RESEARCH PAPER

Exploring Isoquinoline Alkaloids: Synthetic Approaches, Structural Diversification, and Anticonvulsant Potential

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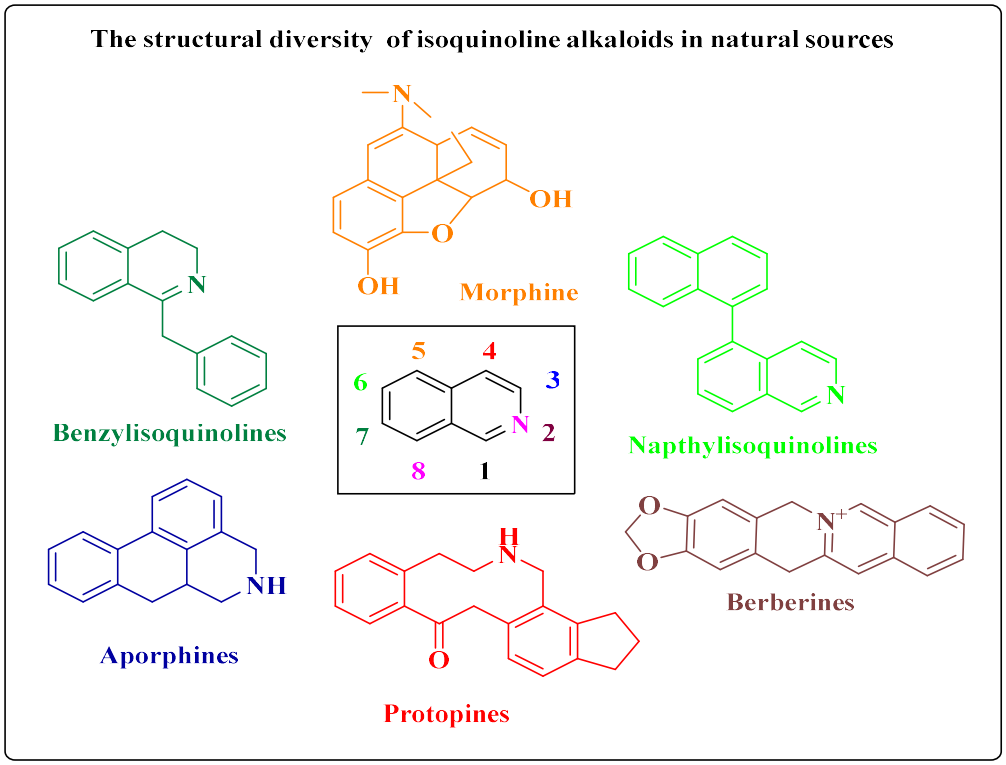

Abstract

Background: Epilepsy is a chronic neurological disorder characterized by recurrent seizures resulting from abnormal

neuronal excitability and an imbalance between excitatory and inhibitory neurotransmission. Despite the availability of antiepileptic drugs, a significant proportion of patients remain pharmacoresistant and experience adverse effects.
Objective: To review recent advances in chemistry, synthesis, structural modification, and anticonvulsant potential of isoquinoline alkaloids in epilepsy management.
Methods: A comprehensive literature review was conducted using databases such as PubMed, ScienceDirect, Google Scholar, SpringerLink, and Wiley Online Library, focusing on studies published between 2020 and 2025.
Results: Isoquinoline alkaloids represent an important class of nitrogen-containing heterocyclic compounds with diverse pharmacological activities. Structural modifications and structure–activity relationship (SAR) studies suggest that substitution patterns and heterocyclic frameworks play a crucial role in enhancing anticonvulsant potential. Mechanistically, these compounds are reported to modulate GABAergic neurotransmission and influence voltage-gated ion channels, contributing to reduced neuronal excitability.
Conclusion: Isoquinoline alkaloids are promising scaffolds for the development of novel antiepileptic agents. However, further studies focusing on detailed SAR, pharmacokinetics, and clinical validation are necessary to establish their therapeutic potential.
Keywords: Isoquinoline alkaloids; Epilepsy; Anticonvulsant activity; Structure–activity relationship; GABAergic modulation; Neuropharmacology; Drug discovery.
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1:Introduction

Epilepsy is one of the most common and serious neurological conditions, affecting more than 50 million people worldwide **[1]**. Epilepsy is a group of chronic non-communicable neurological disorders characterized by spontaneous recurrent seizures **[2,3]**. Epilepsy is the second most common chronic neurological disorder and can greatly affect the quality of life of patients. Nearly four out of five people with epilepsy live in low- and middle-income countries **[4,5]**. Epilepsy is a neurological disease characterized by unprovoked recurrent epileptic seizures that originate in all brain regions or may be localized to specific areas **[6]**. Every year, approximately 250,000 new cases are added worldwide. It is estimated that about 28–30% of patients are resistant to the available medical therapies **[7,8]**. Seizures result from abnormal electrical activity in the brain, and in most cases, treatment begins with antiepileptic drugs. About half of the patients are controlled with single-drug therapy, while nearly 30% of patients require two or three drugs to control seizures. The remaining patients who are resistant to oral antiepileptic drugs require other treatments, including surgery **[9,10,11]**. Despite the development of several new anticonvulsant drugs, epilepsy remains a continuing health concern **[12]**. One out of four epileptic seizures remain inadequately treated **[13,14]**. Epilepsy is characterized by different types of seizures and epilepsy syndromes and is often associated with comorbidities such as depression, anxiety, increased mortality, and other neurological complications **[15,16]**. Epilepsy is commonly considered the result of an imbalance between excitatory and inhibitory neuronal activity, leading to abnormal discharge of cerebral neurons and periodic, unpredictable seizures **[17]**. This situation has stimulated considerable research for the discovery of new antiepileptic drugs, and in this regard, medicinal plants have emerged as an important source for the development of novel anticonvulsant agents **[18]**.

2: Pathophysiology of Epilepsy

The pathophysiology of epilepsy is complex, and several mechanisms are involved in epileptogenesis and epileptogenicity **[19]**. The efficacy of anticonvulsant drugs is associated with different molecular targets that reduce the excitability of neurons involved in seizure onset **[20,21]**. The mechanisms of action of currently available antiepileptic drugs include: (a) induction of prolonged inactivation of sodium (Na^+) channels, (b) blockade of calcium (Ca^{2+}) channel currents, and (c) enhancement of inhibitory γ-aminobutyric acid (GABA)ergic neurotransmission or modulation of excitatory glutamatergic neurotransmission. With respect to the latter pharmacological target, extensive studies have demonstrated that both competitive and non-competitive antagonists of ionotropic glutamate receptors (iGluRs) show promising therapeutic potential in the prevention and treatment of epilepsy **[22,23]**. GABA is an important inhibitory neurotransmitter in the central nervous system (CNS) that reduces neuronal excitation and activity **[24]**. Gamma-aminobutyric acid (GABA) receptors are mainly divided into two types: GABA_A and GABA_B. The GABA_A receptor is a ligand-gated ion channel that mediates the inhibitory effects of GABA. Activation of this receptor increases chloride ion (Cl^-) influx into the neuron, leading to

hyperpolarization of the cell membrane and reduced neuronal excitability **[25,26]**.

3: Mechanism of Epilepsy (GABAergic System)

Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the cerebral cortex and plays a crucial role in maintaining the inhibitory tone that counterbalances neuronal excitation, as shown in fig.1**[27]**. When the balance between excitatory and inhibitory neurotransmission is disturbed, excessive neuronal activity may occur, leading to seizures associated with Epilepsy **[28]**. Excitatory synaptic transmission in the brain is mainly mediated by glutamate, which activates postsynaptic receptors such as NMDA and AMPA/kainate receptors, resulting in sodium and calcium influx and neuronal depolarization, thereby increasing neuronal excitability. GABA is synthesized in GABAergic axon terminals and released into the synaptic cleft, where it acts on two main receptor types, GABA_A and GABA_B receptors. Activation of GABA_A receptors regulate chloride ion influx into neurons, producing rapid inhibitory postsynaptic potentials, whereas GABA_B receptor activation increases potassium conductance, decreases calcium entry, and inhibits the presynaptic release of neurotransmitters, thereby contributing to slower inhibitory responses **[29]**. Following synaptic transmission, GABA is rapidly removed from the synapse through uptake into glial cells and presynaptic terminals and is subsequently metabolized by GABA transaminase. Experimental and clinical studies have demonstrated that alterations in GABAergic function play a significant role in epilepsy, as reduced GABA-mediated inhibition and decreased GABA levels have been observed in epileptic brain tissue. Furthermore, GABA agonists suppress seizures, whereas GABA antagonists and inhibitors of GABA synthesis can induce seizures **[30]**. Consequently, several antiepileptic drugs enhance GABAergic neurotransmission; for example, Vigabatrin inhibits GABA transaminase and increases GABA levels, while Tiagabine blocks GABA reuptake into neurons and glial cells, thereby elevating synaptic GABA concentration and producing an anticonvulsant effect **[31,32]**.

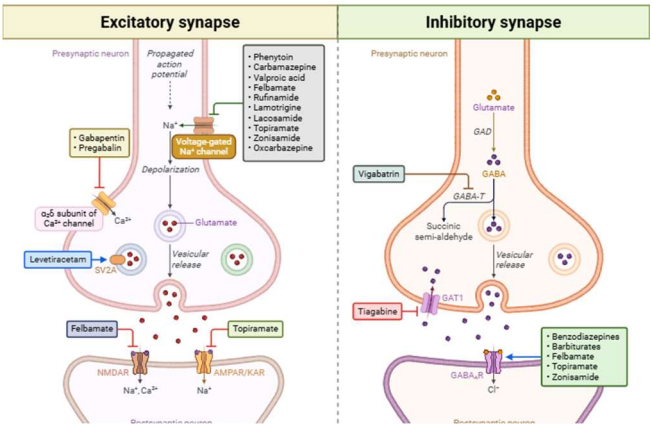


Fig.1: Mechanism of Epilepsy

4: Marketed Antiepileptic Drugs and Their Limitations

Several antiepileptic drugs (AEDs) are currently available for the treatment and long-term management of epilepsy. Commonly prescribed medications include Phenytoin, Carbamazepine, Valproic Acid, Lamotrigine, and Levetiracetam **[33]**. These drugs exert their antiepileptic effects primarily by modulating neuronal excitability through mechanisms such as blocking voltage-gated sodium channels, regulating calcium channels, or enhancing inhibitory neurotransmission mediated by γ-aminobutyric acid (GABA) **[34]**. Through these mechanisms, AEDs help reduce abnormal neuronal firing and prevent seizure propagation. Despite the availability of numerous antiepileptic medications, approximately 30–35% of patients continue to experience uncontrolled seizures, a condition known as drug-resistant epilepsy **[35]**. In addition, long-term therapy with conventional AEDs is often associated with a range of adverse effects. Common side effects include dizziness, sedation, fatigue, cognitive impairment, and gastrointestinal disturbances, which may negatively affect patients' quality of life **[36]**. Some drugs may also cause serious complications such as hepatotoxicity, weight gain, metabolic disturbances, and teratogenic effects during pregnancy **[37]**. Furthermore, many antiepileptic drugs exhibit drug–drug interactions due to hepatic enzyme induction or inhibition, which complicates therapy, particularly in patients receiving multiple medications. The variability in patient response, the narrow therapeutic index, and the risk of chronic toxicity further limits the effectiveness of currently available treatments **[38]**. Therefore, these limitations emphasize the urgent need for the discovery and development of safer, more effective, and well-tolerated therapeutic agents. Natural products and their derivatives have recently gained considerable attention as potential sources of novel antiepileptic compounds due to their structural diversity, multi-

target mechanisms, and relatively lower toxicity profiles **[39]**.

S.NO.	Antileptic Drug	Percentage of Side Effect (%)
1	Phenobarbital	52%
2	Phenytoin	35%
3	Carbamazepine	7%
4	Valproic acid	6%
5	Lamotrigine	10%
6	Levetiracetam	12%

5: Importance of Natural Products in Epilepsy Treatment

Due to the limitations and adverse effects of currently available antiepileptic drugs, natural products have gained considerable attention as potential sources for developing new therapeutic agents **[40]**. Natural compounds derived from medicinal plants often possess diverse biological activities and relatively fewer side effects compared with synthetic drugs, making them promising candidates for drug discovery **[41]**. Among these natural compounds, isoquinoline alkaloids represent an important class of nitrogen-containing heterocyclic molecules widely found in plants **[42]**. These compounds exhibit various pharmacological activities, including neuroprotective, antioxidant, anti-inflammatory, and antimicrobial effects **[43]**. Moreover, several isoquinoline derivatives have shown promising activity in the central nervous system and may influence neurotransmitter systems involved in seizure regulation, particularly by modulating GABAergic and glutamatergic pathways **[44]**. Therefore, isoquinoline-based compounds have emerged as attractive scaffolds for the development of novel anticonvulsant agents. The graph fig.2 shows a steady increase in research on isoquinoline derivatives from 2005 to 2023. This trend indicates growing interest in these compounds as potential anticonvulsant agents. **[45]**.

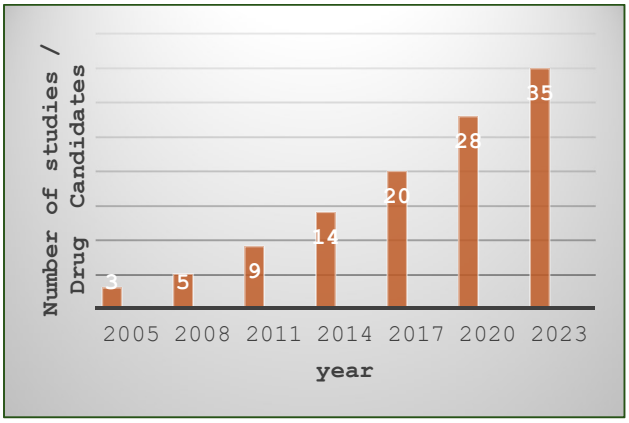


Fig.2: Progress of Isoquinoline Derivatives in Epilepsy

6: Background on Isoquinoline-Containing Natural Moieties

Plants have long been recognized as the cradle of traditional medicine, which has alleviated human ailments for thousands of years **[46]**. The first definition of alkaloids was introduced by W. Meissner in 1818, who defined all organic compounds of plant origin characterized by basicity as alkaloids **[47]**. Alkaloids represent an important and extensive group of natural products. A simple general definition of an alkaloid was first suggested in 1983 as "An alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state and is of limited distribution in living organisms." This definition includes both alkaloids with nitrogen as part of a heterocyclic system and many exceptions with exocyclic nitrogen **[48,49]**. Isoquinoline (ISOQ) is a heterocyclic aromatic organic compound composed of a benzene ring fused to a pyridine ring, referred to as benzopyridines (Figure 3) **[50]**. The chemical formula is C_9H_7N with a molar mass of 129.162 g/mol **[51].** It is a structural isomer of quinoline where the nitrogen atom is present on the 2nd position of the benzene ring **[52]**. This ISOQ ring derives from the natural aromatic amino acid tyrosine **[53]**. It is weakly alkaline in nature but is more basic than quinoline **[54]**. It appears as a yellowish oily liquid, having an unpleasant odour, hygroscopic when solid, has a density of 1.099 g/cm3, a melting point of 26°C to 28°C (79°F to 82°F), the boiling point of 242°C (468°F), and a dipole moment of 2.49 **[55,56]**. The dissolution of ISOQ is well in acetone, diethyl ether, carbon disulfide, and various organic solvents, but is less soluble in water. Several studies have found that ISOQ is also soluble in diluted acids **[57]**. Isoquinoline alkaloids make a large family of natural products showing a wide range of structural diversity and biological activity **[58]**. Isoquinoline alkaloids, an important class of N-heterocyclic bioactive natural products, are common throughout living organisms,

predominantly in the plant kingdom **[59]**. Derived from tyrosine or phenylalanine building blocks, isoquinoline alkaloids are thought to be highly conserved metabolites in ancient vascular plants at the chemotaxonomic level **[60,61]**.

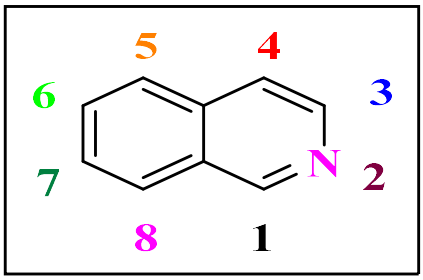


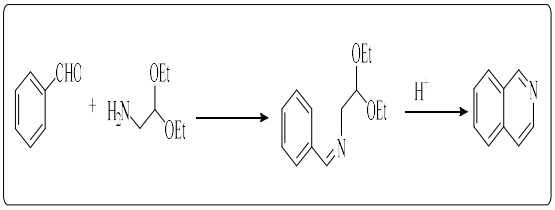
Fig.3: Structure of isoquinoline

7: Chemistry Of Isoquinoline

Isoquinoline (C_9H_7N) is an aromatic benzo-fused pyridine system in which a benzene ring is fused to the β–γ bonds of the pyridine ring, giving a planar 10-π-electron structure that obeys Hückel's rule and confers aromatic stability; the nitrogen lone pair lies in an sp^2 orbital perpendicular to the ring, making isoquinoline a weak but stronger base than quinoline due to better charge delocalization in the protonated form **[62,63]**. Electrophilic substitution (e.g., nitration, halogenation) occurs mainly at positions 5 and 8, with 5 favored, while nucleophilic attack tends to occur at electron-deficient sites such as C-1 or C-3, and the ring can undergo reduction to 1,2- or 3,4-dihydroisoquinolines that may be rearomatized **[64,65]**. Vigorous oxidation cleaves the benzene ring to give phthalic and cinchomeronic acids, confirming the fusion pattern, and classical syntheses such as the Bischler–Napieralski cyclodehydration of β-phenethyl amides followed by dehydrogenation provide convenient access to isoquinoline and its substituted derivatives **[66,67]**.

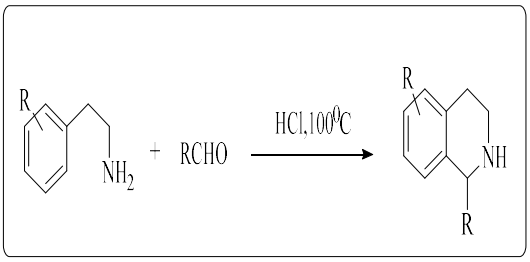
8: Synthesis of Isoquinoline

The synthesis of isoquinoline derivatives is the Pomeranz–Fritsch reaction. This method involves the condensation of benzaldehyde derivatives with amino acetaldehyde acetals, followed by acid-catalyzed cyclization to produce isoquinoline structures. The Pomeranz–Fritsch synthesis has been extensively used for the preparation of various substituted isoquinoline compounds due to its relatively simple reaction conditions and accessibility of starting materials **(Scheme 1) [68,69]**.



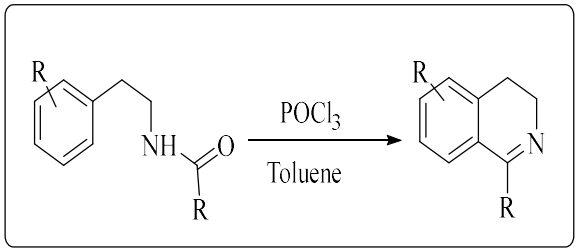
Scheme 1: Pomeranz-Fritsch method

The Pictet–Spengler reaction also plays a significant role in the formation of tetrahydroisoquinoline derivatives, which serve as important intermediates in the synthesis of many biologically active alkaloids. In this reaction, β-arylethylamines react with aldehydes or ketones under acidic conditions to form tetrahydroisoquinoline frameworks through intramolecular cyclization. This method has been widely applied in the synthesis of natural isoquinoline alkaloids and their analogues **(Scheme 2) [70,71]**.



Scheme 2: Pictet–Spengler method

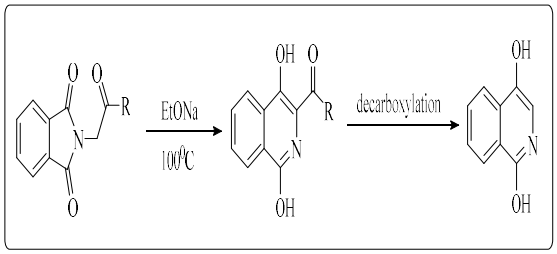
Among these methods, the Bischler–Napieralski reaction is one of the most widely used approaches for the synthesis of isoquinoline and dihydroisoquinoline derivatives. In this reaction, β-phenethyl amides undergo cyclodehydration in the presence of strong dehydrating agents such as phosphorus oxychloride or phosphorus pentoxide to form dihydroisoquinoline intermediates, which can subsequently be oxidized to isoquinoline compounds **(Scheme 3) [72]**.



Scheme 3: Bischler–Napieralski method

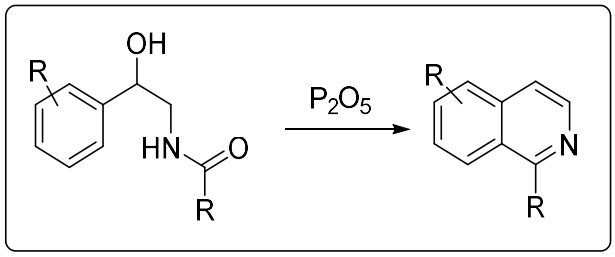
Gabriel and Colman proposed the method that involved phthalimide as the raw material and proceeded via rearrangement upon strong alkaline conditions, leading to isoquinoline derivatives, and

following decarboxylation of those, gave 1,4-dihydroxy isoquinoline **(Scheme 4) [73].**



Scheme 4: Gabriel and Colman method

The Pictet–Gam's reaction is a modification of the Pictet–Spengler reaction used to synthesize isoquinoline derivatives. In this reaction, β-arylethylamides undergo intramolecular cyclization in the presence of strong dehydrating agents such as $POCl_3$, leading to the formation of dihydroisoquinoline or isoquinoline systems. It is an important method for constructing nitrogen-containing heterocycles with pharmaceutical relevance **(Scheme 5) [74,75]**.



Scheme 5: Pictet–Gam's method

Conclusion: Isoquinoline alkaloids represent a promising class of heterocyclic compounds for anticonvulsant drug development. Advances in synthesis and structural modification have enhanced their pharmacological potential, with several derivatives demonstrating significant activity in experimental seizure models. Their ability to modulate GABAergic neurotransmission and ion channels highlights their relevance in epilepsy management. However, further studies focusing on structure–activity relationships, pharmacokinetics, and clinical validation are necessary to optimize their efficacy and ensure successful translation into safe and effective antiepileptic therapies.

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