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The Structure-Activity Relationships of Familiar Antiepileptic Drugs and Na^+ Channels

Esra Nur Cakmak[1] Mahmut Gur[2] Bayram Kiran[3]
[1]Kastamonu University, Department of Genetics and Bioengineering, Kastamonu, Turkey
[2]Kastamonu University, Department of Forest Industrial Engineering, Kastamonu, Turkey
[3]Kastamonu University, Department of Genetics and Bioengineering, Kastamonu, Turkey

ABSTRACT

The aim of this study is to examine the effects of drug active compounds, which are widely used in the treatment of epilepsy, on voltage-gated Na^+ channels are important channels that advance the action potential in the excitation direction by molecular docking method. These molecules have been selected considering the physiopathological effect mechanisms of epilepsy disease. When the action potential is stimulated, Na^+ channels allow sodium ion entry into the cell and cause epilepsy seizures. For this reason, PDB ID: 4PA6 receptor, which acts as an antagonist according to its activity on the canal in the formation of epileptic seizures, was chosen for molecular docking study. As a result of molecular docking studies; Phenytoin gave the best binding affinity for 4PA6 with a value of -7.7 kcal/mol. Other results in descending order (as kcal/mol); Mesuximide (-7.5), Remacemide (-7.3), Tiagabine (-7.1), Ethotoin and Mephenytoin (-7.0), Primidone (-6.9), Topiramate (-6.6), Oxcarbazepine and Lamotrigine (-6.3), Felbamate (-6.0), Lacosamide (-5.9), Zonisamide (-5.8), Levetirecetam and Gabapentin (-5.7), Ethosuximide (-5.6), Trimethadion (-5.1), Valproic Acid (-5.0), Vigabatrin (-4.0), determined as.

Keywords:
Anticonvulsant; Epilepsy; Moleculer docking; Ligand; Receptor

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***Correspondence to**: Esra Nur Cakmak, Kastamonu University, Department of Genetics and Bioengineering, 37150, Kastamonu, Turkey.*
E-Mail: kmrc_1675@hotmail.com
Phone: +90 (539) 5981868

INTRODUCTION

Epilepsy, which is one of the central nervous system diseases, is found in a significant part of the world population [1,2]. 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 [3]. AEDs are classified as first and second generation antiepileptics based on their availability before and after 1990 [4,5]. Until 1990, only six classical drugs (carbamazepine, ethosuximide, phenobarbital, valproic acid, phenytoin, primidone) were available for the treatment of epilepsy, while second generation AEDs (vigabatrin, felbamate, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetirecetam) treatment options have increased [4,6]. New AEDs have advantages such as higher tolerability, less drug interactions, and no inducing effects on hepatic metabolism enzymes [7]. AEDs are not effective on epileptogenesis and can only suppress the onset of seizures. 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]. Looking at the mechanism of epileptic seizures, seizures occur when the balance between synaptic transmission due to voltage-dependent excitation and inhibition-related synaptic transmission is disrupted [3,9]. Excitatory neurotransmitters are acidic amino acids that increase the penetration of Na^+ and Ca^{2+} into the cell, causing the depolarization of the cell [5,10-12]. Inhibitory neurotransmitters are also amino acids that cause hyperpolarization of the cell by increasing Cl^- passage into the cell or increasing K^+ output outside the cell [13,14] and by closing Na^+ and Ca^{2+} channels in the cell membrane and reducing Na^+ and Ca^{2+} entry into the cell. Opening and closing of channels depends on binding of neurotransmitters and voltage changes [15]. Another mechanism is neuronal membrane and molecular channel changes in ionic conduction [16]. The movement of ions in these synaptic transmissions, which occur in the nervous system through neurotransmitters, creates an action potential in the cell membrane that causes epileptic seizures. The cell membrane has a certain negative voltage (membrane potential) depending on the int-

racellular 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 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 [17]. The movement of ions in these synaptic transmissions occurring in the nervous system through neurotransmitters creates an action potential that creates an epileptic seizure in the cell membrane, and a seizure occurs in one area of the brain [3,18].

Treatment methods of epilepsy aim to terminate seizures or reduce the number of seizures with the mentioned mechanisms. Despite the availability of several successful AEDs, some AEDs show toxicity and clinically important drug-drug interactions. Therefore, there is still a need for new drugs with better efficacy and tolerability [19,20]. Therefore, quantitative structure-activity relationship techniques (QSAR and 3D-QSAR) have been widely used approaches in resolving the action mechanisms of known AEDs or in the design and efficacy of new compounds. These techniques help to predict and improve the activities of different compounds and to identify new compounds with less side-effect profiles [21,22].

This study has been focused on the structure-activity relationship of active ingredients used in epilepsy treatment and sodium channel inhibition by using Autodock Vina. The reason for this choice is the interactions between antiepileptic drugs and sodium channel antagonists have been demonstrated in many studies and that the PDBs used in the study have an antagonistic effect on voltage-gated sodium channels by inhibiting sodium transitions from voltage-gated sodium channels. [23].

Before explaining the molecular docking study, it is necessary to touch on computer aided drug design, it is used to identify potential drug molecules according to the binding kinetics between the ligand and the protein and the binding site of the ligand. Predicting situations such as a molecule's affinity for a specific target as well as having the desired physicochemical properties to reach the target site and not showing interest in undesired targets are also the main goals of computer-aided drug design [24,25]. Molecular docking is a method of determining preferred conformations of a preferred molecule when binding to another molecule to form a stable complex. In other words, it is a method that examines the interactions and movements between protein and ligand during binding [11]. The coupling between the ligand and the receptor active site is generally based on the coupling of the solvent accessible surface areas of the molecules. Thus, molecular coupling provides insights into the strength and type of signal transmitted in a biological system [11,26].

When we look at the studies in the literature, it is seen that there are many molecular docking studies. The originality of the work emerges here. Considering the data width, this difference draws attention. To the readers of this article; presents a study in which antiepileptic drugs, which have different mechanisms of action, have a curative effect on the neurological disease epilepsy and act as an active substance in the treatment, are combined with a macromolecule that only inhibits voltage-gated sodium channels, that is, has an antagonistic effect on the channels. Combining 19 antiepileptic drugs with the selected macromolecule differs from other studies in the literature.

MATERIAL AND METHODS

The effects of selected active substances on ion channels are summarized in Table 1. Furthermore, the studied PDB ID: 4PA6 is a macromolecule used as a voltage-gated sodium channel antagonist, acting as an inhibitory neurotransmitter aimed at moving the action potential from a negative voltage to a resting potential.

The mechanisms of action of the active substances were examined and the molecular structures of the 19 active substances included in the research and the molecular structure of the selected macromolecule are shown in Table 2.

4PA6; It is a macromolecule studied on the pore and C-terminal domain structure of NavMS (Magnetococcus marinus) in the presence of channel blocking compound (Figure 1). It was chosen as the molecule with antagonistic effect for the voltage-gated sodium channel. In silico insertion studies show the full extent of the blocking binding site. This information suggests that the NavM channel may be a valuable tool for the screening and rational design of human drugs [27].

The basic principle of molecular docking studies aims to interpret the interaction potentials and bond structures of the two molecules desired to be combined. In other words, it includes determining the conformation that a molecule prefers to bond to another molecule to form a stable complex structure, examine the interactions and movements [28]. Discovery Studio 2020 Client program and Autodock Tolls program, which is the Autodock Vina interface, were used to carry out the docking work. As an example, the 3D view

Table 1. Compounds and their action mechanisms of antiepileptic drugs

Compounds	Action Mechanisms	Compounds	Action Mechanism
Ethotoin	Na^+ channel inhibition	Primidone	GABA increase, Glutamate decrease, Na^+, Ca^{2+} channel inhibition, K^+ channel opening
Ethosuximide	T-type Calcium (Ca^{2+}) channel inhibition	Oxcarbazepine	Sodium channel inhibition, N, P, R type Ca^{2+} channel inhibition
Felbamate	Glutamate inhibition, NMDA receptor blockage, increases GABA levels, Na^+ channel blockade, blockade of voltage-gated Ca^{2+} channels	Tiagabine	Increases GABA concentrations and inhibits GABA-AT
Gabapentin	Increases GABA levels, Calcium channel modification	Topiramate	Glutamate reduction, voltage-transition sodium channel inhibition, activation of potassium currents, AMPA and glutamate inhibition, voltage-transition calcium channel inhibition, NMDA inhibition, increase of GABA concentration, inhibition of carbonic anhydrase isoenzyme
Lamotrigine	Voltage-gated sodium channel inhibition, glutamate reduction, Ca^{2+} channel inhibition	Valproic acid	Na^+ and T type Ca^{2+} channel inhibition, GABA increase, K^+ channel activity
Levetiracetam	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	Vigabatrin	GABA increase opens K^+ (potassium) channels, increases Cl^- channel opening, GABA-AT inhibition effect
Phenytoin	Sodium and calcium channel inhibition activates K^+ channel transmission, increases GABA concentration	Zonisamide	T-type Calcium channel inhibition, Inhibit Carbonic Anhydrase isoenzyme, voltage-gated Na^+ channel inhibition, inhibit glutamate release
Lacosamide	It increases the slow inactivation phase of the Na^+ channel and is responsible for blocking the voltage-gated sodium channel.	Mephenytoin	Inhibits voltage-gated Na^+ channel conduction
Mesuximide	T-type Ca^{2+} channel inhibition, partial NMDA inhibition	Remacemide	Blocks NMDA responses, inhibits voltage-gated Na^+ channel conduction
Trimethadione	T-type Ca^{2+}, Na^+ channel inhibition, partial NMDA inhibition		

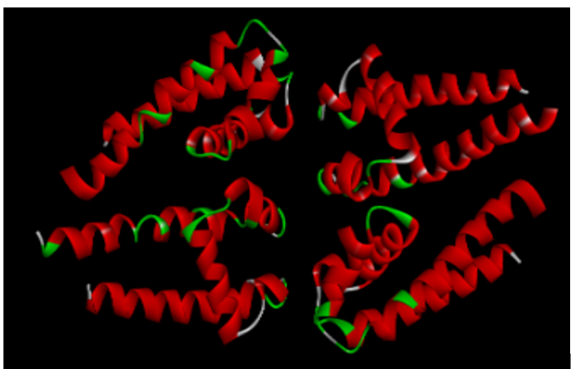


Figure 1. PDB ID:4PA6 macromolecule

of the docking study between 4PA6 and ethosuximide is given in Figure 2.

The 4PA6 macromolecule was selected according to its mechanism of antagonist action for neurotransmitters in epilepsy disease, and it shows the potential to interact well on the action mechanisms of certain ligands in the study. In this study, the A chain, which is the active binding sites of the 4PA6 macromolecule, consisting of four chains A, B, C, D, was chosen randomly. The following amino acid active sites were chosen for the binding sites; TYR 153, ILE 144, ALA 145, PRO 193, ASN 194, TRP 196, PHE 198, VAL 197. The study area was determined as 375 Å spacing, the grid

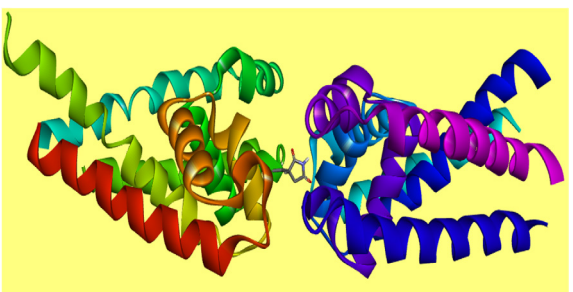


Figure 2. An moleculer docking study 4PA6 with Ethosuximide

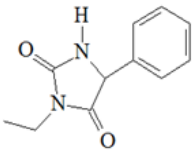
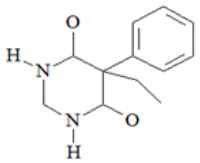
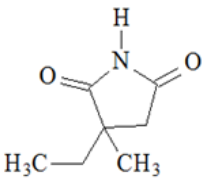
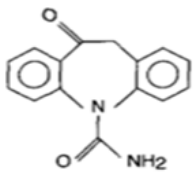
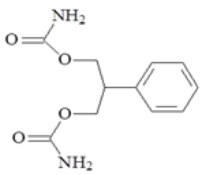
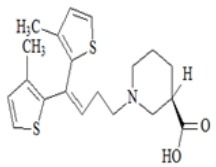
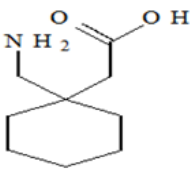
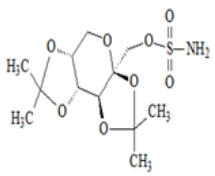
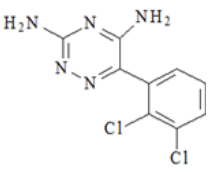
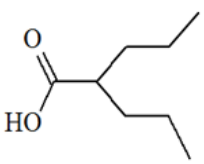
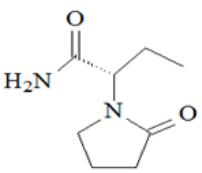
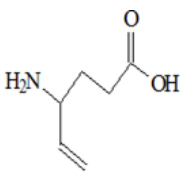
size was determined as 40Å×48Å×52Å for all ligands. The location of this search area is set for all ligands, the X, Y and Z coordinates of the center are set as -20,579, -94,065 and -29,691 and saved for each in the conf.txt file.

RESULTS AND DISCUSSION

Vigabatrin

The affinity value of vigabatrin placed in the macromolecule 4PA6 in the best binding mode was obtained as -4.6 kcal/mol and 2D and 3D pictures of the intermolecular interactions between vigabatrin and macromolecule 4PA6 are given in Figure 3. The resulting ligand-protein interactions are as that; PHEB157, TRPB160 and PROB158

Table 2. Compounds of molecular structures

Compounds	Moleculer structure	Compounds	Moleculer structure
Ethotoin		Primidone	
Ethosuximide		Oxcarbazepine	
Felbamate		Tiagabine	
Gabapentin		Topiramate	
Lamotrigine		Valproic acid	
Levetiracetam		Vigabatrin	

amino acid binding sites, respectively 4,92Å, 3,75Å and 5,43Å with double bonded oxygen atom; Pi-alkyl, pi-alkyl and alkyl bond interaction with lengths of; The GLUc159 amino acid bonding site forms a 2,94Å long conventional hydrogen bond interaction with the amine group (Table 3).

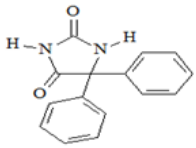
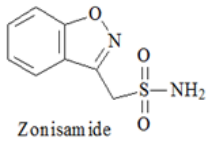
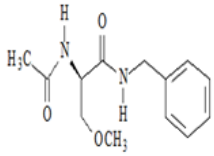
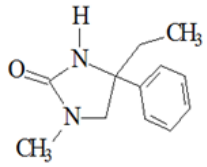
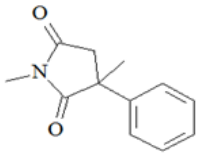
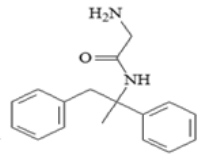
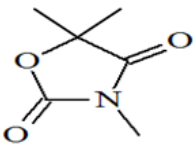
Lamotrigine

The affinity value of lamotrigine was obtained as -5.9 kcal/mol and intermolecular interaction models are presented in Figure 4. The interactions are as follows; TRPb160 amino acid active site length 4.87Å, a bond that interacts with the benzene group in a pi-pi T fashion;

Table 3. Interactions, types and distances between vigabatrin and 4PA6 macromolecule

Vigabatrin			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
PHEb157	O atom in Vigabatrin	4,92	Pi- Alkyl
TRPb160	O atom in Vigabatrin	3,75	Pi-Alkyl
PROb158	O atom in Vigabatrin	5,43	Alkyl
GLUc159	NH_2 compound in Vigabatrin	2,94	Conventional hydrogen bond

TRPb160, PHEb157, PHEb157 and PROc158 amino acid active sites with methyl group; It formed pi-alkyl, pi-alkyl, pi-alkyl and alkyl bond interactions at lengths of 4.24 Å, 4.68 Å, 4.93 Å and 4.26 Å (Table 4).

Phenytoin		Zonisamide	
Lacosamide		Mephenytoin	
Mesuximide		Remacemide	
Trimethadione			

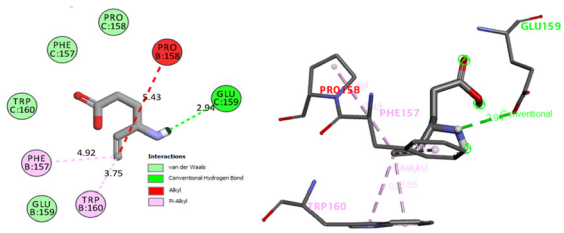


Figure 3. 2D and 3D representation of vigabatrin and 4PA6 macromolecule

Table 4. Interactions, types and distances between lamotrigine and 4PA6 macromolecule

Lamotrigine			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
TRPB160	Benzene group in Lamotrigine	4,87	Pi-pi T-Shaped
TRPB160	CH_3 compound in Lamotrigine	4,24	Pi-Alkyl
PHEB157	CH_3 compound in Lamotrigine	4,68	Pi-Alkyl
PHEB157	CH_3 compound in Lamotrigine	4,93	Pi-Alkyl
PROC158	CH_3 compound in Lamotrigine	4.26	Alkyl

Ethosuximide

Molecular interactions between the ligand with affinity value given as -5.6 kcal/mol and the macromolecule 4PA6 are shown in the Figure 5 and the interactions are the; 2,69Å long pi-donor hydrogen bond interaction with TRPD160 amino acid active site amine group; TRPA160 amino acid active site methyl group 3,96Å long pi-sigma

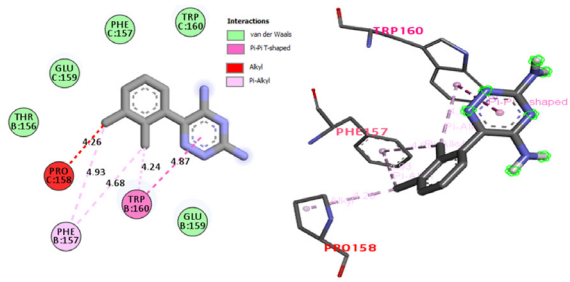


Figure 4. 2D and 3D representation of lamotrigine and 4PA6 macromolecule

bond interaction; PHEA157 amino acid active site formed 5,31Å long pi-alkyl bond interactions with the methylene group (Table 5).

Table 5. Interactions, types and distances between ethosuximide and 4PA6 macromolecule

Ethosuximide			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
TRPD160	NH_2 compound in Ethosuximide	2,69	Pi-Donor hydrogen bond
TRPA160	CH_3 compound in Ethosuximide	3,24	Alkyl
PHEA157	CH_2 compound in Ethosuximide	5,31	Pi-Alkyl

Lacosamide

Molecular interactions between lacosamide and 4PA6 with affinity values of -5.9 kcal/mol are shown in Figure 6. Interactions; Carbon hydrogen bond and pi-sigma inte-

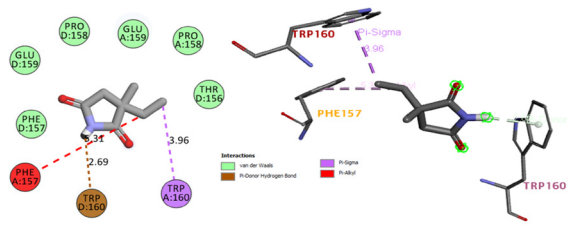


Figure 5. 2D and 3D representation of ethosuximide and 4PA6 macromolecule

raction at 3,56Å and 4,12Å distance with methyl group of amino acid active sites LEUB168 and TRPA192; It is in the form of a pi-pi stacked bond interaction with the benzene group in the PHEB142 amino acid active site at a distance of 3.84A2 (Table 6).

Table 6. Interactions, types and distances between lacosamide and 4PA6 macromolecule

Lacosamide			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
LEUB168	Methyl group in Lacosamide	3,56	Conventional hydrogen bond
TRPA192	CH_3 compound in Lacosamide	4,12	Pi-Sigma
PHEB142	Benzene group in Lacosamide	3,84	Pi-pi Stacked

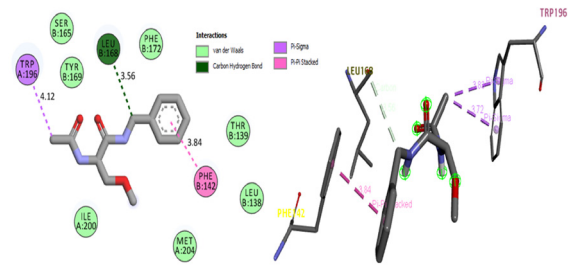


Figure 6. 2D and 3D representation of lacosamide and 4PA6 macromolecule

Zonisamide

The affinity value of the zonisamide ligand placed in the best binding position to 4PA6 was obtained as -5.8 kcal/mol and the interactions between the best binding form of zonisamide and 4PA6 are shown in Figure 7. Obtained ligand-protein interactions; Pi-Sulfur, pi-alkyl and pi-pi stacked bond interaction with the benzoxaline group at the amino acid binding sites METB178, LEUB138 and PHEB142, respectively, at a distance of 4.99Å, 5.46Å and 2.94Å; The PHEB142 and LEUB168 amino acid active sites are in the form of nitrogen atom interaction with the 3.98A8 and 5.06A3 long pi-pi stack and pi-alkyl carbon bond, respectively (Table 7).

Felbamate

The patterns of interactions between the best binding

Table 7. Interactions, types and distances between zonisamide and the 4PA6 macromolecule

Zonisamide			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
METB175	Benzaxazoline group in Zonisamide	4,99	Pi-Sulfur
LEUB138	Benzaxazoline group in Zonisamide	5,46	Pi-Alkyl
PHEB142	Benzaxazoline group in Zonisamide	3,67	Pi-pi Stacked
PHEB142	Benzaxazoline group in Zonisamide	3,98	Pi-Pi Stacked
LEUB168	Benzene group in Zonisamide	5,06	Pi-Alkyl

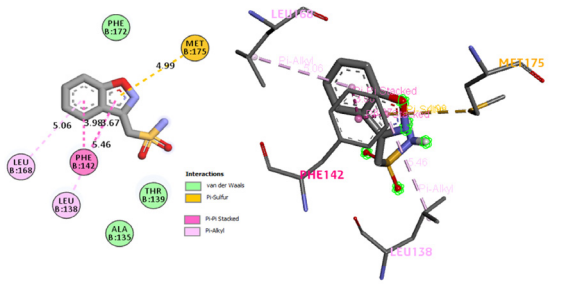


Figure 7. 2D and 3D representation of zonisamide and 4PA6 macromolecule

position of felbamate and 4PA6 with an affinity of -5.7 kcal/mol are shown in Figure 8 and the resulting molecular coupling interactions are as follows; Pi-sulfur, pi-alkyl and pi-pi stacked bond interaction with METB178, LEUB138 and PHEB142 amino acid of 4.99Å, 5.46Å, and 3.46Å length, respectively; The amino acid binding sites PHEB142 and LEUB168 formed pi-pi stacked and pi-alkyl bond interactions with the benzene group, with a length of 3.98Å and 5.06 Å, respectively (Table 8).

Table 8. Interactions, types and distances between felbamate and the 4PA6 macromolecule

Felbamate			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
METB175	The benzene group in Felbamate	5,42	Pi-Sulfur
ASNA264	The benzene group in Felbamate	5,31	Pi- Alkyl
PHEB142	O atom in Felbamate	3,80	Pi-pi Stacked

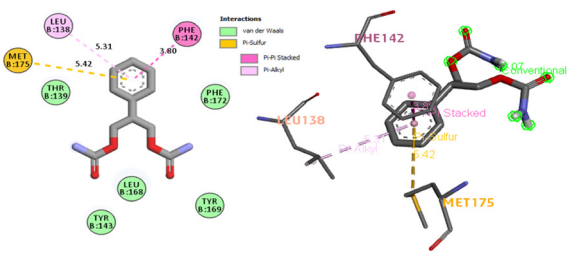


Figure 8. 2D and 3D representation of felbamate and 4PA6 macromolecule

Oxcarbazepine

The binding affinity value of the ligand oxcarbazepine placed in the best binding position to the 4PA6 macromolecule was -7.3 kcal/mol. 2D and 3D visualizations of the intermolecular interactions between the position in the best binding mode of oxcarbazepine and 4PA6 are provided in Figure 9. The resulting ligand-protein interactions; The GLUB159 amino acid bonding site formed a classical hydrogen bond interaction of 2.40Å with the amine group. PROC158 amino acid active site formed a carbon hydrogen bond interaction with the O atom of 4.51Å length. TRPC160 amino acid active site formed a 4.61Å long pi-pi stacked bond interaction with the benzene group (Table 9).

Table 9. Interactions, types and distances between Oxcarbazepine and the 4PA6 macromolecule

Oxcarbazepine			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
GLUB159	NH_2 compound in Oxcarbazepine	2,40	Conventional hydrogen bond
PROC158	O atom in Oxcarbazepine	3,48	Corbon hydrogen bond
TRPC160	Benzene group in Oxcarbazepine	4,61	Pi-pi stacked

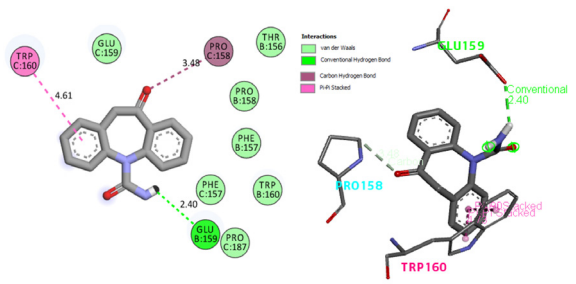


Figure 9. 2D and 3D representation of oxcarbazepine and 4PA6 macromolecule

Tiagabine

The binding affinity value of tiagabine was obtained as -5.7 kcal/mol and the connections between the best binding mode and 4PA6 are shown in Figure 10. Obtained ligand-protein communications; The amino acid binding sites LEUB168, TRPA196 and LEUB168 are with the methylthiophene group, respectively formed pi-sigma, pi-pi stacked and pi-alkyl bond interactions with a length of 4.47Å, 5.34Å and 5.22Å, respectively. TRPA196, TYRB169, PHEB172 and ILEA200 amino acid binding sites are respectively with methyl group, formed pi-alkyl, pi-alkyl, pi-alkyl, alkyl and alkyl interactions with a length of 4.21Å, 5.45Å, 4.93Å, 5.21Å and 4.32Å lenghts; The ILEA200 amino acid active site formed a 4.37Å alkyl bond interaction with the methylene group. The PHEB172 and META204 amino acid active sites formed pi-alkyl and alkyl bond interactions with the benzene group at a length of 5.45Å and 5.25Å, respectively (Table 10).

Table 10. Interactions, types and distances between tiagabine and the 4PA6 macromolecule

Tiagabine			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
LEUB168	Methylthiophene group in Tiagabine	4,47	Pi-sigma
TRPA196	Methylthiophene group in Tiagabine	5,34	Pi-pi stacked
LEUB168	Methylthiophene group in Tiagabine	5,22	Pi-Alkil
TRPA196	CH_3 compound in Tiagabine	4,21	Pi-Alkil
TYRB169	CH_3 compound in Tiagabine	5,45	Pi-Alkil
ILEA200	CH_3 compound in Tiagabine	5,21	Alkil
ILEA200	CH_3 compound in Tiagabine	4,32	Alkil
ILEA200	CH_2 compound in Tiagabine	4,37	Alkil
PHEB172	CH_3 compound in Tiagabine	4,93	Pi-Alkil
PHEB172	Benzen group in Tiagabine	5,45	Pi-Alkil
META204	Benzen group in Tiagabine	5,25	Alkil

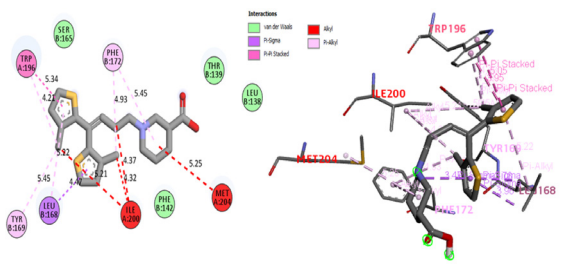


Figure 10. 2D and 3D representation of tiagabine and 4PA6 macromolecule

Gabapentin

The binding affinity value of gabapentin at the best binding position was obtained as -5.7 kcal/mol, and the interaction patterns between gabapentin and 4PA6 are shown in Figure 11. Interactions after molecular coupling study; THRC156 amino acid active sites formed a classical hydrogen bond interaction with the amine compound of 2.53Å and 2.19Å lengths, respectively. TRPB160 amino acid active site formed a 4.97Å long pi-alkyl bond interaction with the benzene group (Table 11).

Valproic Acid

The affinity value of valproic acid placed in the best bin-

Table 11. Interactions, types and distances between gabapentin and the 4PA6 macromolecule

Gabapentin			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
THRc156	NH_2 compound in Gabapentin	2,53	Conventional hydrogen bond
THRc156	NH_2 compound in Gabapentin	2,19	Conventional hydrogen bond
TRPb160	Benzene group in Gabapentin	4,97	Pi-Alkyl

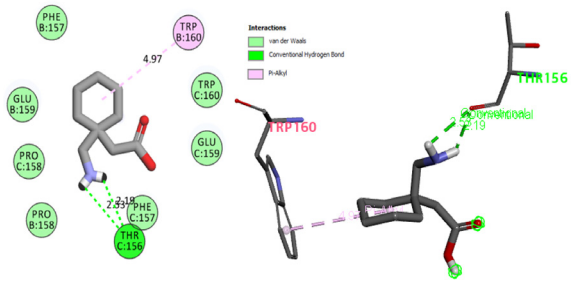


Figure 11. 2D and 3D representation of gabapentin and 4PA6 macromolecule

ding position to 4PA6 was -5.0 kcal/mol, and the molecular interactions between valproic acid and 4PA6 are given in Figure 12. The post-run interactions are as follows; PROc157 amino acid active sites formed a carbon hydrogen bond interaction with a double bonded oxygen atom and a length of 3.23Å. The GLUc159 amino acid active site formed an unfavorable acceptor-acceptor bond interaction with the oxygen atom of 2.71Å length. TRPc160 and TRPb160 amino acid active site formed a pi-sigma bond interaction with the methyl group of 3.38Å and 3.61Å, respectively. TRPb160, TRPc160 and PHEc157 amino acid active sites with the methylene group are 4.28Å, respectively; They formed 4.53Å and 4.89Å long pi-alkyl bond interactions (Table 12).

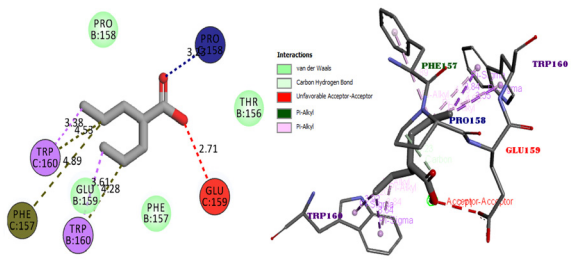


Figure 12. 2D and 3D representation of valproic acid and 4PA6 macromolecule

Primidone

The affinity value of primidone placed in the best binding position to 4PA6 was -6.9 kcal/mol, and the molecular interactions between primidone and macromolecule are given in Figure 13. Formed ligand-protein interactions; TRPd160 amino acid active site formed a 2.83Å long pi-

Table 12. Interactions, types and distances between valproic acid and the 4PA6 macromolecule

Valproic Acid			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
PROc158	Double-bond O atom in Valproic acid	3,23	Carbon hydrogen bond
GLUc159	O atom in Valproic acid	2,71	Unfavorable acceptor-acceptor
TRPb160	CH_3 compound in Valproic acid	3,61	Pi-Sigma
TRPc160	CH_3 compound in Valproic acid	3,38	Pi-Sigma
TRPb160	CH_2 compound in Valproic acid	4,28	Pi-Alkyl
TRPc160	CH_2 compound in Valproic acid	4,53	Pi-Alkyl
PHEc157	CH_2 compound in Valproic acid	4,89	Pi-Alkyl

donor hydrogen bond interaction with the amine group. TRPa160 amino acid active site formed a 3.52Å long pi-sigma interaction with the methyl group. The amino acid active sites PROd186, PHEa157 and PROa158 are 3.44Å with O atom, respectively; 3.79Å and 3.41Å length carbon hydrogen bond interaction formed (Table 13).

Table 13. Interactions, types and distances between primidone and the 4PA6 macromolecule

Primidone			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
TRPd160	NH_2 compound in Primidone	2,83	Pi-Donor hydrogen bond
TRPa160	CH_3 compound in Primidone	3,52	Pi-Sigma
PROd158	O atom in Primidone	3,44	Carbon hydrogen bond
PHEa157	O atom in Primidone	3,79	Carbon hydrogen bond

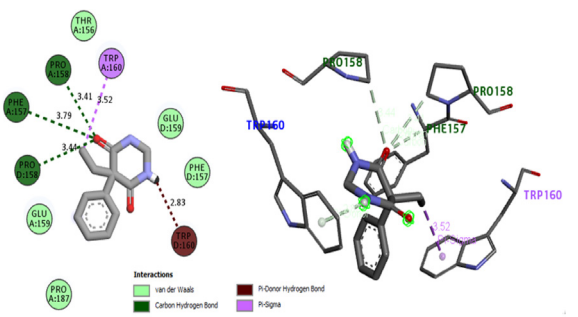


Figure 13. 2D and 3D representation of primidone and 4PA6 macromolecule

Remacemide

The affinity value of remacemide placed in the best binding position to 4PA6 was -7,3 kcal/mol. 2D and 3D fi-

gures of interactions between Remacemide and 4PA6 are presented in Figure 14 and interactions after molecular insertion are; The amino acid active sites PHEB142, TRPA196 and LEUB168 are 3.82Å with the benzene group, respectively; 5.98Å and 4.63Å lengths formed pi-pi stacked, pi-pi stacked and pi-alkyl bond interactions (Table 14).

Table 14. Interactions, types and distances between remacemide and the 4PA6 macromolecule

Remacemide			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
PHEB142	Benzen group in Remacemide	3,82	Pi-Pi Stacked
TRPA196	Benzen group in Remacemide	5,98	Pi-Pi Stacked
LEUB168	Benzen group in Remacemide	4,63	Pi-Alkyl

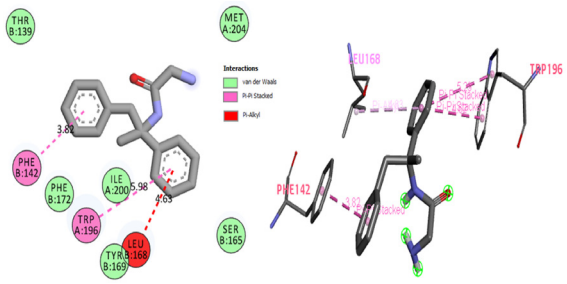


Figure 14. 2D and 3D representation of remacemide and 4PA6 macromolecule

Phenytoin

The affinity value of phenytoin at the best binding position was -7.7 kcal/mol. Pictures of interactions between phenytoin and 4PA6 are presented in Figure 15 and post-study interactions are; GLUA159 amino acid active site formed a 3.55Å long pi-anion bond interaction with the benzene group (Table 15).

Table 15. Interactions, types and distances between phenytoin and the 4PA6 macromolecule

Phenytoin			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
GLUA159	Benzene group in Phenytoin	3,55	Pi-Anion

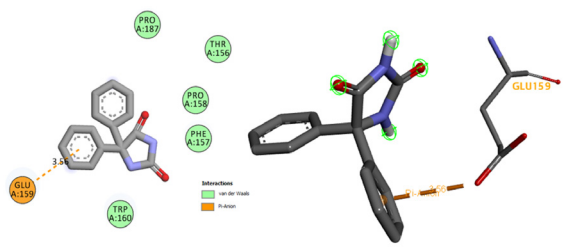


Figure 15. 2D and 3D representation of phenytoin and 4PA6 macromolecule

Ethotoin

The affinity value of ethotoin, which was placed in the best binding position to the 4PA6 macromolecule, was -7.0 kcal/mol, and the pictures of the interactions between ethotoin and 4PA6 are shown in Figure 16. The resulting interactions; The LEUB168 amino acid active site formed a conventional hydrogen bond interaction of 2.46Å with the amine group. The PHEB142 amino acid active site formed a 3.75Å long pi-pi stacked bond interaction with the benzene group. The TRPA146 and ILEA200 amino acid active sites formed pi-alkyl and alkyl bond interactions with the methylene group of 4.85Å and 4.58Å lengths, respectively (Table 16).

Table 16. Interactions, types and distances between ethotoin and the 4PA6 macromolecule

Ethotoin			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
LEUB168	NH_2 compound in Ethotoin	2,46	Conventional hydrogen bond
TRPA196	CH_2 compound in Ethotoin	4,85	Pi-Alkyl
ILEA200	CH_2 compound in Ethotoin	4,58	Alkyl
PHEB142	Benzene group in Ethotoin	3,75	Pi-Pi Stacked

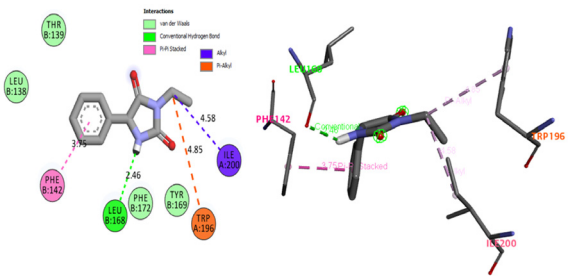


Figure 16. 2D and 3D representation of ethotoin and 4PA6 macromolecule

Trimethadione

The affinity value of trimetadione at the best binding position was obtained as -5.1 kcal/mol, and the 2D and 3D figures of the intermolecular interactions between trimethadione and the macromolecule are shown in Figure 17. Interactions; The amino acid binding sites TRPC160, PHEB157, PHEB157, TRPB160, TRPB160 and PROC158 are 4.01Å with the methyl group, respectively; 5.04Å; 5.04Å; 4.52Å; They formed pi-alkyl, pi-alkyl, pi-alkyl, pi-alkyl, pi-sigma and alkyl bond interactions with a length of 3.87Å and 5.06Å, respectively. The PROC158 amino acid active site formed a 3.27Å long carbon hydrogen bond interaction with the O atom (Table 17).

Table 17. Interactions, types and distances between trimethadione and the 4PA6 macromolecule

Trimethadione			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
TRPc160	CH_3 compound in Trimethadione	4,01	Pi-Alkyl
PHEb157	CH_3 compound in Trimethadione	5,04	Pi-Alkyl
PHEb157	CH_3 compound in Trimethadione	5,04	Pi-Alkyl
TRPb160	CH_3 compound in Trimethadione	4,52	Pi-Alkyl
TRPb160	CH_3 compound in Trimethadione	3,87	Pi-Sigma
PROc158	CH_3 compound in Trimethadione	5,06	Alkyl
PROc158	O atom in Trimethadione	3,27	Carbon hydrogen bond

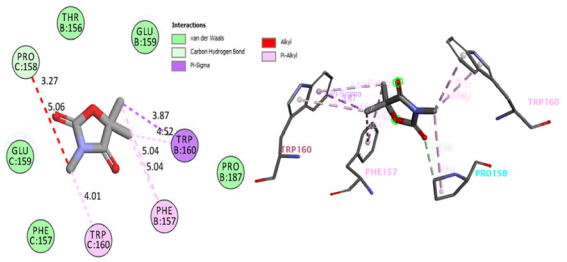


Figure 17. 2D and 3D representation of trimethadione and 4PA6 macromolecule

Table 18. Interactions, types and distances between levetiracetam and the 4PA6 macromolecule

Levetiracetam			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
GLUc159	NH_2 compound in Levetiracetam	2,15	Conventional hydrogen bond
PROc158	O atom in Levetiracetam	3,48	Carbon hydrogen bond
TRPb160	CH_3 compound in Levetiracetam	3,68	Pi-sigma
TRPb160	CH_2 compound in Levetiracetam	4,61	Pi-alkyl
TRPc160	CH_2 compound in Levetiracetam	3,56	Pi-sigma
TRPc160	C atom in Levetiracetam	4,46	Pi-alkyl
PHEc157	C atom in Levetiracetam	5,28	Pi-alkyl

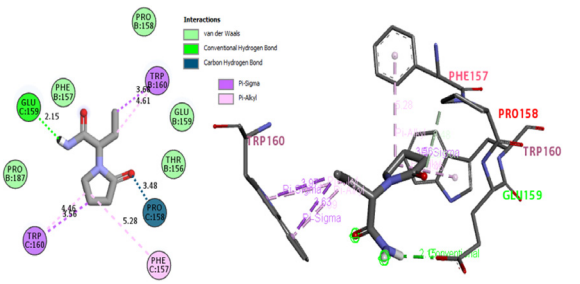


Figure 18. 2D and 3D representation of levetiracetam and 4PA6 macromolecule

Levetiracetam

The affinity value of levetiracetam at the best binding position was obtained as -5.7 kcal/mol, and pictures of the molecular interactions between the best binding position of levetiracetam and 4PA6 are shown in Figure 18. The resulting ligand-protein interactions are as follows; The GLUc159 amino acid binding site formed a 2.15Å-long classical hydrogen bond interaction with the amine group. TRPb160 amino acid active site formed a 3.68Å long pi-sigma bond interaction with the methylene group. PROc158 amino acid active site formed a carbon hydrogen bond interaction with the O atom of 3.48Å length. The TRPb160 and TRPc160 amino acid binding sites formed pi-alkyl and pi-sigma interactions with the methylene group at a length of 4.61Å and 3.56Å, respectively. The TRPc160 and PHEc157 amino acid binding sites formed pi-alkyl interactions with the carbon atom with a length of 4.46A28 and 5.28Å, respectively (Table 18).

Topiramate

The affinity value of topiramate at the best binding position was obtained as -6.6 kcal/mol, and 2D and 3D pictures of the interactions of molecules with 4PA6 are presented in Figure 19. The resulting interactions are as follows; The GLUd158 and PROa187 amino acid active sites formed a conventional hydrogen bond interaction with the amine compound with a length of 2.97Å and 2.15 Å. The PHEa157 amino acid binding site formed a 5.75Å long pi-sulfur bond interaction with the S atom. TRPd160, TRPd160, PHEd157, PHEa157, METc182, PROd158, PROa158 and PROa158 amino acid binding sites with methyl group respectively; length of 4.80Å, 6.25Å, 5.44Å, 4.84Å, 5.47Å, 4.82Å, 4.80Å and 5.35Å; they formed interactions with a pi-alkyl, pi-alkyl, pi-alkyl, pi-alkyl, alkyl, alkyl and alkyl bond (Table 19).

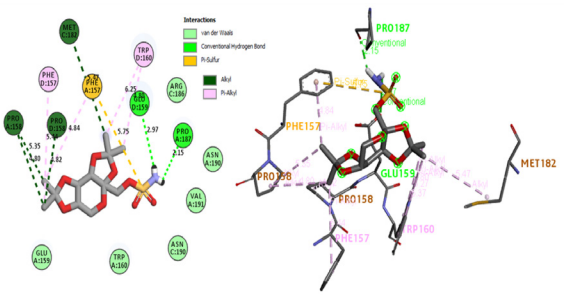


Figure 19. 2D and 3D representation of topiramate and 4PA6 macromolecule

Table 19. Interactions, types and distances between topiramate and the 4PA6 macromolecule

Topiramate			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
GLUD159	NH_2 compound in Topiramate	2,97	Conventional hydrogen bond
PROA187	NH_2 compound in Topiramate	2,15	Conventional hydrogen bond
TRPD160	CH_3 compound in Topiramate	4,80	Pi-Alkyl
TRPD160	CH_3 compound in Topiramate	6,25	Pi-Alkyl
PHED157	CH_3 compound in Topiramate	5,44	Pi-Alkyl
PHEA157	CH_3 compound in Topiramate	4,84	Pi-Alkyl
PHEA157	S atom in Topiramate	5,75	Pi-Sulfur
METC182	CH_3 compound in Topiramate	5,47	Alkyl
PROD158	CH_3 compound in Topiramate	4,82	Alkyl
PROA158	CH_3 compound in Topiramate	4,80	Alkyl
PROA158	CH_3 compound in Topiramate	5,35	Alkyl

Mesuximide

The mesuximide binding affinity value was obtained as -7.5 kcal/mol and the models of molecular interactions between the best binding mode and 4PA6 are presented in Figure 20 and the interactions are as follows; Amino acid active sites PHEB142 and LEUB168 formed a pi-pi stacked and pi-alkyl bond interaction with the benzene group of 3.93Å and 4.99Å lengths, respectively (Table 20).

Table 20. Interactions, types and distances between mesuximide and the 4PA6 macromolecule

Mesuximide			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
PHEB142	Benzene group in Mesuximide	3,93	Pi-Pi Stacked
LEUB168	Benzene group in Mesuximide	4,99	Pi- Alkyl

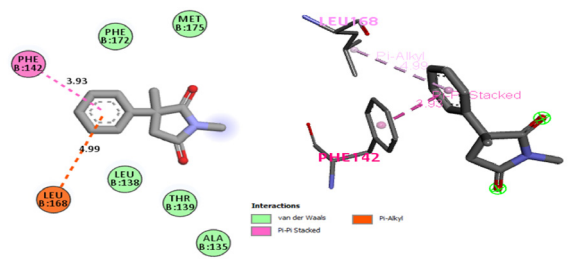


Figure 20. 2D and 3D representation of mesuximide and 4PA6 macromolecule

Mephenytoin

The binding affinity value of mephenytoin at the best binding position was -7.0 kcal/mol, and the molecular interaction patterns between the best binding position and 4PA6 are shown in Figure 21. Ligand-protein interactions; The PROC158 amino acid active site formed a 3.45Å long carbon hydrogen bond interaction with the O atom. The PROB187 amino acid region formed a 5.12Å long pi-alkyl bond interaction with the benzene group. The amino acid binding sites PROC158, TRPC160, PHEC157 and TRPB160 were formed with methyl group with alkyl, pi-sigma, pi-alkyl and pi-sigma bond interactions of 5.07Å, 3.83Å, 5.46Å and 3.63Å length, respectively. The TRPB160 amino acid active site formed a 4.85Å long pi-alkyl bond interaction with the methylene group (Table 21).

Table 21. Interactions, types and distances between mephenytoin and the 4PA6 macromolecule

Mephenytoin			
Residue	**Ligand group**	**Distance (Å)**	**Interaction**
PROC158	O atom in Mephenytoin	3,45	Carbon hydrogen bond
PROC158	CH_3 compound in Mephenytoin	5,07	Alkyl
TRPC160	CH_3 compound in Mephenytoin	3,83	Pi-Sigma
PHEC157	CH_3 compound in Mephenytoin	5,46	Pi- Alkyl
TRPB160	CH_3 compound in Mephenytoin	3,63	Pi-Sigma
TRPB160	CH_2 compound in Mephenytoin	4,85	Pi- Alkyl
PROB187	Benzene group in Mephenytoin	5,12	Pi- Alkyl

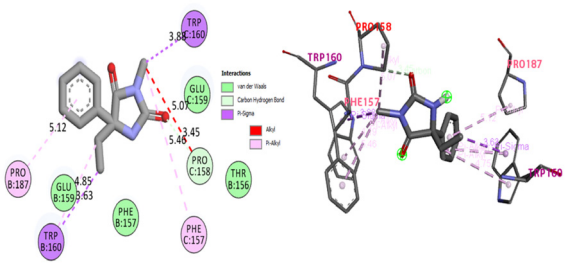


Figure 21. 2D and 3D representation of mephenytoin and 4PA6 macromolecule

After combining the 4PA6 macromolecule with antiepileptic drugs in the Autodock tools program, the interactions of the conformation obtained in the Discovery Studio program with the receptor were observed. The binding affinities obtained as a result of the insertion study are given in Table 22.

The results of molecular coupling of 19 ligand molecu-

Table 22. The binding affinity values of ligands placed in 4PA6 at the best conformation

Ligand's	Best Binding affinity Best Binding affinity (kcal/mol)	Distance from best mode (Å)	
		RMSD l.b	RMSD u.b
Vigabatrin	-4,6	0,000	0,000
Lacosamide	-5,9	0,000	0,000
Zonisamide	-5,8	0,000	0,000
Oxcarbazepine	-6,3	0,000	0,000
Levetirecetam	-5,7	0,000	0,000
Tiagabine	-7,1	0,000	0,000
Topiramate	-6,6	0,000	0,000
Lamotrigine	-6,3	0,000	0,000
Gabapentin	-5,7	0,000	0,000
Felbamate	-6,0	0,000	0,000
Ethosuximide	-5,6	0,000	0,000
Valproic acid	-5,0	0,000	0,000
Mesuximide	-7,5	0,000	0,000
Ethotoin	-7,0	0,000	0,000
Primidone	-6,9	0,000	0,000
Trimethadione	-5,1	0,000	0,000
Phenytoin	-7,7	0,000	0,000
Remacemide	-7,3	0,000	0,000
Mephenytoin	-7,0	0,000	0,000

les obtained by their receptor interactions are combined. It was seen that the phenytoin molecule gave the best affinity value, but when we look at the type of bond it formed, it formed a pi-anion bond instead of the desired hydrogen bond or van der Waals bond. Hydrogen bond types such as carbon hydrogen bond and classical hydrogen bond are desired bond types. Because the stronger the bond between the molecules, the better the interaction. The best interactions in molecular interactions are van der Waals and hydrogen bonding, while the least important interactions are covalent and ionic bonds. One reason is that while cysteine is the only amino acid that will form the covalent disulfide bond, there are many amino acids that will interact with each other through hydrogen bonding and van der Waals interactions. The other reason is that the number of amino acids capable of forming ionic bonds is very few, and the number of units capable of forming hydrogen bonds or van der Waals interactions is innumerable. Although vigabatrin gave the lowest affinity value with the 4PA6 macromolecule among 19 molecules, it gave the conventional hydrogen bond with the amino acid GLUc159. The controversial issue is whether it is the type of bond emerging or the affinity value obtained that matters in docking studies.

When we look at the results, if we compare the bond types formed by the active substances that give the closest affinity values to each other; When looking at phenytoin (-7.7kcal/mol) and mesuximide (-7.5kcal/mol) ligands, it was seen that they gave close affinity values to each other. Although they gave the two highest results among 19 protein-ligand structures, they did not form the desired hydrogen and van der Waals bonds. there are only several pi bonds, and phenytoin made a single interaction with the 4PA6 protein, while mesuximide formed two types of interaction with the two amino acid structures of 4PA6. The following ligands with the highest binding affinity are remacemide (-7.3kcal/mol) and tiagabine (-7.1kcal/mol), respectively. While 3 ligand groups in the structure of remasemide formed pi bonds with the 4PA6 protein, 11 ligand groups in the structure of tiagabine formed various pi and alkyl bonds with the macromolecule structure. Ethotoin and mephenytoin structures with the same binding affinities (-7.0kcal/mol) formed the hydrogen bond, which is one of the strong bond structures for molecular interactions. The ethotoin ligand structure has made 4 types of bonds with the macromolecule, and the best of them is conventional hydrogen bonding. Mephenytoin structure, on the other hand, is bound to 7 amino acids in the active region of the macromolecule in the docking structure that emerged as a result of its combination with the 4PA6 macromolecule, and a carbon hydrogen bond structure emerged in the binding. When we compare primidone (-6.9kcal/mol) and topiramate (-6.6kcal/mol), we see that both ligands form hydrogen bonds with the 4PA6 macromolecule. Primidone formed hydrogen bonds with 3 of 4 ligand groups, while topiramate formed hydrogen bonds with 2 of 11 ligand groups. other bonds are pi and alkyl bonds. Although lamotrigine and oxcarbazepine (-6.3kcal/mol) ligand-receptor structures gave the same binding affinity values, only oxcarbazepine gave the desired hydrogen bond structure with the macromolecule. Although felbamate gave better binding affinity between felbamate (-6.0kcal/mol) and lacosamide (5.9kcal/mol), it was lacosamide that formed hydrogen bonds with the 4PA6 macromolecule. We can say the following for zonisamide (-5.8kcal/mol) and levetiracetam (-5.7kcal/mol), which have very close binding affinities; Levetiracetam formed a stronger bond than zonisamide through ligand insertion into the macromolecule and combined more ligand groups with amino acids than zonisamide. When gabapentin (-5.7kcal/mol) and ethosuximide (-5.6kcal/mol) are examined, it seems that both ligand structures give hydrogen bonds. When looking at the bond types made by trimethadione (-5.1kcal/mol) and valproic acid (-5.0kcal/mol), which have low binding affinity, it is seen that both structures combine 7 ligand groups with the amino acid regions of the macromolecule. and both gave hydrogen bonds with a single ligand group. Finally, when we examined the structure of vigabatrin, we said above that it gives the lowest affinity with its binding affinity of -4.6 kcal/mol. The situation to be looked at here is to compare the bond types that occur, and despite the low affinity, it has been observed that a ligand group in the vigabatrin structure forms a hydrogen bond with the macromolecule.

Considering the studies conducted with antiepileptic drugs in the literature, Najm et al. (2020) obtained a value of -6.1 kcal/mol in the docking studies on the voltage-gated sodium channel PDB ID: 5KAV structure obtained from the protein data bank with the active ingredient of lamotrigine [29], while the result we obtained in the 4PA6 complex, which is a lomotrigine and sodium channel antagonist, was -6.3 kcal/mol in our study. had moles. As a result of the comparison, it can be said that the values are very close to each other. Correa-Basurto et al. (2015) obtained a value of -5.6 kcal/mol from their molecular docking study between SV2A protein and levetiracetam, and when compared with our study, it was seen that -5.7 kcal/mol was obtained from the levetiracetam-4PA6 complex. and the results are very close to each other [30]. In the computer simulation studies on the Binding of HLA Molecules to AEDs in the literature, it was determined that they exhibited high affinity values in the molecular docking process with Carbazepine, Lamotrigine and Oxcarbazepine drugs. When compared with our study, it was seen that close values were obtained [31]. Iman et al. (2013) placed 20 ligand structures on the protein as a result of their research on voltage-gated sodium channels and showed that ligands interact mainly with the II-S6 residues of NaV1.2 by making hydrogen bonds and can inhibit the Na^+ channel efficiently. After the obtained molecular docking results, it is seen that the binding energy of the other 20 ligands is higher than the binding energy of the reference phenytoin drug, and the values vary between approximately -5.40 kcal/mol and -6.46 kcal/mol [32]. In our study, it was observed that phenytoin drug gave a ΔG value of -7.7 kcal/mol in docking process with sodium channel antagonist protein.

In the literature review, as a result of molecular docking studies with known antiepileptics, dg values were found to be similar to the values in our study. In the scan data obtained, it was observed that some ligands made strong bond interactions, while it was determined that some structures did not give the desired bond types, but the affinity values of these structures could be high. When we are going to make a comment that supports the result of our study, it is not only the chelate values that are important for us, but also the bond structures and interaction types. In addition, it is necessary to look at the experimental data when examining the interactions, it should be noted that the molecular insertion method is not a decisive study on its own in scientific studies, and many data should be examined together.

Finally, when looking at the total, it was seen that those with the best affinity values did not make the strongest bonds, but those with the lowest affinities gave the desired hydrogen bond types. When we discuss here, the conclusion to be drawn is that the degree of binding affinity and the number of bonds obtained and the bond structures are not parallel.

CONCLUSION

In the study, Discovery Studio 2020 program and AutoDOCK Vina energy scoring were used, and there are various scoring functions. The results show that the PDB ID: 4PA6 macromolecule, which has an antagonistic effect on voltage-gated sodium channels, also gave good affinity value in its studies with 19 active substances. The types of bonds that emerge as a result of the placement work are important to us. Because even if the obtained affinity value is low, we can say that the stronger the bond they establish, the better the interaction.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR CONTRIBUTION

Esra Nur Cakmak, Mahmut Gur and Bayram Kiran designed the study. ENC performed all experiments. ENC and MG analysed the data. ENC wrote the paper.

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