RESEARCH ARTICLE

Discovery of Novel Phthalimide Analogous based Anti-Epileptic by Molecular Docking

Rajan K. Kurmi*, Reema Sinha, Anurag Agrawal

Abstract

Aim: The development of innovative compounds for managing seizures with greater therapeutic efficacy and fewer side effects by molecular docking.

Introduction: One of the major global problems is epilepsy, a severe brain illness that affects around 1% of people globally. Vigabatrin, sodium valproate, phenytoin, and other strong medications for the treatment of epilepsy causes side effects and patient resistance. Despite the antiepileptic drug development process seems to be successful, more effective and safer, still antiepileptic drugs are needed, especially for the treatment of refractory seizures. The study's focus was on phthalimide analogs with strong GABA-AT inhibitory effects by molecular docking.

Methodology: Since protein-ligand interactions are important for drug design, The protein data bank was used to retrieve the 3D structures of GABA-AT, and the Chem Office tool was used to dock the 3D structures of Novel Ligand (Chem Draw 16.0).

Result: By using Lipinski's rule of five on the novel analogs to assess their anti-epileptic activity, and the drug-likeness property was verified. All the compounds had docking energies over 6.11 kcal/mol for the anti-epileptic GABA-AT receptors

Conclusion: These concluded that novel compounds can be the promising lead for further study as an Anti-Epileptic for the management and prevention of Epilepsy

Keywords: Docking, GABA-AT, Anti-convulsant, Anti-Epileptic

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Introduction

Epilepsy is a severe brain illness affecting around 1% of people globally. One-third of people with active epilepsy don't respond well to medication. Therefore, creating new antiepileptic and/or anti-epileptogenic medications is required to treat the illness.[1] characterized by prolonged neuronal overactivity resulting in abnormal brain electrical activity. Epilepsy is characterized by partial or generalized seizures that happen spontaneously and regularly. Other symptoms of epilepsy include muscular spasms, other signs, and involuntary bodily movements.[2] Less than 80% of people demonstrated that taking the available antiepileptic drugs decreased the frequency and intensity of seizures.[3-6] Therapies sometimes come with negative side effects. The first antiepileptic drug, potassium bromide, was created in the middle of the 19th century.[7,8] Although the precise mechanism of potassium bromide's effect is uncertain, it predominantly works through GABA-activated chloride channels, which might lead to the membranes of neuronal cells being hyperpolarized.(DeLahunta et al.; Silverstein and Hopper). Anti-epileptic medications (AEDs) may not reduce the frequency or intensity of seizures in some circumstances. Once at least two AEDs have been tried and failed to work, it is diagnosed. Changing medications frequently is a common feature of the illness. In between 30 and 40 percent of epileptics, medication-resistant seizures occur. [9-11] When two antiseizure medications, either alone or together, have been properly tested on a patient and they still have incapacitating seizures, the patient is said to have refractory epilepsy.[11] The use of medication combinations in the treatment of epilepsy is highly beneficial. In many instances, the combination produces a stronger impact than when other medications are taken separately.[12]

The study's focus has been on certain phytochemicals with strong GABA-AT effects. Better seizure control, more therapeutic effectiveness, and fewer side effects may result from the discovery of new compounds combined with multi-target therapies. Targeting the activity of receptors such as GABA-AT distinguishes anti-epilepsy. Gamma-aminobutyric acid is important to the initiation and development of epilepsy. According to various current theories on the underlying mechanisms of epilepsy, studies indicate that preventing the reuptake of GABA can significantly boost the amount of GABA in the brain, lowering the frequency and severity of many seizures.[13,14]

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Material and Methods

Compounds are docked into the active sites of enzymes using the completely automated docking technology known as Auto Dock 4.2.

Structure of target proteins

GABA-AT and the sodium channel were chosen as the study's primary therapeutic targets for epilepsy. The following epilepsy target proteins' three-dimensional structures were obtained from the protein data bank using the PDB id 1OHV. Docking of standard anti-epileptic drugs like phenytoin, vigabatrin, and valproate already present in other articles.

Molecular docking using Auto Dock

In the study, various Novel compounds were designed by the Chem Office tool (Chem Draw 16.0). were docked, and several typical protein targets for epilepsy were used to assess their binding affinities. In accordance with the binding affinity energies, the value was determined. the ligand conformation of a total of 6 compounds was done according to the binding affinities with the receptor targets 1OHV. were the co-crystallized structures of LYS329 that are effective against epilepsy and have the corresponding PDB IDs 1OHV. (Figure 1)

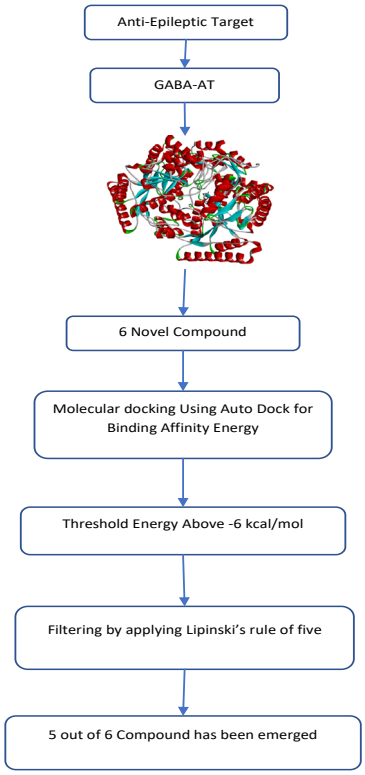


Figure 1: Representation of selection of compounds by different approaches used in the study.

Results and Discussion

Amongst the 6 Novels screened, All the compounds had docking energies over 6.11 kcal/mol for the anti-epileptic GABA-AT and Sodium Channels receptors.

Additionally, the molecular characteristics of the 6 novel compounds were examined using Molinspiration to fit into the Lipinski rule of five, this is essential for achieving the rational drug design and determining the bioactivity score

Table 1: Binding affinity energies (in kcal/mol) of potent compounds active against Epilepsy.

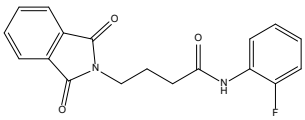
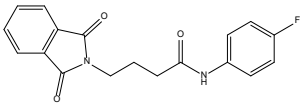
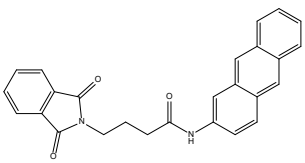
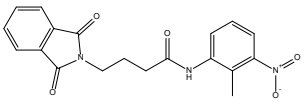
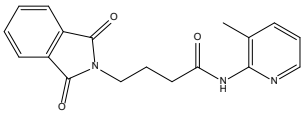
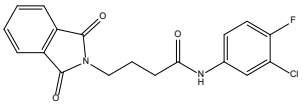
S.no	*Structures*	*Target receptors*	*Binding affinity (in kcal/mol)*
Compound 1		1OHV	-9.67
Compound 2		1OHV	-9.92
Compound 3		1OHV	-10.51
Compound 4		1OHV	-10.48
Compound 5		1OHV	-10.78
Compound 6		1OHV	-9.61

Table 2: List of phytochemicals shortlisted by implementing Lipinski's rule of five and their Molinspiration bioactivity details.

S.no	*miLogP*	*TPSA*	*natoms*	*MW*	*nON*	*nOHNH*	*nviolation*	*nrotb*	*volume*
Compound 1	2.98	68.17	24	326.33	5	1	0	5	282.08
Compound 2	3.03	68.17	24	326.33	5	1	0	5	282.08
Compound 3	5.21	68.17	31	408.46	5	1	1	5	365.14
Compound 4	3.18	114.00	27	367.36	8	1	0	6	317.05
Compound 5	2.37	81.07	24	323.35	6	1	0	5	289.56
Compound 6	3.64	68.17	25	360.77	5	1	0	5	295.62

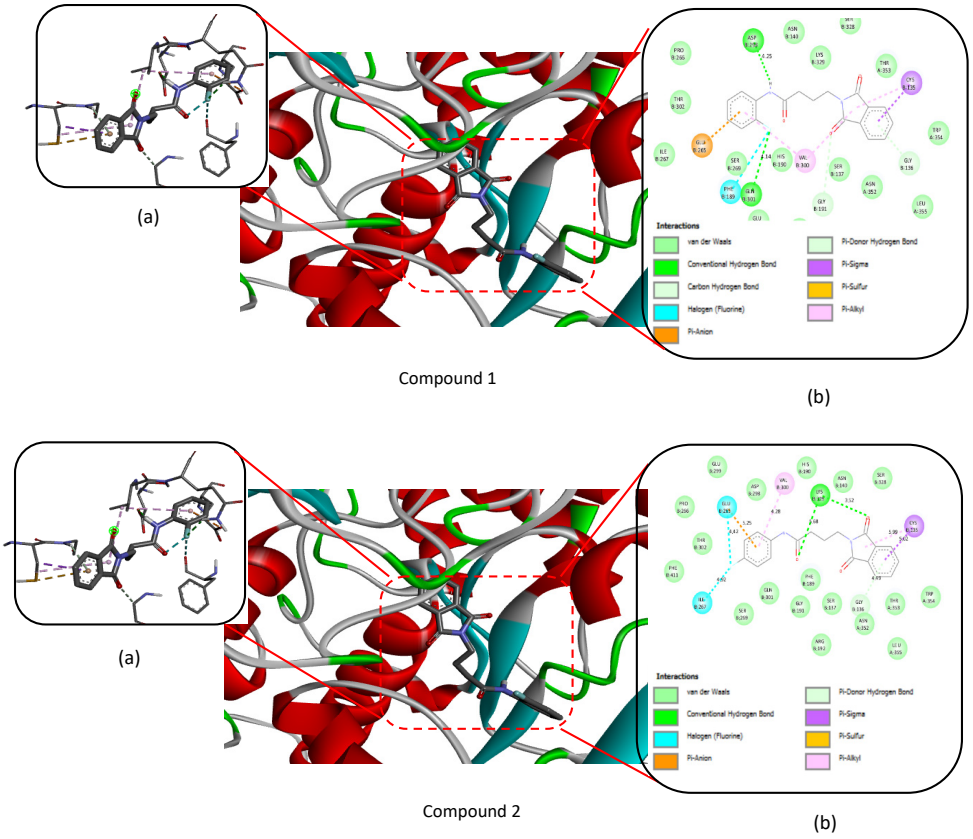


Figure 2: Molecular docking analysis of Compound 1 and 2 (a) Pose view of 3D interaction of compound with receptors 1OHV. (b) Pose view of 3D interaction of the compound with receptors 1OHV.

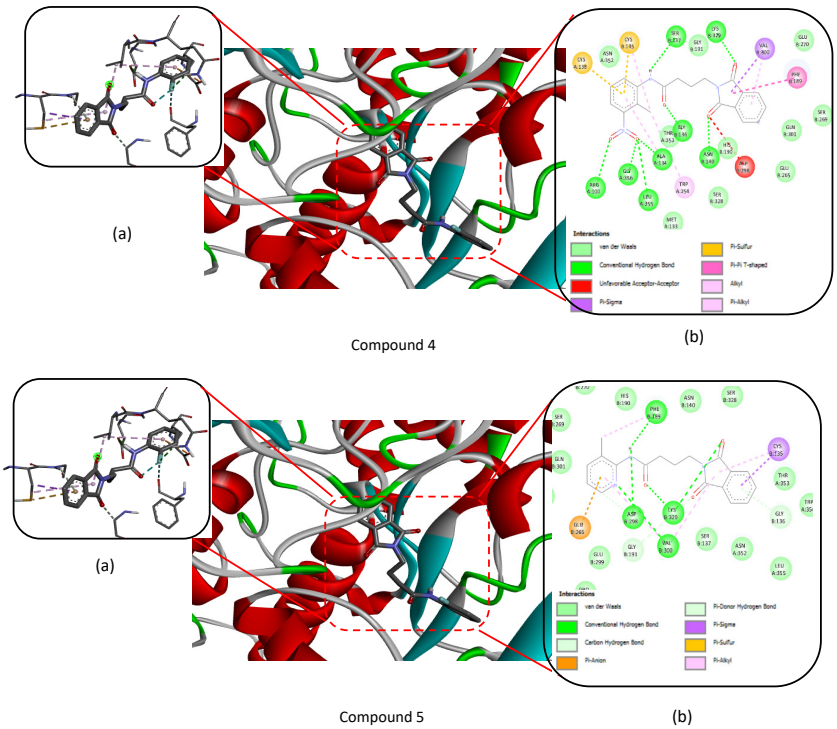
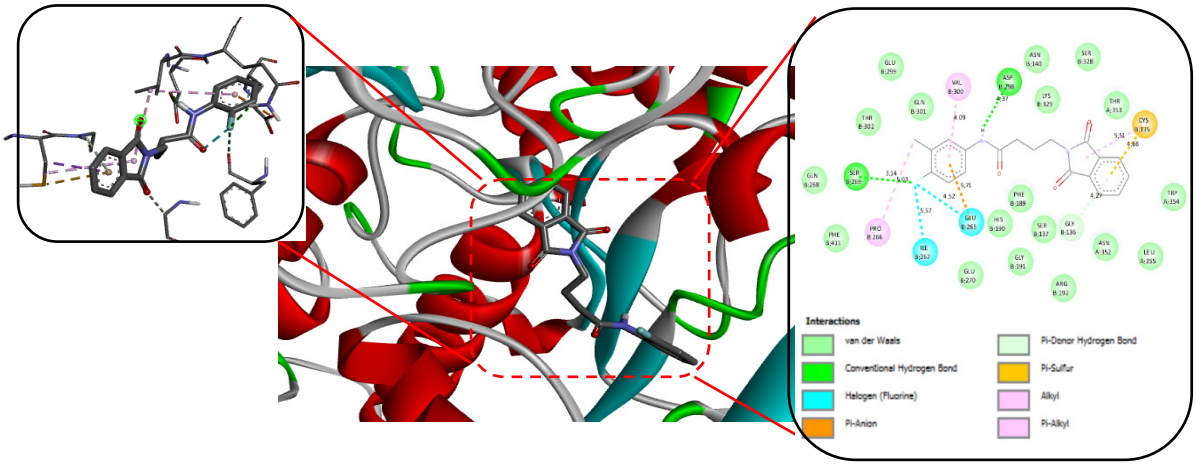


Figure 3: Molecular docking analysis of Compound 4 and 5 (a) Pose view of 3D interaction of compound with receptors 1OHV. (b) Pose view of 3D interaction of compound with receptors 1OHV.



Compound 6

Figure 4: Molecular docking analysis of Compound 4 and 5 (a) Pose view of 3D interaction of the compound with receptors 1OHV. (b) Pose view of 3D interaction of the compound with receptors 1OHV.

for medications designed for oral administration (Molecular properties of all 6 compounds are shown in Table 2). 5 out of 6 compounds were found to show no violations for the Lipinski rule of 5. Figure 1 displays a flow chart of several analyses performed on the all-novel compounds to choose the best choice. All six new compounds that have the greatest IOHV binding affinities were present. Compound 1 was discovered to have the best docking conformation, with binding affinities of -9.67 kcal/mol towards 1OHV, followed by Compound 2 with -9.92 kcal/mol toward 1OHV, Compound 3 with -10.51 kcal/mol, and Compound 4 with -10.48 kcal/mol toward 1OHV, compounds 5 and 6 had binding affinities of -10.78 kcal/mol and -9.61 kcal/mol towards 1OHV, respectively. As Shown in Table 1, all six new compounds showed favorable bioactivity and drug-like characteristics. The most interacting residues in the active sites of 1OHV were likewise revealed by the optimal docking posture. Pose view of the interactions between the chosen novel compound and therapeutic targets are shown in Figures 2-4.

Conclusion

Based on the binding affinities as exhibited by the docking studies supported by molecular characteristics using Molinspiration the study revealed that the five compounds can be considered potent Anti-Epileptic Drugs against 1OHV. Compound 5 had binding affinities of -10.78 These compounds can be the promising lead for further study as Anti-Epileptic for the management and prevention of Epilepsy.

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