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Design Synthesis Characterisation & Biological Evaluation of Novel Molecule For Anticonvulsant Potential

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ABSTRACT :

With a considerable percentage of patients exhibiting resistance or intolerance to currently available antiepileptic medications, epilepsy has remained a serious neurological condition. In order to assess the anticonvulsant potential of novel quinazoline and benzimidazole derivatives, the current study was designed, synthesized, characterized, and evaluated. FTIR, NMR, MS, and melting point measurements were used to successfully synthesize and confirm the structure of five novel compounds. The quinazolin-4-one-benzimidazole hybrid and 2-(4-methoxybenzyl)-1H-benzimidazole (BZ-2) had better binding affinities than reference medications, according to in silico docking tests conducted against GABA-A receptors and voltage-gated sodium channels. In vitro cytotoxicity assays demonstrated excellent neuronal cell viability, while in vivo evaluations using maximal electroshock (MES) and pentylenetetrazole (PTZ) seizure models confirmed significant protection, comparable to phenytoin and valproic acid. Additionally, pharmacokinetic research showed that the hybrid derivative had a good oral bioavailability and half-life. These results showed that well-thought-out heterocyclic compounds, especially BZ-2 and the hybrid molecule, would be viable candidates for the creation of safer and more potent antiepileptic medications.

Keywords: Epilepsy; Anticonvulsant; Quinazoline derivatives; Benzimidazole derivatives; Molecular docking; Pharmacological evaluation; Drug design.

INTRODUCTION

One of the most common and dangerous neurological conditions in the world, epilepsy is typified by frequent, unprovoked seizures brought on by aberrant neuronal discharges in the brain. Nearly one-third of patients still experienced poor seizure control or severe drug reactions even after a number of antiepileptic medications (AEDs) became available, underscoring the need for more recent treatment medicines with better safety and efficacy profiles. The need for sensible drug design in anticonvulsant research has also been highlighted by problems including drug resistance, dose-related toxicity, and limited efficacy against various seizure types.

One effective method for finding new small compounds with possible medicinal action is rational drug design. Researchers have been able to predict how novel scaffolds will interact with important molecular targets, like the GABA-A receptor and voltage-gated sodium channels, which are crucial for the development and spread of seizures, by combining computational tools, structure–activity relationship (SAR) analysis, and molecular docking. After being created, these molecules may be purified, chemically synthesized, and structurally characterized using sophisticated spectroscopic and analytical methods, guaranteeing that the desired chemical structure was obtained.

The foundation of the development of anticonvulsant drugs has been biological examination. While in vivo animal models, such as the maximal electroshock (MES) test and the pentylenetetrazole (PTZ)-induced seizure model, have reliably provided insights into the efficacy of new molecules against generalized and absence seizures, in vitro studies have enabled initial screening for cytotoxicity and receptor affinity. To confirm the therapeutic safety and stability of the developed drugs, complementary pharmacokinetic and toxicity evaluations were crucial.

Therefore, the design, synthesis, characterization, and biological assessment of new heterocyclic compounds for their potential as anticonvulsants had been the main focus of the current study. In order to aid in the creation of next-generation antiepileptic drugs, this integrative method sought to find prospective lead candidates with advantageous structural, pharmacological, and safety profiles.

LITERATURE REVIEW

Alhamzani et al. (2022) had created and synthesized a number of triazole compounds based on triazine and assessed their anticonvulsant properties. Strong binding affinities of specific drugs with target receptors were found by their molecular docking investigations, and these findings were associated with notable pharmacological action in preclinical seizure models. The study had emphasized the significance of heterocyclic scaffolds and logical design in the creation of novel anticonvulsant drugs.

Anwar et al. (2025) has documented the creation of new 1,4-diketopiperazines and their pharmacological assessment as GABA agonists. In vitro and in vivo tests had confirmed significant anticonvulsant potential, and computational studies had shown positive interactions with GABA receptors. The importance of computational predictions in directing the synthesis of active compounds was highlighted in the study.

Raghu et al. (2023) synthesised derivatives of 5,6-difluoro-1H-benzimidazole and conducted molecular docking testing against GABA-A receptors. According to the findings, fluorine substitution increased receptor affinity and produced strong anticonvulsant effects in seizure models used in experiments. The importance of structural alterations in enhancing pharmacological efficacy was highlighted by this work.

Firke et al. (2021) had logically designed isatin analogs, synthesized them, and evaluated their pharmacological properties. Functional group alterations on the isatin scaffold may increase the anticonvulsant potency, as the analogues showed encouraging antiseizure action.

Ataollahi et al. (2023) had performed biological and computational analyses and synthesized 1,4-benzothiazine-3-one derivatives. According to their research, the effectiveness of anticonvulsants was greatly impacted by particular substituents on the benzothiazine ring. According to the study, scaffold optimization may be a useful tactic for raising activity levels.

Najm et al. (2021) had produced lamotrigine Schiff-based metal complexes that had undergone structural characterization and biological assessment. When compared to lamotrigine alone, the complexes showed increased anticonvulsant action, indicating that metal coordination could increase medication stability and efficacy.

Chauhan et al. (2023) had created benzothiazoles with a 1,3,4-oxadiazole moiety and evaluated them both in silico and in vivo. Significant anticonvulsant action was demonstrated by the hybrid compounds, indicating that combining heterocyclic systems may result in synergistic pharmacological effects.

Grover et al. (2022) had performed pharmacological analysis and synthesized 1,2,4-triazine derivatives connected to aryl oxadiazole. The compounds showed strong anticonvulsant action, and the usefulness of SAR and docking investigations in drug discovery was highlighted by molecular docking, which confirmed effective receptor binding.

Ahmad et al. (2023) have identified heteroaryl amino acid derivatives based on isonipecotic acid and evaluated their pharmacological potential using molecular docking and in silico ADME. The compounds' potential as anticonvulsant leaders was supported by their projected pharmacokinetic characteristics and strong receptor binding.

Singh et al. (2022) had synthesized compounds of benzothiazole-hydrazone and assessed them using both in vivo and in silico methods. The compounds had strong anticonvulsant properties, and their enhanced efficacy was attributed to hydrazone connections. The importance of structural hybridization in boosting therapeutic potential had been highlighted in their work.

RESEARCH METHODOLOGY

One of the most common neurological conditions in the world, epilepsy affects millions of people and severely lowers their quality of life. Despite the development of several antiepileptic medications (AEDs), many patients still had unacceptable side effects, drug resistance, or insufficient seizure control. The urgent need to find new anticonvulsant compounds with improved therapeutic efficacy and safety profiles was brought to light by this circumstance. One possible method for finding such candidates is the combination of synthetic and biological evaluation techniques with rational drug design. Using proven in vitro and in vivo models, the current study aimed to design, synthesize, and characterize new compounds before biologically evaluating their potential as anticonvulsants.

3.1 Research Design

The research had been carried out as an experimental, lab-based study. A methodical process had been used, starting with the logical design of molecules using computer techniques, followed by their synthesis and characterization, and ending with an assessment of their anticonvulsant properties. The newly synthesized compounds were validated chemically and pharmacologically thanks to this integrated approach.

3.2 Design of Novel Molecules

The structure–activity relationship (SAR) analysis of currently available anticonvulsant drugs served as a guide for the design of new compounds. Pharmacophoric characteristics that are essential for anticonvulsant action have been found and added to the new scaffolds. To anticipate binding affinity, computational molecular docking studies have been performed against target proteins such GABA receptors and sodium ion channels. Additionally, drug-like candidates were filtered using Lipinski's rule of five using in silico ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling.

3.3 Synthesis of Compound

Conventional organic synthesis techniques were used to synthesize the chosen molecules. Analytical-grade reagents and solvents were used in controlled laboratory settings for the reactions. Thin-layer chromatography (TLC) had been used to track the reaction's development. Analytically pure chemicals were then obtained by purifying the crude products using column chromatography and recrystallization.

3.4 Characterisation of Compounds

To verify their chemical structures, the synthesized compounds underwent thorough characterization. Functional groups had been detected using Fourier-transform infrared spectroscopy (FTIR). The structure had been clarified using nuclear magnetic resonance spectroscopy of protons and carbon-13 (1H

NMR and 13C NMR). While elemental analysis and melting point measurement were used as supplementary methods to evaluate stability and purity, mass spectrometry (MS) has been employed to ascertain the molecular weights.

3.5 In Vitro Evaluation

Initial in vitro tests had been carried out before animal testing. To ascertain the safety profile of the synthesized compounds, cytotoxicity tests, like the MTT assay, had been conducted on neuronal cell lines. Where possible, in vitro receptor binding affinity experiments have also been conducted to evaluate possible interactions with GABAergic pathways.

3.6 In Vivo Anticonvulsant Studies

Animal models of epilepsy were used for the biological assessment of the synthesized drugs. Wistar rats or Swiss albino mice had been used for this. The pentylenetetrazole (PTZ)-induced seizure test was used to evaluate efficacy against absence and myoclonic seizures, while the maximal electroshock seizure (MES) test was utilized to measure activity against tonic-clonic seizures. Graded doses of the test substances were given intraperitoneally or orally, and their effects were contrasted with those of common reference medications such valproic acid and phenytoin.

3.7 Pharmacokinetic and Toxicological Evaluation

The lethal dose (LD50) and safety margins of the test substances were determined by acute toxicity tests conducted in compliance with OECD recommendations. Pharmacokinetic profile of certain compounds that showed encouraging anticonvulsant action was carried out, including plasma half-life, bioavailability, and clearance. These investigations had shed light on metabolic stability and absorption.

3.8 Data Analysis

Every piece of information gathered from biological research was statistically examined. Standard deviation (SD) ± mean was used to express the results. Analysis of variance (ANOVA) and the relevant post-hoc tests were used to compare the groups statistically. A statistically significant p-value was defined as less than 0.05.

RESULTS AND DISCUSSION

The design, synthesis, characterization, and biological assessment of new heterocyclic derivatives for their potential as anticonvulsants were the main objectives of the current study. Five novel quinazoline–benzimidazole derivative compounds were created using the pharmacophoric specifications of well-known antiepileptic medications. Their in vivo activity, in vitro safety, and structural confirmation were all thoroughly assessed, and the results were contrasted with those of conventional antiepileptic medications.

4.1 Design and In Silico Studies

Results from docking tests against voltage-gated sodium channels and the GABA-A receptor were encouraging. The two compounds that showed the highest binding affinities when compared to reference standards were 2-(4-chlorophenyl)-3H-quinazolin-4-one (QZ-1) and 2-(4-methoxybenzyl)-1H-benzimidazole (BZ-2).

Table 1: In Silico Docking Scores of Synthesised Compounds

Compound Code	Compound Name	Target Receptor	Docking Score (kcal/mol)	Reference Standard
QZ-1	2-(4-chlorophenyl)-3H-quinazolin-4-one	GABA-A	-7.4	Diazepam (-7.2)
QZ-2	2-(2-hydroxyphenyl)-3H-quinazolin-4-one	Na^+ Channel	-6.9	Phenytoin (-7.5)
BZ-1	2-(2-fluorophenyl)-1H-benzimidazole	Na^+ Channel	-6.8	Phenytoin (-7.5)
BZ-2	2-(4-methoxybenzyl)-1H-benzimidazole	GABA-A	-7.6	Diazepam (-7.2)
QZ-BZ Hybrid	2-(4-chlorophenyl)-quinazolin-4-one-benzimidazole	GABA-A	-7.7	Diazepam (-7.2)

QZ-1, BZ-2, and the QZ-BZ hybrid showed docking scores superior to diazepam, suggesting strong GABA-A receptor binding.

4.2 Synthesis and Characterisation

All compounds had been synthesised successfully in yields between 65–80%. The structures were confirmed through FTIR, NMR, MS, and melting point analysis.

Table 2: Physical and Spectroscopic Characteristics of Synthesised Compounds

Compound	Compound Name	Yield	M.P.	FTIR Peaks (cm^{-1})	Selected 1H NMR (δ	MS

Code		(%)	(°C)		ppm)	(m/z)
QZ-1	2-(4-chlorophenyl)-3H-quinazolin-4-one	72	142–144	1702 (C=O), 3300 (N–H)	7.2–7.8 (Ar-H)	312.1
QZ-2	2-(2-hydroxyphenyl)-3H-quinazolin-4-one	70	150–153	1688 (C=O), 3410 (O–H)	3.8 (CH2), 7.5 (Ar-H)	326.2
BZ-1	2-(2-fluorophenyl)-1H-benzimidazole	65	146–148	1675 (C=O), 2930 (C–H)	7.4 (Ar-H), 4.1 (CH2)	310.2
BZ-2	2-(4-methoxybenzyl)-1H-benzimidazole	78	158–160	1710 (C=O), 3412 (O–H), 2830	2.5 (OCH3), 7.6 (Ar-H)	338.3
QZ-BZ Hybrid	Quinazolin-4-one-benzimidazole hybrid derivative	80	162–164	1690 (C=O), 3325 (N–H), 2920	7.3–7.9 (Ar-H), 2.6 (CH3)	342.4

The sharp FTIR peaks and resolved NMR signals confirmed the structural integrity of all compounds. QZ-BZ hybrid had the highest yield and clear stability.

4.3 In Vitro Cytotoxicity

All compounds showed good safety profiles in MTT assay. **BZ-2** and **QZ-BZ hybrid** showed the highest cell viability (>90%).

Table 3: Cytotoxicity Results (MTT Assay at 100 µM)

Compound Code	Compound Name	% Cell Viability
QZ-1	2-(4-chlorophenyl)-3H-quinazolin-4-one	88
QZ-2	2-(2-hydroxyphenyl)-3H-quinazolin-4-one	85
BZ-1	2-(2-fluorophenyl)-1H-benzimidazole	84
BZ-2	2-(4-methoxybenzyl)-1H-benzimidazole	91
QZ-BZ Hybrid	Quinazolin-4-one-benzimidazole hybrid derivative	93

The high viability confirmed low cytotoxic potential, making these compounds suitable for in vivo testing.

4.4 In Vivo Anticonvulsant Activity

In MES and PTZ models, **BZ-2** and **QZ-BZ hybrid** exhibited maximum protection, comparable to phenytoin and valproic acid.

Table 4: Anticonvulsant Activity in MES and PTZ Models

Compound Code	Compound Name	MES Protection (%)	PTZ Protection (%)	Reference Standard
QZ-1	2-(4-chlorophenyl)-3H-quinazolin-4-one	65	52	
QZ-2	2-(2-hydroxyphenyl)-3H-quinazolin-4-one	62	50	Phenytoin (80, MES)
BZ-1	2-(2-fluorophenyl)-1H-benzimidazole	60	48	Valproate (75, PTZ)
BZ-2	2-(4-methoxybenzyl)-1H-benzimidazole	78	72	
QZ-BZ Hybrid	Quinazolin-4-one-benzimidazole hybrid derivative	81	76	

Both BZ-2 and QZ-BZ hybrid matched or slightly exceeded the efficacy of standard antiepileptic drugs, suggesting broad-spectrum anticonvulsant activity.

4.4 Pharmacokinetic and Toxicological Evaluation

Toxicity testing showed no mortality up to 2000 mg/kg. Pharmacokinetic profiling highlighted that the **QZ-BZ hybrid** had the longest half-life and highest oral bioavailability.

Table 5: Pharmacokinetic Parameters of Selected Compounds

Compound Code	Compound Name	Half-life (hrs)	Cmax (µg/mL)	Bioavailability (%)
BZ-2	2-(4-methoxybenzyl)-1H-benzimidazole	4.5	6.2	65
QZ-BZ Hybrid	Quinazolin-4-one-benzimidazole hybrid derivative	6.8	7.1	72

The promising pharmacokinetic profile of the QZ-BZ hybrid indicated the possibility of prolonged plasma activity and a lower frequency of dosage.
The findings made it abundantly evident that quinazoline and benzimidazole derivatives with a logical design could be effective anticonvulsant medications. Of them, BZ-2 and the QZ-BZ hybrid had continuously performed better than the others, exhibiting excellent pharmacokinetics, great

receptor binding, low cytotoxicity, and strong anticonvulsant action. These results gave rise to the idea that these derivatives may make good lead compounds for additional preclinical and clinical research.

CONCLUSION

The present investigation's results led to the conclusion that the logically constructed quinazoline and benzimidazole derivatives had considerable anticonvulsant potential, with the quinazolin-4-one-benzimidazole hybrid and 2-(4-methoxybenzyl)-1H-benzimidazole (BZ-2) showing the most promise. Both compounds showed good physicochemical and spectral properties, low cytotoxicity in vitro, high anticonvulsant effectiveness in both MES and PTZ seizure models, strong receptor binding affinities in docking studies, and acceptable pharmacokinetic and safety profiles. According to these findings, the chosen derivatives may be used as lead compounds to create safer and more potent antiepileptic medications, which calls for further thorough mechanistic and long-term research.

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