ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 19, Issue 3, 2026

Online - 2455-3891
Print - 0974-2441

Review Article

STRUCTURAL DIVERSIFICATION AND ECO-FRIENDLY SYNTHESIS OF PHENYTOIN ANALOGS

POORNIMA PANDEY, ANJU SINGH, SHARDA SHAKYA, RAJENDIRAN A*

Department of Pharmacy, School of Pharmaceutical Sciences, CSJM University, Kanpur, Uttar Pradesh, India.
***Corresponding author: A. Rajendiran; Email: arajendiran12@gmail.com**

Received: 05 November 2025, Revised and Accepted: 13 January 2026

ABSTRACT

Phenytoin is a traditional anti-epileptic drug of the hydantoin class, universally employed for seizure control in generalized tonic–clonic and focal seizures. Although effective, phenytoin is plagued by limitations such as low aqueous solubility, dose-dependent pharmacokinetics, and toxicity following chronic administration. These limitations have prompted the synthesis of several hydantoin analogs to enhance therapeutic effects, pharmacokinetics, and drug selectivity. This review focuses on chemically modified phenytoin derivatives, prepared using methods such as N-substitution, para-aryl functionalization, and heterocyclic hybridization, among others. Structural alteration was examined in their literature-cited pharmacological activities. Classical and advanced synthetic methods, such as microwave-assisted synthesis, solvent-free grinding, ultrasound irradiation, and continuous flow chemistry, were also assessed for efficacy, sustainability, and yield of the product. Derivatives including mephenytoin, fosphenytoin, Schiff bases, and hybrid molecules incorporating thiazole, quinazolinone, and imidazole showed improved anticonvulsant, anti-inflammatory, antioxidant, antimicrobial, and anticancer activity. PEGylation and prodrug formation (e.g., fosphenytoin) improved delivery and solubility profiles. Modern green synthesis techniques, particularly microwave and solvent-free reactions, significantly reduce reaction times while minimizing the environmental footprint. These methods not only enhanced synthetic efficiency but also benefited sustainable medicinal chemistry practices. Structural modification of phenytoin has given rise to derivatives possessing better pharmacological profiles and broader therapeutic uses. The incorporation of green and highly efficient synthesis routes presents an exciting avenue for future drug discovery. Phenytoin continues to be a useful template in the field of medicinal chemistry, with continued application in the design of safer, better anticonvulsant drugs.

Keywords: Phenytoin, Schiff base, Hybrid molecules, Voltage-gated sodium channels, PEGylation.

 DOI: http://dx.doi.org/10.22159/ajpcr.2026v19i3.57389. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Epilepsy is a chronic, long-standing neurological disorder with recurrent seizures due to abnormal neuronal discharges [1]. Despite the availability of traditional anti-epileptics, the quest for newer drugs with better efficacy and reduced toxicities remains a high-priority goal. Hydantoin derivatives, especially phenytoin, have been extensively explored due to their wide-spectrum anticonvulsant activity and voltage-gated sodium channel-blocking mechanism [2]. Phenytoin, 5,5-Diphenylimidazolidine-2,4-dione, the classic hydantoin, remains a cornerstone in the treatment of generalized tonic–clonic and partial seizures [3].

Structural alterations have been made to the phenytoin core scaffold, leading to a wide range of analogs with improved pharmacological profiles [4]. These modifications include N-alkylation, para-substitution on the aryl ring, thio-derivatives, Schiff base formation, and hybrid conjugation with other bioactive heterocycles like thiazole, quinazolinone, and imidazole. Substitution at the various positions of the hydantoin ring system has been shown to have a deep impact on the pharmacological profile, i.e., potency, selectivity, and pharmacokinetics [5]. Simultaneously, synthetic strategies have evolved significantly. Conventional methods, such as the Bucherer–Bergs reaction, are now complemented by advanced green chemistry approaches, including microwave-assisted synthesis, solvent-free grinding, and ultrasound-aided techniques, which offer faster reactions, better yields, and more eco-friendly conditions [6]. For instance, microwave-assisted synthesis has been described as a fast, green, and efficient process with a significant reduction in reaction time and enhanced yields [7]. This review focuses on the structural diversification and green synthesis of multiple phenytoin derivatives, using 5,5-diphenylhydantoin as a core scaffold. The aim is to highlight both classical and modern methodologies alongside the therapeutic potential of each analog, contributing to future drug development in epilepsy and beyond.

Despite the extensive clinical use of phenytoin, challenges such as poor aqueous solubility, nonlinear pharmacokinetics, and long-term toxicity necessitate continued structural optimization. Therefore, this review aims to comprehensively summarize structural diversification strategies of phenytoin analogs along with advancements in eco-friendly synthetic methodologies, highlighting their pharmacological significance and future potential in drug development.

HISTORICAL OVERVIEW

Throughout the decades, numerous phenytoin derivatives have been found through structural modification to maximize pharmacokinetics, reduce toxicity, and expand therapeutic application [8]. The table summarizes 10 notable derivatives, with a focus on alkylation, hydroxylation, halogenation, and hybrid conjugation with other heterocycles. Such structural modification has yielded compounds with broadened anticonvulsant, antimicrobial, anticancer, and anti-inflammatory activity. Of greatest importance, prodrug species such as fosphenytoin improved injectable solubility, and metal complexes and PEGylation improved stability and bioavailability. Such structural advancement parallels ongoing medicinal chemistry to further optimize the hydantoin template for additional clinical applications beyond epilepsy.

Evolution of phenytoin synthesis techniques

Synthesis of phenytoin has travelled a long way since its initial discovery in 1908. Initially synthesized through the Bucherer–Bergs reaction of benzil, urea, and base, the classical method dominated for decades [19]. With the emergence of green chemistry, techniques such as microwave-assisted synthesis, solvent-free grinding, and ultrasound irradiation have gained popularity, offering improved yields, reaction times, and environmentally friendly conditions [20]. More recent developments involve mechanochemical approaches and flow chemistry, further enhancing process efficiency and scalability [21]. These developments are reflective of enhanced emphasis toward efficient and sustainable

processes in pharmaceutical synthesis, allowing continued optimization of phenytoin and its analogs for drug use [22].

SYNTHESIS METHODOLOGY

Classical synthesis (Bucherer–Bergs reaction)

The traditional phenytoin synthesis is the Bucherer–Bergs reaction, a time-tested method found in the early 20th century [19]. It starts with the condensation of benzil and urea with a strong base such as sodium ethoxide or potassium hydroxide, under reflux (Fig. 1). The reaction constructs the hydantoin ring by cyclization and dehydration reactions to yield phenytoin as the product. Although easy and preferred, the process normally involves long reaction times and severe conditions. However, it is still a point of departure for phenytoin synthesis in academia and small-scale pharmaceutical synthesis.

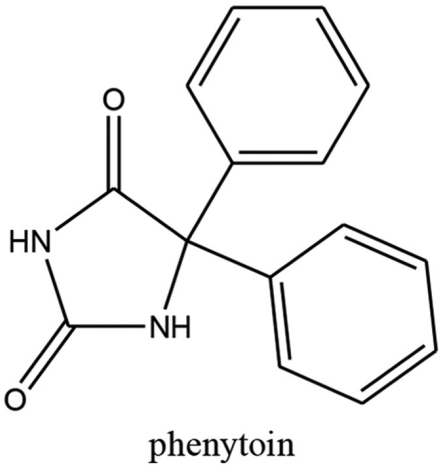

Fig. 1: Phenytoin

Microwave-assisted synthesis

Microwave-assisted synthesis is a sophisticated method employed to synthesize phenytoin efficiently compared to traditional heating [23]. Here, the starting materials, such as benzil and urea, are combined with a catalytic base and irradiated with microwaves [24]. The microwaves efficiently heat the reactants quickly and uniformly, extremely shortening reaction time hours, reducing them to mere minutes, and also enhancing yields in many cases. The method reduces the use of solvent, which fits the tenets of green chemistry (Fig. 3). The high energy input makes it possible to close the ring and dehydrate quickly, and thus it is a method of choice for lab-scale synthesis as well as eco-friendly pharmaceutical synthesis of phenytoin and its analogs.

Solvent-free (mechanochemical or grinding) synthesis

Solvent-free synthesis or mechanochemical synthesis is a process of ball milling the solid reactants – most often benzil and urea – jointly in the presence of a catalytic base without the use of any solvent (Fig. 4) [25]. It encompasses manual grinding using a mortar and pestle or mechanical grinding using a ball mill. Mechanical energy generated leads to molecular interaction and induces the reaction, resulting in the formation of the product, i.e., phenytoin [26]. It is a green synthesis process that eliminates toxic solvents, conserves energy, and minimizes waste. It is cost-effective, eco-friendly, and suitable for small-scale and sustainable chemistry reactions [27].

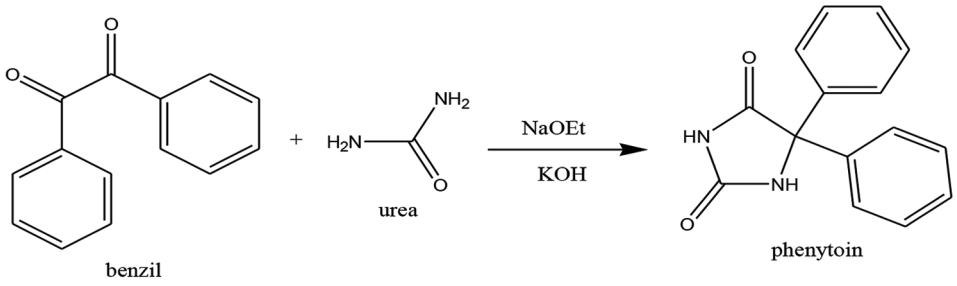

Fig.2: Classical synthesis (Bucherer–Bergs reaction)

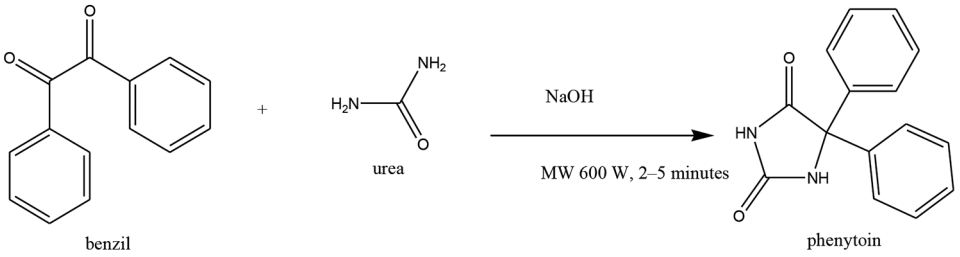

Fig. 3: Microwave-assisted synthesis

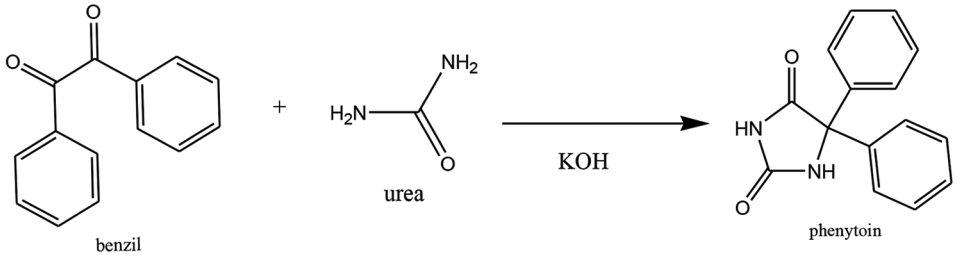

Fig. 4: Solvent-free (mechanochemical or grinding) synthesis

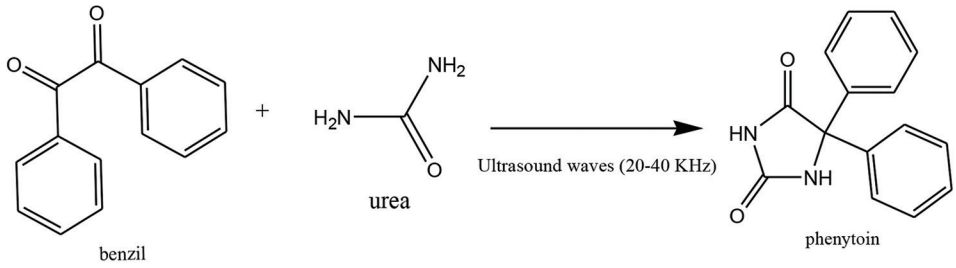

Fig. 5: Ultrasound-assisted synthesis

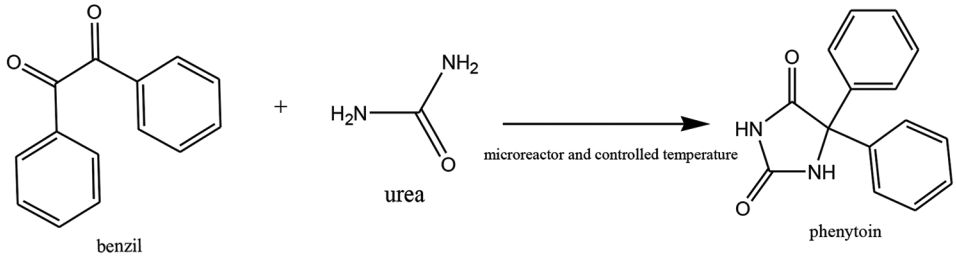

Fig. 6: Flow chemistry/continuous flow synthesis

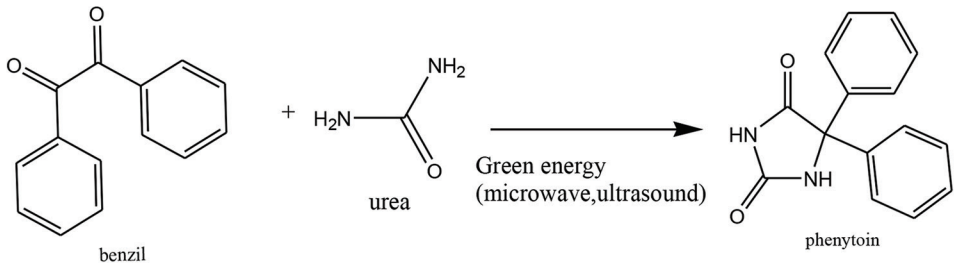

Fig. 7: Green chemistry approaches

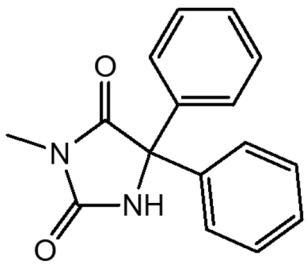

Fig. 8: Mephenytoin (3-methyl-5,5-phenylimidazolidine-2,4-dione)

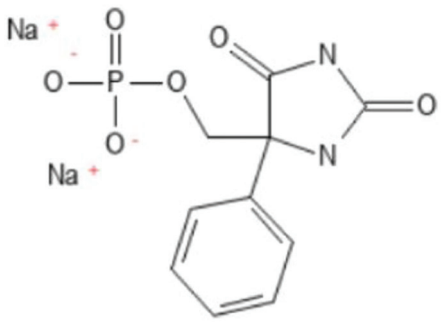

Fig. 9: Ethotoin (3-ethyl-5-phenylimidazolidine-2,4-dione)

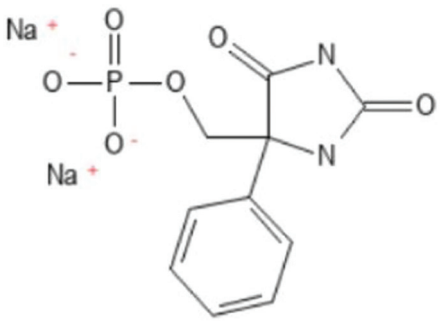

Fig. 10: Fosphenytoin (disodium [2-(phenytoin-5-ylmethoxy) ethyl] phosphate)

Ultrasound-assisted synthesis

Ultrasound-assisted synthesis uses high-frequency sound waves to aid the chemical reaction between benzil and urea in the presence of a base [28-30]. Ultrasonic waves form cavitation bubbles within the reaction mixture, which collapse violently and generate localized high pressure and temperature. This energy increases mass transfer, increases collision rates among reactants, and accelerates ring closure in hydantoin formation. This leads to quicker synthesis of phenytoin with higher yields and milder conditions compared to conventional methods. This green process is beneficial for increasing the efficiency of the reaction (Fig. 5).

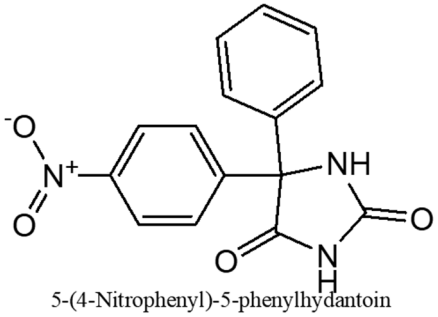

Fig. 11: 5-(4-nitrophenyl)-5-phenylhydantoin

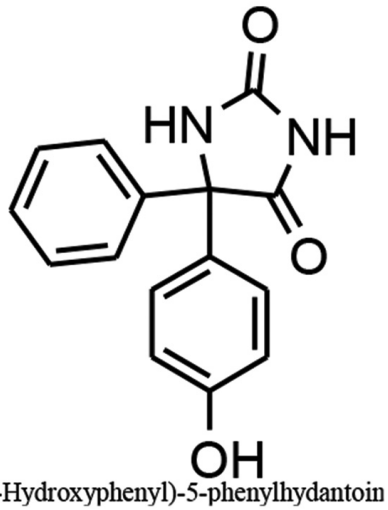

Fig. 12: 5-(4-hydroxyphenyl)-5-phenylhydantoin

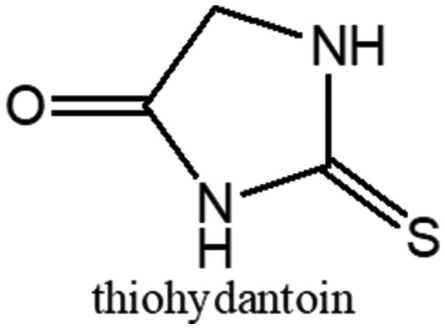

Fig. 13: Thiohydantoin (2-thioxoimidazolidine-4-one)

Flow chemistry/continuous flow synthesis

Flow chemistry, or continuous flow synthesis, is the method of conducting chemical reactions in a continuous flowing stream rather than in batches [31,32]. Solutions of benzil, urea, and base are pumped into a microreactor or flow tube under controlled temperature and pressure in this procedure (Fig. 6) [33]. Reaction conditions, residence time, mixing, and heat are precisely controlled, and this gives reproducible and scalable phenytoin synthesis. It is best applied to industrial-scale synthesis, yielding high purity and yield, and following today's sustainable manufacturing practices.

Green chemistry approaches

Green chemistry-guided synthesis of phenytoin aims at minimizing environmental impact by using environmentally friendly reagents, renewable catalysts, and energy-saving processes [34]. These pathways

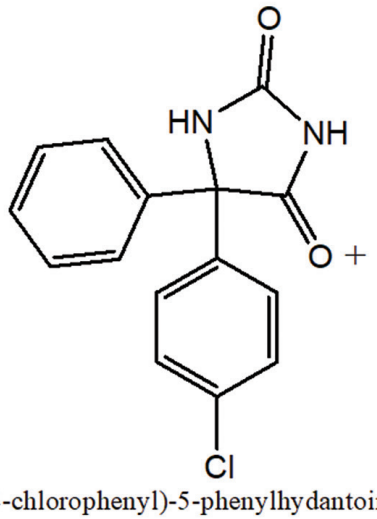

Fig. 14: 5-(4-chlorophenyl)-5-phenylhydantoin

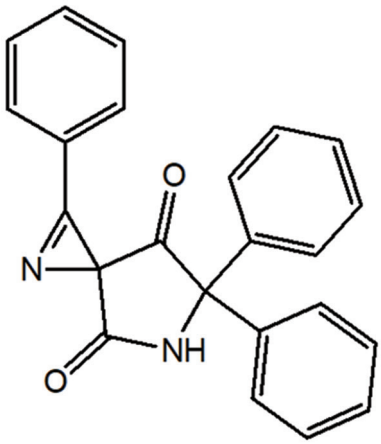

Fig. 15: Schiff base of phenytoin

can include the use of bio-based or recyclable solvents, solid-phase catalysts, or enzyme-catalyzed reactions (Fig. 7) [34,35]. The goal is to replace unsafe chemicals, save energy, and achieve maximum atom economy. Green synthesis is the future of drug synthesis, integrating environmental responsibility with effective phenytoin and derivative production [36].

PHENYTOIN DERIVATIVES: STRUCTURES, SYNTHESIS, MECHANISM, AND BIOLOGICAL EVALUATION

Mephenytoin

Mephenytoin (3-methyl-5,5-phenylimidazolidine-2,4-dione) is synthesized by N3-methylation of phenytoin with methyl iodide under a base such as potassium carbonate or sodium hydride (Fig. 8) [9,37,38]. The 3-position nitrogen atom is deprotonated under microwave irradiation and methylated by Substitution Nucleophilic Bimolecular Reaction (SN2) with methyl iodide very rapidly to produce mephenytoin. The reaction is usually carried out in acetone or Dimethylformamide (DMF), and the microwave energy significantly reduces the reaction time with increased yield. Although mephenytoin was discovered to have greater CNS activity, it was later withdrawn due to toxicity [39-41].

Reaction mechanism

The reaction is a classic SN2 reaction. The acidic hydrogen is first removed by the strong base from the N3 nitrogen of phenytoin and yields a reactive anionic intermediate. The nitrogen is a nucleophile and

attacks the electrophilic carbon atom of the methyl iodide, resulting in the removal of the iodide ion and the formation of an N-C bond. The product is mephenytoin, where the N3 position is methylated, and the ring is intact. The alkylation reaction is effective and can be performed using microwave-assisted synthesis, which shortens the reaction time significantly [42,43].

Biological evaluation of mephenytoin

Mephenytoin was originally developed as an anticonvulsant medication and proved to be extremely successful in treating the vast majority of types of seizures, especially tonic-clonic and partial seizures(see table 1). Mephenytoin stabilizes neuronal membranes and retards repetitive neuronal firing, similar to phenytoin, by blocking voltage-sensitive sodium channels [9, 44, 45, 51].In the standard Maximal Electroshock Seizure MES test in mice, Mephenytoin demonstrated an ED_50 (median effective dose) of 12.5 mg/kg .This value indicates potency comparable to the parent drug, phenytoin, which typically exhibits an ED_50 of approximately 10.0 mg/kg in the same experimental model [46].However, its use in the clinic was brief due to extreme side effects, including inhibition of the bone marrow, hepatotoxicity, and hypersensitivity. Mephenytoin is also metabolized in the liver by CYP2C19 and exhibits extremely variable pharmacokinetics between individuals, especially poor metabolizers [47].

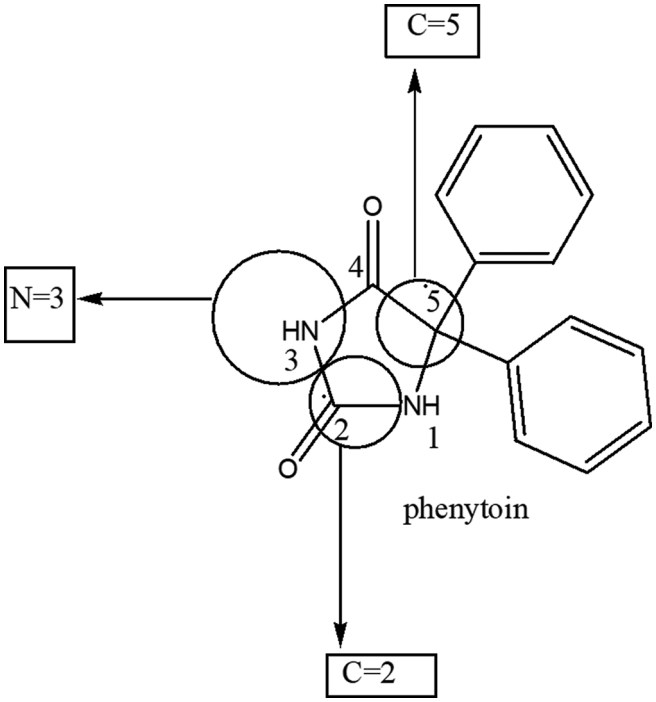

Fig. 16: Modification sites in phenytoin

Ethotoin

Ethotoin (3-Ethyl-5-phenylimidazolidine-2,4-dione) is prepared through the base-catalyzed condensation of urea and benzaldehyde in the presence of a catalyst, potassium cyanide KCN (Fig. 9). Benzaldehyde and urea couple together under microwave irradiation to produce an intermediate, which subsequently undergoes intramolecular cyclization to give the hydantoin ring with a single phenyl group at the 5-position. A methyl group is incorporated at the 3-position, resulting in the final product, ethotoin. The reaction is usually solvent-free or performed in ethanol, and microwave energy significantly reduces the reaction time. Ethotoin has anticonvulsant activity and is structurally less complex than phenytoin, but has been superseded largely because of pharmacokinetic constraints [10,48,49].

Biological evaluation of ethotoin

Ethotoin is a hydantoin derivative that has been traditionally employed as an anticonvulsant agent in the management of epilepsy(see table 1). Its action is comparable to phenytoin in the sense that it stabilizes neuronal membranes and inhibits recurrent neuronal firing by altering the voltage-gated sodium channels [50, 51].In in vivo experiments, Ethotoin has exhibited dose-dependent anticonvulsant efficacy in traditional models [52]. The compound is usually moderately potent relative to phenytoin; for example, in the Maximal Electroshock Seizure MES test in rats, Ethotoin exhibited an ED_50 of 36 mg/kg, which is significantly higher than the ED_50 of phenytoin in the same model approx. 10 mg/kg. It possesses a shorter half-life and reduced toxicity in animal models [53, 54].

Fosphenytoin

Fosphenytoin (Disodium [2-(phenytoin-5-ylmethoxy)ethyl] phosphate) is done through initial hydroxymethylation of phenytoin at the N3 position by formaldehyde (Fig. 10) [55,56]. The latter is phosphorylated with phosphoric acid or phosphorus oxychloride to yield the phosphonooxymethyl group. Fosphenytoin, in the water-soluble prodrug form of phenytoin, is more suitable for parenteral application due to increased solubility and patient tolerance [57].

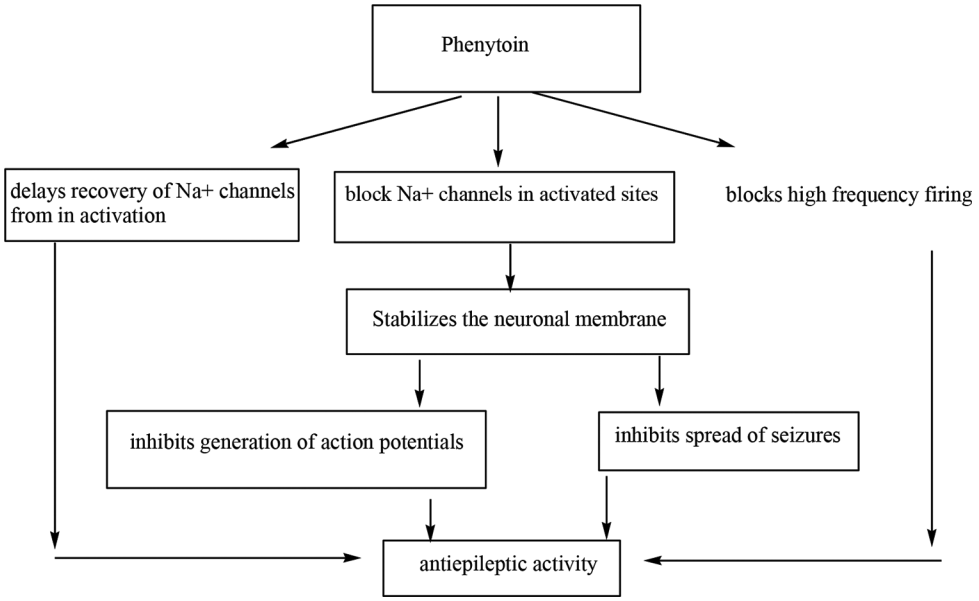

Fig. 17: Mechanism of action of phenytoin

Table 1: Phenytoin derivatives table

Sr. No.	Derivative name/code	Modification type	Pharmacological Activity	Remarks	Year	References
1	Mephenytoin	N3-methylation	Anticonvulsant	Historical use.	1945	[9]
2	Ethotoin	N3-ethylation	Anticonvulsant	Less potent.	1957	[9,10]
3	Fosphenytoin	Phosphate ester (prodrug)	Injectable anticonvulsant	Water-soluble prodrug.	1996	[11]
4	5-(4-Nitrophenyl)- 5-phenylhydantoin	Para-nitro substitution	Anticonvulsant	Electron-withdrawing groups enhance activity.	1974	[12]
5	5-(4-Hydroxyphenyl)-5-phenylhydantoin	Para-hydroxy substitution	Antioxidant, Central nervous system active	Improves BBB permeability.	1986	[13]
6	Thiohydantoin	O replaced with S	Anti-inflammatory, anticancer	Common modification.	1979	[14]
7	3-Amino-5,5-diphenylhydantoin	NH_2 at N3	Anti-epileptic	SAR-based study.	1989	[15]
8	5-(4-Chlorophenyl)- 5-phenylhydantoin	Para-chloro substitution	Anticonvulsant	SAR candidate.	1990	[16]
9	Benzylhydantoin	Benzyl ring fused	CNS-active	Improves lipophilicity.	2001	[17]
10	Schiff base of phenytoin	Imine linkage with aldehydes	Antimicrobial, anticancer	Hybrid scaffold.	2011	[18]

Table 2: Modifications at different positions in phenytoin

Position	Modification	Resulting property/activity
N3	Alkyl group	Increases lipophilicity; high toxicity risks
N3	Phosphate ester	Dramatic increase in aqueous solubility; safe for Intravenous use
N3	Schiff base	Broadened activity; enhanced safety index
C5 (Para)	Nitro group	Enhances binding/permeability; mutagenic potential
C5 (Para)	Hydroxyl group	Enhances solubility; lowers toxicity; antioxidant potential
C2	Sulfur (Thio)	Potent anticancer and anti-inflammatory activity

Biological evaluation of fosphenytoin

Fosphenytoin is an intravenous prodrug of phenytoin designed to avoid the solubility issue with intravenous phenytoin (Table 1). It is rapidly metabolized to active phenytoin by plasma phosphatases following injection. It is equally effective as an anticonvulsant and is especially useful in emergencies for status epilepticus due to its rapid onset, better tolerability, and reduced rate of local tissue injury [58, 59]. Fosphenytoin demonstrates dramatically enhanced solubility, measured at 142 mg/mL compared to phenytoin's aqueous solubility of approximately 0.02 mg/mL. This increased solubility permits a significantly faster maximum administration rate of 150 mg PE/min (Phenytoin Equivalents), compared to phenytoin's maximum rate of 50 mg/min, without the risk of crystallization or local irritation. It is also less likely to induce cardiac arrhythmias and hypotension compared with phenytoin [60, 61].

5-(4-Nitrophenyl)-5-phenylhydantoin

This compound is synthesized by cyclocondensation of 4-nitrobenzil and urea in a base such as KOH. The reaction is based on the nucleophilic attack of deprotonated urea at one of the 4-nitrobenzil carbonyl carbons (Fig. 11) [19]. Cyclization and dehydration reactions are carried out under microwave irradiation, which results in the formation of the hydantoin ring with a phenyl and a 4-nitrophenyl group at the 5-position. Microwave energy enhances the reaction efficiency, reduces the amount of solvent, and delivers the product in minutes. The nitro group increases the electron-withdrawing quality and can serve as a handle for future modification [23,24].

Reaction mechanism

The base abstracts a proton from the urea in the initial step to generate a nucleophilic nitrogen. The nitrogen attacks the electrophilic carbonyl carbon of 4-nitrobenzil to generate the tetrahedral intermediate. Cyclization is the second step, as the second nitrogen of the urea attacks the other carbonyl group and undergoes dehydration to give the imidazolidine-2,4-dione ring (hydantoin). The product contains a phenyl and a 4-nitrophenyl group at the 5-position due to the symmetry of 4-nitrobenzil. The nitro substituent enhances the electrophilicity of the benzil to render the reaction favorable [19,62].

Biological evaluation of 5-(4-nitrophenyl)-5-phenylhydantoin

This nitro-analogue of phenytoin has been investigated for antimicrobial and anticonvulsant activity(see table 1). The nitro group, being an electron-withdrawing functionality, increases CNS target binding affinity and, potentially, blood–brain barrier permeability [62, 63].The compound has been shown to be an effective anticonvulsant in model systems. Specifically, it displayed an ED_50 of approximately 14.8 mg/kg in the Maximal Electroshock Seizure MES test, confirming its anticonvulsant potential.However, this structural feature introduces a crucial trade-off: The potential therapeutic benefit of enhanced CNS penetration must be critically weighed against the known risks associated with the nitro functionality, which includes concerns for cytotoxicity and mutagenicity. This risk necessitates that the compound either be structurally optimized (e.g., by reduction or bioisosteric replacement) or a prodrug designed to mitigate these safety concerns before therapeutic purposes can be considered.

5-(4-Hydroxyphenyl)-5-phenylhydantoin

This derivative is prepared through the reaction of 4-hydroxybenzil with urea under alkaline conditions in the presence of KOH as a catalyst Fig. 12. Upon microwave irradiation, deprotonated urea nucleophilically attacks one of the carbonyls of 4-hydroxybenzil, which initiates cyclization to result in the hydantoin ring. The reaction drives out water and results in the final product with a phenyl and 4-hydroxyphenyl group at the 5-position. The hydroxyl group confers polarity and potential hydrogen-bonding capability to the molecule [64-66].

Biological Evaluation Of 5-(4-nitrophenyl)-5-phenylhydantoin

This phenol derivative, often referred to as 4'-HPPH (5-(4-Hydroxyphenyl)-5-phenylhydantoin), is most significant as the major human metabolite of phenytoin. It is formed by CYP2C9 and CYP2C19 metabolism of phenytoin, and then largely excreted as a glucuronide conjugate [65, 66, 67].

Detoxification/Toxicity: Glucuronidation of HPPH is considered a detoxification pathway, as HPPHmay be bioactivated to a reactive intermediate by peroxidase, which can oxidize lipids, proteins, and DNA.

Anticonvulsant Activity: The compound maintains moderate anticonvulsant activity in seizure models (MES and PTZ (Pentylenetetrazole)) but is specifically defined by reduced toxicity (due to rapid detoxification) and enhanced aqueous solubility (it has an approximate solubility of >40.2 μg/mLat pH 7.4).

Antioxidant Potential: The phenolic moiety also allows for conjugation with other pharmacophores and is suitable for further design in drug delivery systems. The hydroxy group gives the compound antioxidant properties(see table 1) [66, 67, 68].

Thiohydantoin

Thiohydantoin (2-Thioxoimidazolidine-4-one) is synthesized by the condensation of thiourea with benzil in the presence of a base such as KOH [69]. Thiourea is first deprotonated to render the nitrogen atom nucleophilically active to attack one of the benzil carbonyl groups. Ring closure and dehydration proceed to construct the thiohydantoin ring Fig. 13, one of the carbonyl oxygens being replaced by a sulfur atom. The reaction is highly efficient under microwave irradiation, which reduces the reaction time and enhances the product purity. Sulfur addition enhances biological reactivity and potential coordination capability [70,71].

Reaction mechanism

The reaction begins with the deprotonation of thiourea by the base, which activates the nucleophilic nitrogen center. The nucleophile attacks one of the electrophilic carbonyl carbons of benzil, forming a tetrahedral intermediate. Ring closure begins with a nucleophilic attack of the second nitrogen atom of thiourea on the second carbonyl group. The reaction is completed by a dehydration reaction that forms the five-membered imidazolidine ring, now carrying a thioxo group at position. The thiohydantoin product thus formed structurally resembles phenytoin but with one carbonyl oxygen replaced by a sulfur atom, which enhances its chemical reactivity and alters biological interactions [71-73].

Biological evaluation of thiohydantoin

Thiohydantoin derivatives are synthesized by replacing one or more oxygen atoms of the hydantoin ring with sulfur, a structural change known to expand the therapeutic spectrum beyond classic anticonvulsant activity. Thiohydantoin analogues are known to exhibit anti-inflammatory and potent anticancer properties (see table 1)[73, 74].Studies have demonstrated that key Thiohydantoin analogues exhibit significant cytotoxicity. For example, a C2-substituted thio-analogue demonstrated an IC50 of 2.5 μM against the A549 human lung cancer cell line, a potency superior to the reference drug 5-fluorouracil IC50 = 4.2 μM. The sulfur atom's presence is linked to enhanced cytotoxicity, and these compounds are excellent ligands for forming metal complexes, which can further boost bioactivity [74].

5-(4-chlorophenyl)-5-phenylhydantoin

This compound is prepared by base-catalyzed condensation of 4-chlorobenzil and urea Fig. 14. The reaction involves cyclization and dehydration reactions under microwave irradiation to form the final hydantoin ring with a phenyl and a 4-chlorophenyl group. The chloro substituent enhances lipophilicity and may be a location of further substitution [75,76].

Biological evaluation of 5-(4-chlorophenyl)-5-phenylhydantoin

This analogue maintains high anticonvulsant activity due to its structural resemblance to phenytoin. The chlorine substituent would enhance lipophilicity and, therefore, CNS penetration and metabolic stability [77].It has exhibited encouraging activity against seizure models. Specifically, the 5-(4-chlorophenyl) analogue displayed an ED50 of 18.5 mg/kg in the Maximal Electroshock Seizure MES test, confirming its high activity and rigid structure make it a good core for the synthesis of more active CNS agents. It is also sought after for anti-inflammatory activity [78].

Schiff base of phenytoin

Phenytoin Schiff base is prepared by condensing the N3 position of phenytoin with an aromatic aldehyde such as benzaldehyde or salicylaldehyde. Under acidic or thermal conditions, the aldehyde is forced to react with the NH group of phenytoin to give an imine C=N linkage. The reaction is conducted in methanol or ethanol and initiated by microwave irradiation. The condensation yields the stable Schiff base, which is used as a ligand or further substituted in an attempt to improve its bioactivity (Fig. 15) [79,80].

Reaction mechanism

The reaction is a nucleophilic attack of the free pair of electrons on the N3 nitrogen of phenytoin on the carbonyl carbon of the aldehyde. This forms the hemiaminal of the intermediate, which dehydrates (loses water) to yield the final product with the C=N (imine) bond. Microwave irradiation facilitates the reaction with uniform distribution of heat and lowering of activation energy, resulting in clean and efficient condensation. The reaction follows the general principles of Schiff base formation, also referred to as imine formation [79-81].

Biological evaluation of Schiff bases of phenytoin

Phenytoin Schiff base derivatives have been investigated for anticonvulsant, anti-inflammatory, and antimicrobial activity. The imine group C=N is the pharmacophore, and the attached aromatic or heteroaromatic ring may be varied to increase binding [81]. Studies involving novel phenytoin Schiff bases have confirmed their anticonvulsant potential. For example, a key analogue (SB2-Ph) was evaluated using the Maximal Electroshock (MES) test in mice, exhibiting an ED50 value of 8.29 mg/kg, demonstrating potency comparable to the reference drug phenytoin (ED50 = 5.96 mg/kg). Critically, the combination of phenytoin with this specific Schiff base resulted in an additive anticonvulsant effect and increased the protective index (PI) by more than sevenfold, suggesting a potential for enhanced safety in combination therapy.They are primarily metal chelating, and Cu (II), Zn(II), or Ni(II)complexes of Schiff bases have been found to exhibit enhanced bioactivities, especially in antioxidant and anticancer bioassays [80, 81].

SAR OF THE PHENYTOIN SCAFFOLD

Phenytoin (5, 5-diphenylimidazolidine-2,4-dione) consists of a hydantoin ring with two phenyl groups at the C5 position. Modifications at specific positions significantly alter its potency, solubility, and therapeutic profile. The basic structure consists of a five-membered heterocyclic ring containing two nitrogens (a glycolylurea). The nitrogen at position 3 (N3) is weakly acidic. This allows Phenytoin to form water-soluble salts (like Phenytoin Sodium), which are essential for intravenous administration. The cyclic uride structure is necessary for binding to the voltage-gated sodium channels in their inactive state (Fig. 16) [9, 82, 83].

Substitutions at the N3 position

Adding a methyl group at N3 (e.g., Mephenytoin) creates a "prodrug" effect. The body must de-alkylate the drug to make it active. While it remains an effective anticonvulsant, N3-alkylated derivatives are often associated with higher incidences of sedation and skin rashes. Fosphenytoin is a phosphate ester prodrug attached to the N-3 position. It is highly water-soluble and safer for IM or IV injection because it is rapidly converted to Phenytoin in the blood [83].

Modifications at the N3 position

The N-3 position is the most common site for modification to alter pharmacokinetics and solubility. Replacing the N-3 hydrogen with a methyl group (Mephenytoin) or an ethyl group (Ethotoin) increases lipophilicity and CNS activity(see table 2). While Mephenytoin shows potency ED50 = 12.5 mg/kg. Comparable to phenytoin (ED50 = 10.0 mg/kg), it introduces significant metabolic variability via CYP2C19 and severe side effects like bone marrow inhibition. Replacing the N-3 hydrogen with a phosphate ester group dramatically improves aqueous solubility (142 mg/mL vs. 0.02 mg/mL for phenytoin) this modification allows for safe parenteral administration at high rates (150 mg PE/min) without crystallization or local tissue irritation. Integrating an imine linkage (C=N) at N-3 expands the biological profile Some Schiff bases (e.g., SB2-Ph) maintain high anticonvulsant activity (ED50 = 8.29 mg/

kg) while significantly increasing the Protective Index (PI) by more than seven-fold compared to phenytoin [84, 85, 86].

Substitutions at the C5 position

The C-5 position is the most critical site for determining the spectrum of anticonvulsant activity. Two phenyl groups at the C-5 position (as seen in Phenytoin) provide maximum activity against generalized tonic-clonic seizures and partial seizures. If the phenyl groups are replaced by smaller alkyl groups (like methyl or ethyl), the drug becomes more effective against absence seizures (Ethotoin is an example) but loses potency against tonic-clonic seizures. One phenyl and one ethyl group (Nirvanol) results in a different activity profile and higher toxicity. At least one aromatic ring at C-5 is generally required for the "Phenytoin-like" effect on sodium channels. The presence of an electron-withdrawing nitro group (NO2) increases electrophilicity and potential CNS target binding affinity It maintains effective anticonvulsant activity (ED50 = 14.8 mg/kg) but introduces risks of cytotoxicity and mutagenicity. A hydroxyl group (OH) increases polarity and water solubility it serves as a detoxification pathway through rapid glucuronidation, resulting in reduced toxicity compared to the parent compound while maintaining moderate anticonvulsant activity adding a chlorine atom increases lipophilicity and metabolic stability. The chloro-analogue remains highly active (ED50 = 18.5 mg/kg), demonstrating that halogenation is well-tolerated at the Para-position [87, 88, 89].

Modifications at the C2 position (Isosteric replacement)

Replacing the C-2 carbonyl oxygen with a sulfur atom (Thiohydantoin) shifts the therapeutic focus from epilepsy to anti-inflammatory and anticancer activity (Table 2). . The sulfur atom increases chemical reactivity and coordination capability with metal ions, leading to potent cytotoxicity against cancer cell lines like A549 (IC50 ~ 2.5 μ\M), often superior to standard drugs like 5-fluorouracil [90].

MECHANISM OF ACTION OF PHENYTOIN

Phenytoin works by blocking voltage-gated sodium channels and keeping them in their inactive state for longer. This extends the refractory period, so neurons cannot fire repeatedly as easily. It acts on sodium channels in both brain and heart cells. In the brain, it mainly affects neurons that are firing very rapidly, like those involved in seizures, with a particular focus on the motor cortex. By doing this, it helps stop seizure activity from spreading and reduces the overactive brain stem signals that cause the stiffening (tonic phase) seen in tonic-clonic seizures (Fig. 17). In the heart, phenytoin slightly shortens the cardiac action potential and increases the time before the next impulse can occur [91, 92].

DISCUSSION

Structural modification of phenytoin has been a successful strategy in precluding its pharmacokinetic drawbacks and increasing its therapeutic scope. By intentional substitutions like N-alkylation, para-aryl functionalization, and heterocyclic hybridization, some analogs have shown enhanced anticonvulsant, antioxidant, anti-inflammatory, and antimicrobial activities.

Comparative analysis of structural diversification strategies

The structural modifications to the phenytoin core highlight distinct design philosophies, often involving trade-offs between potency, safety, and delivery.

Prodrugs versus N-Alkylation (Delivery vs. Metabolism)

The major limitation of injectable phenytoin (low solubility) was directly overcome by the rational design of the prodrug Fosphenytoin. Its solubility of 142 mg/mL allows for a significantly faster administration rate 150 mg PE/min compared to phenytoin, addressing a critical clinical need for status epilepticus. Conversely, simple N-alkylation (e.g., Mephenytoin) initially yielded compounds with comparable anticonvulsant potency (ED50sim 12.5 mg/kg vs. 10.0 mg/kg for phenytoin), but this structural change introduced severe toxicity and variable metabolism (CYP2C19 dependence), leading to its withdrawal. This exemplifies a key design lesson: optimizing delivery (Fosphenytoin) was more impactful than optimizing potency via simple N-substitution (Mephenytoin) [93].

Functionalization on the aryl rings leads to varied pharmacological profiles, demonstrating the impact of electronic effects.The nitro group (5-(4-Nitrophenyl) derivative, ED50sim 14.8 mg/kg is thought to enhance CNS affinity but introduces a critical safety trade-off. The electron-withdrawing nature, while potent, raises concerns regarding potential cytotoxicity and mutagenicity, demanding further optimization.In contrast, the hydroxyl group (5-(4-Hydroxyphenyl), or 4) is associated with detoxification as the major human metabolite, exhibiting enhanced aqueous solubility and antioxidant properties, making it a safer template for conjugation [94, 95].

Hybridization and functional expansion

Coupling the hydantoin core with other pharmacophores yields multi-functional agents. Schiff bases exhibit potency comparable to phenytoin (ED50sim 8.29 mg/kg) and, when used in combination, significantly enhance the protective index by over seven-fold, suggesting a major safety advantage. Similarly, Thiohydantoin analogues, modified at the C-2 position, expand the focus to non-epileptic uses, showing potent anticancer activity against cell lines like A549 IC50 sim 2.5 μM), often surpassing reference drugs like 5-FU [95, 96].

Impact of green chemistry on sustainable synthesis

Equally important as the use of green chemistry in synthesis is the use of methods like microwave-assisted reactions, solvent-free grinding, ultrasound irradiation, and continuous flow synthesis.Microwave-assisted reactions provide rapid and uniform heating, shortening reaction times from hours to mere minutes, significantly enhancing synthetic efficiency.Techniques such as solvent-free grinding represent the ultimate commitment to the 12 Principles of Green Chemistry by eliminating the use of toxic organic solvents and minimizing waste generation.Continuous flow synthesis allows for precise control of parameters (temperature, pressure, residence time), which is critical for safety, reproducibility, and industrial-scale production of high-purity derivatives.The synergy between diversification of structures and green synthetic pathways has the potential to fashion futuristic antiepileptic drugs that are safer, more efficient, and environmentally friendly [97, 98, 99, 100].

CONCLUSION

The structural diversity of phenytoin has led to a promising series of derivatives with improved pharmacokinetic and pharmacodynamic properties. Site-directed substitutions such as N-alkylation, aryl functionalization, and hybrid conjugation with heterocycles have resulted in several analogs with improved anticonvulsant, antioxidant, anticancer, and antimicrobial activity. The incorporation of quantitative data, such as the ED_{50} of the Schiff base analogs, sim. 8.29 mg/kg and the IC_{50} data for Thiohydantoin (sim. 2.5 μM for anticancer activity), validate the potential for these new derivatives to offer comparable potency to phenytoin while expanding the therapeutic spectrum. Prodrugs like Fosphenytoin, with their superior aqueous solubility 142 mg/mL), demonstrate the success of rational molecular design in overcoming clinical formulation limitations. Furthermore, the synthesis of hybrid molecules that enhance the PI suggests new avenues for safer combination therapies. Modern green synthetic techniques, particularly microwave-assisted and solvent-free protocols, have significantly enhanced the efficiency and environmental acceptability of phenytoin synthesis. This shift in methodology allows for rapid, scalable, and environmentally conscious synthesis of derivatives with shorter reaction times and higher yields. Overall, phenytoin continues to be a robust scaffold for anticonvulsant drug discovery, with new analogs having breakthrough potential for safety and efficacy. The advancement of medicinal chemistry with eco-sustainable synthetic methodologies holds promise for the continued development of next-

generation hydantoin-based therapeutics to meet modern clinical and regulatory demands [101-104].

ACKNOWLEDGMENT

The authors acknowledge the support and guidance received from the School of Pharmaceutical Sciences, CSJM University, Kanpur, for its resources and encouragement necessary to complete this work. Finally, the Authors thank the scientific community for its continuous efforts toward advancing greener synthesis, biological evaluation, and clinical translation of heterocyclic scaffolds, which have inspired and shaped the direction of this article.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

None.

REFERENCES

1. Raj T, Sylvia A, Chidambaranathan S, Nirmala P. A prospective study of drug utilization pattern of anti-epileptic drugs and their adverse effects in a tertiary care hospital. Henry Daniel. Int J Curr Pharm Res. 2018;10(4):50-3.
2. Sarma P, Bhattacharyya A. Models of epilepsy used in antiepileptic drug discovery: A review. J Pharm Pharm Sci. 2014 Oct;6:1-7.
3. Wadghane S, Bhor R, Shinde G, Kolhe M, Pooja R. A review on the some biological activities of the hydantoin derivatives. J Drug Deliv Ther. 2023 Jan 15;13(1):171-8. doi: 10.22270/jddt.v13i1.5904
4. Guerrab W, Lgaz H, Kansiz S, Mague JT, Dege N, Ansar M, *et al*. Synthesis of a novel phenytoin derivative: Crystal structure, Hirshfeld surface analysis and DFT calculations. J Mol Struct. 2020 May 15;1205:127630. doi: 10.1016/j.molstruc.2019.127630
5. Cho S, Kim SH, Shin D. Recent applications of hydantoin and thiohydantoin in medicinal chemistry. Eur J Med Chem. 2019 Feb 15;164:517-45. doi: 10.1016/j.ejmech.2018.12.066, PMID 30622025
6. Sarkar A, Santra S, Kundu SK, Hajra A, Zyryanov GV, Chupakhin ON, *et al*. A decade update on solvent and catalyst-free neat organic reactions: A step forward towards sustainability. Green Chem. 2016;18(16): 4475-525.
7. Katre SD. Microwaves in organic synthetic chemistry – a greener approach to environmental protection: An overview. Int J Chem Sci. 2007;5(2):489–501.
8. Pal R, Singh K, Paul J, Khan SA, Naim MJ, Akhtar MJ. Overview of chemistry and therapeutic potential of non-nitrogen heterocyclics as anticonvulsant agents. Current Neuropharmacology. 2022;20(8):1519-53.
9. Bialer M. Chemical properties of antiepileptic drugs (AEDs). Adv Drug Deliv Rev. 2012 Jul 1;64(10):887-95. doi: 10.1016/j.addr.2011.11.006, PMID 22210279
10. Vardanyan R, Hruby V. Synthesis of Essential Drugs. Netherlands: Elsevier; 2006 Mar 10.
11. McCleane GJ. Intramuscular fosphenytoin reduces neuropathic pain: A randomized, double-blind, placebo-controlled, crossover study. Analgesia. 1999 Jan 1;4(4):479-82.
12. Vatannavaz L, Sabounchei SJ, Sedghi A, Karamian R, Farida SH, Rahmani N. Synthesis, characterization, theoretical study and biological activity studies of the mercury (II) complexes of 5-methyl-5-(4-nitrophenyl)-hydantoin. J Chin Chem Soc. 2021 Nov;68(11): 2140-50. doi: 10.1002/jccs.202100135
13. Ohashi T, Takahashi S, Nagamachi T, Yoneda K, Yamada H. A new method for 5-(4-hydroxyphenyl) hydantoin synthesis. Agric Biol Chem. 1981 Apr 1;45(4):831-8.
14. Khirallah SM, Ramadan HM, Shawky A, Qahl SH, Baty RS, Alqadri N, *et al*. Development of novel 1,3-disubstituted-2-thiohydantoin analogues with potent anti-inflammatory activity; *In vitro* and *in silico* assessments. Molecules. 2022 Sep 23;27(19):6271. doi: 10.3390/molecules27196271, PMID 36234810
15. Abida MD, Tauquir Alam M, Asif M. Study of some hydantion derivatives as anticonvulsant agents. Prog Chem Biochem Res. 2020;3(2):93-104. doi: 10.33945/SAMI/PCBR.2020.2.2
16. Konnert L, Lamaty F, Martinez J, Colacino E. Recent advances in the synthesis of hydantoins: The state of the art of a valuable scaffold. Chem Rev. 2017 Dec 13;117(23):13757-809. doi: 10.1021/acs.chemrev.7b00067, PMID 28644621
17. Cherneva E, Buyukliev R, Shivachev B, Rusew R, Bakalova A. A new synthetic route for preparation of 5-methyl-5-benzylhydantoin: X-ray analysis and theoretical calculations. Molbank. 2025 Jan 22;2025(1):M1956. doi: 10.3390/M1956
18. Tchekalarova J, Todorov P, Rangelov M, Stoyanova T, Todorova N. Additive anticonvulsant profile and molecular docking analysis of 5,5'-diphenylhydantoin Schiff bases and phenytoin. Biomedicines. 2023 Oct 27;11(11):2912. doi: 10.3390/biomedicines11112912, PMID 38001914
19. Kalník M, Gabko P, Bella M, Koóš M. The Bucherer-Bergs multicomponent synthesis of hydantoins-excellence in simplicity. Molecules. 2021 Jun 30;26(13):4024. doi: 10.3390/molecules26134024, PMID 34209381
20. Banerjee S, Periyasamy S, Muthukumaradoss K, Deivasigamani P, Saravanan V. Revolutionizing organic synthesis through green chemistry: Metal-free, bio-based, and microwave-assisted methods. Front Chem. 2025;13:1656935. doi: 10.3389/fchem.2025.1656935, PMID 40832566
21. Chetry AB. Mechanochemistry: A new frontier in chemical synthesis. J Chem Res. 2025 May;49(3):299. doi: 10.1177/17475198251339299
22. Ahmad S, Jaiswal R, Yadav R, Verma S. Recent advances in green chemistry approaches for pharmaceutical synthesis. Sustain Chem One World. 2024 Dec 1;4:100029. doi: 10.1016/j.scowo.2024.100029
23. Kappe CO, Stadler A. Microwave-assisted organic synthesis. 2nd ed. Weinheim: Wiley-VCH; 2013.
24. Nagar MK, Waghmare KR, Dhabale PN, Chanekar PD, Bhatia S. Microwave assisted synthesis and characterization of phenytoin. Asian J Res Chem. Apr 2011;4(4):619-20.
25. Wenger LE, Hanusa TP. Synthesis without solvent: Consequences for mechanochemical reactivity. Chem Commun (Camb). 2023;59(96):14210-22. doi: 10.1039/D3CC04929A, PMID 37953718
26. Jin Z, Yan C, Chu H, Huang Q, Wang Z. Synthesis of benzoin under supramolecular catalysis involving cyclodextrins in water: Application for the preparation of the antiepileptic drug phenytoin. RSC Adv. 2022;12(17):10460-6. doi: 10.1039/D1RA09062C, PMID 35424977
27. Pagola S. Outstanding advantages, current drawbacks, and significant recent developments in mechanochemistry: A perspective view. Crystals. 2023 Jan 10;13(1):124. doi: 10.3390/cryst13010124
28. Siddique M, Rashid R, Ali A. Fundamentals of acoustic cavitation, ultrasound-assisted processes, and sonochemistry. In: In Modeling and Simulation of Sonogr-Processes. Netherlands: Elsevier; 2025 Jan 1. p. 3-17. doi: 10.1016/B978-0-443-23651-8.00001-2
29. Safari J, Naeimi H, Ghanbari MM, Sabzi Fini O. Preparation of phenytoin derivatives under solvent-free conditions using microwave irradiation. Russ J Org Chem. 2009 Mar 1;45(3):477-9. doi: 10.1134/S1070428009030270
30. Yang B, Zhai X, Mei R, Wang P, Mei Y. An improved ultrasound-assisted synthesis of phenytoin suitable for undergraduate education. Ultrason Sonochem. 2025 Jan 1;112:107207. doi: 10.1016/j.ultsonch.2024.107207, PMID 39718079
31. Baxendale IR, Brocken L, Mallia CJ. Flow chemistry approaches directed at improving chemical synthesis. Green Process Synth. 2013 Jun 1;2(3):211-30. doi: 10.1515/gps-2013-0029
32. Buglioni L, Raymenants F, Slattery A, Zondag SD, Noël T. Technological innovations in photochemistry for organic synthesis: Flow chemistry, high-throughput experimentation, scale-up, and photoelectrochemistry. Chem Rev. 2021 Aug 10;122(2):2752-906. doi: 10.1021/acs.chemrev.1c00332, PMID 34375082
33. Longstreet AR, McQuade DT. Organic reaction systems: Using microcapsules and microreactors to perform chemical synthesis. Acc Chem Res. 2013 Feb 19;46(2):327-38.
34. Ganesh KN, Zhang D, Miller SJ, Rossen K, Chirik PJ, Kozlowski MC, *et al*. Green chemistry: A framework for a sustainable future. ACS Omega. 2021 Jun 15;6(25):16254-8. doi: 10.1021/acsomega.1c03011, PMID 34235294
35. Sheldon RA. Metrics of green chemistry and sustainability: Past, present, and future. ACS Sustainable Chem Eng. 2018 Jan 2;6(1): 32-48. doi: 10.1021/acssuschemeng.7b03505
36. Kurul F, Doruk B, Topkaya SN. Principles of green chemistry: Building a sustainable future. Discov Chem. 2025 Apr 7;2(1):68. doi: 10.1007/s44371-025-00152-9
37. Elbarki A, Guerrab W, Laabaissi T, Benhiba F, Rouifi Z, Oudda H, *et al*. Chemical, electrochemical and theoretical studies of 3-methyl-5, 5'-diphenylimidazolidine-2, 4-dione as corrosion inhibitor for mild

steel in HCl solution. Chem Data Collect. 2020 Aug 1;28:100454. doi: 10.1016/j.cdc.2020.100454
38. Guerrab W, Akrad R, Ansar M, Taoufik J, Mague JT, Ramli Y. 3-methyl-5, 5-diphenylimidazolidine-2, 4-dione. IUCrData. 2017 Oct 28;2(10):x171534. doi: 10.1107/S2414314617015346
39. Al-Nuzal SM, Al-Dulaimi MF, Hassan AT. Synthesis and spectrometric study of some nucleophilic reactions of the antiepileptic molecule; 5, 5-diphenyl imidazolidine-2,4-dione. J Univ Anbar Pure Sci. 2018 Jan 1;12(1):38-53.
40. Guerrab W, Mague JT, Ramli Y. Synthesis and crystal structure of 3-octyl-5, 5-diphenylimidazolidine-2, 4-dione, C23H28N2O2. Z Kristallogr - New Cryst Struct. 2020 Oct 27;235(6):1425-7. doi: 10.1515/ncrs-2020-0347
41. Han L, Wang P, Wang Y, Zhao Q, Zheng F, Dou Z, *et al*. Rapid discovery of the potential toxic compounds in *Polygonum multiflorum* by UHPLC/Q-orbitrap-MS-based metabolomics and correlation analysis. Front Pharmacol. 2019 Apr 16;10:329. doi: 10.3389/fphar.2019.00329, PMID 31057397
42. Hulshoff A, Renema J, Roseboom H, Loriaux B, Rook B. Gas chromatographic alkylation studies of phenytoin, mephenytoin and primidone: Investigation of butylated derivatives. J Pharm Biomed Anal. 1983 Jan 1;1(2):169-79. doi: 10.1016/0731-7085(83)80024-7, PMID 16867815
43. Gordos J, Schäublin J, Spring P. Micro-determination of plasma diphenylhydantoin by gas-liquid chromatography. J Chromatogr. 1977 Mar 1;143(2):171-81. doi: 10.1016/S0378-4347(00)81822-8, PMID 838829
44. Hutt AJ, Hadley MR, Tan SC. Enantiospecific analysis: Applications in bioanalysis and metabolism. Eur J Drug Metab Pharmacokinet. 1994 Sep;19(3):241-51. doi: 10.1007/BF03188927, PMID 7867667
45. Buchwald AL. Mephenytoin overdose--phenytoin poisoning incognito? Case report and mephenytoin/phenytoin comparison. J Toxicol Clin Toxicol. 2000 Jan 1;38(7):781-5. doi: 10.1081/CLT-100102392, PMID 11192466
46. Kupferberg HJ, Yonekawa W. The metabolism of 3-methyl-5-ethyl-5-phenylhydantoin (mephenytoin) to 5-ethyl-5-phenylhydantoin (nirvanol) in mice in relation to anticonvulsant activity. Drug Metab Dispos. 1975 Jan 1;3(1):26-9. doi: 10.1016/S0090-9556(25)05616-8
47. Bettio L, Bankar G, Dubé CM, Nelkenbrecher K, Filipovic M, Singh S, *et al*. The pharmacokinetic and pharmacodynamic relationship of clinically used antiseizure medications in the maximal electroshock seizure model in rodents. Int J Mol Sci. 2025 Jul 22;26(15):7029. doi: 10.3390/ijms26157029, PMID 40806162
48. Kappe CO. Recent advances in the Biginelli dihydropyrimidine synthesis. New tricks from an old dog. Acc Chem Res. 2000 Dec 19;33(12): 879-88. doi: 10.1021/ar000048h, PMID 11123887
49. Nageshwaran S, Ledingham D, Wilson HC, Dickenson A, editors. Drugs in Neurology. Oxford: Oxford University Press; 2017 Jan 26.
50. Fujii J, Higashi A, Inotsume N, Matsuda I, Nakano M. Studies on pharmacokinetics of ethotoin in epileptic children and adolescents using a stable isotope. Rinshoyakuri/Japanese Clin Pharmacol Ther. 2001 Mar 31;32(2):59-64.
51. Troupin AS, Friel P, Lovely MP, Wilensky AJ. Clinical Pharmacology of mephenytoin and ethotoin. Ann Neurol. 1979 Nov;6(5):410-4. doi: 10.1002/ana.410060506, PMID 42344
52. Porcheddu A, Charnay C, Delogu F, Colacino E. From solution-based nonconventional activation methods to mechanochemical procedures: The hydantoin case. In: Nontraditional Activation Methods in Green and Sustainable Applications. Netherlands: Elsevier; 2021 Jan 1. p. 421-52. doi: 10.1016/B978-0-12-819009-8.00003-7
53. Schneider H, Janz D, Gardner-Thorpe C, Meinardi H, Sherwin AL, editors. Clinical pharmacology of anti-epileptic drugs. In: Workshop on the Determination of Anti-Epileptic Drugs in Body Fluid II (WODADIBOF II) Held in Bethel, Bielefeld, Germany, 24-25 May, 1974. Berlin: Springer Science+Business Media; 1974.
54. Johannessen SI. Pharmacokinetics of anti-epileptic drugs and their clinical significance. Behav Neurol. 1990;3(1):1-11. doi: 10.3233/BEN-1990-31S102, PMID 24487080
55. Di L, Kerns EH. Drug-Like Properties: Concepts, Structure Design and Methods from ADME to Toxicity Optimization. United States: Academic Press; 2015 Dec 17.
56. Elati CR, Gangula S, Naredla A, Ashok S, Bhattacharya A, Bandichhor R. Novel synthesis of fosphenytoin: Anti-convulsant prodrug. Synth Commun. 2008 Aug 18;38(17):2950-7.
57. Agrawal S, Gaikwad S, Patel R, Shinde L, Deshmukh A. Synthesis and formulation development of phenytoin by inclusion complexation. Indian J Pharm Sci. 2021 Sep 1;83(5):955-62. doi: 10.36468/pharmaceutical-sciences.848
58. Noval M, Seung H, Armahizer M. Evaluation of fosphenytoin therapeutic drug monitoring in the neurocritical care unit. Drugs R D. 2020 Mar;20(1):17-22. doi: 10.1007/s40268-019-00292-1, PMID 31925752
59. Martinho J, Simão AY, Barroso M, Gallardo E, Rosado T. Determination of antiepileptics in biological samples-a review. Molecules. 2024 Oct 2;29(19):4679. doi: 10.3390/molecules29194679, PMID 39407608
60. Knapp LE, Kugler AR. Clinical experience with fosphenytoin in adults: Pharmacokinetics, safety, and efficacy. J Child Neurol. 1998 Oct;13 Suppl 1(1 Suppl):S15-8; discussion S30-2. doi: 10.1177/088307389801300105l, PMID 9796747
61. Popławska M, Borowicz KK, Czuczwar SJ. The safety and efficacy of fosphenytoin for the treatment of status epilepticus. Expert Rev Neurother. 2015 Sep 2;15(9):983-92. doi: 10.1586/14737175.2015.1074523, PMID 26289487
62. Mahdizade Ari M, Dashtbin S, Ghasemi F, Shahroodian S, Kiani P, Bafandeh E, *et al*. Nitrofurantoin: Properties and potential in treatment of urinary tract infection: A narrative review. Front Cell Infect Microbiol. 2023 Jul 27;13:1148603. doi: 10.3389/fcimb.2023.1148603, PMID 37577377
63. Ji W, Li CL, Chen H, Yu ZX, Liao X. A newly designed heterodiene and its application to construct six-membered heterocycles containing an N-O bond. Chem Commun (Camb). 2019;55(80):12012-5. doi: 10.1039/C9CC05694G, PMID 31538167
64. Choudhary U, Kumar V, Dwivedi T, Ahmed W, Vishavjeet V, Rathi J, *et al*. Study of anticonvulsant drug (phenytoin) along with synthesis and pharmacological effect. Int J Med Sci Pharm Res. 2022 Dec 15;8(4): 13-5. doi: 10.22270/ijmspr.v8i4.52
65. Zeb A, Ali H, Khan JZ, Shah FA, Alattar A, Alanazi FE. *In silico* molecular docking and molecular dynamic simulation of transferrin coated phenytoin loaded SLNs with molecular targets of epilepsy. PLOS One. 2025 Jun 20;20(6):e0325772. doi: 10.1371/journal.pone.0325772, PMID 40540445
66. Poupaert JH, Cavalier R, Claesen MH, Dumont PA. Absolute configuration of the major metabolite of 5, 5-diphenylhydantoin, 5-(4'-hydroxyphenyl)-5-phenylhydantoin. J Med Chem. 1975 Dec;18(12):1268-71. doi: 10.1021/jm00246a024, PMID 1195283
67. Arboix M, Pantarotto C. Determination of 5, 5-diphenylhydantoin and its major metabolites in biological specimens by gas chromatography and selected ion-monitoring. Chromatographia. 1982 Aug;15(8): 509-13. doi: 10.1007/BF02260285
68. Ieiri I, Goto W, Hirata K, Toshitani A, Imayama S, Ohyama Y, *et al*. Effect of 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) enantiomers, major metabolites of phenytoin, on the occurrence of chronic-gingival hyperplasia: *In vivo* and *In vitro* study. Eur J Clin Pharmacol. 1995 Nov;49(1-2):51-6. doi: 10.1007/BF00192358, PMID 8751021
69. Muccioli GG, Fazio N, Scriba GK, Poppitz W, Cannata F, Poupaert JH, *et al*. Substituted 2-thioxoimidazolidin-4-ones and imidazolidine-2,4-diones as fatty acid amide hydrolase inhibitors templates. J Med Chem. 2006 Jan 12;49(1):417-25. doi: 10.1021/jm050977k, PMID 16392827
70. Abd Elhady H, El Desoky S, Al-Shareef HF, El-mekawy R. Synthesis, reactions, and applications of hydantoin and 2-thiohydantoin derivatives. Acta Pol Pharm Drug Res. 2019 Dec 29;76(6):971-86. doi: 10.32383/appdr/112124
71. Errayes A, Darwish M, Alzaedi A. Chemical synthesis strategies for thiohydantoin derivatives: A comprehensive review. Mediterr J Chem. 2025 Sep 29;15(2):241-55.
72. Kobyłka K, Żuchowski G, Tejchman W, Zborowski KK. Synthesis, spectroscopy, and theoretical calculations of some 2-thiohydantoin derivatives as possible new fungicides. J Mol Model. 2019 Sep; 25(9):268. doi: 10.1007/s00894-019-4146-9, PMID 31446500
73. González MT, Ariza JL, Pino F, Villanova RG. Derivatives of 2-thiohydantoin as spectrophotometric analytical reagents. Talanta. 1978 Jun 1;25(6):331-7. doi: 10.1016/0039-9140(78)80137-4, PMID 18962269
74. Khodair AI, Bakare SB, Awad MK, Al-Issa SA, Nafie MS. Design, synthesis, and computational explorations of novel 2-thiohydantoin nucleosides with cytotoxic activities. J Heterocycl Chem. 2022 Apr;59(4):664-85. doi: 10.1002/jhet.4405
75. Arani NM, Safari J. A rapid and efficient ultrasound-assisted synthesis of 5,5-diphenylhydantoins and 5,5-diphenyl-2-thiohydantoins. Ultrason Sonochem. 2011 Mar 1;18(2):640-3. doi: 10.1016/j.ultsonch.2010.09.001, PMID 20920873
76. Siopa F, Perry MJ, Francisco AP, Afonso CA. Batch and continuous

synthesis of 5, 5-diphenylhydantoin, an active pharmaceutical ingredient. J Chem Educ. 2025 Jul 15;102(8):3491-6. doi: 10.1021/acs.jchemed.4c01286
77. Sagratella S. Characterization of the *in vitro* antiepileptic activity of new and old anticonvulsant drugs. General Pharmacology: The Vascular System. 1998;30(2):153-60.
78. Castel-Branco MM, Alves GL, Figueiredo IV, Falcão AC, Caramona MM. The maximal electroshock seizure (MES) model in the preclinical assessment of potential new antiepileptic drugs. Methods Find Exp Clin Pharmacol. 2009;31(2):101-6. doi: 10.1358/mf.2009.31.2.1338414, PMID 19455265
79. Murtaza S, Akhtar MS, Aslam A, Riaz T, Kousar N. Schiff bases of 2, 4-dihydroxybenzaldehyde as potential anticonvulsant compounds; in vivo and docking studies. Acta Poloniae Pharmaceutica. 2017;74(6):1717-28.
80. Mallesha L, Mohana KN, Veeresh B. Synthesis and biological activities of Schiff bases of gabapentin with different aldehydes and ketones: a structure–activity relationship study. Medicinal Chemistry Research. 2012;21(1):1-9.
81. Batra N, Batra S, Nagori BP. Design, synthesis and evaluation of Schiff bases &thiazolidinone derivatives for anticonvulsant activity. J Appl Pharm Sci. 2014 Jan 30;4(1):105-12. doi: 10.7324/JAPS.2014.40118
82. Pal R, Kumar B, Akhtar MJ, Chawla PA. Voltage gated sodium channel inhibitors as anticonvulsant drugs: A systematic review on recent developments and structure activity relationship studies. Bioorg Chem. 2021 Oct 1;115:105230. doi: 10.1016/j.bioorg.2021.105230, PMID 34416507
83. Meijer JW, Meinardi H, Binnie CD. The development of antiepileptic drugs. In: Discoveries in Pharmacology-Volume 1-Nervous System and Hormones. Vol. 247. Netherlands: Elsevier Science; 2022 Sep 9.
84. Eichelbaum M, Kroemer HK, Fromm MF. Impact of P450 genetic polymorphism on the first-pass extraction of cardiovascular and neuroactive drugs. Adv Drug Deliv Rev. 1997 Sep 15;27(2-3):171-99. doi: 10.1016/S0169-409X(97)00042-2, PMID 10837557
85. Donnelly DM, Meegan MJ, Katritzky AR. Comprehensive heterocyclic chemistry. Ed. AR Katrizky. N.-Y.: Pergamon Press. 1984;4:657.
86. Allah AE, Guerrab W, Mague JT, Ramli Y. Novel approach to the synthesis of alkylated phenytoin scaffold. Moroccan J Heterocycl Chem. 2024 Nov 1;23(1):27-36.
87. Deodhar M, Sable P, Bhosale A, Juvale K, Dumbare R, Sakpal P. Synthesis and evaluation of phenytoin derivatives as anticonvulsant agents. Turkish Journal of Chemistry 2009;33(3):367-73.
88. Yaari Y, Selzer ME, Pincus JH. Phenytoin: Mechanisms of its anticonvulsant action. Ann Neurol. 1986 Aug;20(2):171-84. doi: 10.1002/ana.410200202, PMID 2428283
89. Barton ME, Klein BD, Wolf HH, White HS. Pharmacological characterization of the 6 Hz psychomotor seizure model of partial epilepsy. Epilepsy Res. 2001 Dec 1;47(3):217-27. doi: 10.1016/S0920-1211(01)00302-3, PMID 11738929
90. Poupaert JH, Vandervorst D, Guiot P, Moustafa MM, Dumont P. Structure-activity relationships of phenytoin-like anticonvulsant drugs. J Med Chem. 1984 Jan;27(1):76-8. doi: 10.1021/jm00367a015, PMID 6690687
91. Patocka J, Wu Q, Nepovimova E, Kuca K. Phenytoin-an anti-seizure drug: Overview of its chemistry, pharmacology and toxicology. Food Chem Toxicol. 2020 Aug 1;142:111393. doi: 10.1016/j.fct.2020.111393, PMID 32376339
92. Debnath S, Kannadasan M, Ghosh S, Ghosh NS, Chakraborty R, Sen S. Antiepileptic activity of the hydroalcoholic extract of *Erythrina fusca* lour bark against the animal models of mes, ptx and ptz induced epileptic seizure models. Int J Chem Res. 2010 Jan 1;1:6-10.
93. Wankhede S, Badule A, Chaure S, Damahe A, Damahe M, Porwal O. Challenges and strategies in prodrug design: A comprehensive review. J Adv Sci Res. 2025 Jun 30;16(6):1-20. doi: 10.55218/JASR.2025160601
94. Lamssane H, Haoudi A, Thiruvalluvar AA, Hökelek T, Varadharajan V, Chakroune S, *et al*. N-alkylated 5,5-diphenylhydantoin derivatives: Synthesis, X-ray, spectroscopic characterization, Hirshfeld surface analysis, DFT, molecular docking, molecular dynamics simulations, and cholesterol oxidase binding affinity estimation. ACS Omega. 2025 Jul 7;10(27):29267-84. doi: 10.1021/acsomega.5c02215, PMID 40686988
95. Prabhu G, Basavaprabhu N, Narendra N, Vishwanatha TM, Sureshbabu VV. Amino acid chlorides: A journey from instability and racemization toward broader utility in organic synthesis including peptides and their mimetics. Tetrahedron. 2015 May 13;71(19):2785-832. doi: 10.1016/j.tet.2015.03.026
96. Rasmussen JK, Heilmann SM, Krepski LR, Smith HK, Katritzky AR, Sakizadeh K. Poly (2-imidazolin-5-ones)-a new class of heterocyclic polymers. J Polym Sci A Polym Chem. 1986 Nov;24(11):2739-47. doi: 10.1002/pola.1986.080241103
97. Kadam A, Jangam S, Oswal R. Application of green chemistry principle in synthesis of phenytoin and its biogical evaluation as anticonvulsant agents. J Chem. 2011;8(S1):S47-52. doi: 10.1155/2011/159430
98. Kar S, Sanderson H, Roy K, Benfenati E, Leszczynski J. Green chemistry in the synthesis of pharmaceuticals. Chem Rev. 2021 Dec 15;122(3):3637-710. doi: 10.1021/acs.chemrev.1c00631, PMID 34910451
99. Ahsan H, Islam SU, Ahmed MB, Lee YS, Sonn JK. Significance of green synthetic chemistry from a pharmaceutical perspective. Curr Pharm Des. 2020 Dec 1;26(45):5767-82. doi: 10.2174/1381612826666200928160851, PMID 32988346
100. Gupta P, Mahajan A. Green chemistry approaches as sustainable alternatives to conventional strategies in the pharmaceutical industry. RSC Adv. 2015;5(34):26686-705. doi: 10.1039/C5RA00358J
101. Gupta M, Tripp J. Phenytoin. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2025 Jan.
102. Botros S, Khalil NA, Naguib BH, El-Dash Y. Synthesis and anticonvulsant activity of new phenytoin derivatives. European journal of medicinal chemistry. 2013;60:57-63.
103. Sari SP, Salma SNK, Rianti A. Monitoring of anticonvulsant drug side effects in outpatients with epilepsy. Int J Appl Pharm. 2018 Dec 1;10(1):303-6. doi: 10.22159/ijap.2018.v10s1.67
104. Melkani I, Kumar B, Pandeynk NK, Singh S, Baghel DS, Sudhakar K. Therapeutic impact of nanomedicine for the treatment of neuropathic pain: Principle, prospective and future. Int J App Pharm. 2024; 16(5):46-58.