileptic seizures.

Introduction

Epilepsy is a common neurological disease characterized by seizures caused by sudden, irregular, excessive and intense electrical discharges in the gray matter of the brain due to the high excitability of neurons in the brain. Although there is not much information about the cellular and molecular mechanisms of epileptic seizures, the most well-known mechanism is excessive neuronal firing, which is caused by the disruption of the balance between excitatory and inhibitory voltage-dependent/synaptic transmission. Neurotransmitters are divided into excitatory neurotransmitters and inhibitory neurotransmitters. Excitatory neurotransmitters are acidic amino acids that cause depolarization of the cell by increasing the passage of Na^+ and Ca_2^+ into the cell. Inhibitory neurotransmitters are amino acids that cause hyperpolarization of the cell by increasing the passage of Cl^- into the cell or increasing the outflow of K^+ and closing the Na^+ and Ca_2^+ channels in the cell membrane and reducing the entry of Na^+ and Ca_2^+ into the cell. This imbalance in the nervous system results from functional disorders in macromolecules involved in excitatory and inhibitory transmission in the epileptic brain, resulting in the development of epilepsy in a specific region of the brain (1). The cell membrane has a certain negative voltage (membrane potential) depending on the intracellular and extracellular ion concentration. A nerve cell in the resting phase is polarized and has a membrane potential of about -70 mV to -80 mV. This potential is balanced by ion pumps and ion channels, creating a concentration gradient across the membrane with a greater negative

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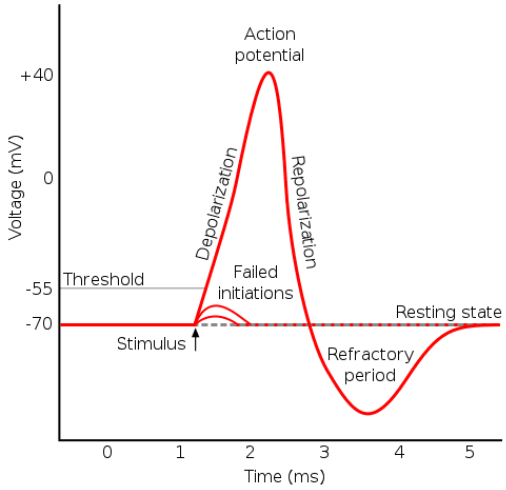
charge inside the cell. With the positive shift of the membrane voltage, the depolarized membrane action potential (AP) is formed, and nerve and muscle cells are stimulated by this potential. AP transmitted along the axon in neurons is transferred to the next neuron via neurotransmitters at the axon tip and neuronal firing is provided. After depolarization, the membrane becomes hyperpolarized by reaching a voltage below the resting potential (Figure 1) (2,3). This is a response to prevent excessive excitability as a result of successive firings in a healthy nervous tissue, and the membrane quickly returns to the resting phase (polarization). Therefore, the state of extreme excitability; increased excitatory synaptic neurotransmission, decreased inhibitory synaptic neurotransmission, or a change in ion concentration on both sides of the membrane causing depolarization or multiple synchronized sub-threshold excitatory stimuli (4).



Şekil 1: Phases of an action potential depending on the membrane voltage.

The aim of epilepsy treatment is to prevent or control seizures and to improve medical and neuropsychiatric comorbidities. The first discovered antiepileptic drugs (bromide, phenobarbital) that suppress the occurrence, spread and severity of seizures have negative properties in terms of keeping seizures under control and side effects (5). AEDs are classified as first- and second-generation antiepileptics based on their availability before and after 1990 (6). Until 1990, only six classical drugs (carbamazepine, ethosuximide, phenobarbital, valproic acid, phenytoin, primidone) could be used for the treatment of epilepsy, while the discovery of second-generation AEDs (vigabatrin, felbamate, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levexamide) has increased treatment options (with lamotrigine, topiramate, tiagabine, oxcarbazepine, laxamide, leve, lavomid) (7). AEDs act through different molecular mechanisms to modify the excitability of neurons. Thus, they prevent the firing of neurons associated with epileptic seizures and ensure the transmission of normal signals between neurons (8). Sodium channel blockers, calcium channel blockers, glutamate receptor antagonists, GABA receptor agonists and carbonic anhydrase inhibitors are used in the treatment of epilepsy. Glutamate blockers; Glutamate, an excitatory neurotransmitter, enters the cell by sodium and calcium ions; it performs excitation by providing the movement of potassium and chloride ions out of the cell (9). The NMDA receptor (NMDA-R) consists of two different protein subunits, NMDA-R1 and NMDA-R2, on ligand-opened ion channels. With the overstimulation of NMDA receptors, the active sites of NMDA receptors act as high

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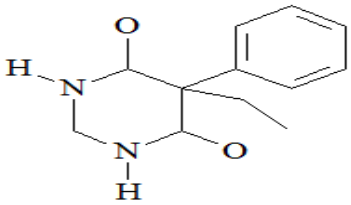
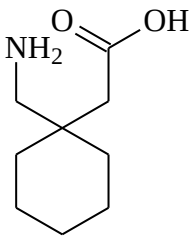
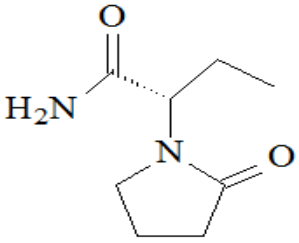
conduction channels by allowing Na^+ and Ca_2^+ to enter target cells. The NMDA receptor is known to have some affinity for the glycine recognition site. The NMDA receptor is linked to a sodium and calcium ion channel and contains a number of binding sites, including the glycine binding site (10). 5UN1; It is a macromolecule that has been studied on the mechanism of NMDA receptor channel block. Memantine, an antagonist-containing macromolecule suitable for the treatment of epilepsy, is an antagonist of the NMDA receptor. This crystal structure, together with long-term simulations of molecular dynamics, provides work on how MK-801 and memantine (a drug approved for the treatment of Alzheimer's disease) bind to the ion channel entrance site, promote ion channel gate closure, and physically block the ion permeability M3-helix beam transition and M2-pore rings (11).

Materials and Methods

PDB ID: 5un1 macromolecule obtained from the RCSB PDB database is a macromolecule studied on the mechanism of NMDA receptor channel block. This macromolecule has been selected among molecules that have an antagonistic effect for the N-Methyl-D-Aspartate receptor. Considering that NMDA receptors play an active role in the treatment of epilepsy, the 5UN1 structure was chosen as a macromolecule suitable for the action mechanism of ligands. The nomenclature, molecular structures and mechanisms of action of the AED active ingredients used in this study are presented in Table 1: Vigabatrin, Locosamide, Levetiracetam, Gabapentin, Primidone and their 3D structures are accessed from the PubChem database.

Table 1: Structural information of antiepileptics

Names	Mechanisms of Action	Chemical Structures
Primidon	GABA increase, Glutamate decrease, Na^+, Ca^{2+} channel inhibition, K+ channel opening	
Gabapentin	Increases GABA levels, Calcium channel modification	
Levetirasetam	Modulation of synaptic vesicle proteins, N, T-type Ca^{2+} Channel inhibition, increases voltage-gated potassium channel conductivity, increases GABA concentration, and inhibits glutamate system by stimulating	

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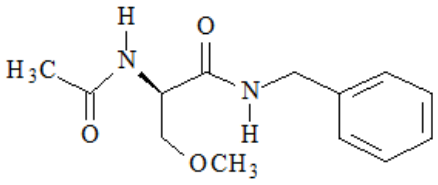
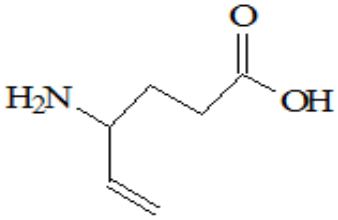
Lacosamide	It increases the slow inactivation phase of the Na^+ channel and is responsible for blocking the voltage-gated sodium channel.	
Vigabatrin	GABA increase opens K^+ (potassium) channels, increases Cl^- channel opening, GABA-AT inhibition effect	

Molecular docking analysis was applied to determine the interactions between the active ingredients determined according to their high potential on ion channels for the treatment of epilepsy and the protein targeting their mechanisms and to calculate the binding energy. In the study carried out with this method, firstly, the structures previously studied were extracted from the receptor structure in the Discovery Studio 2020 Client (12) and the ligand structures were recorded in .pdb format. In the second step, the structures saved in .pdb format were converted to .pdbqt format by following the necessary steps in the Autodock Vina program (13,14), which is the Autodock Tools interface. Then, the conformational structure with the best binding affinity was sent into the receptor and the interactions were examined.

The 5UN1 macromolecule is selected according to its mechanism of antagonistic action to the NMDA receptor for neurotransmitters in epilepsy, and the G chain, which is the active binding sites for chelation, of the 5UN1 macromolecule, consisting of eight chains consisting of G, A, B, H, E, F, C, D, was randomly selected in this study. PRO 514, LEU 515, THR 516, ARG 521, PHE 482, SER 678, ASP 722, PHE 748. The study area was 375 Å spacing, grid size was determined as 46Å×40Å×40Å for all ligands.

The location of this research area was set for all ligands, the X, Y and Z coordinates of the center were 0.386, -31.287 and 12.087 and recorded for each in the conf.txt file. The vina.exe file prepared by The Scripps Research Institute, which enables the vina program to run before the docking phase starts, is called over the script system, then the folder containing the conf.txt file to be used in the docking phase is called. Then, the program was run and the out.pdbqt file containing 10 conformations was created.

Results

In the Discovery Studio 2020 Client program, the conformation that gives the best value was placed inside the 5UN1 macromolecule to see 2D and 3D structures. The binding affinity values obtained for ligands as a result of this calculation are summarized in Table 2.

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Table 2: The binding affinity values of ligands placed in 5UN1 at the best conformation

Ligand's	Best Binding affinity (kcal/mol)	Distance from best mode (Å)	
		RMSD l.b	RMSD u.b
Vigabatrin	-5,1	0,000	0,000
Levetiracetam	-4,9	0,000	0,000
Gabapentin	-5,6	0,000	0,000
Primidone	-6,4	0,000	0,000
Locasamide	-6,1	0,000	0,000

Vigabatrin

The affinity value of vigabatrin placed in the 5UN1 macromolecule in the best binding mode was -5.1 kcal/mol, and 2D and 3D pictures of the intermolecular interactions between vigabatrin and macromolecule 4KFM are given in figure 2. The resulting ligand-protein interactions are as follows; The amino acid binding sites ILEG517 and LEUH764 formed an alkyl bond interaction with the double bonded oxygen atom in lengths of 3.91Å and 5.44Å, respectively. The PROH521 amino acid active site formed a conventional hydrogen bond interaction with the amine of 2.82Å and 2.79Å lengths, respectively (Table 2).

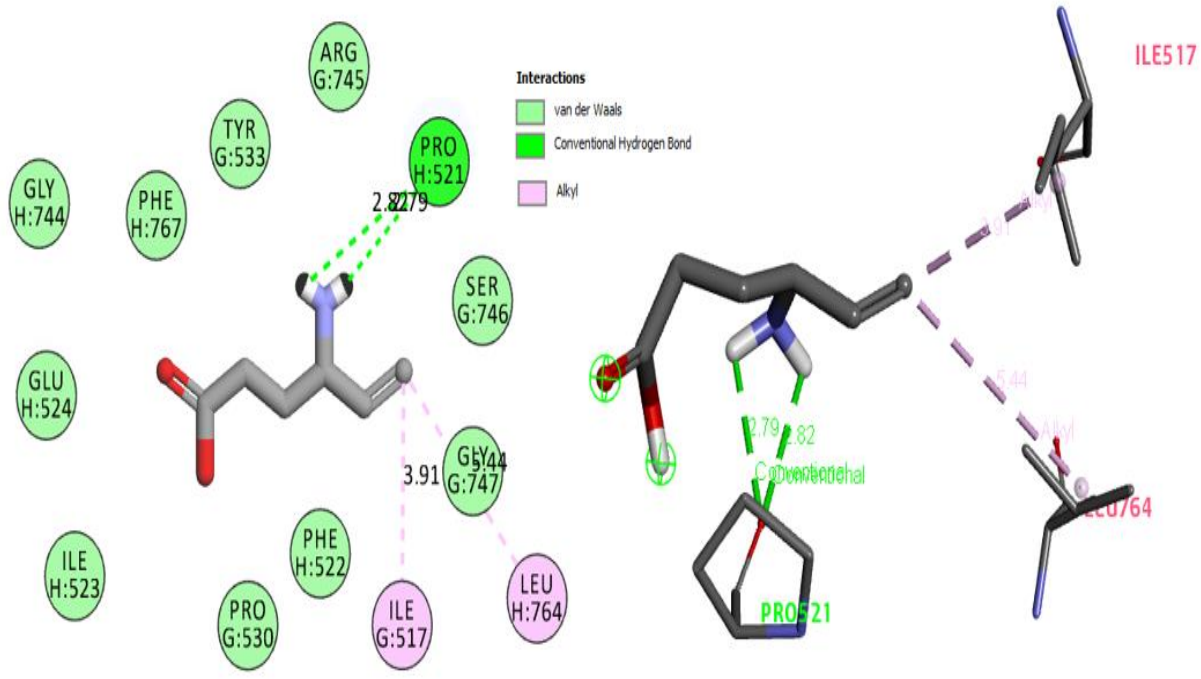

Figure 2: 2D and 3D representation of the interaction of vigabatrin and macromolecule (5UN1)

Table 2: Interactions, types and distances between vigabatrin and 5UN1

Amino acids	Ligand group	Distance (Å)	Interaction
PRO_H521	The NH2 compound in vigabatrin	2,82	Conventional Hydrogen Bond
PRO_H521	The NH2 compound in vigabatrin	2,79	Conventional Hydrogen Bond
ILE_G517	O atom in vigabatrin	3,91	Alkyl
LEU_H764	O atom in vigabatrin	5,44	Alkyl

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Levetiracetam

Patterns of interactions between levetiracetam best binding position and 5UN1 with an affinity of -4.9 kcal/mol are shown in figure 3. The resulting molecular binding interactions are as follows; The PHEG527 and GLUG526 amino acid binding sites formed a conventional hydrogen bond interaction with the amine group of 2.45Å and 2.30Å lengths, respectively (Table 3).

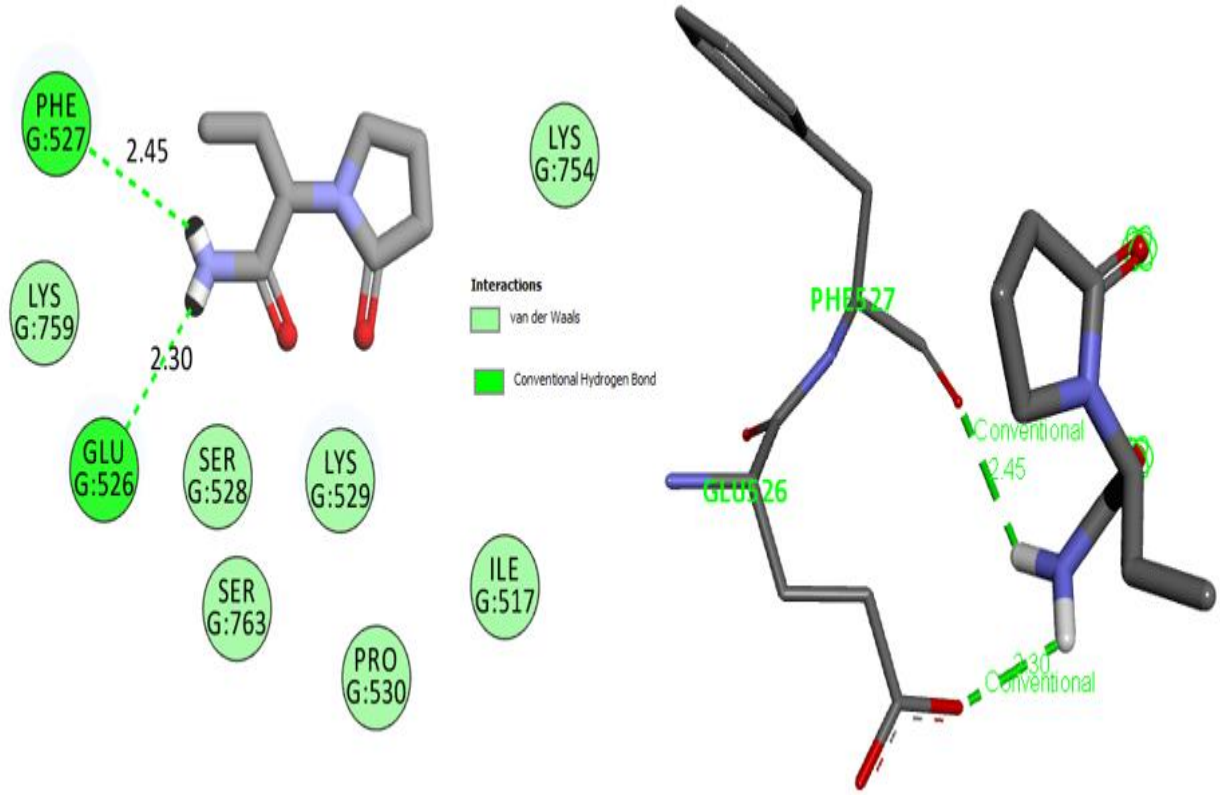

Figure 3: 2D and 3D representation of the interaction of levetirecetam and macromolecule (5UN1)

Table 3: Interactions, types and distances between levetiracetam and 5UN1

Amino acids	Ligand group	Distance (Å)	Interaction
PHE_G527	The NH2 compound in levetirecetam	2,45	Conventional Hydrogen Bond
GLU_G526	The NH2 compound in levetirecetam	2,30	Conventional Hydrogen Bond

Gabapentin

The affinity value of gabapentin at the best binding position was -5.6 kcal/mol, and the interaction between gabapentin and 5UN1 is shown in figure 4. The interactions after the molecular docking study were as follows; PROH521 amino acid active site formed a conventional hydrogen bond interaction of 2.27Å length with the amine compound. The ARGG725 amino acid active site formed a 4.28Å alkyl bond interaction with the benzene group (Table 4).

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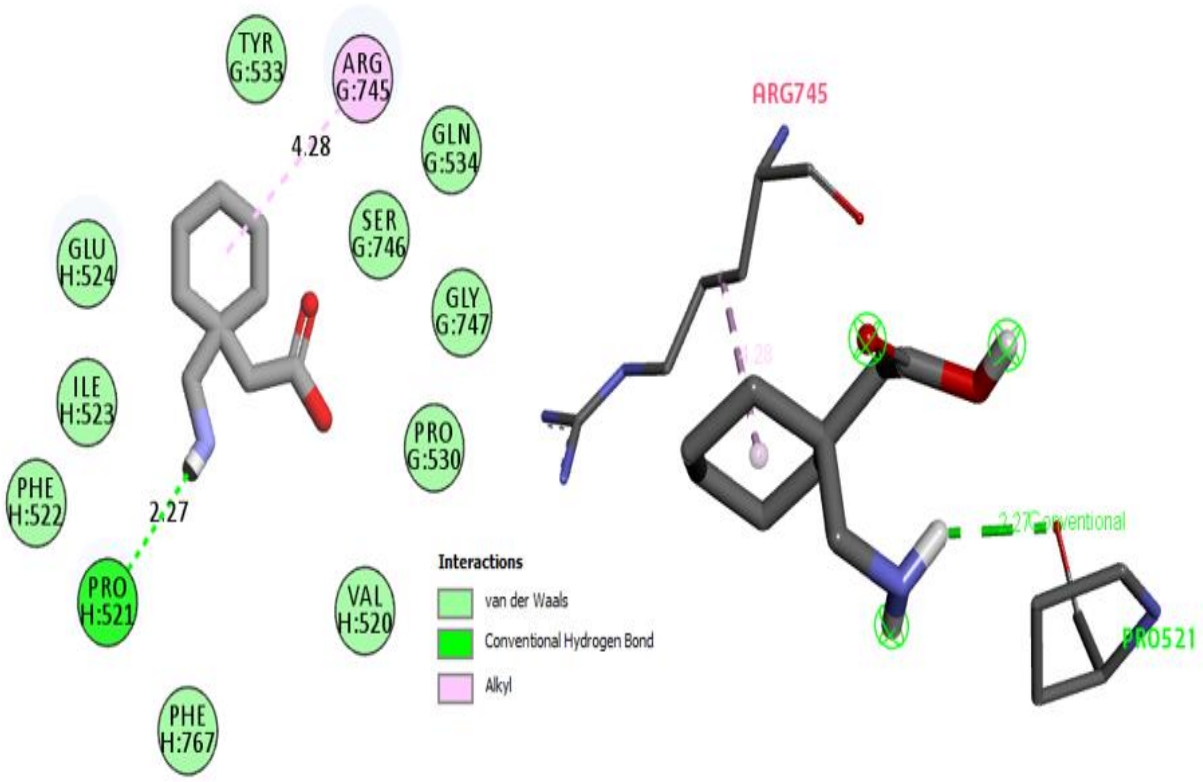

Figure 4: 2D and 3D representation of the interaction of gabapentin and macromolecule (5UN1)

Table 4: Interactions, types and distances between gabapentin and 5UN1

Amino acids	Ligand group	Distance (Å)	Interaction
PRO_H521	The NH2 compound in gabapentin	2,27	Conventional Hydrogen Bond
ARG_G725	The benzene group in gabapentin	4,28	Alkyl

Primidone

The affinity value of primidone placed in the best binding position in 5UN1 was obtained as -6.4 kcal/mol, and the molecular interactions between primidone and macromolecule are given in figure 5. The resulting ligand-protein interactions are as follows; The GLUG423 amino acid active site formed a conventional hydrogen bond interaction of 2.15Å with the amine group. The TYRG410 amino acid active site formed a 4.45Å long pi-alkyl bond interaction with the methylene group. ARGG784 amino acid active site formed a carbon hydrogen bond interaction with the O atom of 3.35Å length. TRPG782, ILEG426 and ILEG431 amino acid active sites with the benzene group are 4.49Å, respectively; 4.94Å and 4.96Å lengths of pi-pi stacked formed pi-alkyl and pi-alkyl bond interactions (Table 5).

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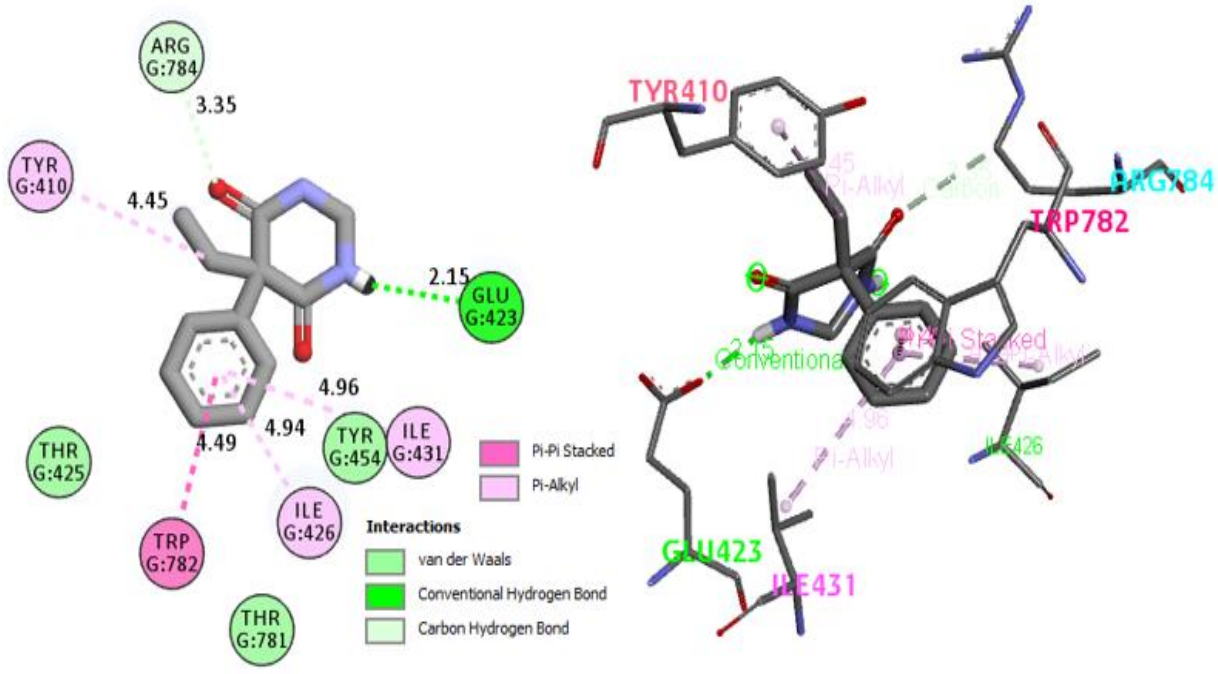

Figure 5: 2D and 3D representation of the interaction of primidone and macromolecule (5UN1)

Table 5: Interactions, types and distances between primidone and 5UN1

Amino acids	Ligand group	Distance (Å)	Interaction
GLU_G423	The NH2 compound in primidone	2,15	Conventional Hydrogen Bond
TYR_G410	CH2 compound in primidone	4,45	Pi-Alkyl
ARG_G784	Primidondaki O atomu	3,35	Carbon Hydrogen Bond
TRP_G782	The benzene group in primidone	4,49	Pi-Pi Stacked
ILE_G426	The benzene group in primidone	4,94	Pi- Alkyl
ILE_G431	The benzene group in primidone	4,96	Pi- Alkyl

Locosamide

Molecular interactions between locosamide and 5UN1 with affinity values of -6.1 kcal/mol are shown in figure 6. The interactions are as follows; ASPA760 amino acid active sites are conventional hydrogen bond interaction with amine group at length of 2.58Å and 2.86Å, respectively. The amino acid binding sites ASPA760, ALAG522, VALH520 and PHEG527 formed a 3.80Å long pi-anion, 5.33Å long pi-alkyl, 5.66Å long pi-alkyl and 3.84Å long pi-sigma bonds with the benzene group, respectively. And the GLUG526 amino acid binding site formed a carbon hydrogen bond interaction with the carbon atom in lengths of 3.62Å, respectively (Table 6).

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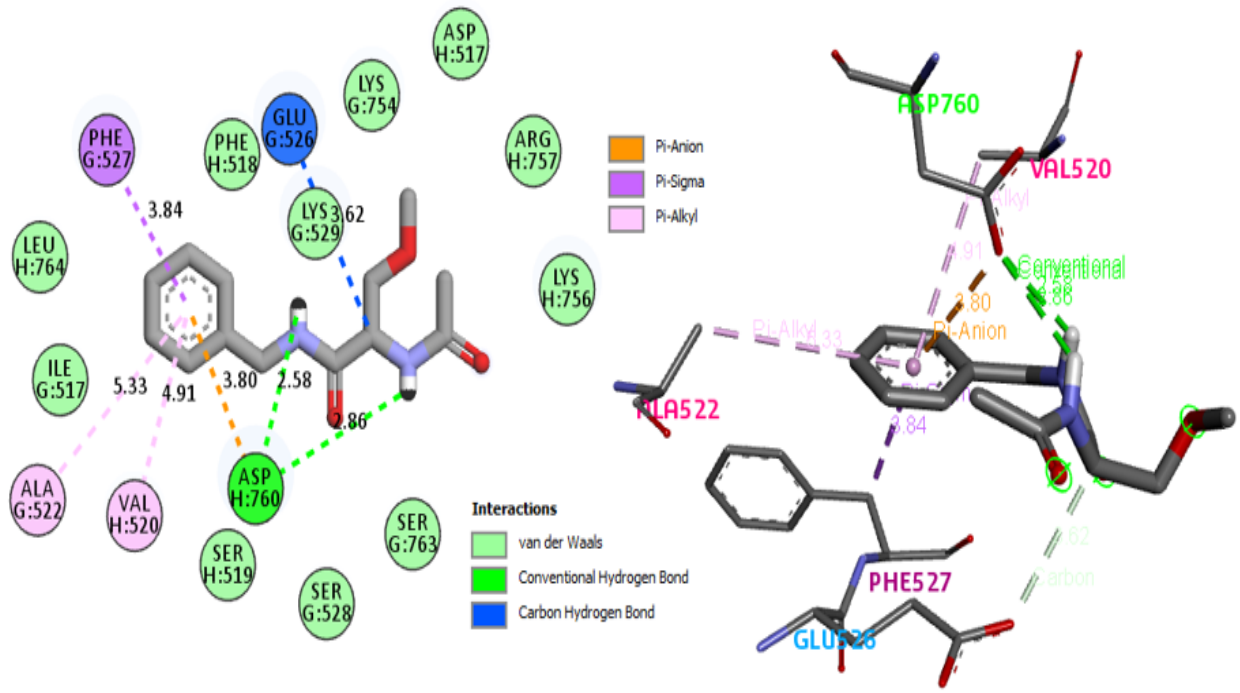

Figure 6: 2D and 3D representation of the interaction of locosamide and macromolecule (5UN1)

Table 5: Interactions, types and distances between locosamide and 5UN1

Amino acids	Ligand group	Distance (Å)	Interaction
ASP_A760	The NH2 compound in locosamide	2,58	Conventional Hydrogen Bond
ASP_A760	The NH2 compound in locosamide	2,86	Conventional Hydrogen Bond
ASP_A760	The benzene group in locosamide	3,80	Pi-Anion
ALA_G522	The benzene group in locosamide	5,33	Pi-Alkyl
VAL_H520	The benzene group in locosamide	5,66	Pi-Alkyl
PHE_G527	The benzene group in locosamide	3,84	Pi-Sigma
GLU_G526	C atomu in locosamide	3,62	Carbon Hydrogen Bond

Discussion

In another study, Vigabatrin, Levetiracetam, Gabapentin, Primidone and Locasamide ligand structures were studied, and when we compared the obtained data with the data in our study, it was seen that levetiretam gave the lowest result in both studies, while gabapentin gave the highest result in the other study, and primidone antiepileptic in this study. However, the data consists of approximately close values (15). In another study, an affinity value of -2,803 kcal/mol was obtained as a result of the 1HOV-vigabatrin docking study, but here a higher affinity value was obtained for vigabatrin in the 5UN1-vigabatrin structure (16). Another coupling study was performed between the active ingredients of gabapentin and vigabatrin and the hGAT1 macromolecule. Compared to molecular insertion with 5UN1, 5UN1 gave higher

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affinity value within the two ligand structures. The data discussed indicate that AEDs are frequently used materials in molecular insertion studies (17).

Conclusion

Only DOCK energy scoring was used in the study, and there are also various scoring functions. The results show that the 5UN1 coded macromolecule can best achieve its effect on NMDA receptors, which has a significant effect on its role in epilepsy treatment, with primidone. Another piece of information provided by the docking study is that the conventional hydrogen bond and carbon-hydrogen bond formation between the receptor and ligands form a strong bond, and the appearance of these bonds can have a good effect on the resulting complex structure. For this reason, structures that form strong bonds give better results than others. If we compare the data obtained as a result of molecular coupling of ligands with the PDB ID file 5UN1, studied as an NMDA receptor antagonist, the highest binding affinities were -6.4 kcal/mol with the 5UN1-pyrimidone complex structure. Then -6.1 kcal/mol locosamide; gabapentin with -5.6 kcal/mol; followed by vigabatrin with -5.1 kcal/mol and finally levetiracetam macromolecule with -4.9 kcal/mol. As a result, when we look at the data, it is seen that the NMDA receptor has the best potential to suppress the ion flow into the cell, and primidone is the best active ingredient.

In Table 6, the antiepileptic and interaction bond ratios that form the conventional hydrogen bond with the 5UN1 macromolecule are given. The bonding energy of the structure was compared despite conventional hydrogen bonding.

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In Table 6, the antiepileptic and interaction bond ratios that form the conventional hydrogen bond with the 5UN1 macromolecule are given. The bonding energy of the structure was compared despite conventional hydrogen bonding.

According to the results; Although primidone gave the best binding energy, it was able to make two of the desired hydrogen bonds out of the 6 bonds that occurred. Locosamide, which gave the best binding energy right after, made a total of seven bonds and made three bonds from the hydrogen bond type, which is a strong bond. Gabapentin, on the other hand, gave conventional hydrogen bonds in one of the two types of bonds. Looking at Vigabatrin, it gave four bonds and two of them form hydrogen bonds. Finally, when levetiracetam is examined, it is seen that there is a hydrogen bond in the two bonds formed. Here, although levetiracetam gives the lowest binding affinity, it appears to form hydrogen bonds at the same rate as the ligand-macromolecule structure giving the highest affinity. Although locosamide had the highest number of hydrogen bonds, it was determined that it did not achieve the highest affinity. Nevertheless, it is possible to say that all ligand structures, regardless of the binding energy, form the desired hydrogen bond structure with the 5UN1 macromolecule.

These ligands, which are the active ingredients of antiepileptic drugs used in molecular placement studies and applied to inhibit seizures, seem to be promising in research for the treatment of epileptic seizures. It can be said that more studies and applications can be done in order to combine the 5UN1 macromolecule, which has an antagonistic effect on the NMDA receptor used in the study and the chance to convulse epileptic seizures, and antiepileptic ligands, and to bring a perspective on its effectiveness in becoming a drug.

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There is no conflict of interest between the authors and institutions.

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