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(REVIEW ARTICLE)

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Computational study on gabapentin as a potential therapy for partial seizures

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Abstract

US Food and Drug Administration (USFDA) approved gabapentin as an adjuvant treatment for refractory partial seizures and several diverse disorders. The drug has a relatively safe profile and is well tolerated; however, awareness is required to monitor the patient's medication, its misuse, and how to approach better patient fate. Despite the enormous scientific hypothesis encircling the drug, there is a requisite to research further about the novelty of the drug.

The review delineates the drug profile, synthesis, pharmacology, ADME properties, and computational study of gabapentin.

Keywords: Gabapentin; Anticonvulsants; Synthesis; Molecular docking; Spectral information

1. Introduction

Gabapentin, an anticonvulsant drug, was first developed in the 1970s as a second-generation AEDs [1]. Initially, the drug was used as a muscle relaxant and antispasmodic, but its anticonvulsive properties and potential as a supplement to more effective anticonvulsants were discovered later [2,3,4]. Gabapentin is a structural counterpart of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) which received FDA approval in the United States in 1993 [5]. It was first created as an anti-epileptic drug to treat specific seizures. Gabapentin is sold under a variety of brand names, including Neurontin. It is a type of anticonvulsant drug that is used to treat partial seizures and neuropathic pain[6,7]. The drug is a first-line treatment for diabetic neuropathy, postherpetic neuralgia, and significant discomfort induced by neuropathic pain [8]. It is only modestly effective- roughly 30-40% of people who have taken gabapentin for diabetic neuropathy or postherpetic neuralgia see a significant improvement [9]. In addition to neuropathic pain, the Neurontin brand is used to treat seizures in adults and children over the age of 3. Gabapentin has FDA approval for the following uses: -

- Postherpetic neuralgia
- Adjunctive therapy for partial seizures with or without secondary generalization in epilepsy patients above the age of 12 and the pediatric population, 3- to 12-year-olds with a partial seizure.
- Severe to moderate restless leg syndrome (RLS).

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- Physicians have recommended some Gabapentin brand forms
- Gabapentin, under the brand name Gralise, is only for treating neuropathic pain, not epilepsy.
- Horizant is a medication that is used to treat nerve pain and restless leg syndrome (RLS).

The past three decades are known as the modern era of anticonvulsants, as several new AEDs have been approved worldwide, along with gabapentin (Table.1).

Table 1 Chronological development of AEDs (Anti-epileptic drugs)

Name of AEDs	Year
Felbamate	1993
Gabapentin	1993
Lamotrigine	1994
Fosphenytoin	1996
Topiramate	1996
Tiagabine	1997
Levetiracetam	1999
Zonisamide	2000
Oxcarbazepine	2000
Pregabalin	2004

2. Drug profile

- Generic name: Gabapentin
- Brands Name: Gralise®, Neurontin ®,Horizant®
- Synonyms: Gabapentin , Gabapentina , Gabapentine , Gabapentinum , Gabapentin
- IUPAC Name: 2-[1-(Aminomethyl)cyclohexyl]acetic acid
- Molecular Formula: $C_9H_{17}NO_2$
- Molecular weight: 171.240g/mol

The 2D and 3D structures of gabapentin are shown in [Fig.1,2] and their brand names are represented in [Fig.3]

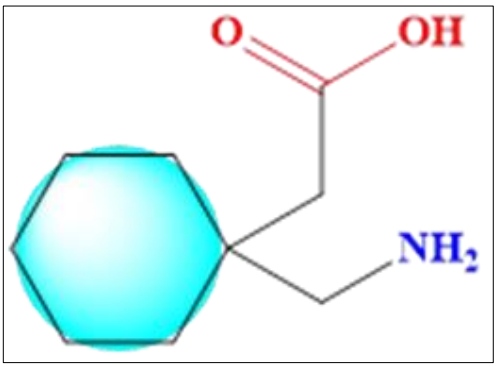


Figure 1 2D structure

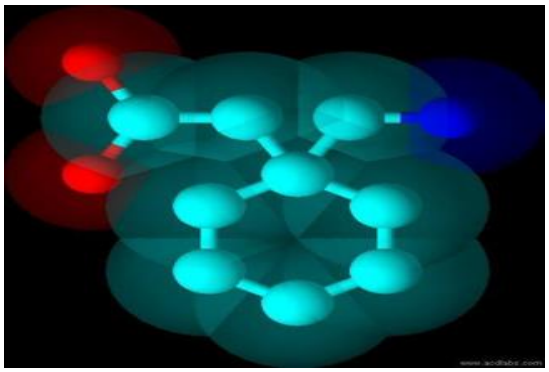


Figure 2 3D structure

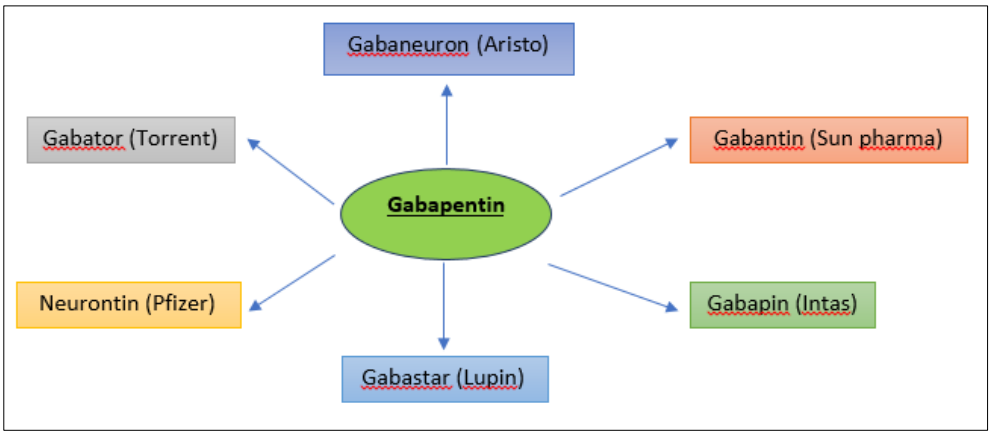
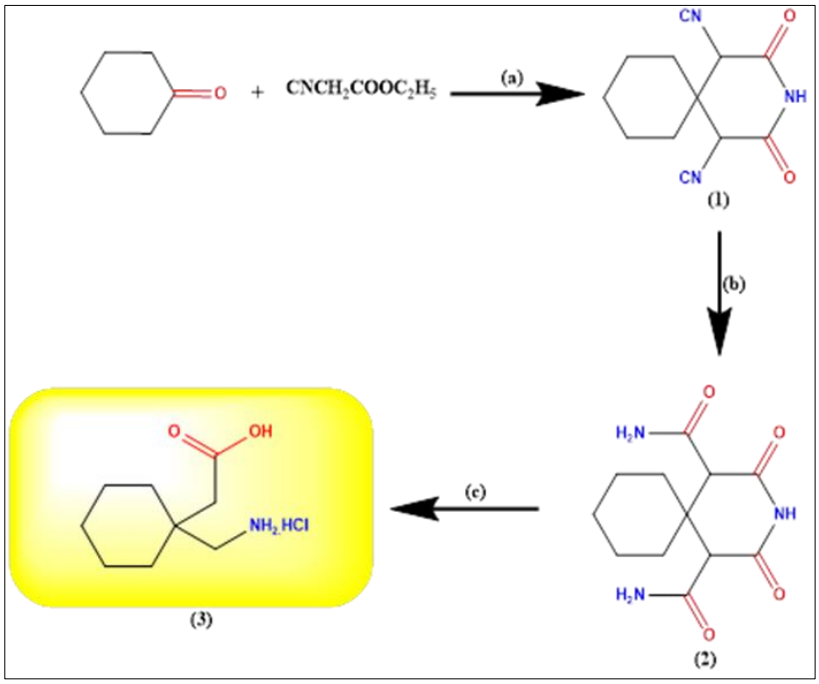


Figure 3a Brand Names (Manufacturers)

2.1. Synthesis



(1)1,5-Dicyano-2,4-dioxo-3-azaspiro [5,5]-undecane; (2)1,5-diaminoformyl-2,4-dioxo-3-azaspiro[5,5]-undecane; (3)Gabapentin hydrochloride

Reagents: (a) NH_3, CH_3CH_2OH;(b) H_2SO_4, H_2O; (c) KOH, NaClO

Figure 3b Synthetic route of Gabapentin [10]

2.2. Mechanism of action

The exact mechanism through which gabapentin works as a pain reliever is unknown [5,11]. The auxiliary α2δ-1 subunit of voltage-gated calcium channels appears to be the principal target (although a poor affinity for the α2δ-2 subunit has also been found) [12-14]. The primary function of these subunits is to assist the migration of calcium channel pore-forming α1 subunits from the endoplasmic reticulum to the cell membrane of presynaptic neurons [12]. Chronic pain has been linked to an increase in the expression of α2δ subunits, and these alterations have been linked to hyperalgesia [13]. Gabapentin seems to block the activity of α2δ-1 subunits, resulting in a reduction in the density of presynaptic voltage-gated calcium channels and the subsequent release of excitatory neurotransmitters [12]. This inhibition is likely also responsible for the anti-epileptic effects [14].

Gabapentin has also been shown to act on adenosine receptors and voltage-gated potassium channels, though the clinical significance of this action is unknown.

2.3. Pharmacodynamics

Gabapentin works by inhibiting the release of excitatory neurotransmitters, allowing it to be used to treat pathologic neurotransmission including neuropathic pain and seizures [5,15]. It has a broad therapeutic index, with dosages of up to 8000 mg/kg in rats failing to cause death[16].

2.4. Pharmacokinetics

Gabapentin is believed to be absorbed solely through enhanced transport by the LAT1 transporter in the intestines [17]. Because this mechanism is saturable, gabapentin's oral bioavailability is inversely related to the administered dose: a 900mg/day regimen has around 60% bioavailability, while a 4800mg/day regimen has only 27% bioavailability[5,18]. Gabapentin's Tmax has been calculated to be 2-3 hours [12,18]. The absorption of gabapentin is unaffected by food [5,18].

After IV treatment, gabapentin has an apparent volume of distribution of 58±6L [5,11]. The medication is found in the CSF in amounts of 9-20% of those in plasma, and similar concentrations are present in breast milk as seen in plasma [5,11,17]. Nearly 3% of the orally delivered dosage of gabapentin is bound to plasma protein.

Gabapentin is less metabolized in humans; approx. 1% of the drug of the administered dose is present as metabolites, while the remaining is eliminated in urine. Gabapentin is only excreted as an unaltered medication in the urine. Cimetidine, a tubular secretion inhibitor, lowers clearance by around 12%, suggesting the role of tubular secretion in gabapentin renal elimination. Gabapentin has a half-life of 5-7 hours in persons with normal renal function. The elimination half-life of gabapentin was reported to be around 52 hours in patients having a creatinine clearance of less than 30 mL/min. Gabapentin's plasma and renal clearances are closely related to the patient's creatinine clearance as it is primarily eliminated through the kidneys (renal elimination) [5,11,17].

2.5. Side effects

Common side effects of gabapentin may include:

- Fever, chills, sore throat, body aches, unusual tiredness.
- Jerky movements
- Headache
- Double vision
- Swelling of legs and feet
- Tremors
- Dizziness, drowsiness, tiredness
- Problems with balance or eye movements
- Nausea, vomiting

2.6. Toxicity

Toxicity symptoms include:

- Dizziness
- Sleepiness
- Slurred speech
- Lethargy
- Loss of consciousness
- Diarrhea

Overdoses, especially in combination with other CNS depressants like Opioids, can result in coma and death.

2.7. Therapeutic uses

- Gabapentin is used with other medications to prevent and control epileptic seizures.
- Gabapentin is also prescribed in nerve pain following shingles (a painful rash due to herpes zoster infection) in adults.
- Gabapentin is also used to treat moderate to severe primary restless legs syndrome (RLS).

2.8. Spectral information

Based on the structure of gabapentin, the IR values were predicted theoretically. ChemDraw Professional 16.0 was used to create hypothetical ^{1}HNMR spectra [Fig.7] and Mass spectra [Fig.8].

3. Computational study

3.1. Molecular Docking

The molecular docking study was conducted to assess their interaction and binding modes with target receptors and good biological activity using Glide extra precision (XP) Maestro 10.1 Schrodinger, running on Linux 64 operating system. The 2D structure for synthesized compounds was generated and then converted to their respective 3D structures using Ligprep. The X-ray crystal structure of 2COJ (PDB id) was downloaded from Protein Data Bank and solved at a resolution of 2.4 Å. The protein was prepared using the protein preparation wizard, and a grid was generated for the co-crystal ligand. The water residues beyond 5 Å were eliminated. The protein was optimized by assigning H-bonds and minimization at OPLS 2005 force field. Molecular docking studies mainly involve selecting and preparing appropriate protein, grid generation, and ligand preparation, followed by docking & its analysis. The docking score and, hydrogen bonds & pi-pi interaction formed with the enclosed amino acids were used to conclude theirbinding affinities and proper alignment of these compounds at the receptor's active site. The ligands and the receptors were prepared using LigPrep and Protein preparation wizard. The binding poses for the compound were analyzed by examining their free energy scores.

4. Results and discussion

The molecular docking studies were performed to establish the binding ability of the gabapentin to the human cytosolic branched-chain aminotransferase (hBCATc). The docking score was found to be -5.231 KCal/mol. The 2D ligand interaction diagram of gabapentin is represented in Fig.4. The gabapentin fits nicely into the hBCATc enzyme making four hydrogen bond interactions with the most essential active site residues.

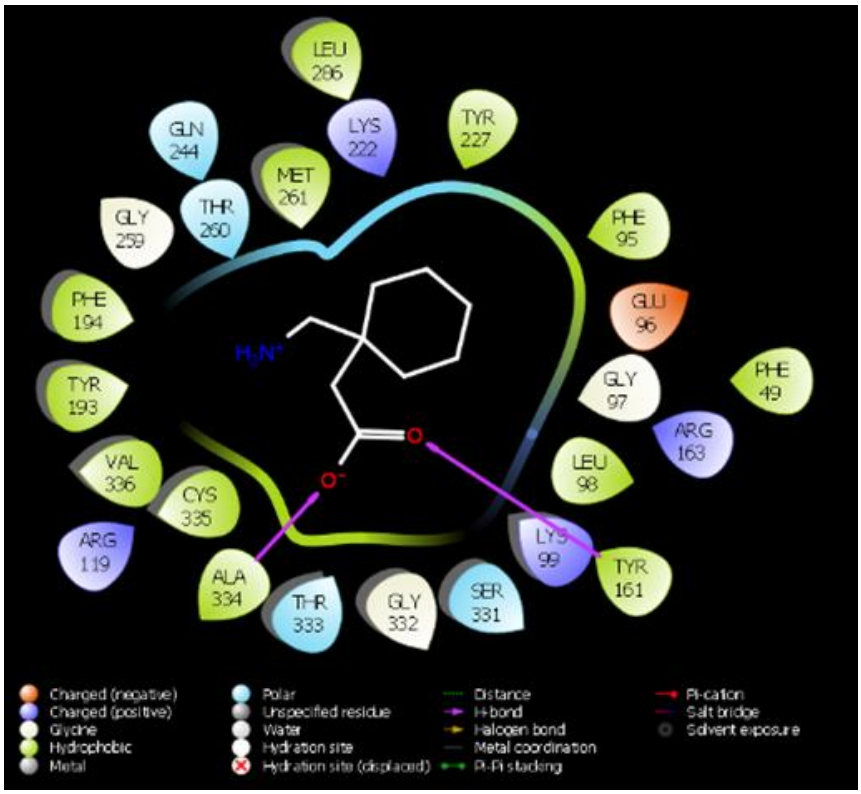


Figure 4 2D Ligand interaction of gabapentin using Lig Plot

The docking study performed,displayed a hydrogen bonding with the side chains of THR 260, TYR 161 and backbone of THR 333 and ALA 334, depicted in Fig.5. The receptor surface view of gabapentin was represented in Fig.6. The

molecular docking protocol was validated by re-docking of the gabapentin back into the same active site of hBCATc and found to be almost same interaction. The docking of gabapentin against the generated grid showed almost the same docking mode with RMSD value of 1.7; therefore, the docking protocol was validated by the generated grid.This result justifies that gabapentin has a high affinity for hBCATc.

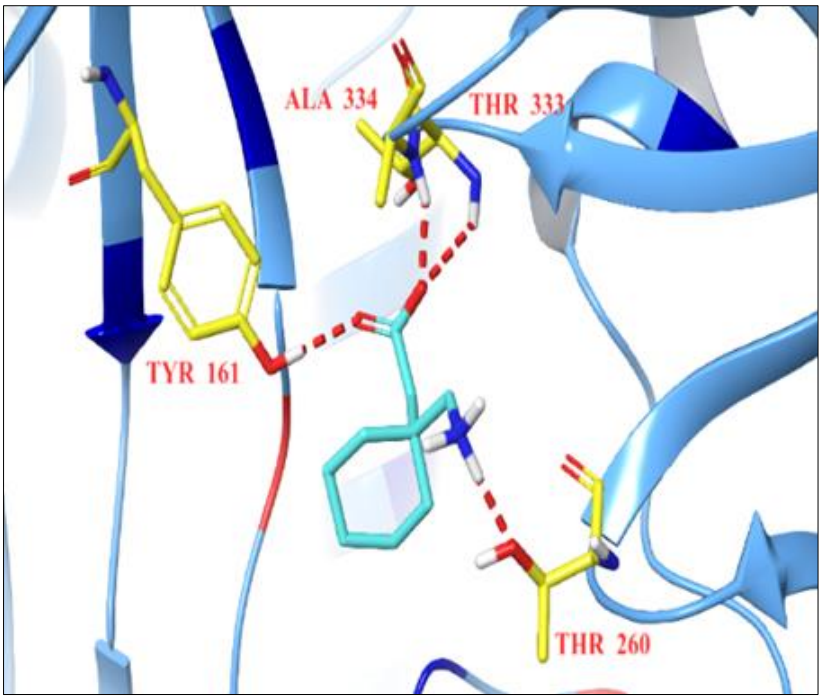


Figure 5 Docked Pose of gabapentin (turquoise color) represented as the stick in the binding site of hBCATc showing hydrogen bond interaction (red dash lines)

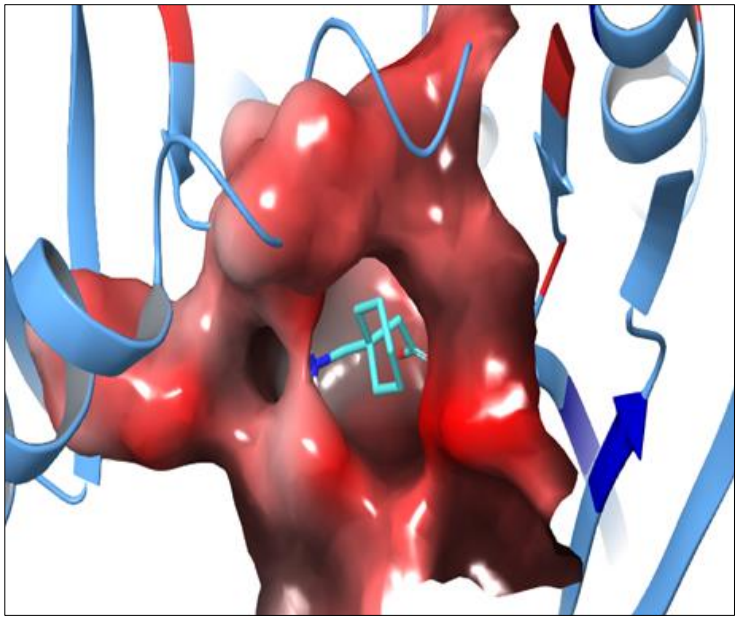


Figure 6 A receptor surface view and gabapentin (turquoise color) represented as the stick in the binding site of hBCATc

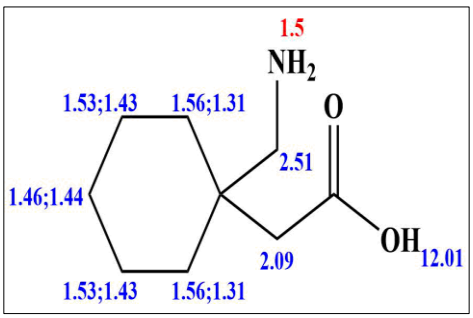


Figure 7 Chem ^{1}HNMR Estimation

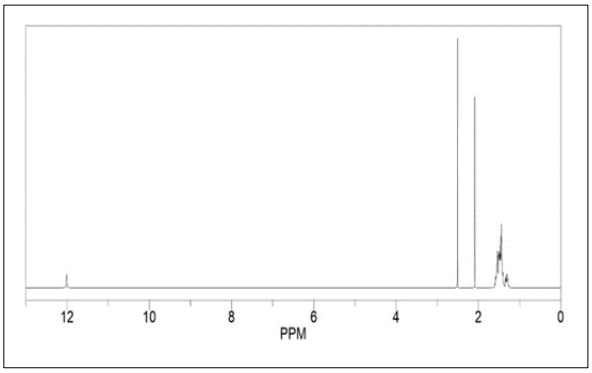


Figure 8 Mass Spectrum

Spectral prediction: IR (cm^{-1}) δmax: 3350 (NH_2), 3020(OH), 2860(CH_2-alip), 1690(C=O); ^{1}HNMR (300 MHz) δppm: 1.46-1.56 (s,10H,CH_2), 1.50 (s,2H,NH_2), 2.09-2.51 (s,4H,CH_2), 12.01 (s,1H, OH, D_2O exchangeable).

5. Conclusion

This study reviews the drug Profile, chemical, and structural characteristics, *In silico* studies, adverse side effects, and its clinical efficacy. Gabapentin is a well-tolerated, safe drug for treating focal epilepsy with an approving pharmacokinetic profile processing a broad therapeutic index. It is necessary to perceive the pharmacological rationale for its diversified manifestations and harmful side effects.

Compliance with ethical standards

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Disclosure of conflict of interest

All the authors have no conflict of interest.

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