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Pyrazoline as a Promising Scaffold for Antiepileptic Drug Development: A Comprehensive Review

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Abstract: Epilepsy is a prevalent neurological condition affecting millions of people worldwide, with significant social and economic burdens. Despite the availability of various antiepileptic drugs (AEDs), many patients continue to experience uncontrolled seizures or adverse effects, highlighting the need for novel therapeutic agents. Heterocyclic compounds, especially five-membered rings like pyrazoline, have gained attention in drug discovery due to their diverse pharmacological activities. Pyrazoline, characterized by a dihydropyrazole ring, exhibits promising physiological properties relevant to the CNS. This review explores epilepsy's pathophysiology and common mechanisms of existing AEDs, including modulation of ion channels and neurotransmitter balance. Pyrazoline derivatives demonstrate broad-spectrum activity and significant antiepileptic potential by targeting GABAergic and glutamatergic systems. Several studies report effective pyrazoline-based compounds with improved safety and efficacy profiles. This review includes proposed mechanisms, reaction schemes for synthesis, and a summary of reported pyrazoline derivatives as potential antiepileptic agents, reinforcing their role in future drug development.

Keywords: *Pyrazoline, Heterocyclic Compound, Epilepsy, AED.*

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I. INTRODUCTION

A. Overview of Epilepsy and Global Impact

The World Health Organization (WHO) has a longstanding commitment to supporting individuals with epilepsy. Because of its distinguishing features, epilepsy is commonly acknowledged as a public health concern. People of various racial backgrounds, socioeconomic classes, and geographic locations are impacted. Although it can manifest at any age and impacts both males and females, the disorder is most frequently identified in early childhood, puberty, and old life. When a person has at least two unprovoked seizures that are not brought on by sudden metabolic changes or alcohol or drug departure, epilepsy is diagnosed [1].

Epilepsy's prevalence and frequency are somewhat greater in males than in females, with a peak occurrence in the elderly, indicative of the increased incidence of stroke, neurological disorders, and malignancies within this demographic. In both children and adults, focal seizures are more prevalent than generalized seizures. Although the etiology of epilepsy differs depending on the sociodemographic of the affected populations and the scope of the diagnostic workup, around 50% of cases from high-income countries (HIC) still lack a known cause. According to seizure freedom, most patients with epilepsy have a good overall prognosis. Prevalence and remission rates from low- and middle-income countries (LMICs), where most epilepsy patients go untreated, are similar to those from HICs. Since epilepsy seems to be more common in most LMICs, misdiagnosis, acute symptomatic seizures, and early

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mortality can account for the overlapping prevalence. Research has consistently demonstrated that a sustained seizure remission occurs in almost half of instances [2].

There are currently 210 nations, and ES has expanded its reach into both the developed and developing worlds. The demand aimed at then construction of ES services, diagnoses, actions, result assessment, quality-of-life matters, employment, and wellbeing financial valuation are just a few of the economic topics that are being discussed more and more amongst doctors. Based on Medline reports since 1991 to November 1999 [3-7] and abstracts of epilepsia supplements from the 19th –23rd ILAE International Epilepsy Congresses (IECs) 1991–1999, we updated the worldwide ES. Because it might be expensive for people from underdeveloped nations to attend an IEC or publish in an international publication, the existence of ES in any given nation can only be estimated. DCRES or nations that report having started or maintained ES-not on individual Epilepsy Surgical Centers since 1990 was the focus of our search. ES was revealed in the selected reports under a variety of restrictions and at different levels. Reports of vagal nerve stimulator implantation were regarded as ES activity if there were more than a few occurrences. Case reports and surgical procedures that were not documented or referred to as lesionectomies for epilepsy (such as tumors and angiomas) were not included.

We believe our coverage of ES is quite well-founded, despite the fact that Medline does not feature all medical journals. We discovered nine DCRES between 1991 and 1999 using Medline, and abstracts of the 1991–999 IECs showed that there were at least 26 (18.3%) DCRES in 142 developing nations.

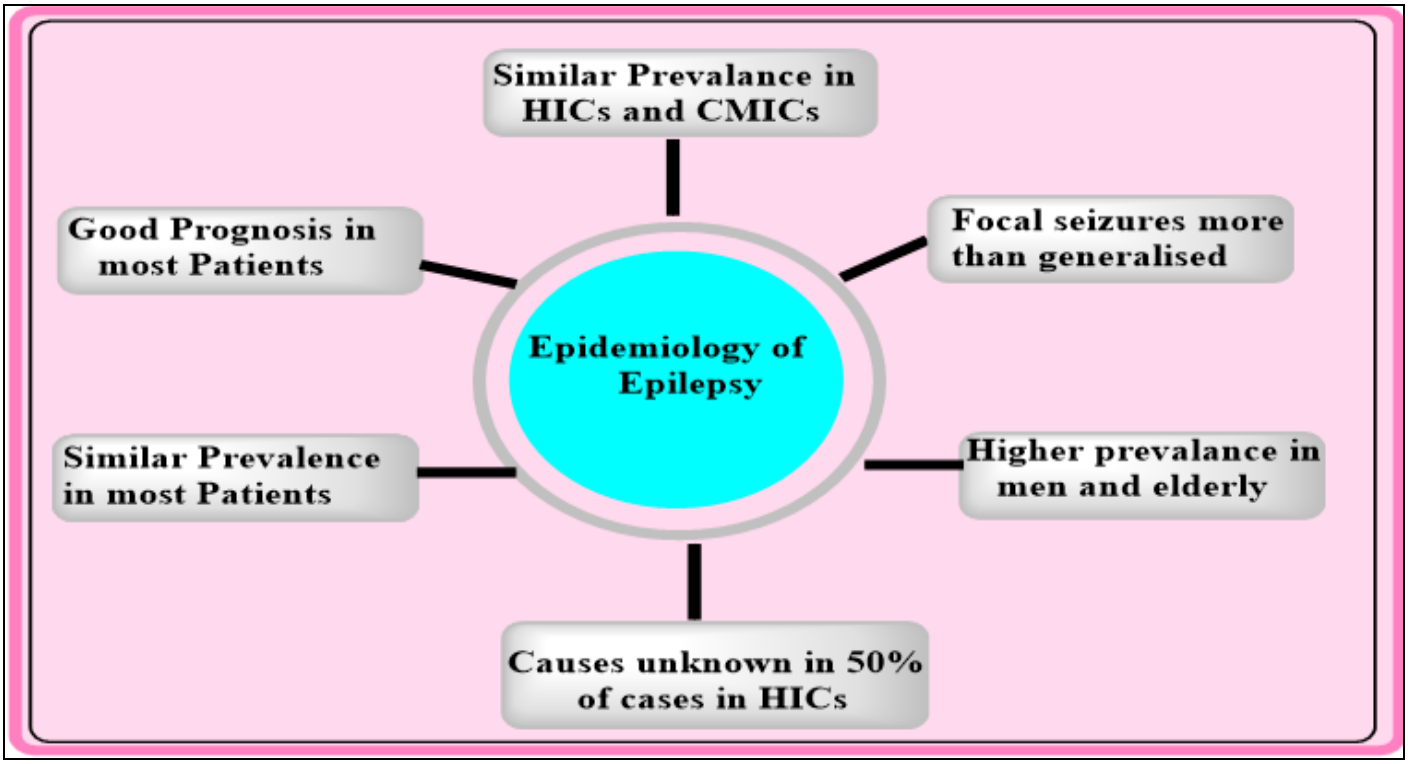

Fig 1 Epidemiology of Epilepsy

The WHO publishes reports on world health concerns [8]. Some of the data from the third monitoring report, which came to the conclusion that the "world population growth rate started to decline slowly in 1990," is presented here. The most pervasive risk is still the absence of access to a sufficient supply of clean drinking water and sanitary facilities. Although the gap is narrowing, there are still significant differences in maternal, newborn, and under-five mortality. Nearly 80% of the 50 million deaths that take place each year take place in underdeveloped nations. Infectious diseases are connected to half of them. Over 2 million people die each year from diseases that can be prevented by vaccination. Every year, 3 million people die from tuberculosis. Malaria, which kills over a million people annually, affects half of the world's population. Some of the data from the third monitoring report, which came to the conclusion that the "world population growth rate started to decline slowly in 1990," is presented here. The most pervasive risk is still the absence of access to a sufficient supply of clean drinking water and sanitary facilities. Although the gap is narrowing, there are still significant differences in maternal, newborn, and under-five mortality. Nearly 80% of the 50 million deaths that take place each year take place in underdeveloped nations. Infectious diseases are connected to half of them. Over 2 million people die each year from diseases that can be prevented by vaccination. Every year, 3 million people die from tuberculosis. Malaria, which kills over a million people annually, affects half of the world's population.

B. Need for Novel Antiepileptic Agents

The basic biological mechanisms through which AEDs function include attenuation of excitatory (particularly glutamate-mediated) transmission, enhancement of GABA-mediated inhibitory neurotransmission, and modification of voltage-dependent ion channels (Na+, Ca2+, and K+) [9].

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In recent years, molecular targets for AEDs have been identified. [9]

In recent years, molecular targets for AEDs have been identified. These consist of the α2δ type 1 and 2 subunits of voltage-gated calcium channels (PGB), SV2A synaptic vesicle protein (LEV, brivaracetam), A- or M-type voltage-gated potassium channels (retigabine), glutamatergic AMPA receptors (talampanel and perampanel), metabotropic glutamate receptors, hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, connections (gap junctions), and vesicular transporters for glutamate and GABA.

Other molecular targets for AEDs have been discovered in recent years. These consist of the α2δ type 1 and 2 subunits of voltage-gated calcium channels (PGB), SV2A synaptic vesicle protein (LEV, brivaracetam), A- or M-type voltage-gated potassium channels (retigabine), glutamatergic AMPA receptors (talampanel and perampanel), metabotropic glutamate receptors, hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, connections (gap junctions), and plasma membrane and vesicular transporters for glutamate and GABA. more, such as oxidative stress processes, cation chloride co-transporters, inflammatory pathways, peroxisome proliferator activated receptors, and the mammalian target of rapamycin (mTOR) [10].

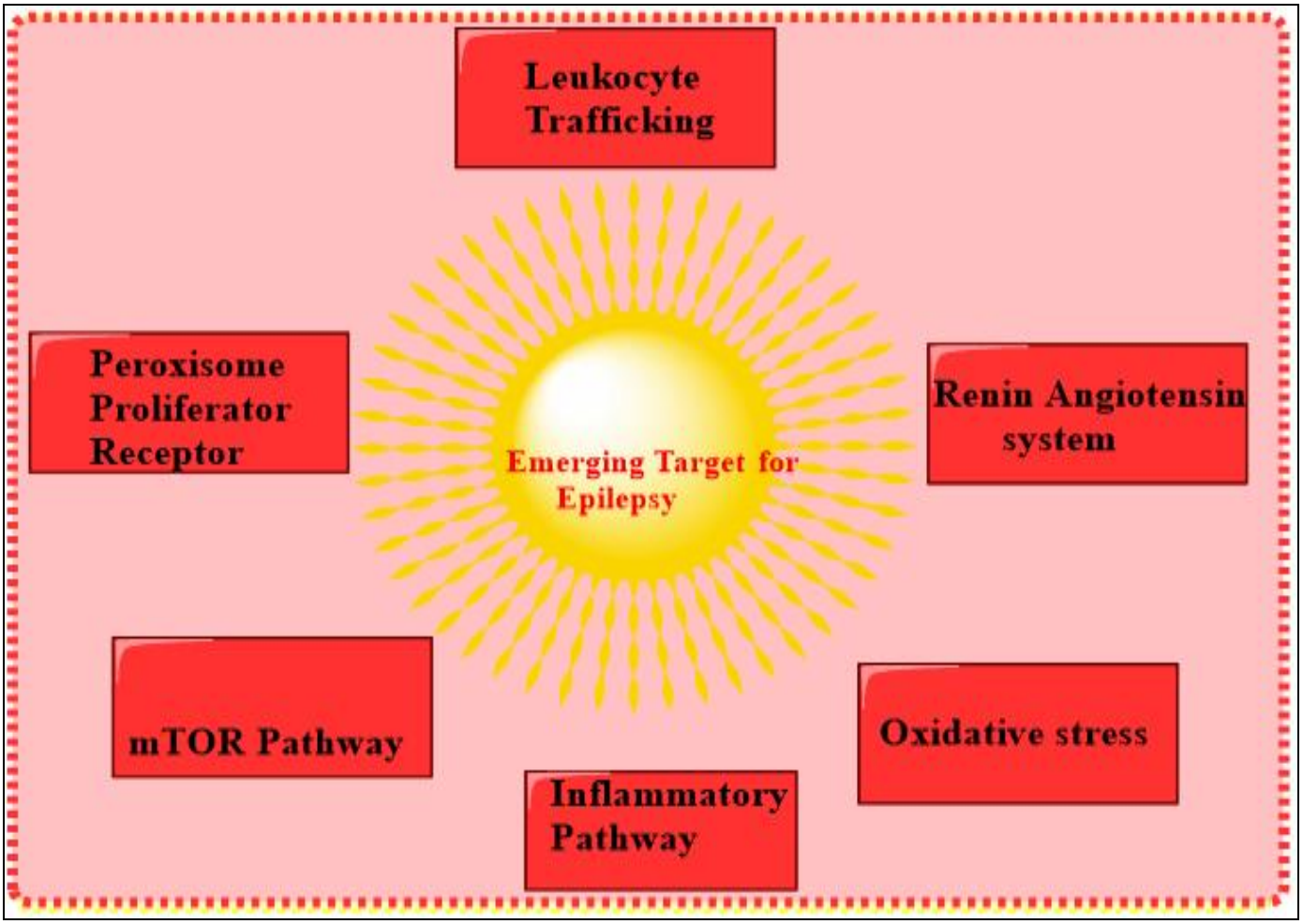

Fig 2 Emerging Target for Epilepsy

C. Role of Heterocyclic Compounds in Drug Development

In our day-to-day lives, heterocyclic compounds are highly interesting. One or more heteroatoms can be found in the structure of heterocyclic compounds. They could be either cyclic or non-cyclic. There are several uses for heterocyclic compounds. Their main applications are as veterinary goods, agrochemicals, and medicines. Additionally, they are used as copolymers, sanitizers, developers, antioxidants, corrosion inhibitors, and dyes. Other organic compounds are synthesized using them as vehicles [11].

For medicinal chemists, new developments in synthetic techniques that enable quick access to a large range of functionalized heterocyclic compounds are crucial because they increase the amount of drug-like chemical space that is available and promote more effective drug discovery program delivery. Additionally, the creation of reliable synthetic pathways that can easily produce large amounts of a target chemical aid in quickening the drug development process. The pharmaceutical business is being significantly impacted by the development of novel heterocyclic syntheses that permit various bond formation techniques, even if conventional synthetic methodologies are frequently employed throughout a drug discovery cycle [12].

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D. Pyrazoline: Structure and Physiological Significance

Fig 3 Structure of Pyrazoline

Pyrazoline is a heterocyclic molecule with five members that contains two nitrogen atoms next to each other. It is basic in nature and contains only one endocyclic double bond. 2-pyrazolines appear to be the most researched pyrazoline type chemicals among its several derivatives [2]. One type of cyclic hydrazine moiety is pyrazoline. The structure of the five-membered dihydropyrazole ring exhibits an envelope conformation, according to the X-ray analysis. The C5 atom deviates from the heterocyclic ring's almost planar arrangement of the other four atoms. It is widely utilized as helpful synthons in organic synthesis and is essential to the advancement of heterocyclic chemistry theory [13-15].

E. Physicochemical Properties

Due to its lipophilic nature, pyrazoline is soluble in propylene glycol but insoluble in water. It is well known that compounds containing a 2-pyrazoline group that lack a substituent at the heterocyclic ring's 1-position can react with benzaldehyde to produce 4-benzylidine derivatives at high temperatures (200 °C) and in an inert atmosphere. Because of their high blue fluorescence in solution, pyrazoline derivatives—typical ICT (Intramolecular Charge Transfer) compounds—are referred to as a type of fluorescent brightening agent.

They have a tendency to transport. It has been reported to have an intramolecular conjugated charge transfer process in the excited state. The nitrogen atom at position one and the carbon atom at position three are electron-donating and withdrawing moieties, respectively, in the conjugated section (–N1–N2–C3–) of the ring. The above-conjugated portion does not conjugate with the carbon atoms at positions 4 and 5. Its fluorescence spectrum shows a significant redshift as solvent polarity increases. Due to double bond hindrance brought on by cyclization, these compounds exhibit greater fluorescence.

Bulky groups in the 4- and 5-positions enhanced the molecule's stability to light and fluorescence efficiency. It is important for pyrazoline whitening agent design. The spiroconjugated charge transfer quenching of pyrazoline fluorescence is likewise caused by the aryl group at position 5 [16-19].

F. Spectrum of Activity

Pyrazolines exhibit a wide range of possible pharmacological actions and are found in several pharmacologically active compounds, including azolid/tandearil anti-inflammatory), indoxacarb (insecticidal), anturane (uricosuric), phenazone/amidopyrene/methampyrone (analgesic and antipyretic), etc. The pyrazoline structure has drawn a lot of attention. The discovery of this class of medications highlights the unpredictable nature of pharmacological action resulting from structural alteration of a prototype drug molecule and offers an excellent case study of contemporary drug development. It has a wide range of therapeutic uses [20-23]. Potential antipyretic, analgesic, muscle relaxant, psychoanaleptic, antiepileptic, antidepressant, anti-inflammatory, insecticidal, antibacterial, and antihypertensive properties have been discovered for pyrazoline derivatives. Additionally, it was shown that their derivatives had herbicidal, cytotoxic, and cannabinoid CB1-receptor modulating properties as well as the ability to prevent platelet aggregation. They also have strong biological activity that selectively targets certain receptors, such as inhibitors of nitric oxide synthase (NOS). Interest in pyrazoline was also shown in dyes and dye couplers [24, 25].

G. Synthetic Strategies for Pyrazoline Derivatives

➢ *Biological and Therapeutic Importance of Pyrazoline*

- *Cannabinoid CB1 Receptor Antagonists:*

In addition to their extremely beneficial therapeutic properties, cannabinoid receptor type 1 (CB1) antagonists are one of the most appealing topics of extensive study on pyrazoline derivatives. CB1 receptor antagonists have promising futures in a variety of therapeutic domains, including alcohol and tobacco addiction and cognitive impairment. A number of pharmaceutical corporations and

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academic research organizations have recently revealed novel chemical entities (NCEs) with CB1 antagonistic characteristics that are structurally linked to rimonabant 1.

Many CB1 antagonists are bioisosteres that are generated from rimonabant (1) by substituting various heterocyclic analogs, such as pyrazoline, for the pyrazole component.

A one-pot cinchonidine salt of (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxylic acid (2) was recently described by Marti et al. and is helpful as an intermediary in the synthesis of cannabinoid CB1 neutral antagonists.

The process is effective at preventing intermediate isolation and yields a high-quality product with enantiomeric excess [26]. Additionally, Yoo *et al.* synthesized 3, 4-diphenyl-4, 5-dihydro-pyrazole-1-carboxylic acid hydrazide 3, which is employed as a CB1 modulator [27].

Pyrazoline 4 hydrochloride demonstrated 97% affinity at 3 μM in the CB1 receptor binding assay. Thus far, pyrazoline derivatives of general structure 5 have been proposed as effective treatments for schizophrenia and obesity.

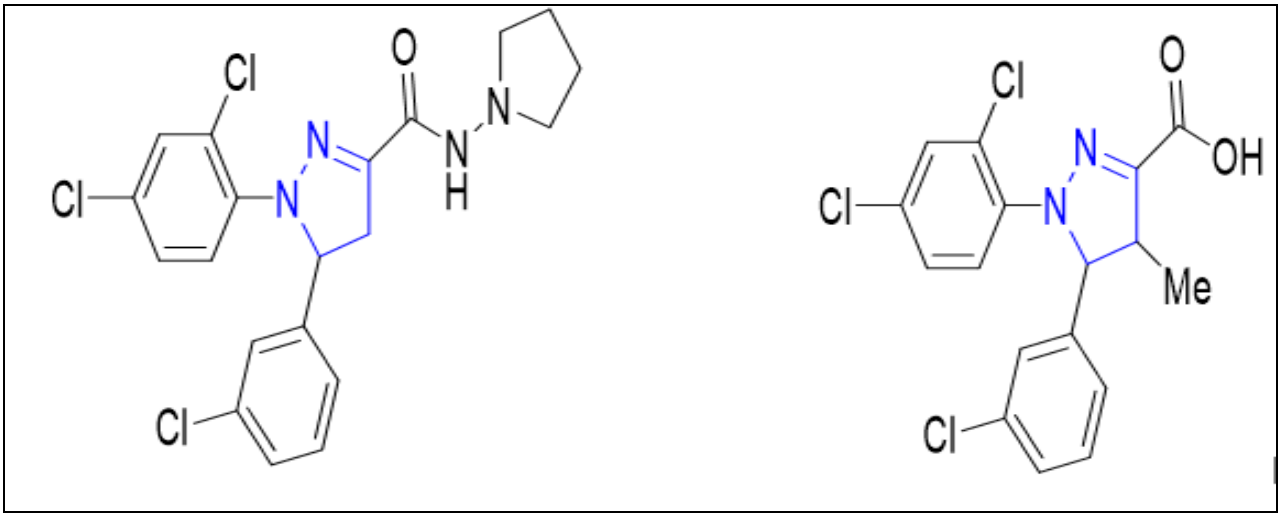

Fig 4 & 5 5-(3-Chlorophenyl)-1-(2, 4-Dichlorophenyl)-N-(Pyrrolidin-1-Yl)-4, 5-Dihydro-1H-Pyrazole-3-Carboxamide & 5-(3-Chlorophenyl)-1-(2, 4-Dichlorophenyl)-4-Methyl-4, 5-Dihydro-1H-Pyrazole-3-Carboxylic Acid

H. Antidepressent Activity

Using SwissWebster mice and the "Porsolt Behavioural Despair Test," Palaska et al. synthesized ten novel 3, 5-Diphenyl-2-pyrazoline derivatives and assessed their antidepressant properties. 3-(4-Methoxyphenyl)-5-(3, 4-dimethoxyphenyl)-2-pyrazoline [9], 3-(4-methoxyphenyl)-5-(2-chloro-3, 4-dimethoxyphenyl)-2-pyrazoline [10] and 3-(4-chlorophenyl)-5-(2-chloro-3, 4-dimethoxyphenyl)-2-pyrazoline [11] decreased 41.94-48.62% immobility times at 100 mg.kg-1 dose level. Furthermore, it was shown that the antidepressant activity was enhanced by 4-methoxy and 4-chloro substituents on the phenyl ring at position 3 of the pyrazoline ring; activity was diminished when same groups were substituted with bromo and methyl substituents.

Fig 6, 7 & 8: 5-(3,4-dimethoxyphenyl)-3-(3-methoxyphenyl)-4,5-dihydro-1H-pyrazole, 5-(6-chloro-4,5-dimethoxycyclohexa-1,3-dien-1-yl)-3-(3-methoxyphenyl)-4,5-dihydro-1H-pyrazole & 5-(2-chloro-3,4-dimethoxyphenyl)-3-(3-chlorophenyl)-4,5-dihydro-1H-pyrazole

Prasad *et al.* synthesized five new 1, 3, 5-Triphenyl-2-pyrazolines and another five new 3-(2" Hydroxynaphthalen1"-yl)-1, 5-diphenyl-2-pyrazolines and evaluated their antidepressant activity by the Porsolt behavioural despair test on Swiss-Webster mice. 1-Phenyl-3-(2"-hydroxyphenyl)-5- (4'-dimethylaminophenyl)-2-pyrazoline [12], 5-(4'- Dimethylaminophenyl)-1,3-diphenyl-2-pyrazoline, 1-Phenyl3-(2"-hydroxynaphthalen-1"-yl)-5-(3',4',5'- trimethoxyphenyl)-2-pyrazoline, 1-Phenyl-3-(4"-methylphenyl)-5-(4'-dimethylaminophenyl)-2-pyrazoline [13] and 1-Phenyl-3-(4"-bromophenyl)-5-(4'-dimethyl amino phenyl)-2-pyrazoline reduced immobility times 25.63-59.25% at 100 mg.kg-1 dose level. Furthermore, it was shown that the antidepressant activity was enhanced by 4-methoxy and 4-chloro substituents on the phenyl ring at position 3 of the pyrazoline ring; activity was diminished when same groups were substituted with bromo and methyl substituents.

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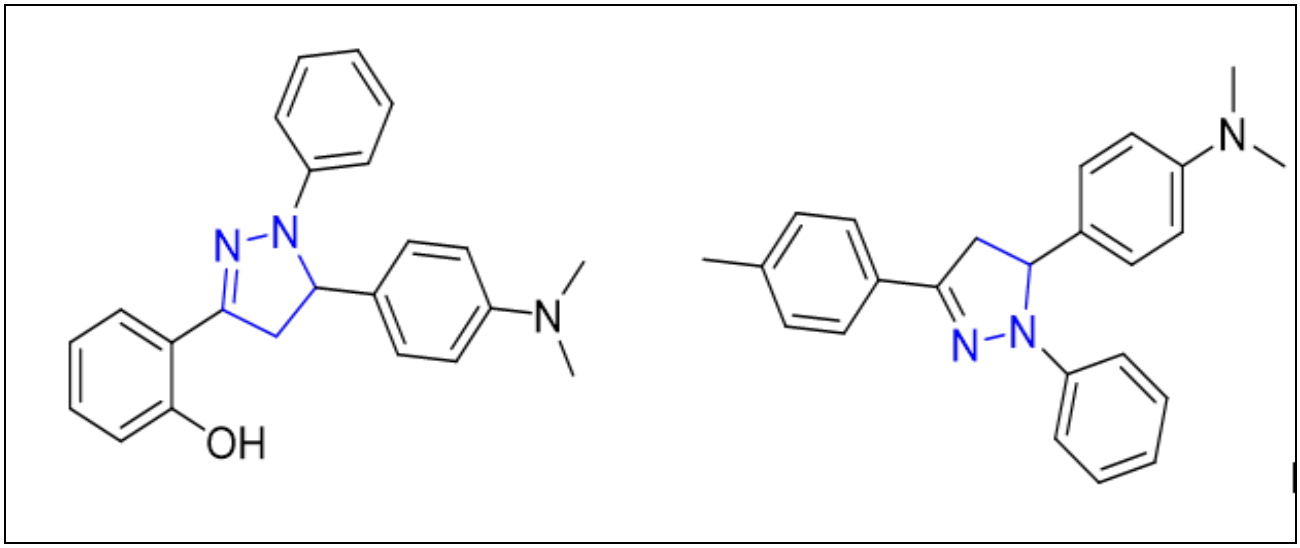

Fig 9 & 10 2-(5-(4-(Dimethylamino) Phenyl)-1-Phenyl-4, 5-Dihydro-1H-Pyrazol-3-Yl) Phenol & N, N-Dimethyl-4-(1-Phenyl-3-(P-Tolyl)-4, 5-Dihydro-1H-Pyrazol-5-Yl) Aniline

I. Antimicrobial Activity

A series of bispyrazolines were created by Yusuf et al. (2017) by refluxing bischalcone with phenylhydrazine in a dry, acidic ethanol medium. According to the Claisen-Schmidt condensation process, 2-furfuraldehyde and p-hydroxy acetophenone react to produce chalcone.

The structures of the bischalcones and bispyrazolines were confirmed by means of 1H NMR, 13C NMR, IR, and mass spectroscopy. In contrast to the standard drugs amoxicillin and fluconazole, newly synthesized compounds were evaluated for their antimicrobial potency against five fungus strains (A. sclerotium, Penicillium glabrum, A. niger, A. janus, and Fusarium oxysporum) and seven bacterial strains (E. coli, K. pneumonia, P. fluorescens, S. aureus, P. aeruginosa, B. subtilis, and S. pyrogen) using the serial tube dilution method [28].

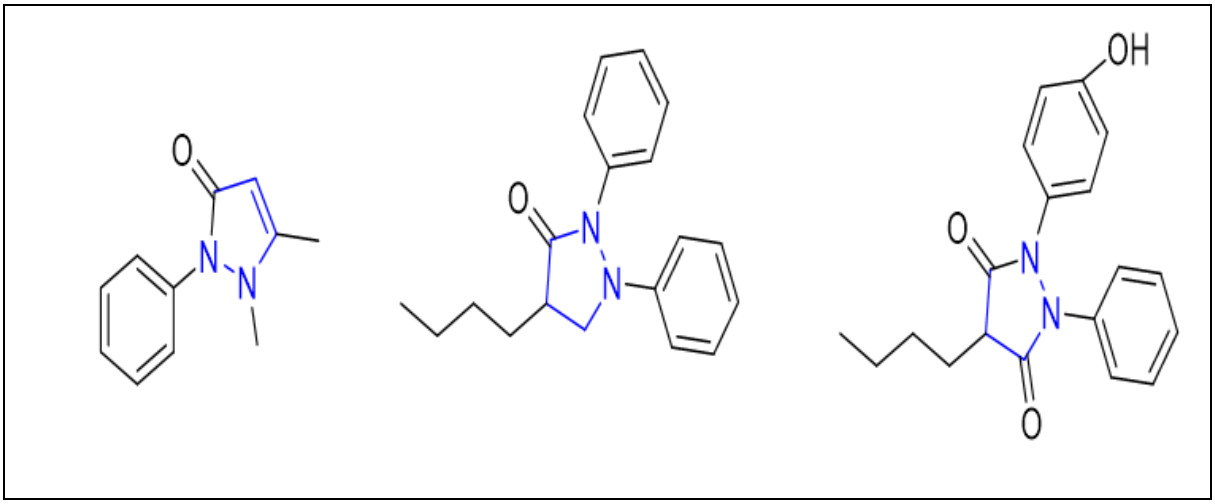

Fig 11, 12 & 13 1, 5-dimethyl-2-phenyl-1, 2-dihydro-3H-pyrazol-3-one, 4-butyl-1, 2-diphenylpyrazolidin-3-one & 4-butyl-1-(4-hydroxyphenyl)-2-phenylpyrazolidine-3, 5-Dione

Asad *et al.* (2020) synthesized a series of N-propionyl 2-pyrazolines from the chalcones by reacting propionic acid with hydrazine hydrate. All new compounds were evaluated for antibacterial activity against gram-positive bacterial strain (B. Subtilis, S. Aureus) and gram-negative bacterial strain (E. Coli, P. Peli). All new compounds showed significant activity against bacteria [29].

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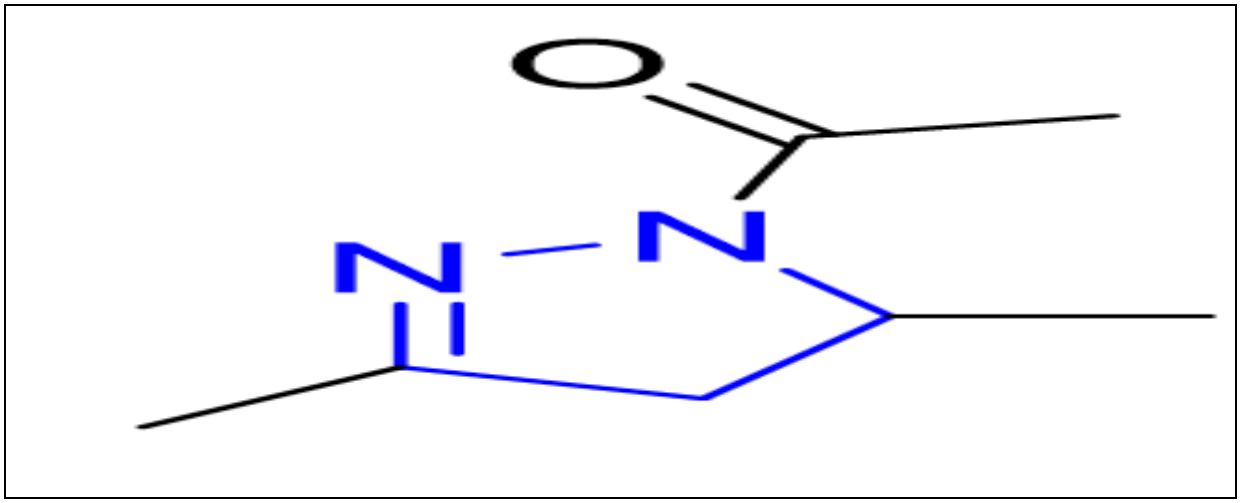

Fig 14: 1-(3, 5-Dimethyl-4, 5-Dihydro-1H-Pyrazol-1-Yl) Ethan-1-One

J. Anticancer Activity

In 2018, a number of thiazole-pyrazoline hybrids were reported by Edrees et al. [34]. The process of creating these derivatives involves reacting N-thiocarbamoylpyrazoline, the starting material, with various haloketone derivatives to produce the final compounds 9, 10, and 11. In addition, compounds 9, 10, and 11 exhibit moderate inhibitory activity against the human hepatocellular carcinoma cell line (HepG2), with IC50 values of 3.54 μM, 2.98 μM, and 1.70 μM, respectively. The most active pyrazoline derivative was discovered to be number eleven; a SAR analysis shows that activity is increased by substitution on the C-4 position of the phenyl ring [30].

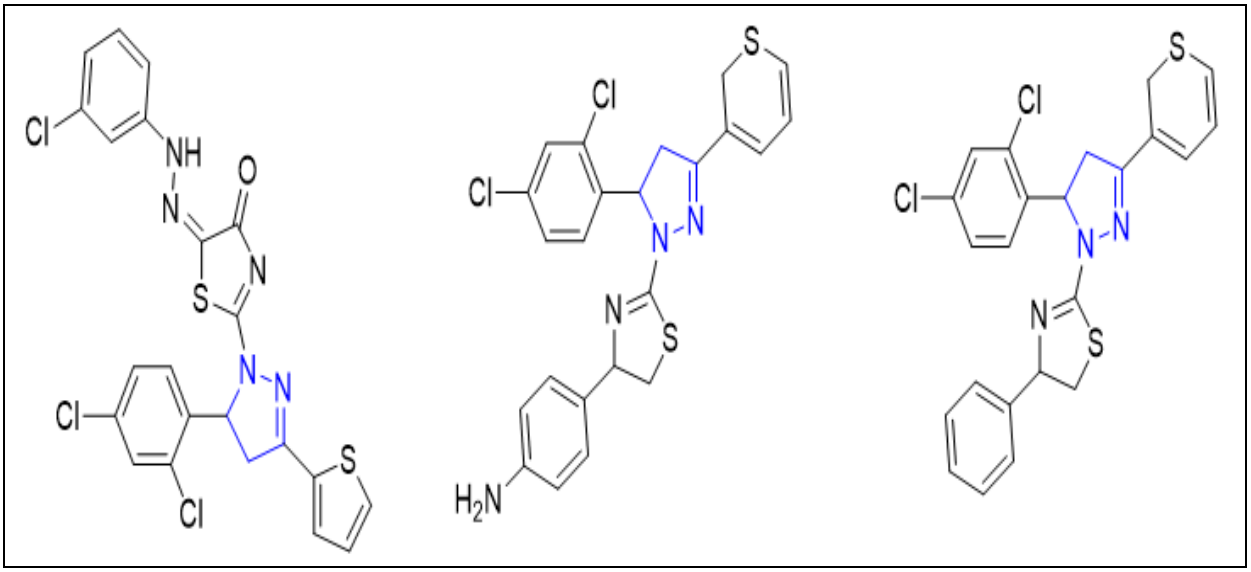

Fig 15, 16 & 17: (E)-5-(2-(3-Chlorophenyl)Hydrazono)-2-(5-(2,4-Dichlorophenyl)-3-(Thiophen-2-Yl)-4,5-Dihydro-1H-Pyrazol-1-Yl)Thiazol-4(5H)-One, 4-(2-(5-(2,4-Dichlorophenyl)-3-(2H-Thiopyran-3-Yl)-4,5-Dihydro-1H-Pyrazol-1-Yl)-4,5-Dihydrothiazol-4-Yl)Aniline & 2-(5-(2,4-Dichlorophenyl)-3-(2H-Thiopyran-3-Yl)-4,5-Dihydro-1H-Pyrazol-1-Yl)-4-Phenyl-4,5-Dihydrothiazole

K. Anti-inflammatory Activity

In the vivo acute carrageenan-induced paw edema standard technique in rats, the bis (3-aryl-4, 5-dihydro-1H-pyrazole-1-carboxamide) derivatives 70–71 were synthesized and evaluated for their anti-inflammatory qualities [85]. At a dose level of 50 mg/kg [85], this group of pyrazoline also showed a respectable inhibitory effect against the fever-causing prostaglandin E2 (PGE2) [86–88]. Significant anti-inflammatory effects were demonstrated by the bis-pyrazoline derivative 70 [85]. With decreased ulcer index values, compounds 70 and 71 demonstrated exceptional anti-inflammatory properties in comparison to indomethacin, a common reference [31].

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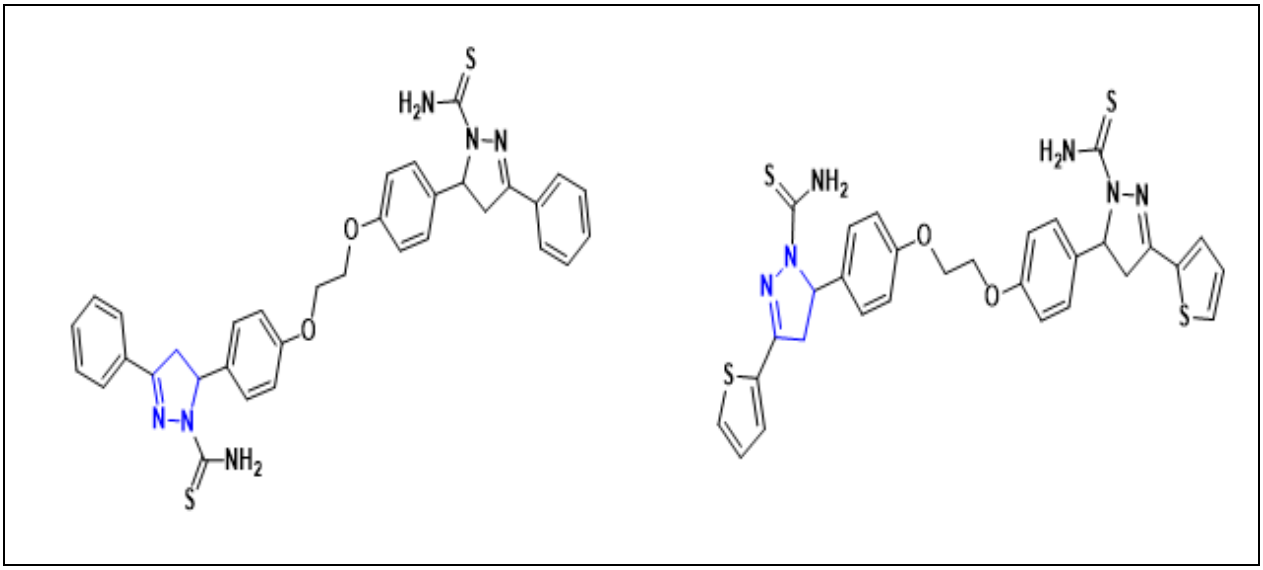

Fig 18 & 19: 5,5'-((Ethane-1,2-Diylbis(Oxy))Bis(4,1-Phenylene))Bis(3-Phenyl-4,5-Dihydro-1H-Pyrazole-1-Carbothioamide) & 5,5'-((Ethane-1,2-Diylbis(Oxy))Bis(4,1-Phenylene))Bis(3-(Thiophen-2-Yl)-4,5-Dihydro-1H-Pyrazole-1-Carbothioamide)

L. Antioxidant Activity

A number of pyrazoline derivatives were synthesized by Babu et al. [32], and their antioxidant potential was assessed in comparison to the common medication ascorbic acid. Comparing compound 60, 61 the former demonstrated superior antioxidant activity. Activity of Polarity Probes: Svechkarev et al., [33] synthesized two new 1, 3, 5-Triphenyl-2-pyrazoline moiety-containing derivatives of 3-hydroxychromone [61] and talked about the potential for using these compounds, which have high solvatofluorochromism, as efficient ratiometric polarity probes in analytical chemistry and biophysics based on information about their fluorescent properties [34].

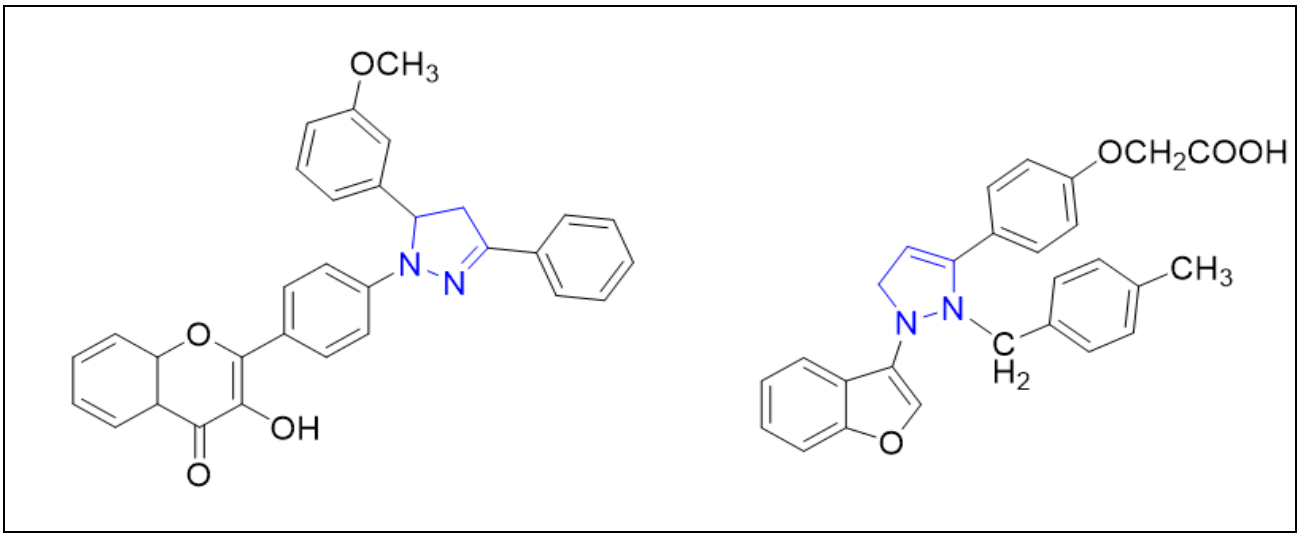

Fig 20 & 21: 3-Hydroxy-2-(4-(5-(3-Methoxyphenyl)-3-Phenyl-4,5-Dihydro-1H-Pyrazol-1-Yl)Phenyl)-4a,8a-Dihydro-4H-Chromen-4-One & 2-(4-(1-(Benzofuran-3-Yl)-2-(4-Methylbenzyl)-2,5-Dihydro-1H-Pyrazol-3-Yl)Phenoxy)Acetic Acid

M. Antiepileptic Activity

New 2-pyrazoline derivatives (8a) were synthesized by Maruthi Rao B et al. [35], who also assessed their antiepileptic properties. Comparing the compounds to standards, they demonstrated good antiepileptic action. The maximal electroshock seizure (MES) method was used to screen for anticonvulsant activity in the 3, 5-diphenyl2-pyrazoline-1-carboxamide derivatives (8b) that Ravinesh Mishra et al. [36] produced. Male albino mice were used in a rotorod toxicity test to assess neurotoxicity. At dose levels of 100–300 mg/kg, it was demonstrated that every tested chemical was protective against MES.

Stiripentol (STP) derived compounds (8c) were created by M.N. Aboul-Enein et al. 85 as potential anticonvulsant drugs. The PTZ and MES methods were used to screen the compounds. A number of 2-pyrazoline derivatives (8d) were synthesized by N. Beyhan et al. [37], who then tested them for anticonvulsant properties. Among the substances that were evaluated, 2-pyrazoline-1-carboxamide derivatives with 5-bromothiophen, 5-chlorothiophen, and 2, 6-dichlorophenyl groups were shown to have significant PTZ test activity.

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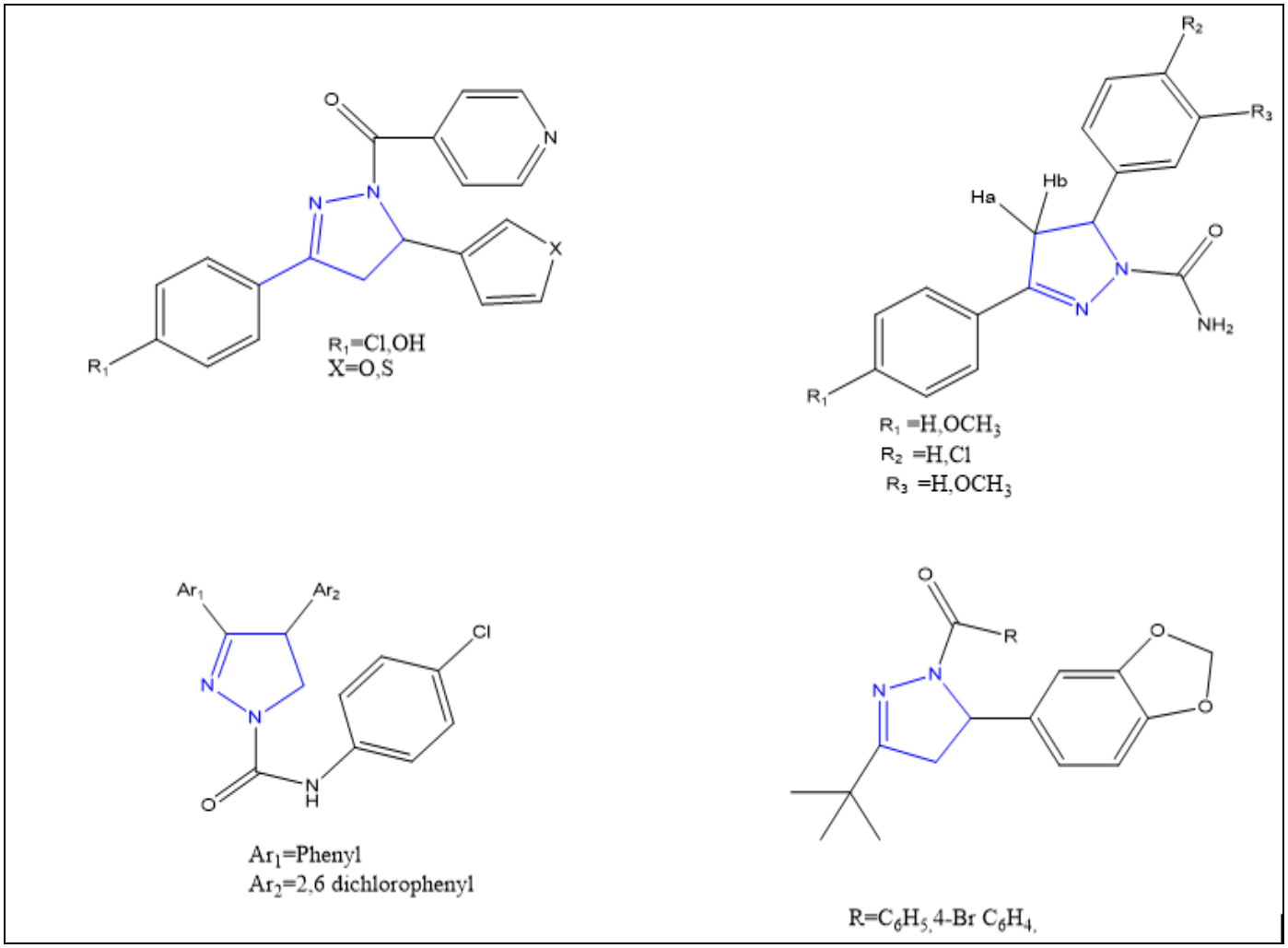

Fig 22, 23, 24 & 25: New 2-Pyrazoline Derivatives, 3, 5-Diphenyl2-Pyrazoline-1-Carboxamide Derivatives, Stiripentol (STP) Derived Compounds & 2-Pyrazoline Derivatives

II. MECHANISM OF ACTION OF ANTIEPILEPTIC DRUGS

AEDs' methods of action can be divided into two categories: post-synaptic suppression of neuronal impulse production or effects on the neuronal action potential. The activation of voltage-gated channels implicated in the electrical propagation of the seizure is usually the focus of inhibition of the neural action potential. Neuronal depolarization and the action potential depend on sodium channels. Usually, when an action potential is fulfilled, a neurotransmitter is released, which either causes a terminal effect on the brain or other neurons leading to extracranial organs, or it further spreads the signal at a neuronal synapse [38].

Numerous novel antiepileptic medications (AEDs) have been developed recently, opening up a variety of epilepsy treatment options. When choosing medications for specific epilepsy patients, knowledge of the mechanisms of action of AEDs is helpful. AEDs can be divided into those that act on the extrasynaptic neuronal membrane, at the excitatory or inhibitory synapse, or by a variety of different methods [39].

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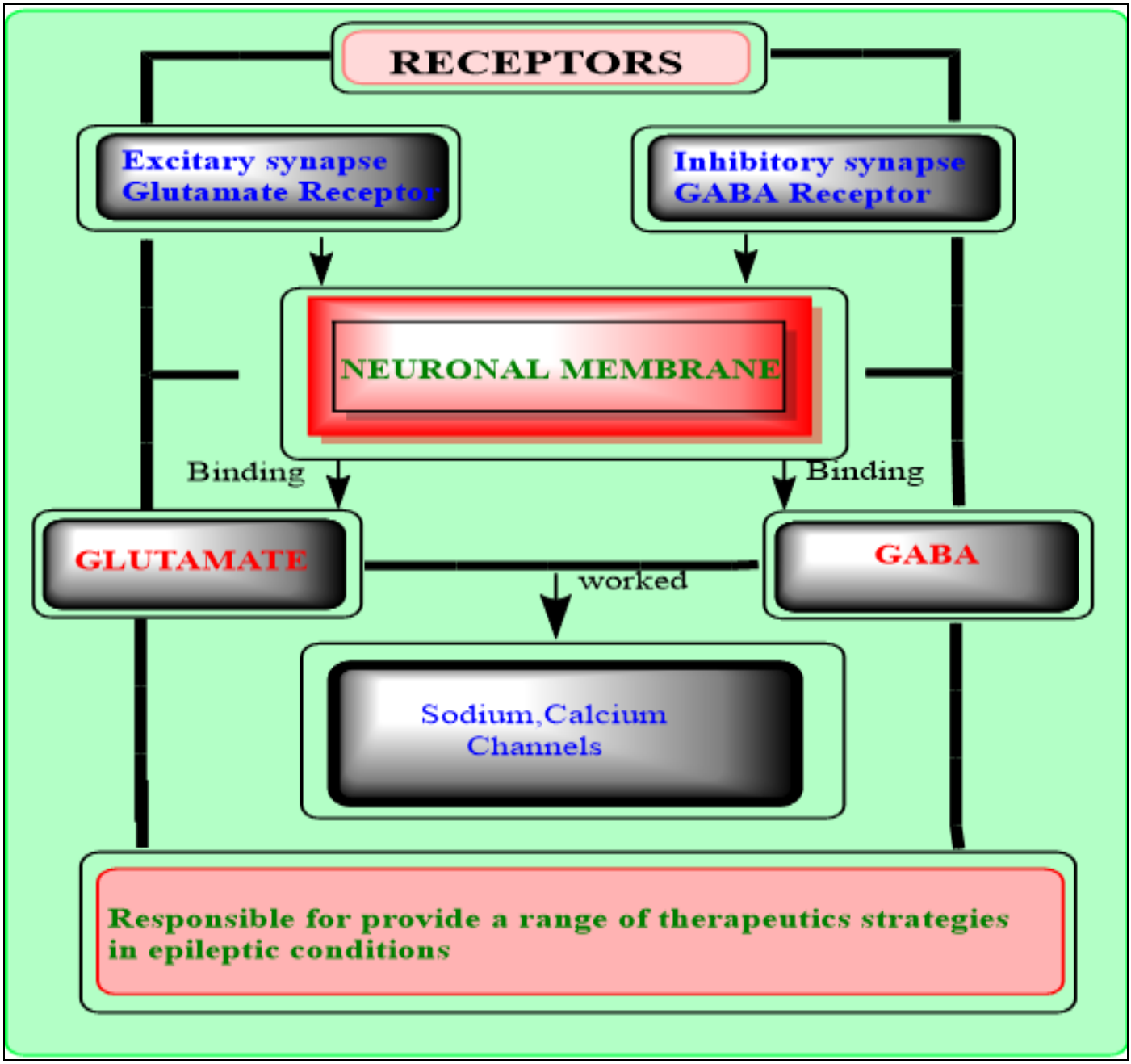

Fig 26 Mechanism of Action of Antiepileptic Drug

III. PATHOPHYSIOLOGY OF EPILEPSY

An overly prolonged and coordinated firing of a cluster of neurons causes epileptic seizures. An ongoing rise in neuronal excitability is the one characteristic shared by all epileptic disorders. Numerous causal events, including trauma, oxygen deprivation, malignancies, infections, and metabolic disturbances, can be linked to abnormal cellular discharges. However, in roughly half of epileptic individuals, no particular causal factors are identified. For certain types of epilepsy, such as monogenic epilepsies and epilepsies brought on by abnormalities in neuronal migration, the underlying causes and pathophysiological mechanisms are (partially) understood. The current understanding of a number of additional forms of epilepsy is still incomplete [40].

IV. DISORDERS OF NEURONAL MIGRATION

The process of evolution is the source of the human brain's intricate structure. The growth of the entire complement of neurons in the brain and their migration to certain locations across the central nervous system (CNS) is the processes that take place throughout brain development.

Additionally, a series of organized biological processes leads to the formation of the complex neuronal circuitry of the human brain, along with the development of the myelin sheath that insulates these circuits. These processes begin after the first month of pregnancy and continue into adulthood. Disruptions in brain development can result from various prenatal and perinatal injuries that occur during critical stages of growth. Moreover, genetic abnormalities can emerge during brain development, giving rise to numerous (genetic) disorders. The most profound effects on

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central nervous system function are seen in conditions that affect neuronal proliferation. These include chromosomal abnormalities, focal cortical dysplasia and related disorders, growth-related disturbances, microcephaly, macrocephaly, unilateral macrocephaly, and neurocutaneous syndromes [41].

V. GENETICS OF HUMAN EPILEPSY

Genetic linkage studies have pinpointed regions in the genome that may harbor genes contributing to epilepsy susceptibility. Advancements in genomic technologies now enable the detection of both common genetic variations and structural changes like copy number variants (CNVs) through comprehensive genome-wide analyses. Furthermore, specific point mutations can be discovered using methods such as exome or whole-genome sequencing. Research into the genetics of epilepsy encompasses both rare Mendelian forms and more common types that likely follow an oligo- or polygenic inheritance pattern, involving a combination of rare variants, common polymorphisms, and CNVs. These genetic alterations may affect long-term brain development, potentially disrupting brain structure and function, increasing the risk of seizures, and contributing to specific types of temporal lobe epilepsy and associated co-morbid conditions. Despite these advances, the precise role of many mutations in the development of epilepsy remains uncertain [42].

VI. PATHOPHYSIOLOGY OF DISTINCT TYPES OF EPILEPSY

A. Mesial Temporal Lobe Epilepsy

Temporal lobe epilepsy (TLE) is often linked to hippocampal sclerosis, which may result from an initial brain injury occurring long before the onset of neurological symptoms. This form of epilepsy is typically resistant to pharmacological treatment and often necessitates surgical removal of the mesial temporal regions where seizures originate. However, even surgery does not always provide lasting relief. While preventing hippocampal damage and epileptogenesis following the initial injury could offer a promising strategy for TLE management, the absence of definitive insights into the underlying pathophysiological mechanisms limits the development of targeted therapies. Current research explores the mechanisms potentially involved in epileptogenesis and investigates novel treatment strategies aimed at prevention. Along with the loss of principal neurons and specific interneurons, structural changes in neural networks—such as axonal sprouting and increased neurogenesis—play a significant role. These changes are further influenced by alterations in receptor and ion channel function, as well as modifications in other cellular components [43].

B. Gelastic Epilepsy

Less than 1% of epilepsies are gelastic seizures [44], which are primarily linked to hypothalamic hamartomas in children. These seizures typically start in infancy, even in the neonatal stage, and progress over time, sometimes involving additional focal or generalized seizures. In most situations, the surface EEG is normal. A significant improvement is achieved when the hamartoma is treated surgically or radiosurgically [45]. These kids may also have cognitive impairment and premature puberty [46]. Gelastic seizures can result from a variety of lesions, including tumors, malformations of cortical development, tuberous sclerosis, and postinfectious foci, but invasive EEG recordings and electrical stimulation have demonstrated that they originated from the hypothalamic hamartomas [47]. As far as we are aware, this is the first instance of GS-related neurocysticercosis. Although the physiological underpinnings of joy and laughter are not entirely understood, laughter is described as unmotivated or emotion-free in patients who have gelastic seizures without a consciousness impairment. This could be interpreted as a dissociation between the motor and emotional components of laughter.

C. Rasmussen Encephalitis

- *Rasmussen Encephalitis (RE)*

Is a rare, progressive neurological disorder characterized by chronic inflammation that primarily affects one hemisphere of the brain, most often in children. This review aims to provide a comprehensive narrative overview of existing literature on RE, including its historical background, underlying mechanisms, and treatment approaches. RE typically arises in individuals who had previously normal development, and its incidence is low, with only a small number of new cases identified annually in epilepsy centers. Although most cases occur in children, about 10% are diagnosed in adolescents and adults.A defining characteristic of RE is drug-resistant focal seizures, frequently presenting as *epilepsia partialis continua*. Over time, patients often experience a gradual decline in both motor and cognitive functions. Neuroimaging commonly reveals progressive atrophy of the affected brain hemisphere. Histopathological findings are marked by T-cell-mediated encephalitis, along with activated microglia and reactive astrogliosis. Current treatment guidelines identify cerebral hemispherotomy as the most effective intervention for seizure control in RE, although it may lead to considerable neurological impairment. Alternatively, pharmacological therapies, including antiseizure drugs and immunomodulatory treatments, are also employed [48].

VII. COMMON MECHANISM OF EXISTING ANTIEPILEPTIC DRUGS

A. Voltage-Gated Ion Channels

Epileptic encephalopathies are widely believed to result from imbalances in neural excitation and inhibition. Voltage-gated ion channels, both excitatory and inhibitory, are essential targets for antiepileptic medications, as they play a central role in modulating neuronal excitability and synaptic communication. Emerging studies emphasize the critical involvement of these ion channels in multiple facets of epilepsy, such as presynaptic neurotransmitter release**,** intrinsic neuronal responsiveness, and neuronal network synchronization. Moreover, genetic mutations affecting these ion channels in both excitatory principal neurons and inhibitory interneurons have been identified as significant factors in the pathogenesis of various forms of epilepsy [49].

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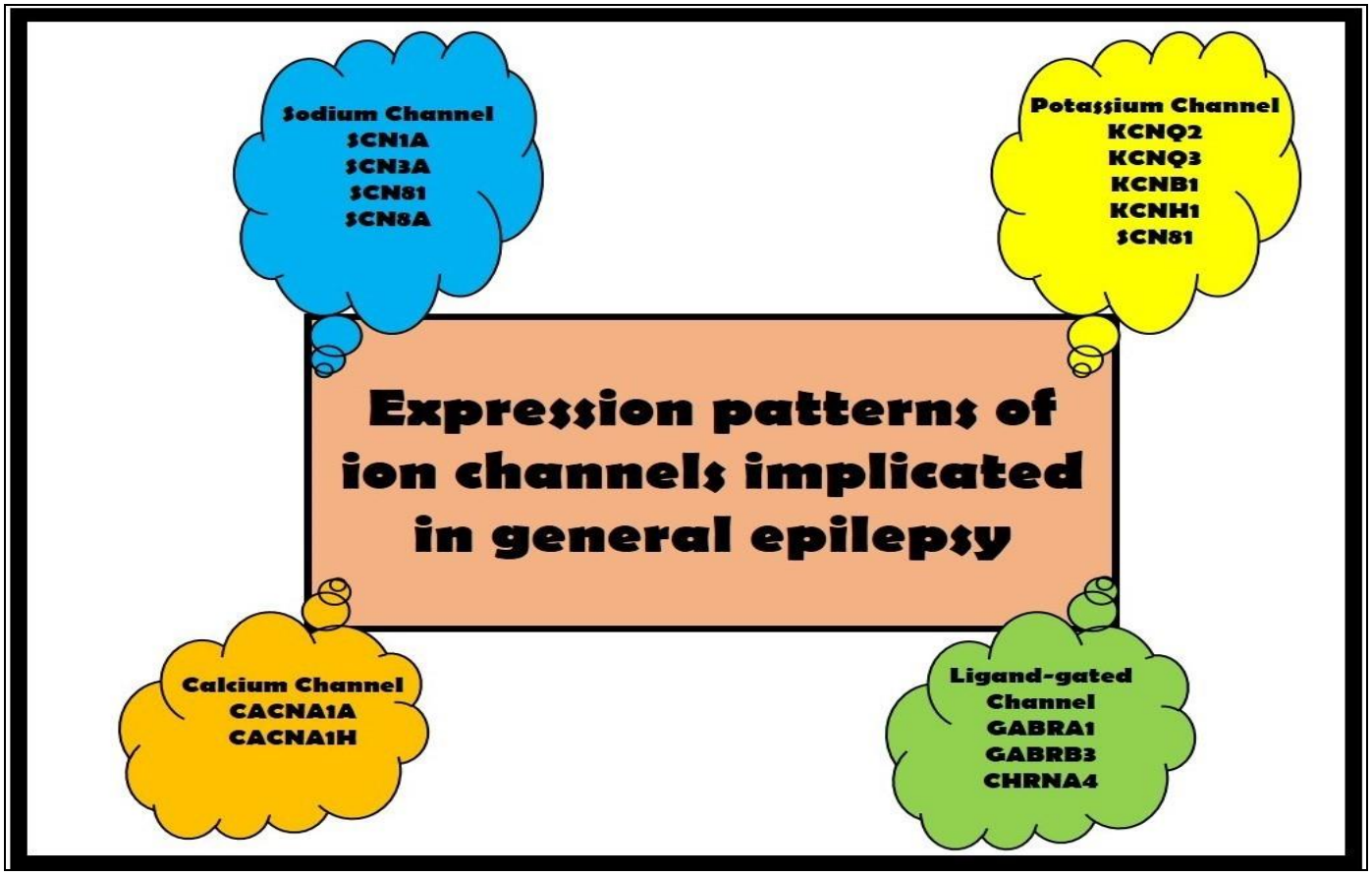

Fig 27 Expression Patterns of Ion Channels Implicated in Genetic Epilepsy. Gene Groups are Represented by Different Colors.

B. Inhibitory Neurotransmission

GABA receptor-mediated neurotransmission is the most common form of inhibitory signaling in the brain and has long been recognized as a crucial component in both the development and treatment of epilepsy. For over a century, GABA receptors have served as primary targets for antiseizure drugs. Research has now shown that GABA's effects are complex and involve multiple receptor subtypes, influencing brain function in ways that go beyond merely counteracting excitatory signals. A deeper understanding of GABA mediated inhibition within neural circuits holds promise for the creation of more targeted therapies aimed at correcting the network abnormalities associated with epilepsy [50].

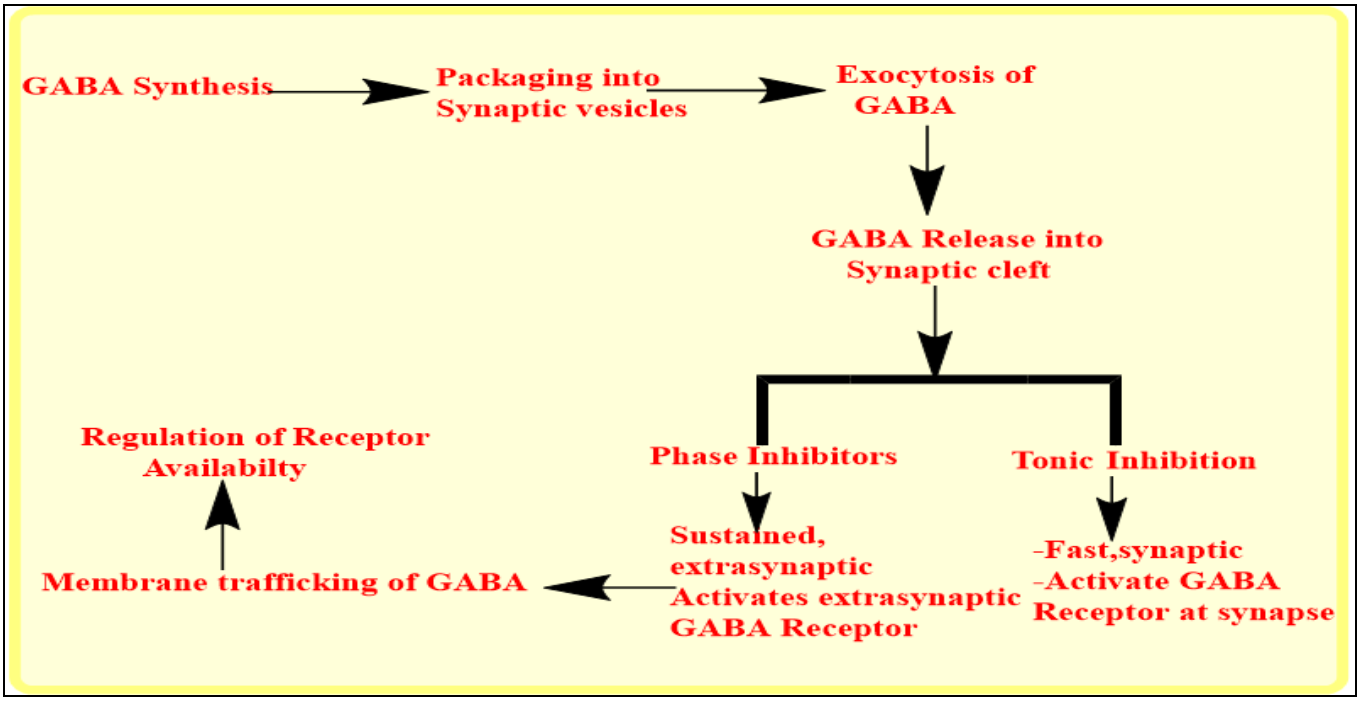

Fig 28 Inhibitory Neurotransmission

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C. Excitatory Neurotransmission

Evidence is reviewed that suggests an excitatory neurotransmission abnormality may be a contributing factor to epileptic phenomena in a number of animal and human syndromes. Certain genetic syndromes may be influenced by altered glutamate transport or metabolism, and different acquired forms of epilepsy may be significantly impacted by increased responsiveness to NMDA receptor activation. Decreasing glutamatergic neurotransmission provides a rational therapeutic approach to epilepsy. Potent anticonvulsant effects are seen with the acute administration of NMDA antagonists in a wide range of animal models. Some competitive antagonists acting at the NMDA/ glutamate site show prolonged anticonvulsant activity following oral administration at doses free of motor side effects and appear suitable for clinical trial [51].

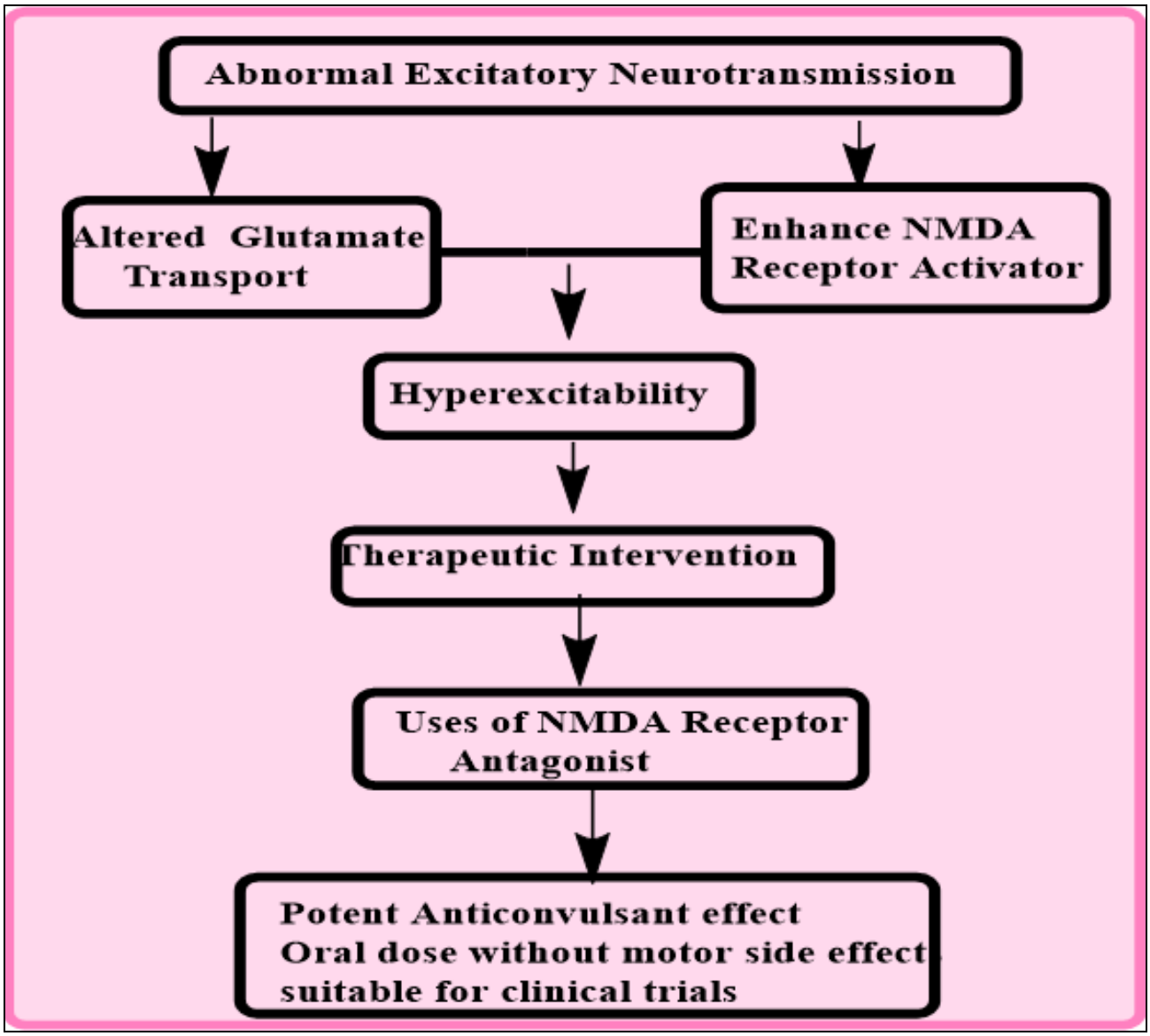

Fig 29 Excitatory Neurotransmission

D. Modulation of Synaptic Vesicle Proteins

Since the 1970s, researchers have explored how synaptic vesicles (SVs) are locally formed and reused at synapses. Heuser and Reese suggested that, following stimulation, SVs are regenerated at the neuromuscular junction through the development of coated vesicular intermediates at the plasma membrane.

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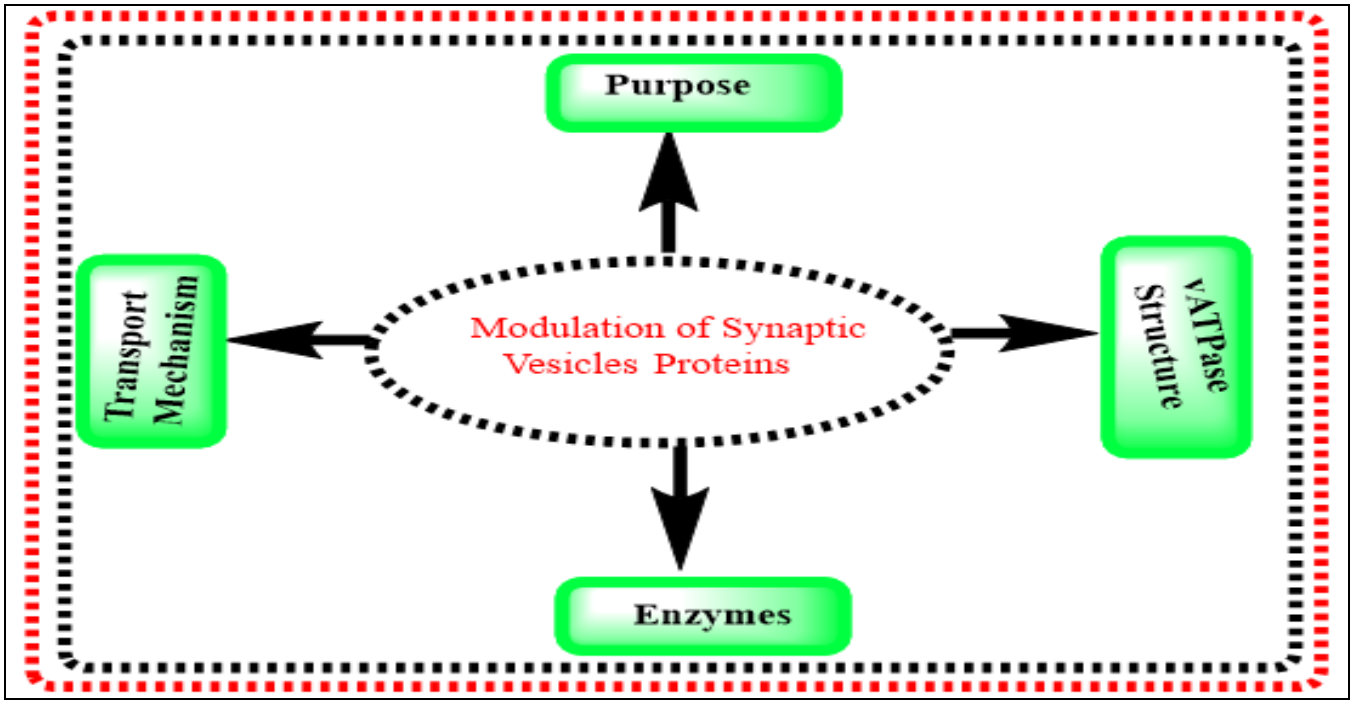
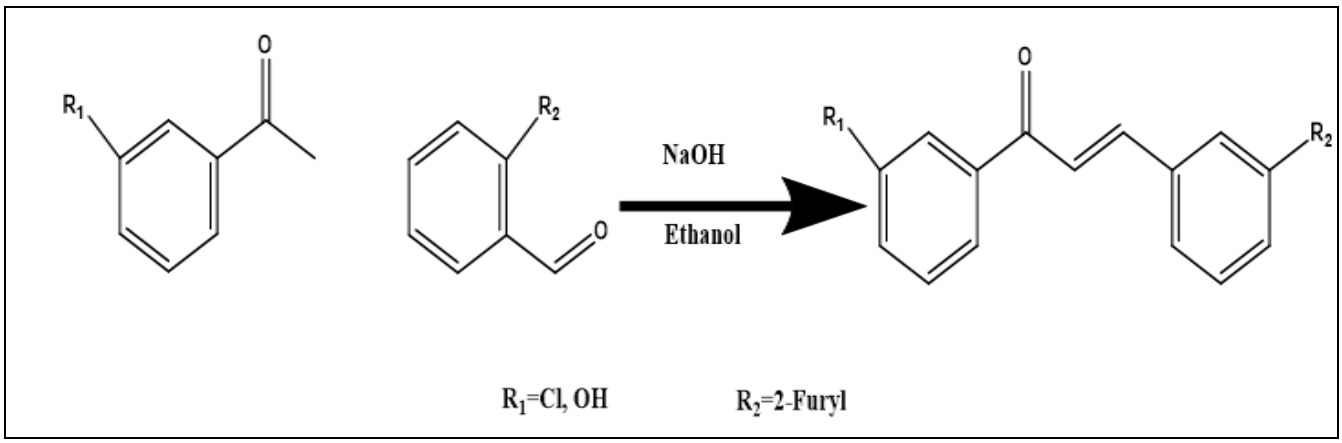


Fig 30 Modulation of Synaptic Vesicle Proteins

E. Mechanism of SV (Re) Acidification

Acidification of synaptic vesicles (SVs) is crucial for proper neurotransmitter uptake and effective synaptic transmission. This acidification is facilitated by the vacuolar H^+-ATPase (vATPase), which hydrolyzes ATP to actively transport protons (H^+) into the vesicle. This proton influx creates an acidic environment and establishes an electrochemical gradient ($\Delta\mu H^+$). Vesicular transporters rely on this gradient to move neurotransmitters like glutamate and GABA into SVs. The vATPase consists of two main components: the V1 domain (located in the cytoplasm, responsible for ATP hydrolysis) and the Vo domain (embedded in the membrane, responsible for proton movement). Typically, each SV contains one or two vATPase complexes. Besides synaptic vesicles, vATPases also acidify other organelles such as endosomes, lysosomes, the Golgi apparatus, and secretory vesicles. These enzymes contribute to essential functions including protein breakdown, activation of enzymes, and cargo trafficking. Additionally, vATPases are involved in physiological activities (such as in bones and kidneys) and are implicated in diseases like cancer [52].

VIII. PYRAZOLINE DERIVATIVES AS ANTIEPILEPTIC TREATMENT WITH SYNTHETIC SCHEME



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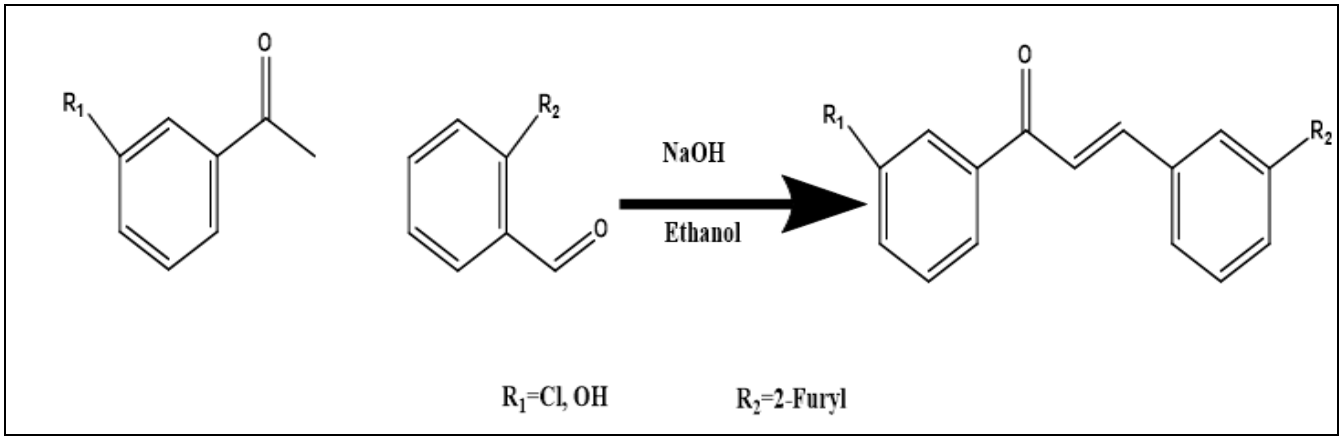


Fig 31 Scheme 1 for the Synthesis of Pyrazoline Derivatives

A solution containing equimolar amounts of acetophenone (0.01 mol) and an aryl aldehyde (0.01 mol) was prepared in 30 mL of ethanol and stirred thoroughly. To this mixture, 15 mL of 40% aqueous potassium hydroxide (KOH) was added gradually. The reaction mixture was then allowed to stand at room temperature overnight. The next day, it was poured onto crushed ice and acidified using hydrochloric acid (HCl). The resulting solid was collected by filtration and purified by recrystallization from ethanol.

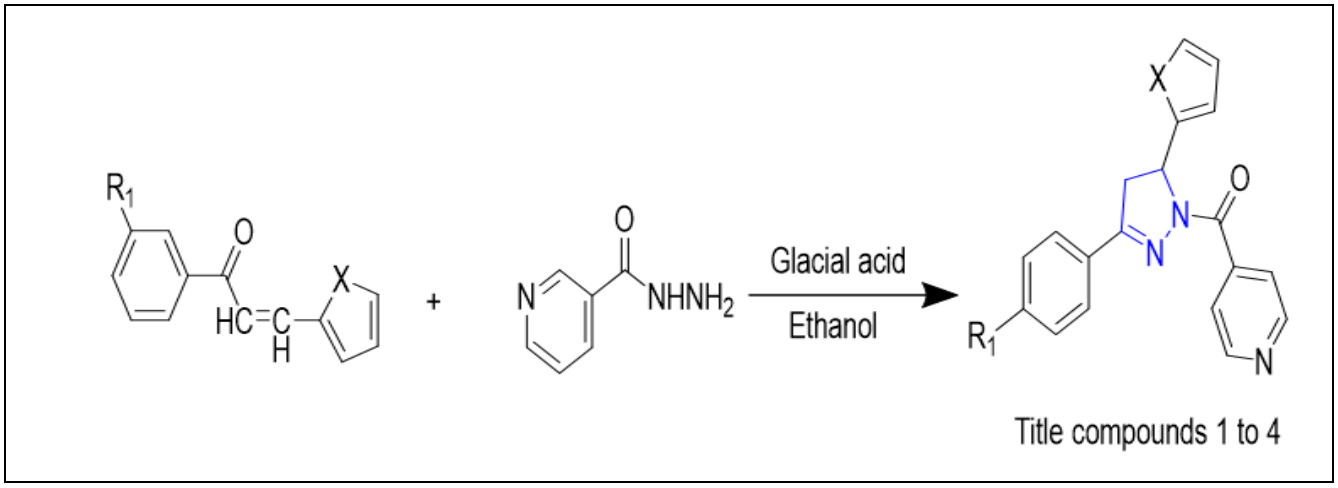
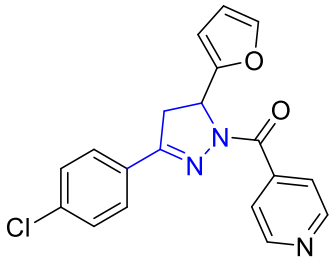
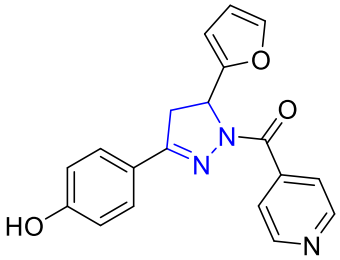


Fig 32 Scheme 2 for the Synthesis of Pyrazoline Derivatives

Table 1 Various Derivatives of Pyrazoline

Compound	R_1	X	Structures
1	Cl	O	
2	OH	O	

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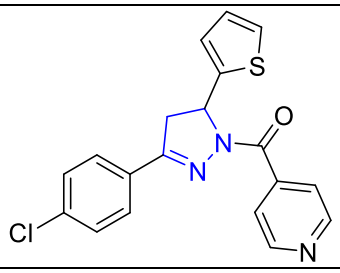
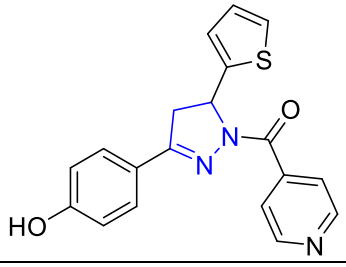
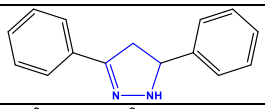
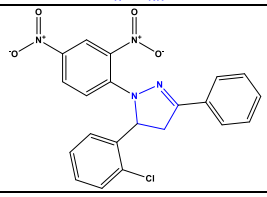
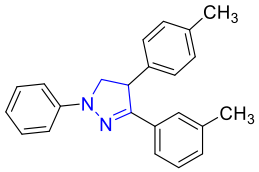
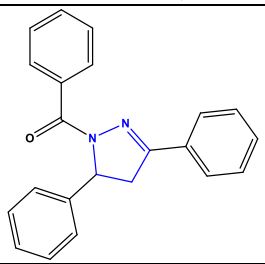
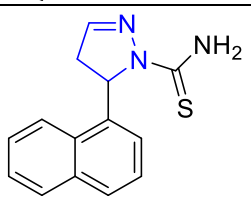
3	Cl	S	
4	OH	S	

Compounds 1-4 (0.01 mol) were dissolved in 30 mL of absolute ethanol, and an equimolar amount of the corresponding hydrazine derivative (0.01 mol) was added along with a few drops of glacial acetic acid. The reaction mixture was then refluxed for 8 hours. After completion, the excess solvent was evaporated, and the crude product was poured into ice-cold water. The resulting solid was collected by filtration and purified through recrystallization using ethanol [53].

IX. REPORTED PYRAZOLINE BASED ANTIEPILEPTIC COMPOUNDS [54]

Table 2 Reported Compounds of Pyrazoline

S. No.	Compound	Key Substituents	Activity Model	Dose (mg/kg)	Reference (Journal/DOI)
1		Phenyl rings at 3 & 5	MES/PTZ	20–100	Int J Pharm Sci Res 2014 [55]
2		DNP & Cl substitutions	MES	20	IJPSR 2014 [56]
3		Acetoamino	PTZ	30	Med Chem Res 2010 [57]
4		Benzoyl	AMPA antagonism	—	Med Chem Res 2010 [58]
5		Naphthalene, Thiocarbamide	MES/PTZ	100	Springer Link 2013 [59]

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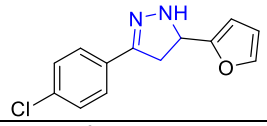
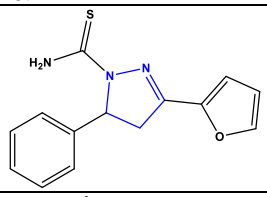
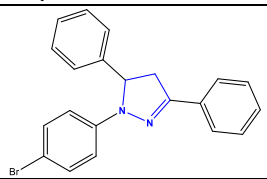
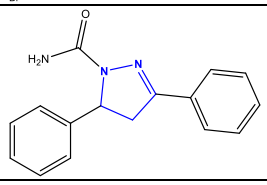
6		Cl-Phenyl, Furyl	MES	30–100	EJMC 2010 [60]
7		Furyl, Thiocarbamide	MES/PTZ	30–300	Med Chem Res 2010 [61]
8		Br-Phenyl	MES	50	Med Chem Res 2010 [62]
9		NH–CO–R substitutions	MES/PTZ	30–300	Hilaris Publisher 2014 [63]

X. CHALLENGES AND FUTURE PROSPECTIVE

Pyrazoline is gaining attention as a valuable scaffold for developing antiepileptic drugs due to its broad spectrum of pharmacological properties. However, its progress is limited by several challenges, including insufficient clinical evidence, ambiguous mechanisms of action, possible toxicity, and suboptimal pharmacokinetic characteristics. Nevertheless, the future outlook remains positive. Innovations in structure-activity relationship analysis, advanced drug delivery systems like nanotechnology, and computational modeling can significantly improve its therapeutic profile. Creating multi-targeted pyrazoline derivatives and conducting thorough preclinical and clinical research may lead to breakthrough treatments. Ongoing studies suggest pyrazoline-based molecules could offer effective options for resistant and varied forms of epilepsy.

XI. LIMITATIONS IN CURRENT RESEARCH

Research on pyrazoline as a potential scaffold for antiepileptic drug development is still limited in several key areas. Most investigations are restricted to preclinical models, offering minimal insight into its safety and effectiveness in humans. The specific molecular targets and mechanisms through which pyrazoline acts are not yet clearly identified, hindering its clinical translation. Additionally, many derivatives have not undergone detailed pharmacokinetic or toxicity evaluations. The broad range of seizure disorders further complicates consistent assessment of its therapeutic potential. Moreover, long-term studies and direct comparisons with current antiepileptic drugs are often missing, underscoring the need for more robust, interdisciplinary research.

XII. FUTURE DIRECTIONS IN DRUG DEVELOPMENT

The future development of pyrazoline-based antiepileptic drugs offers several promising avenues. Prioritizing structure-activity relationship (SAR) analysis is crucial to enhance therapeutic effectiveness while reducing adverse effects. Innovative drug delivery methods, such as liposomes and nanoparticles, can improve bioavailability and facilitate efficient brain targeting. The use of computational approaches, including molecular docking and AI-driven screening, may significantly speed up the discovery and refinement of lead compounds. Creating pyrazoline derivatives that act on multiple targets could provide better treatment options for drug-resistant epilepsy. Furthermore, comprehensive preclinical testing followed by detailed clinical trials is vital to confirm their safety and therapeutic potential.

XIII. CONCLUSION

Pyrazoline derivatives exhibit considerable promise as antiepileptic agents, owing to their wide-ranging pharmacological effects, particularly in modulating ion channels and neurotransmitter systems. This review underscores their flexible chemical structure, broad therapeutic potential, and encouraging outcomes in preclinical seizure models. Nonetheless, their clinical translation is hindered by factors such as limited human trials, insufficient pharmacokinetic data, and poorly defined mechanisms of action. To advance their development, future research should emphasize structure-activity relationship optimization, innovative drug delivery strategies, and comprehensive clinical testing. The application of computational modeling and multi-target drug design may further improve their efficacy. With sustained multidisciplinary research, pyrazoline-based drugs may become valuable therapies for various and drug-resistant epilepsies.

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