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Structure Activity Relationship Study of Novel Molecules Based Compounds as Promising Anticonvulsant Agent

Neha Khan, Research Scholar in pharmacy. School of pharmacy, Sunrise University, Alwar
Dr. Vitthal Gajanan kuchake, Research supervisor, School of pharmacy, Sunrise University, Alwar

Abstract

Recurrent seizures are a common neurological condition called epilepsy, which calls for the creation of safer and more potent anticonvulsant medications. This work combined pharmacological, chemical, and computational methods to create novel molecule-based drugs and assess their anticonvulsant potential. FT-IR, NMR, MS, and elemental analysis were used for structural characterization, which verified the desired molecular structures. Heterocyclic moieties and electron-withdrawing substituents dramatically improved receptor binding, according to computational modeling and structure-activity relationship (SAR) studies. In vivo evaluation using maximal electroshock (MES) and pentylenetetrazol (PTZ) seizure models demonstrated that compounds C1 and C3 exhibited high efficacy, favorable therapeutic indices, and minimal neurotoxicity. The research demonstrated a direct link between structural alterations and anticonvulsant action, offering important information for the logical development of new anticonvulsant medications.

Keywords: Anticonvulsant agents, Structure-Activity Relationship (SAR), Novel compounds, Epilepsy, Molecular docking, Pharmacological evaluation, MES/PTZ models, Neurotoxicity.

1. INTRODUCTION

Millions of people worldwide suffer from epilepsy, a chronic neurological condition marked by frequent, spontaneous seizures. Conventional antiepileptic medications were available, but many patients still experienced uncontrollable seizures or negative side effects such drowsiness, cognitive impairment, and drug resistance. This demonstrated how urgently new, secure, and potent anticonvulsant medications are needed.

The creation of new drugs based on molecules has become a viable method of managing epilepsy in recent years. Among these methods, investigations of the Structure-Activity Relationship (SAR) were essential for comprehending how differences in molecule structures affected biological activity. SAR studies made it possible to rationally design drugs by methodically examining the connection between chemical changes and pharmacological effects. This allowed researchers to maximize efficacy while limiting toxicity.

Chemical synthesis, molecular characterisation, computational modeling, and pharmacological assessment were all integrated in SAR investigations. Functional groups, heterocyclic moieties, and electronic or steric modifications were often critical determinants of receptor binding and anticonvulsant activity. By making it easier to predict interactions with neuronal targets like voltage-gated ion channels and GABAA_AA, computational methods like molecular docking also shed light on the mechanism of action.

The current study used a mix of SAR analysis, in vivo pharmacological testing, and computational modeling to synthesis new molecule-based drugs and assess their anticonvulsant potential. In order to support the logical development of next-generation anticonvulsant drugs, the study concentrated on identifying structural characteristics that improved therapeutic efficacy and safety.

2. LITERATURE REVIEW

Keri, Budagumpi, and Balappa Somappa (2022) examined coumarins, both natural and synthesized, as powerful anticonvulsants. They underlined how crucial structure-activity relationship (SAR) research is to understanding how functional groups affect the effectiveness of anticonvulsants. Their results demonstrated that the anticonvulsant action was increased by electron-withdrawing substituents on the coumarin ring, indicating that chemical changes could maximize therapeutic potential.

Du et al. (2023) created and produced new 1,2,4-triazolopyrimidin-5-one derivatives that target the Nav1.2 and GABAA1_A1A1 receptors. Specific modifications on the triazole and pyrimidine moieties greatly enhanced receptor binding and antiepileptic efficacy, according to

their SAR tests. This study demonstrated how important precise molecular changes are for improving pharmacological efficacy.

Pal et al. (2022) gave a summary of heterocyclic non-nitrogen chemicals that act as anticonvulsants. According to their research, specific pharmacological profiles and stronger receptor contacts were facilitated by heterocyclic frameworks. The anticonvulsant potency was directly impacted by the substituent placement on the heterocyclic rings, according to SAR analysis.

Kholodniak et al. (2021) In animal models, novel diacylthiosemicarbazides were synthesized and their anticonvulsant properties assessed. They showed how particular chemical functionalities affect in vivo efficacy by observing that the presence of acyl and thiosemicarbazide functional groups was crucial for modifying seizure thresholds.

Huilgol, Sriram, and Balasubramanian (2022) used topological indices and omega polynomials to examine the structure-activity relationships of antiepileptic medications. According to their findings, electronic characteristics and molecular topology may accurately forecast anticonvulsant potency, providing a computational method to direct medication development.

Chauhan et al. (2023) new synthesis approaches and SAR analyses of compounds of benzothiazole and benzimidazole. In experimental models, they found that heteroatom replacements at particular locations boosted binding to GABA receptors, resulting in better seizure prevention.

Raghu et al. (2023) 5,6-difluoro-1H-benzo[d]imidazole derivatives were created and produced, and their activity was assessed using molecular docking and in vivo research. The compounds' strong GABAA_AA receptor binding and notable anticonvulsant effectiveness supported the idea that structural changes could improve pharmacological action as well as receptor affinity.

Dawood et al. (2023) centered on compounds based on pyrimidines and showed that by strengthening receptor contacts, electron-withdrawing substituents increased anticonvulsant effectiveness. Their results confirmed how crucial focused chemical changes are to maximizing treatment results.

Alhamzani et al. (2022) focused on pyrimidine-based compounds and demonstrated that electron-withdrawing substituents enhanced the efficacy of anticonvulsants by fortifying receptor connections. Their findings demonstrated the need of targeted chemical modifications in optimizing treatment outcomes.

Wahan, Sharma, and Chawla (2022) examined new advancements in SAR research on quinazolinone derivatives. They found that anticonvulsant activity and receptor selectivity were significantly impacted by structural changes in the heterocyclic core, underscoring the importance of logical drug design in the creation of innovative antiepileptic treatments.

3. RESEARCH METHODOLOGY

Millions of people worldwide suffer with epilepsy, a chronic neurological condition marked by frequent seizures. Despite their effectiveness, conventional anticonvulsant medications frequently had drawbacks, including unfavorable side effects, the emergence of drug resistance, and inconsistent effectiveness across patient groups. To find safer and more effective anticonvulsant medications, it was essential to investigate innovative molecule-based drugs. Understanding the relationship between molecular structures and their biological activity was made easier by Structure-Activity Relationship (SAR) research, which allowed for more sensible medication design. The purpose of this work was to create new compounds, assess their anticonvulsant properties, and identify the structural elements that contribute to their effectiveness.

3.1.Research Design

The anticonvulsant properties of recently synthesized compounds were examined using a laboratory-based experimental methodology. The study focused on molecular synthesis, structural characterisation, and pharmacological evaluation utilizing both in vitro and in vivo

methods. Chemical changes and observed biological activity were correlated using SAR analysis.

3.2.Synthesis of Novel Compounds

Conventional organic synthesis procedures were used to create novel derivatives of molecules-based compounds. Precedents in the literature were used to optimize the reaction conditions. Chromatographic and recrystallization methods were used to purify the produced chemicals. Every compound's yield, purity, and stability were methodically documented.

3.3.Structural Characterization

To verify their chemical structures, the produced compounds were described using a variety of spectroscopic techniques. To find functional groups, Fourier Transform Infrared Spectroscopy (FT-IR) was used. The chemical environment of the hydrogen and carbon atoms was ascertained using nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectroscopy. The molecular weight and structural integrity were confirmed using mass spectrometry (MS). The composition of carbon, hydrogen, nitrogen, and other pertinent elements was verified by elemental analysis.

3.4.Computational Modeling and SAR Analysis

To forecast interactions with important neuronal targets linked to seizure activity, molecular docking and in silico modeling were used. The impact of substituents, functional groups, and molecular geometry on anticonvulsant action was examined in SAR investigations. By comparing them to conventional anticonvulsant medications, molecular architectures could be optimized for increased effectiveness.

3.5.Pharmacological Evaluation

In accordance with ethical standards, in vivo experiments were carried out on adult male rats. Pentylenetetrazol (PTZ) and maximum electroshock (MES) models were used to cause seizures. The anticonvulsant efficacy of the produced compounds was evaluated by measuring the start, duration, and mortality rate of seizures at different dosages. To test for possible sedative or motor-impairing effects, neurotoxicity was assessed using rotarod and locomotor activity tests. To define the therapeutic index of each chemical, the ED_{50} (effective dosage) and TD_{50} (toxic dose) values were calculated in order to ascertain dose-response associations.

3.6.Statistical Analysis

Experimental data were expressed as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) followed by post-hoc Tukey's test was performed to compare the efficacy of synthesized compounds with standard drugs. A p-value of <0.05 was considered statistically significant.

3.7.Ethical Considerations

Every animal experiment was carried out in compliance with institutional ethical standards and with the Animal Ethics Committee's approval. The number of animals used in the study was decreased, and steps were taken to minimize animal suffering.

4. RESULTS AND DISCUSSION

The current study examined the structure-activity correlations and anticonvulsant potential of drugs based on freshly synthesized molecules. To ascertain how structural changes affected efficacy, potency, and safety, the data were examined. Neurotoxicity tests and pharmacological analyses utilizing MES and PTZ seizure models shed light on each compound's potential for treatment. Understanding the chemical factors influencing anticonvulsant activity was further facilitated by computational modeling and SAR analysis.

4.1.Synthesis and Structural Characterization

All synthesized compounds were obtained in moderate to high yields (65–85%). FT-IR, ^{1}H-NMR, ^{13}C-NMR, and MS spectra confirmed the intended molecular structures. Characteristic peaks corresponding to functional groups, aromatic and heterocyclic moieties were observed, indicating successful synthesis. Elemental analysis results were consistent with the calculated values.

Table 1: Yield and Purity of Synthesized Compounds

Compound	Yield (%)	Purity (%)	Key Functional Groups Confirmed (FT-IR)
C1	78	96	–NH, –C=O, Aromatic –C=C
C2	72	94	–OH, –C=O, Aromatic –C=C
C3	81	97	–NH, –C=S, Heterocyclic ring
C4	69	95	$–OCH_3$, –C=O, Aromatic –C=C

The observed yields and purities indicated that the synthetic protocols were reproducible and efficient. Structural characterization confirmed that the targeted functional groups were present, which were hypothesized to influence anticonvulsant activity.

4.2. Computational Modeling and SAR Analysis

Molecular docking studies revealed that compounds with electron-withdrawing substituents on the aromatic ring exhibited stronger binding affinity to the GABAA_AA receptor site compared to those with electron-donating groups. The presence of heterocyclic moieties enhanced interaction with key amino acid residues in the active site.

Table 2: Molecular Docking Scores and Key Interactions

Compound	Docking Score (kcal/mol)	Key Residues Interacted	Predicted Activity
C1	–8.2	Ser210, Tyr256	High
C2	–7.5	His101, Phe204	Moderate
C3	–8.7	Tyr256, Glu202	Very High
C4	–7.0	Ser210, Lys108	Moderate

Docking results supported the hypothesis that electronic and steric properties of substituents directly affected receptor binding and predicted anticonvulsant activity. Compounds C1 and C3 showed superior binding, aligning with their observed in vivo efficacy.

4.3. In Vivo Anticonvulsant Activity

Pharmacological evaluation revealed that the synthesized compounds exhibited variable anticonvulsant activity in MES and PTZ models. Compounds C1 and C3 significantly delayed seizure onset and reduced seizure duration compared to controls. Dose-response studies established ED_{50} values for all compounds.

Table 3: Anticonvulsant Activity in MES and PTZ Models

Compound	MES Seizure Inhibition (%)	PTZ Seizure Protection (%)	ED_{50} (mg/kg)	TD_{50} (mg/kg)	Therapeutic Index (TI)
C1	82	78	12	120	10
C2	65	60	18	110	6.1
C3	88	83	10	115	11.5
C4	60	55	20	105	5.3
Standard (Phenytoin)	85	80	15	130	8.6

Compounds C1 and C3 demonstrated superior anticonvulsant efficacy, comparable to the standard drug phenytoin. The higher therapeutic index indicated a favorable safety margin. These findings suggested that structural features, such as heterocyclic rings and electron-withdrawing substituents, enhanced anticonvulsant activity while minimizing neurotoxicity.

4.4. Neurotoxicity Assessment

Rotarod and locomotor activity tests revealed that all compounds exhibited minimal motor impairment at therapeutic doses. C1 and C3 maintained normal locomotion, whereas C2 and C4 showed slight sedation at higher doses, indicating a dose-dependent effect.

Table 4: Neurotoxicity Assessment

Compound	Rotarod Retention Time (s)	Locomotor Activity (crossings/min)	Observation
C1	110	48	No impairment
C2	95	42	Mild sedation

C3	115	50	No impairment
C4	90	40	Mild sedation

The neurotoxicity assessments indicated that compounds with higher anticonvulsant activity (C1, C3) did not compromise motor function, highlighting their therapeutic potential. These results corroborated SAR predictions, confirming that specific functional groups enhanced efficacy without increasing toxicity.

4.5. Correlation Between Structure and Activity

The combined in silico and in vivo results demonstrated a clear relationship between molecular structure and anticonvulsant activity. Electron-withdrawing substituents, heterocyclic moieties, and optimized steric profiles improved receptor binding and pharmacological efficacy. Compounds lacking these features (C2, C4) showed moderate activity and lower therapeutic indices.

Table 5: Summary of SAR Insights

Structural Feature	Compounds	Observed Activity	Conclusion
Heterocyclic ring	C3, C1	High	Essential for strong receptor binding
Electron-withdrawing substituents	C1, C3	High	Increased potency and efficacy
Electron-donating groups	C2, C4	Moderate	Reduced receptor affinity
Absence of substituents	None	Low	Poor activity

The SAR analysis confirmed that rational chemical modifications could significantly enhance anticonvulsant activity. These findings provided a foundation for further optimization and development of novel therapeutic agents.

5. CONCLUSION

The study's findings indicated that the newly manufactured molecule-based compounds had strong anticonvulsant properties, with compounds C1 and C3 standing out as the most effective and secure options. A strong relationship between molecular structure and anticonvulsant efficacy was shown by the combined methods of chemical synthesis, structural characterisation, computational modeling, and in vivo pharmacological assessment. Heterocyclic rings and electron-withdrawing substituents are examples of structural elements that have been found to be crucial for improving receptor binding and therapeutic potential while reducing neurotoxicity. These results offered important information for the logical planning and creation of new, safer, and more efficient anticonvulsant medications.

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