MOLECULAR DOCKING OF ANTIEPILEPTIC ACTIVITY OF NOVEL PIRACETAM DERIVATIVES

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ABSTRACT

On the newly synthesized 16 piracetam butanamide derivatives (antiepileptic drugs), molecular docking investigations were done. The molecular docking of all the antiepileptic drugs was carried out using Pyrx software's Autodock Vina version 4.0. Gamma-aminobutyric acid aminotransferases (GABAAT) were used in molecular docking analyses to determine which piracetam butanamide derivatives (antiepileptic drugs) had the highest binding affinity, which was determined to be -3.7 kcal/mol. When enhancing the inhibitory actions of the piracetam butanamide derivatives against the GABAAT enzyme, which causes epilepsy, physicochemical characteristics must be taken into account.

KEYWORDS: Epilepsy, GABA, Molecular Docking

INTRODUCTION

According to Goodman (1996), Rang and Dale (1991), epilepsy is a disease of brain function characterized by the unpredictable and recurrent occurrence of seizures. Because of hyper-synchronous discharges from a group of CNS neurons, seizures are brief changes in behavior. Seizures are caused by epilepsy, and depending on how they affect the central nervous system, they can have a variety of negative side effects. The signs can range from mild to dangerous and include entire or partial loss of awareness, loss of speech, erratic engine behavior, and unexpected physical interactions.[1]

The most well-known true neurological condition, epilepsy is responsible for significant morbidity and mortality due to the seizures and the readily available medications. With the exception of febrile seizures, around 5% of the world's population, or about 50 million people, have epilepsy and experience at least one seizure during their lifetimes. Epilepsy affects 0.5–1% of the population. Additionally, in industrialized countries, there are 50–70 instances for every 100,000 people, but in poor countries, there are up to 190 cases for every 100,000 people. About 80% of epilepsy sufferers live in developing nations.[2,3,4,5]

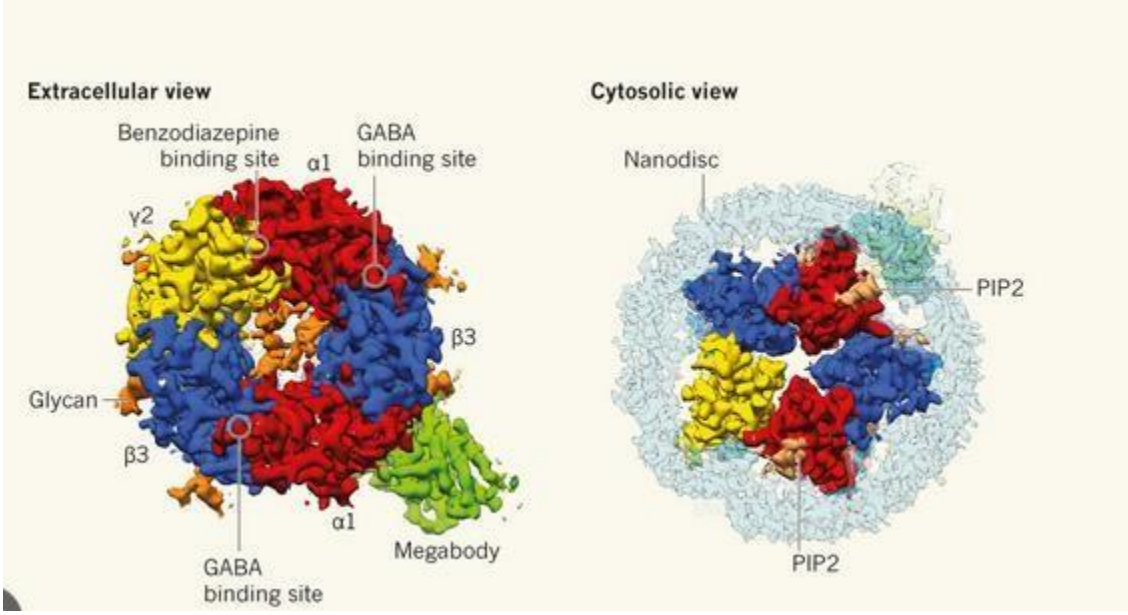

Figure 1: Structural view of GABA recptor

According to studies, the primary inhibitory neurotransmitter in the mammalian central nervous system that modulates central inhibition is gamma aminobutyric acid (GABA). According to the literature review, convulsions have been linked to reduced concentrations of gamma aminobutyric acid.[7] While increased brain GABA levels have an anticonvulsant effect.[6] The selective deactivation of gamma-aminobutyric acid aminotransferases results in an increase in GABA concentration in the brain, making it a proven receptor for anti-convulsant medications. This knowledge of the neurotransmitter gamma aminobutyric acid prepared the way for subsequent research and some of the first effective treatments for the upheaval. Following the development of the commonly used antiepileptic medications, several novel substances, including zonisamide, vigabatrin, and gabapentin, have come into use.[7,8,9]

Better therapies for epilepsy, and eventually a cure, are actively sought after by scientists and medical professionals today. As a result, finding safer and more effective anticonvulsants remains a top objective for drug designers, and finding safer and more potent antiepileptic medications has become a significant problem for medical researchers. [10]

In silico research methods have evolved into a close substitute for experiments in the study of biological systems' molecular components. To find new hits for various therapeutic targets, computational techniques like molecular docking is frequently used. [7.10]

Molecular docking studies show how two or more molecular structures interact with one another, such as how a protein receptor and an enzyme do. Drug research is where molecular docking software is most frequently employed. Virtual screening is docking software's most significant use. From an existing database, virtual screening chooses the most intriguing and promising chemicals for further study. This places demands on the computational method's use, which must be quick and trustworthy. The hunt for effective piracetam butanamide derivatives was the main focus of this research project's molecular docking studies. [11,12,13]

MATERIAL AND METHOD

Based on our earlier techniques, a molecular modelling and docking strategy has been presented. In a nutshell, it is a homology model of the crystal structures of the K channel that was used to construct a model of the open pore of the Na channel. AutoDock 4.2 software was used to perform docking calculations, and a model of the open pore of the Na channel was used as the receptor. To complete the molecular docking investigations, the Lamarckian Genetic Algorithm (LGA) was used. The docking log (dlg) files were analysed using the AutoDock Tools (version 1.5.6), and the final docked conformations were clustered using a tolerance of 1 A root mean square deviation (RMSD).

RESULT AND DISCUSSION

The docking studies were mainly done to accesses the compound with higher antiepileptic activity and to filter out the compounds with lower potency. The drug receptor interactions were studied on calcium channel, sodium channel and GABAA receptors and based on the binding

energy the compound is selected for further activity. Based on the procedure explained in the experimental section, the predicted binding energy is listed in table 1.

Receptors	**With Calcium channel (6KZV)**	**With GABAA (4COF)**	**With Sodium channels (2KAV)**
Compound No.	**kcal/mol affinity**		
Compound 1	-5.7	-5.1	-4.2
Compound 2	-5.8	-5.2	-4.5
Compound 3	-5.6	-5.5	-4.5
Compound 4	-5.8	-6.4	-4.2
Compound 5	-5.4	-4.7	-4.2
Compound 6	-3.8	-3.9	-3.2
Compound 7	-5.3	-5.3	-4.4
Compound 8	-5.3	-4.9	-4.1
Compound 9	-5.6	-5.4	-4.6
Compound 10	-5.2	-4.8	-3.7
Compound 11	-5.6	-5.5	-4.4
Compound 12	-5.6	-5.5	-4.5
Compound 13	-5.5	-4.6	-3.8
Compound 14	-5.1	-5.2	-3.9
Compound 15	-5.5	-5.6	-4.5
Compound 16	-5.7	-5.6	-4.5

Table 1 Docking score of the synthesized derivatives

Table 2: Physicochemical Properties of synthesized compounds

compound	I.U.P.A.C name	Molecular formula	Molecular weight	Melting point	Percentage yield
Compound 1	2-(4-ethyl-2-oxopiperazin-1-yl)acetamide	C8H15N3O2	185.22	89-92	87.2
Compound 2	2-(2-oxo-4-propylpiperazin-1-yl)acetamide	C9H17N3O2	199.25	87-90	83
Compound 3	2-(4-butyl-2-oxopiperazin-1-yl)acetamide	C10H19N3O2	213.28	91-92	89.1
Compound 4	tert-butyl 4-(2-amino-2-oxoethyl)-3-oxopiperazine-1-carboxylate	C11H19N3O4	257.29	77-81	84.8
Compound 5	2-(2-oxopiperazin-1-yl)acetamide TFA salt	C6H11N3O2	157.17	89-92	79.9
Compound 6	2-(3-oxothiomorpholino)acetamide	C6H10N2O2S	174.22	81-83	88.2
Compound 7	(R)-2-(2-isopropyl-3-oxothiomorpholino)acetamide	C9H16N2O2S	216.30	78-80	82.4

Compound 8	(R)-2-(2-methyl-3-oxothiomorpholino)acetamide	C7H12N2O2S	188.25	82-84	78.7
Compound 9	(R)-2-(2-isobutyl-3-oxothiomorpholino)acetamide	C10H18N2O2S	230.33	74-77	77.8
Compound 10	(S)-2-(2-methyl-3-oxothiomorpholino)acetamide	C7H12N2O2S	188.25	91-94	83.9
Compound 11	(S)-2-(2-isopropyl-3-oxothiomorpholino)acetamide	C9H16N2O2S	216.30	87-91	88
Compound 12	(S)-2-(2-isobutyl-3-oxothiomorpholino)acetamide	C10H18N2O2S	230.33	74-77	87.9
Compound 13	2-(3-oxomorpholino)acetamide	C6H10N2O3	158.16	70-73	87.2
Compound 14	(R)-2-(2-methyl-3-oxomorpholino)acetamide	C7H12N2O3	172.18	81-83	82.4
Compound 15	(R)-2-(2-isopropyl-3-oxomorpholino)acetamide	C9H16N2O3	200.23	77-79	79.1
Compound 16	(R)-2-(2-isobutyl-3-oxomorpholino)acetamide	C10H18N2O3	214.26	83-87	87.8

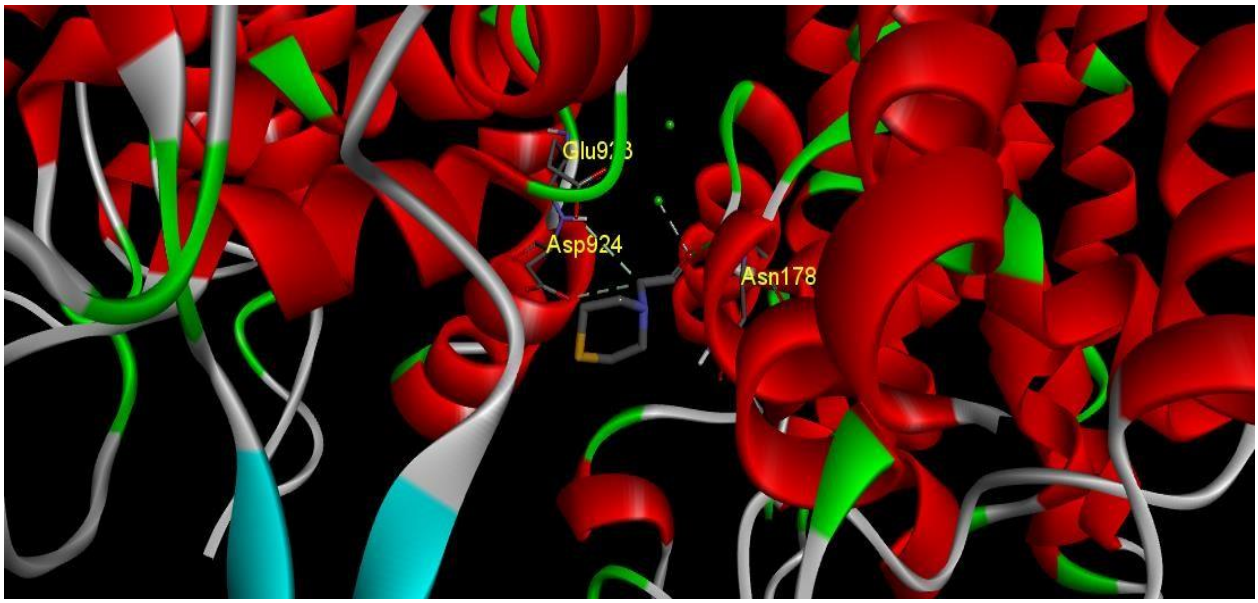

Fig.2 Interaction of compound 6 with Calcium channel (6KZV)3D view

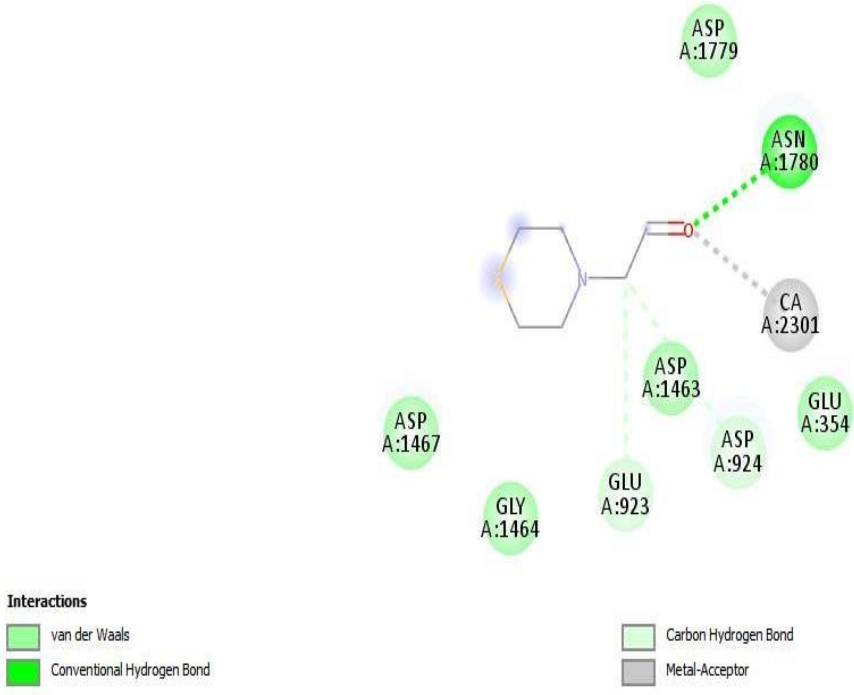

Fig.3 Interaction of compound 6 with Calcium channel (6KZV)2Dview

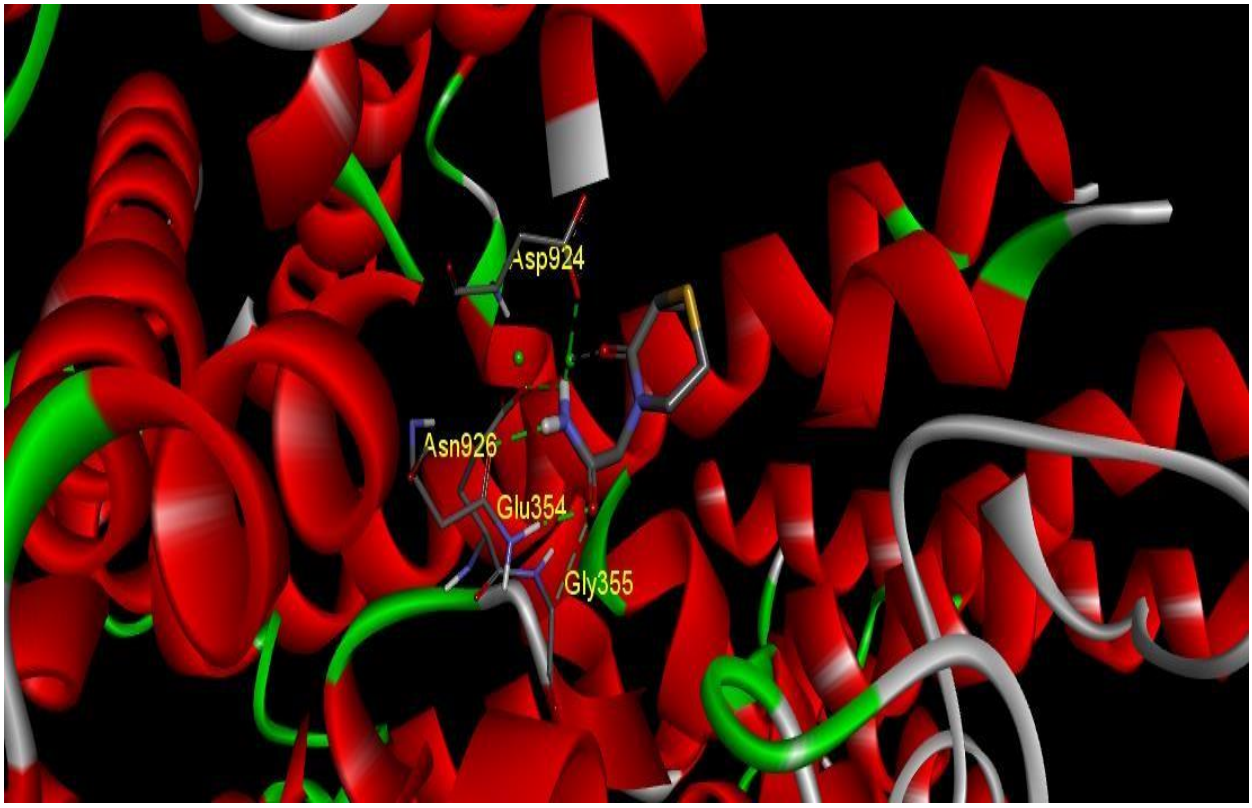

Fig.4 Interaction of compound 10 with Calcium channel (6KZV)3D view

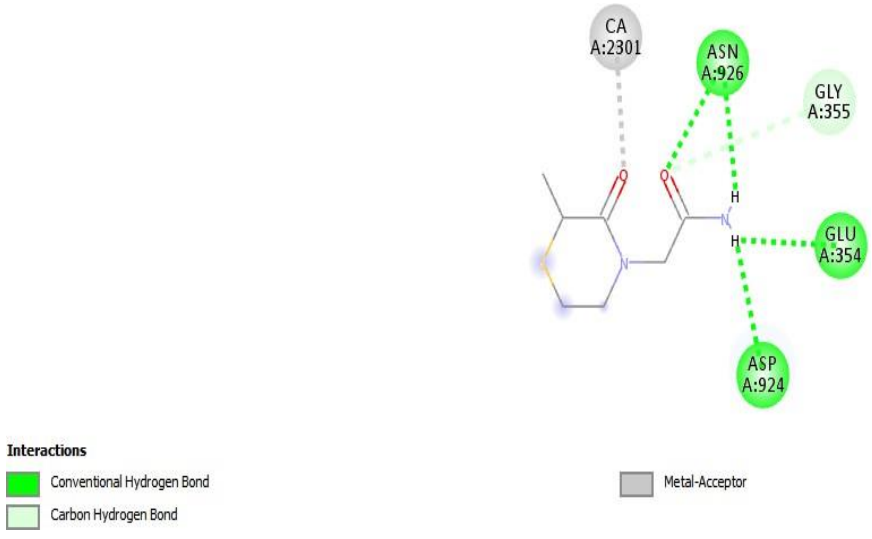

Fig.5 Interaction of compound 10 with Calcium channel (6KZV)2D view

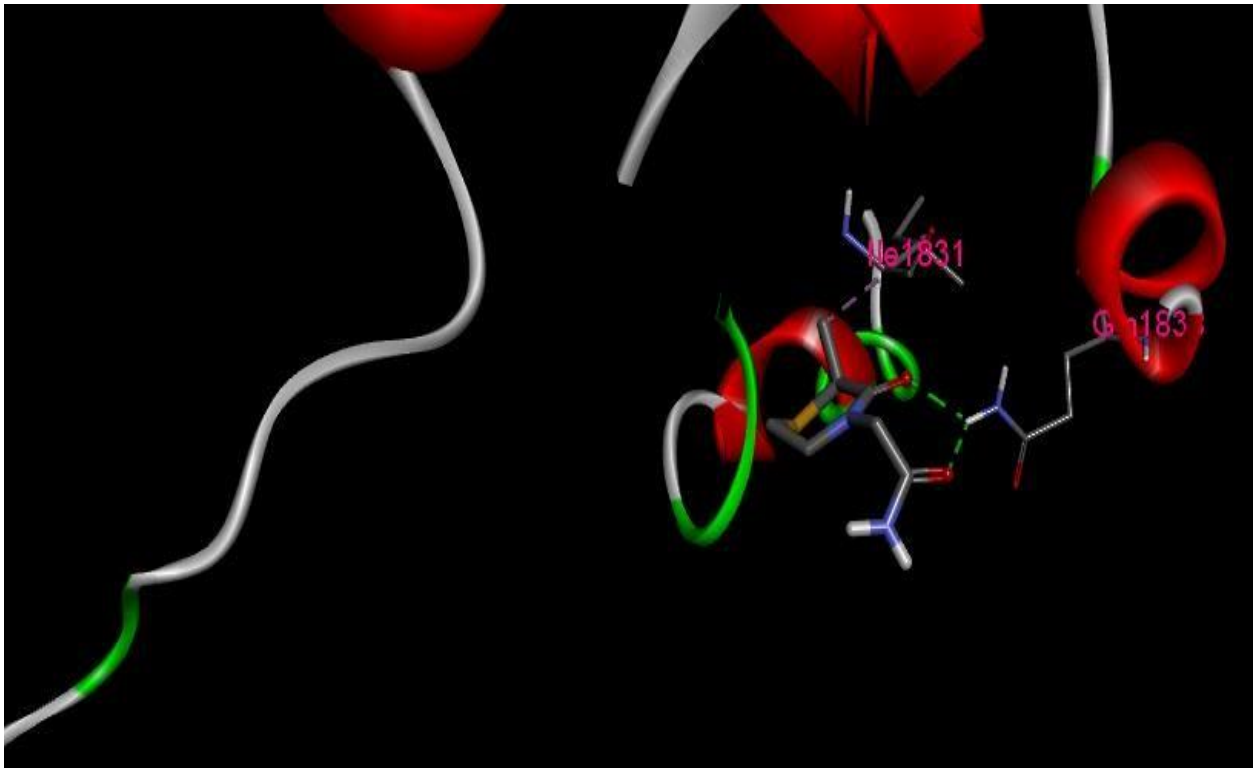

Fig.6 Interaction of compound 10 with Sodium channels (2KAV)3D view

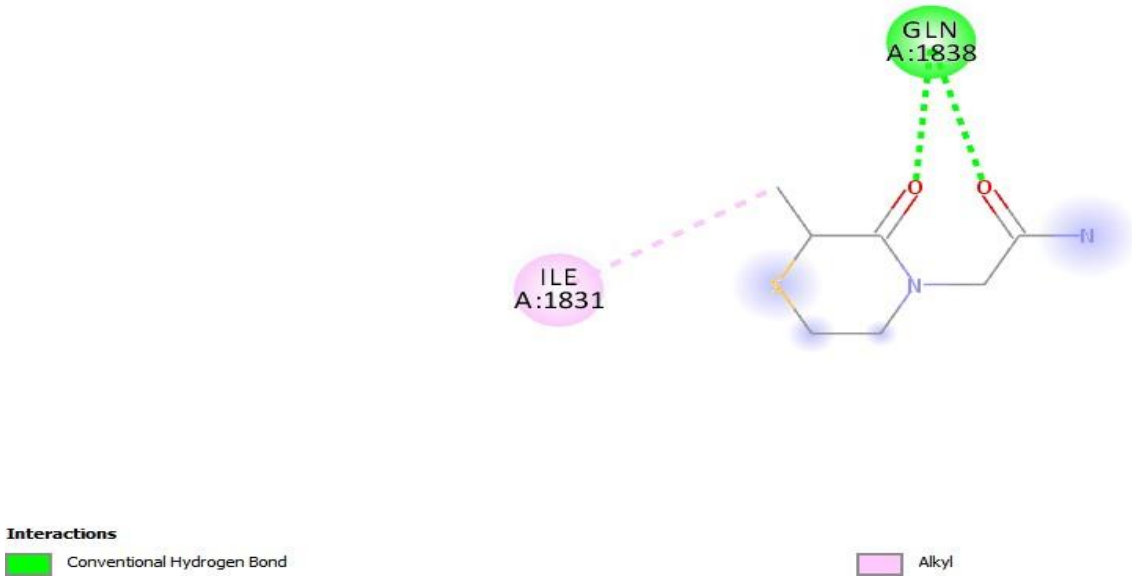

Fig.7 Interaction of compound 10 with With Sodium channels (2KAV)2D view

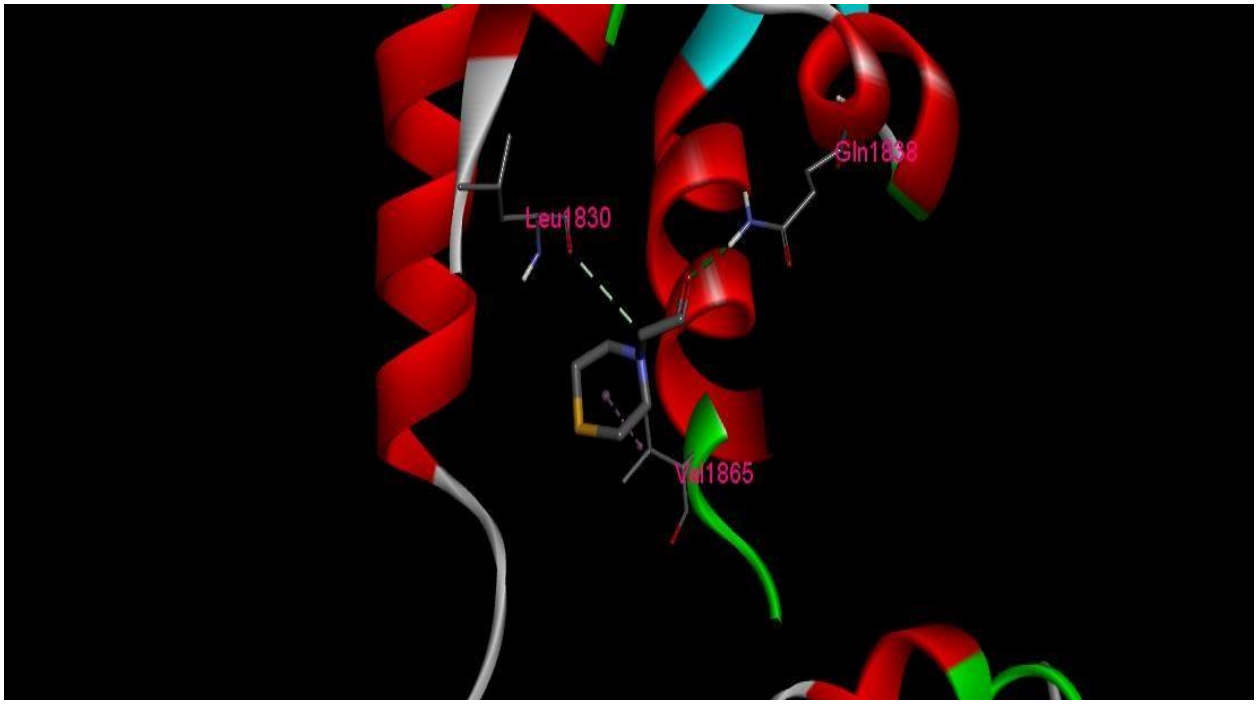

Fig.8 Interaction of compound 6 with Sodium channels (2KAV)3D view

Fig.9 Interaction of compound 6 with Sodium channels (2KAV)2D view

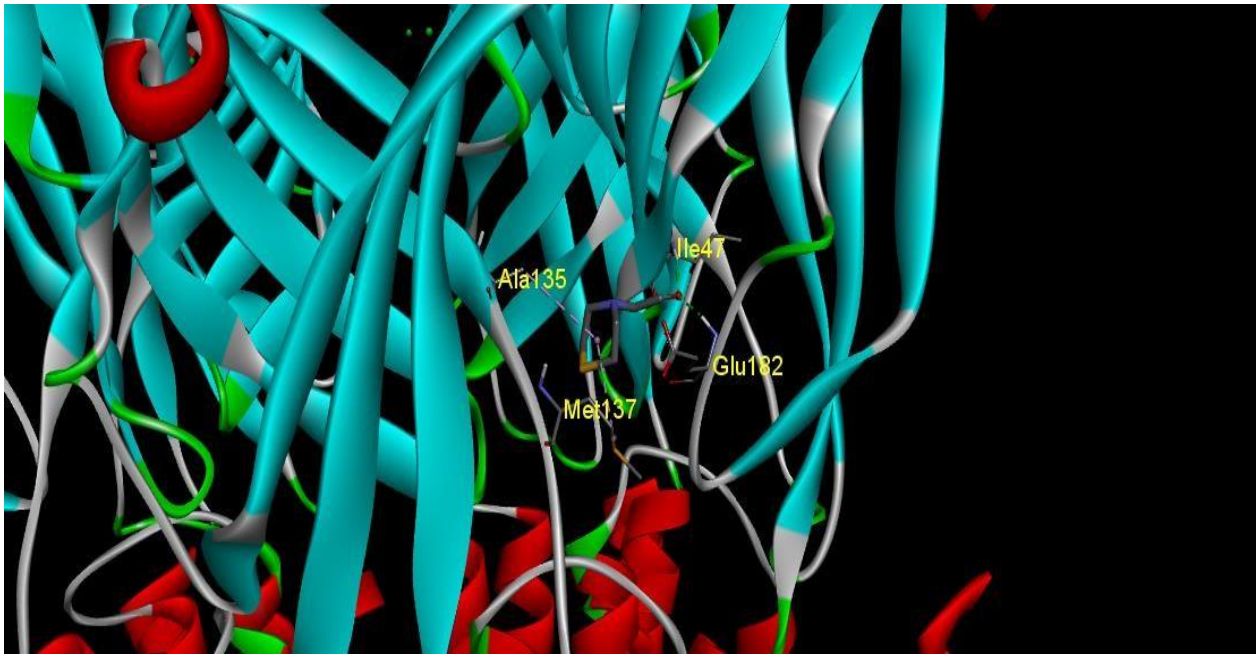

Fig.10 Interaction of compound 10 with GABAA (4COF)3D view

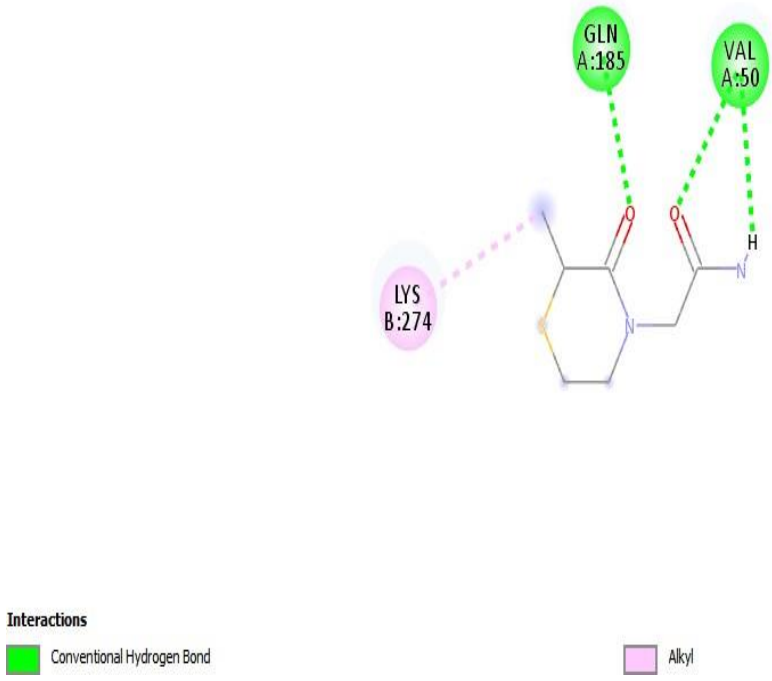

Fig.11 Interaction of compound 10 with GABAA (4COF)2D view

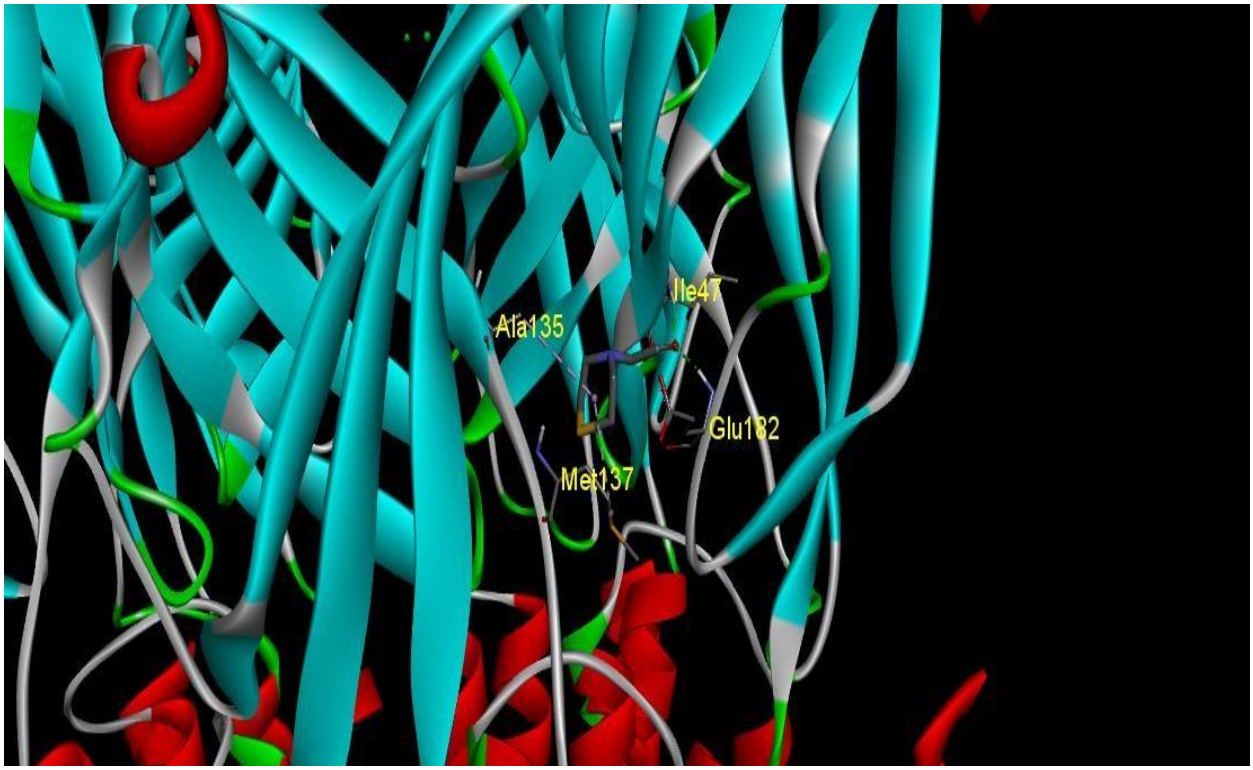

Fig.12 Interaction of compound 6 with GABAA (4COF)3D view

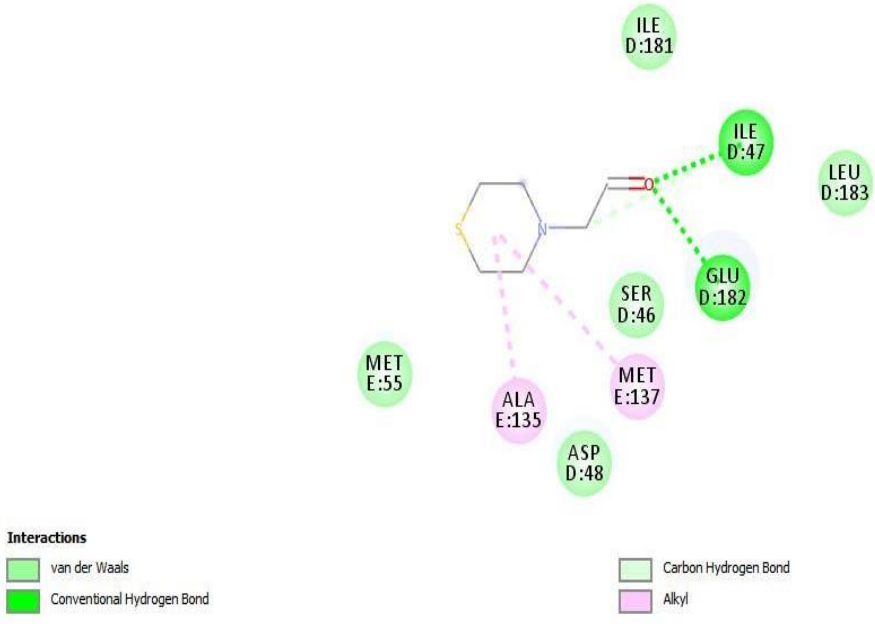

Fig.13 Interaction of compound 6 with GABAA (4COF) 2D view

CONCLUSION

Antiepileptic activity of novel synthesized piracetam butanamide derivatives was assessed as per the docking studies with the drug receptor interaction studies and binding energy. Based on the binding energy the compound 06 and compound 10 was found to be more active.

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CONFLICT OF INTEREST

Authors have no conflict of interest

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