UDC 615.214.2/.012(477)
DOI: 10.15587/2519-4852.2025.337842

STRUCTURAL-FRAGMENT ANALYSIS OF ACTIVE PHARMACEUTICAL INGREDIENTS OF ANTIEPILEPTIC DRUGS IN GROUP N03A OF THE UKRAINIAN PHARMACEUTICAL MARKET AND THEIR PHARMACOPHORIC FEATURES

Maryna Stasevych, Mykhailo Hoidyk, Olexandra Roman, Roksolana Konechna, Andriy Karkhut, Andrii Lozynskyi, Svyatoslav Polovkovych, Roman Lesyk

Epilepsy affects approximately 50 million people globally, with one-third of patients remaining resistant to available therapies, emphasizing the need for new and safer anticonvulsants. Although fragment-based and in silico approaches are effective for drug discovery, a unified structural analysis of antiepileptic APIs on the Ukrainian market remains unexplored.

The aim of the study. *To analyze 16 antiepileptic APIs registered in Ukraine using fragment-based methods to identify shared pharmacophoric features, structural similarities, and correlations between structural fragments and ADME properties (including drug-likeness patterns for structure-property insights) as a basis for rational anticonvulsant design.*

Materials and methods. *Data were collected from the State Register of Medicinal Products of Ukraine and Compendium (June 2025) using ATC code N03A. Literature review used PubMed, PubChem, DrugBank, Scopus, Elicit, and ResearchRabbit. Structural analysis was performed using Python libraries.*

Results. *The study classified 16 active pharmaceutical ingredients (APIs) into structural clusters (e.g., barbiturates, dibenzazepines, amino acid derivatives) based on Tanimoto similarity coefficients and ECFP4 molecular fingerprints. Commonly identified fragments included carbonyl, amino, amide, carboxyl groups, and aromatic rings. ADME profiling revealed consistent relationships between structural features and physicochemical properties: high lipophilicity in benzodiazepines and good absorption characteristics in gabapentinoids. This analysis was performed to identify structure-dependent ADME patterns, providing a basis for fragment-based design of novel anticonvulsants.*

Conclusions. *Despite chemical diversity, the analyzed APIs exhibit shared spatial pharmacophore arrangements with recurring groups supporting activity at NaV, CaV, GABA-A, SV2A, and GABA-T. ADME profiling and structure–property correlations provide a basis for pharmacophore fragment modelling and CNS-oriented fragment-library design to enable rational discovery. Future design should leverage the identified pharmacophoric fragments to build multitarget molecules within a CNS ADME window*

Keywords: *antiepileptic drugs, APIs, FBDD, pharmacophore, structural clustering, ADME, Tanimoto similarity, NaV, GABA-A, SV2A, carbonic anhydrase, Ukrainian pharmaceutical market*

How to cite:
Stasevych, M., Hoidyk, M., Roman, O., Konechna, R., Karkhut, A., Lozynskyi, A., Polovkovych, S., Lesyk, R. (2025). Structural-fragment analysis of active pharmaceutical ingredients of antiepileptic drugs in group N03A of the Ukrainian pharmaceutical market and their pharmacophoric features. ScienceRise: Pharmaceutical Science, 4 (56), 20–34. http://doi.org/10.15587/2519-4852.2025.337842

1. Introduction

Epilepsy is one of the most widespread chronic neurological disorders globally. According to the World Health Organization, approximately 50 million people suffer from it, with more than 70% of cases occurring in low- and middle-income countries [1]. Despite the availability of a wide range of pharmacotherapies, about one-third of patients remain pharmacoresistant, highlighting the need to identify new, more effective, and safer antiepileptic agents [2].

Computer-aided methods, particularly fragment-based design and *in silico* screening, have demonstrated high efficiency in the discovery and optimization of drugs, including anticonvulsants [3, 4]. There are documented cases of rational structural modifications that significantly reduced toxicity (e.g., the transition from carbamazepine to oxcarbazepine) or improved bioavailability through prodrug forms and molecular stereospecificity. However, the literature lacks a systematic comparison of all antiepileptic active pharmaceutical ingredients (APIs) currently available on the Ukrainian market within a unified fragment-based field capable of outlining the "chemical space" of effective anticonvulsant agents.

According to data from the State Register of Medicinal Products of Ukraine [5] and the Compendium information resource [6], antiepileptic drugs used in the therapy of anticonvulsant conditions are represented by group N03A, which includes the following subgroups: N03A A Barbiturates and their deriva-

tives (N03A A02 Phenobarbital, N03AA05 Benzobarbital), N03A B Hydantoin derivatives (N03A B02 Phenytoin), N03A E Benzodiazepine derivatives (N03A E01 Clonazepam), N03A F Carboxamide derivatives (N03A F01 Carbamazepine, N03A F02 Oxcarbazepine, N03A F04 Eslicarbazepine), N03A G Fatty acid derivatives (N03A G01 Valproic acid, N03A G04 Vigabatrin), N03A X Other antiepileptics (N03A X09 Lamotrigine, N03A X11 Topiramate, N03A X14 Levetiracetam, N03A X15 Zonisamide, N03A X18 Lacosamide, and gabapentinoids – N03A X12 Gabapentin and N03A X16 Pregabalin).

In total, antiepileptic drugs on the Ukrainian pharmaceutical market are represented by 16 unique APIs, classified within ATC subgroup N03A. The majority of these substances (43.75%) belong to subgroup N03A X – Other antiepileptic drugs, which demonstrates the highest degree of structural and mechanistic diversity. This is followed by N03A F (18.75%) – Carboxamide derivatives, and two equally represented subgroups – N03A A (barbiturates) and N03A G (fatty acid derivatives) – each accounting for 12.5%. The smallest shares belong to N03A B (hydantoins) and N03A E (benzodiazepines), each comprising 6.25%. This distribution underscores both the historical development of epilepsy treatment and the broad chemical space explored in the design of anticonvulsant agents.

Despite the availability of a broad spectrum of antiepileptic drugs, approximately 30% of patients remain resistant to therapy, creating a pressing need for the development of new, more effective and safer medications. Antiepileptic drugs exhibit diverse mechanisms of action, yet their efficacy and side effect profiles vary considerably. This variability necessitates the search for new therapeutic agents capable of overcoming the limitations of current antiepileptic medications [7–9].

Antiepileptic drugs presented on the pharmaceutical market of Ukraine are the result of decades of research and clinical trials. They represent successful examples of molecules with proven antiepileptic activity, characterized by significant diversity in chemical structure, mechanisms of action, and therapeutic spectra.

In this context, structural analysis of antiepileptic drugs serves two key purposes. First, it enables the identification of recurrent and unique pharmacophoric elements that determine selectivity toward primary molecular targets. Second, it lays the analytical foundation for subsequent fragment-oriented design of novel molecules capable of overcoming pharmacoresistance and improving safety profiles.

The aim of this study was to conduct a comprehensive fragment-based analysis of 16 antiepileptic APIs, which form the basis of numerous medicinal products registered in Ukraine. The analysis involved the evaluation and systematization of their chemical similarity, pharmacophoric structural frequency, identification of key substructures, and assessment of basic ADME parameters, together establishing a basis for the rational design of novel anticonvulsant agents.

2. Planning (methodology) of the research

The planning of the study was based on an integrative cheminformatics strategy aimed at the systematic analysis of the structural and pharmacophoric properties of antiepileptic APIs registered in Ukraine. The research design followed a multistep algorithm encompassing the rational selection of study objects, data extraction from validated sources, and computational modelling using modern open-access tools. The methodological strategy was grounded in the principles of Quality by Design (QbD) to ensure systematic planning, reproducibility, and predictive analytical value.

The planning stage involved the following key components: object selection, data extraction, analytical algorithm and outcome orientation. The study focused on 16 antiepileptic APIs from ATC group N03A, identified through Ukrainian regulatory sources. This ensured a broad representation of diverse chemical scaffolds and mechanisms of action among antiepileptic agents.

The experimental plan followed a logical and reproducible sequence (Fig. 1).

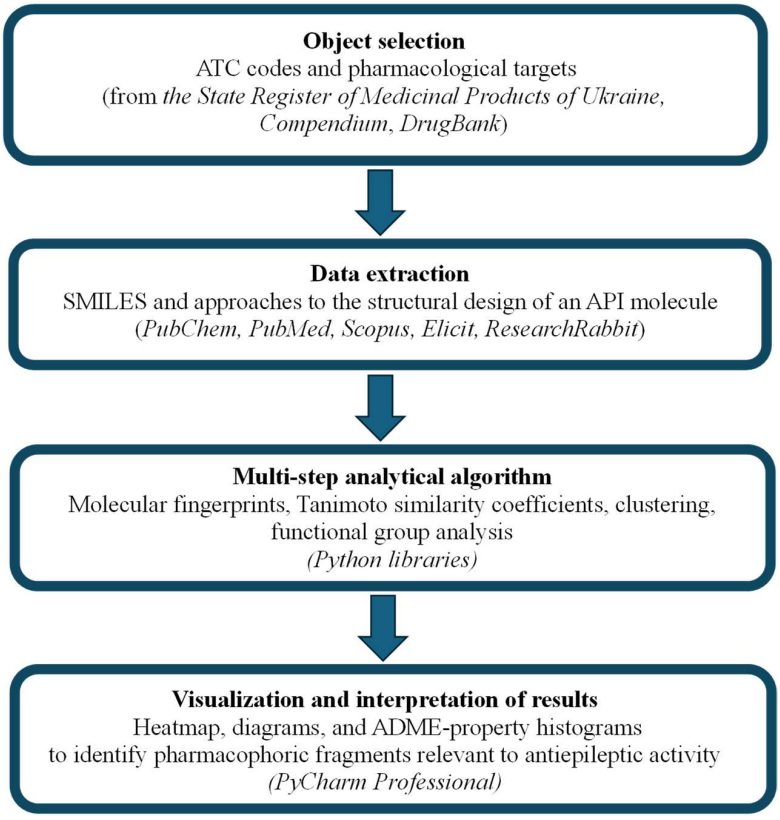


Fig. 1. Algorithm of the structural-fragment analysis of 16 antiepileptic APIs

For each API, molecular structures (SMILES), ATC classification, and pharmacological targets were collected from validated public databases and recent scientific literature, including AI Research Assistants Elicit and ResearchRabbit. The research followed a multi-step analytical algorithm:

1) structural data collection;

2) generation of molecular fingerprints (ECFP4);

3) assessment of structural similarity (Tanimoto coefficients);

4) clustering analysis (KMeans algorithm);

5) functional group and scaffold extraction;

6) visualization and interpretation of structure-activity-property relationships.

Clustering was conducted to group structurally related APIs into distinct clusters. Similarity between 16 APIs was evaluated using Tanimoto coefficients. The planned outcome was to identify frequent and unique pharmacophoric fragments relevant to antiepileptic activity. These insights were intended to support rational design of novel anticonvulsant candidates and development of fragment libraries.

3. Materials and methods

Data on antiepileptic APIs registered on the Ukrainian pharmaceutical market were obtained from the State Register of Medicinal Products of Ukraine [5] and the Compendium information resource [6] (accessed June 2025). An advanced search in the State Register was performed using the ATC code N03A.

A systematic literature search was conducted using the databases PubMed, PubChem, DrugBank, Scopus, as well as AI-based search assistant tools Elicit and ResearchRabbit. The data collected were processed through analytical, comparative, and generalization methods.

Computational work was performed using Python 3.10. Molecular structures (SMILES) for 16 antiepileptic APIs were retrieved from PubChem. Calculation of circular molecular fingerprints (ECFP4) and Tanimoto similarity coefficients was performed using RDKit 2023.03.4 (RDKit: Open-source cheminformatics). Clustering was carried out using the k-means method from the scikit-learn 1.3.0 library. Functional group analysis was applied to identify shared pharmacophoric patterns. Graphical visualizations (diagrams, heatmap, ADME histograms) were created using matplotlib 3.8.0 and seaborn 0.13.0. All scripts were developed, debugged, and executed in PyCharm Professional 2024.1 with the integrated Python interpreter. Graphs were previewed via the SciView IDE module, and final images were exported in PNG format at 300 dpi resolution.

The ADME profiling, including evaluation of drug-likeness criteria (e.g., Lipinski's rule), was conducted not as a primary screening tool but to uncover relationships between identified structural fragments and physicochemical properties, facilitating insights for the rational design of new anticonvulsant candidates.

4. Results

Fragment-Based Drug Design (FBDD) or fragment analysis is a powerful and versatile approach in the modern discovery of novel pharmaceuticals. Applying fragment analysis principles to the structure of already existing, clinically effective antiepileptic drugs is a valuable strategy for identifying key structural elements (pharmacophores) responsible for anticonvulsant activity. This can significantly aid in the development of new molecules with enhanced selectivity, reduced toxicity, and improved antiepileptic efficacy.

To date, a few studies have employed fragment-based approaches in the molecular design of compounds with anticonvulsant properties [10–15]. However, the mentioned studies have either applied fragment-based design, structural optimization, or *ab initio* calculations for selected compounds only. There has been no documented attempt to apply a unified structural and fragment-based approach to the full list of 16 antiepileptic APIs.

Thus, a structural analysis of the full set of these 16 antiepileptic active substances is crucial for the rational development of new chemical entities with selective anticonvulsant action. This analysis enables:

– identification of molecular fragments frequently occurring or unique among clinically effective antiepileptic drugs, regardless of their specific mechanisms of action;

– detection of shared structural motifs among compounds with different chemical scaffolds but similar pharmacological effects, which may indicate "convergent" evolution of effective structures;

– understanding the "chemical space" associated with successful antiepileptic molecules, offering insight into the preferred size, flexibility, polarity, and other physicochemical characteristics of effective structural fragments;

– creation of a library of "active" fragments derived from known antiepileptic drugs, which can serve as starting points or building blocks for designing entirely new chemical entities;

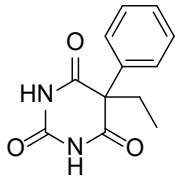
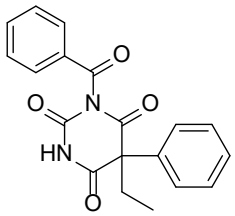
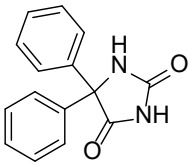
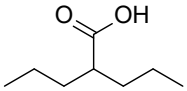
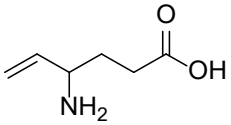
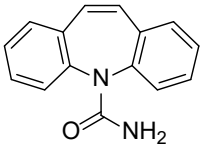
– providing a rational basis for combining, expanding, or modifying identified fragments to generate novel molecular structures with improved properties, potentially enhanced efficacy, better safety profiles, or new mechanisms of action.

In the first phase of this study, we analyzed the historical data on molecular design, chemical structure, and mechanisms of action for each API (Table 1). In addition to classical databases such as PubMed, PubChem, DrugBank, and Scopus, advanced AI-driven platforms Elicit and ResearchRabbit were used to retrieve recent open-access research relevant to molecular design strategies for the listed antiepileptic APIs.

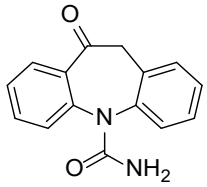
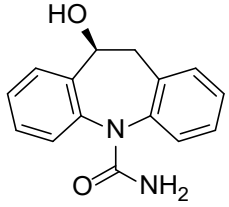
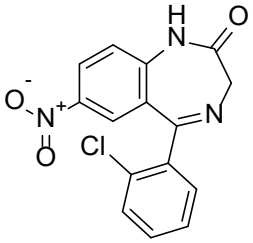
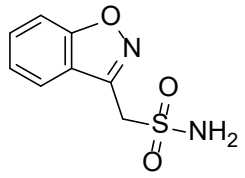
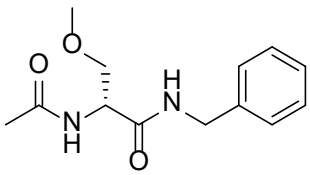
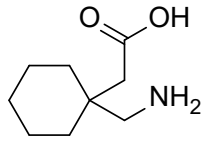
Analysis of the molecular structures of antiepileptic APIs across all six subgroups of ATC group N03 A (Table 1) reveals structural diversity. Besides the five well-defined subgroups (N03A A – N03A G), classified by structural characteristics, the sixth subgroup – N03A X (Other antiepileptics), includes 7 APIs. While some of these share structural similarities, others do not. This subgroup comprises hetero(carbocyclic) compounds based on benzoisoxazole (zonisamide), 1,2,4-triazine (lamotrigine), and β-D-fructopyranose (topiramate) cores, as well as aliphatic amino acid derivatives (gabapentin, pregabalin, levetiracetam, lacosamide).

Table 1

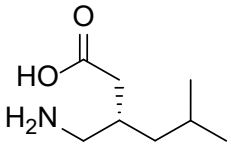
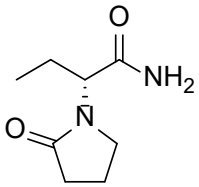
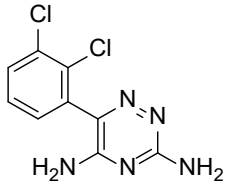
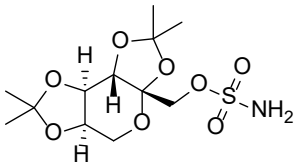
Data on molecular structure, mechanism of action (MoA), and molecular design approaches of antiepileptic APIs on the Ukrainian pharmaceutical market

INN/ATC code/Structure /MoA	Approaches to the structural design of an API molecule
1	2
Phenobarbital (N03A A)  Allosteric modulator of GABA-A receptors [16]	Modifications at the 5th position: – introduction of a phenyl group increases the lipophilicity of the molecule and enhances its ability to cross the blood-brain barrier; incorporation of (halo)aryl substituents improves both activity and lipophilicity; – the presence of alkyl groups (Me, Et, iPr) influences the duration of the pharmacological effect; specifically, the ethyl group is responsible for the prolonged action and anticonvulsant effect, whereas the introduction of an amyl moiety leads to a decrease in anticonvulsant efficacy. The presence of keto groups is essential for binding to GABA-A receptors. Simultaneous substitution of hydrogen atoms at the amino positions in the secondary amine groups of the barbiturate ring reduces anticonvulsant activity [17–25]
Benzobarbital (N03A A)  Allosteric modulator of GABA-A receptors [26, 27]	It is an *N*-benzoyl derivative of phenobarbital, representing a pharmacophore-optimized version of phenobarbital focused on achieving a balance between lipophilicity, duration of action, and pharmacological activity. This modification enhanced the anticonvulsant properties while minimizing undesired sedative effects. The benzoyl group increased the aromatic character of the molecule, thereby improving lipophilicity and blood-brain barrier (BBB) permeability, as well as enhancing interaction with target receptors. A number of studies have been directed toward identifying various [25, 28–31]
Phenytoin (N03A B)  Blocks voltage-gated sodium channels (NaV1.1-1.6) [32]	The hydantoin system mimics certain properties of barbituric acid. The presence of two phenyl groups increases the molecule's lipophilicity and confers high affinity for NaV channels. Unsubstituted secondary NH groups enable hydrogen bonding within the active site of the target protein. The molecular structure allows phenytoin to selectively block sodium channels in their activated state without affecting the GABAergic system, which is a major advantage over the barbiturate subgroup. Substitution of one phenyl ring with an alkyl group reduces both anticonvulsant activity and lipophilicity. Incorporation of trifluoromethyl groups into the structure significantly decreased anticonvulsant activity due to steric hindrance during receptor binding [33–38]
Valproic acid (N03A G)  Inhibits GABA transaminase, activates glutamate decarboxylase, blocks sodium channels (NaV), inhibits T-type calcium channels [39]	The structural modification is characterized by sequential chemical changes aimed at increasing anticonvulsant activity and reducing undesirable toxic effects, particularly hepatotoxicity and teratogenicity. The carboxyl group facilitates protein binding. Amides and esters (such as sodium valproate and valpromide) have improved solubility and modified release profiles. Amide derivatives, notably valpromide and valnoctamide, exhibit enhanced blood-brain barrier (BBB) permeability and increased anticonvulsant activity compared to the parent acid. Another important direction of chemical modifications involves altering the molecule's alkyl chains by introducing unsaturated fragments. Incorporation of triple-bond fragments into the molecule has led to the discovery of new (antitumor) properties [40–44]
Vigabatrin (N03A G)  Inhibits GABA transaminase [45]	Derived through structural modification of GABA, the vinyl fragment forms a covalent bond with the active site of GABA transaminase (GABA-T), while the presence of a primary amino group mimics the α-amino group of GABA, which is essential for recognition and binding to the target enzyme. The carboxyl group acts analogously to the γ-carboxyl group of GABA. A six-carbon alkyl chain ensures spatial compatibility with the enzyme's binding site. Only the S(+)-enantiomer exhibits high affinity for GABA-T and is responsible for the primary pharmacological activity, whereas the R(-)-enantiomer is essentially inactive [46–49]
Carbamazepine (N03A F)  Blocks voltage-gated sodium channels (NaV), exerts weak effects on GABA or calcium channels [50]	The development of the carbamazepine molecule was based on chemical modification of dibenzazepine (iminostilbene) aimed at simultaneously improving pharmacokinetic properties and reducing toxicity. The carbamoyl group is essential for binding to sodium channels and significantly influences pharmacokinetics. Its substitution with other functional groups leads to the loss of antiepileptic activity. Substitutions in the azepine ring disrupt their conformation, negatively affecting anticonvulsant efficacy. The introduction of a carbonyl group into the azepine ring converts it into a prodrug, paving the way for the development of oxcarbazepine and eslicarbazepine [38, 41]

Continuation of Table 1

1	2
Oxcarbazepine (N03A F)  Inhibits sodium and calcium channels; activates potassium channels [46]	The introduction of a carbonyl group in the azepine ring led to a reduction in hepatotoxic metabolites. Replacing the carbonyl group at position 10 with a hydroxyl group resulted in the formation of eslicarbazepine, which exhibits enhanced antiepileptic activity. The substitution of the aromatic groups leads to a loss of affinity for sodium channels. Replacement of the carbamoyl group results in loss of activity [21, 38, 41, 46]
Eslicarbazepine (N03A F)  Inhibits sodium and calcium channels [51]	Eslicarbazepine represents the culmination of rational structural modifications aimed at improving efficacy, tolerability, and pharmacokinetic properties compared to earlier dibenzazepine-based antiepileptic drugs – carbamazepine and oxcarbazepine. The chemical strategy involved the use of the active metabolite of oxcarbazepine – (S)-eslicarbazepine which was synthesized in a prodrug (acetate) form to enhance bioavailability, controlled release, and stereoselectivity. The (S)-configuration provides higher antiepileptic activity and lower toxicity, along with significantly greater affinity for NaV sodium channels. The hydroxyl group is essential for interaction with sodium channels. Even minimal alterations to the molecular “core” lead to a loss of activity or increased toxicity [41, 46, 52–57]
Clonazepam (N03A E)  Positive allosteric modulator of the GABA-A receptor [58]	The 1,4-benzodiazepine core is a key pharmacophore for interaction with the GABA-A receptor. Modifications of the secondary amine group affect pharmacokinetics but rarely enhance anticonvulsant activity. The 2-chlorophenyl group increases the molecule’s lipophilicity and improves blood-brain barrier (BBB) penetration. Substitution of the chlorine atom with other halogens alters activity. The presence of a nitro group at position 7 is crucial for anticonvulsant efficacy; replacing it with H or CH_3 leads to reduced anticonvulsant activity. The keto group at position 2 is responsible for binding to the allosteric site of GABA-A. Substitution of the keto group with -OH alters the duration of action. Modification of the keto group to generate annelated triazole derivatives (e.g., clonazolam) increases affinity for GABA-A receptors. The absence of a chlorine atom in the phenyl moiety (e.g., nitrazepam) results in weakened anticonvulsant activity and increased sedative effects. Replacing the nitro group with a hydroxyl group (e.g., lorazepam) leads to prolonged duration of action. Substitution of the secondary amino group in the diazepine ring with a methyl group and replacement of chlorine with fluorine in the phenyl residue (e.g., flunitrazepam) results in pronounced hypnotic and sedative activity [52, 59–62]
Zonisamide (N03A X)  Inhibits sodium and calcium channels, inhibits carbonic anhydrase [45]	Originally developed as an antibacterial sulfonamide (due to its structural similarity to sulfamethoxazole), this compound lacks classical pharmacophores typical of barbiturates, diazepines, or hydantoins, and therefore exhibits a combined mechanism of action. The molecule is small and possesses good lipophilicity. The benzoxazole core facilitates BBB penetration. The sulfonamide group contributes to the inhibition of sodium and calcium channels. Substitution of the benzisoxazole ring with other heterocycles results in reduced activity, while the absence of the sulfonamide group diminishes anticonvulsant efficacy. Replacing the sulfonamide group with a pyrrolidine-2,5-dione substituent retains anticonvulsant activity [38, 45, 63–68]
Lacosamide (N03A X)  Selectively modulates slow inactivation of NaV channels [46]	The (R)-configuration at the C-3 center is critical for pharmacological activity, as the (S)-enantiomer is nearly inactive. Substituting the (R)- with the (S)-configuration results in a loss of activity. The *N*-benzyl group contributes to lipophilicity and BBB penetration and is also essential for interaction with NaV channels. The introduction of a methoxy group was decisive in enhancing anticonvulsant activity. It also improves water solubility and metabolic stability. Replacing the methoxy group with halogens increases toxicity and deteriorates pharmacokinetic properties [46, 68–71]
Gabapentin (N03A X)  Binds to the $\alpha_2\delta$-1 subunit of voltage-gated calcium channels [46]	The cyclohexane ring stabilizes the molecule and mimics the spatial arrangement of GABA without affecting its acid-base properties. The aminomethylene group is crucial for binding to the $\alpha_2\delta$ subunit of calcium channels. The carboxyl group mimics the polar portion of GABA and retains comparable acidity [41, 46, 72, 73]

Continuation of Table 1

1	2
Pregabalin (N03A X)  Binds to the $\alpha_2\delta$ subunit of voltage-gated calcium channels [46]	Pregabalin was developed as a stereospecific derivative of gabapentin, in which the (S)-enantiomer proved to be significantly more active than the (R)-enantiomer. The primary objective of its development was to improve affinity for the $\alpha_2\delta$-1 subunit of voltage-gated calcium channels in the central nervous system, thereby enhancing efficacy in the control of pain and seizures. To achieve this, the cyclohexane ring present in gabapentin was replaced with an isobutyl moiety, improving the molecule's lipophilicity [41, 46, 74–81]
Levetiracetam (N03A X)  Binds to the synaptic vesicle protein SV2A [46], inhibits N-type potassium and calcium channels [82]	During structural modification of piracetam aimed at enhancing neuronal activity, anticonvulsant properties were discovered accidentally. The pyrrolidone moiety improves BBB permeability. The acetamide side chain is essential for binding to target sites. The (S)-stereocenter confers high bioactivity, whereas the R-enantiomer is virtually inactive. Modification of the pyrrolidone fragment (as in brivaracetam) led to increased affinity for SV2A [38, 41, 46, 83–87]
Lamotrigine (N03A X)  Blocks voltage-gated sodium channels [87], inhibits serotonin receptors [46]	Over the years, numerous strategies have been employed to modify the structure of this compound in order to improve solubility, bioavailability, and safety, as well as to fine-tune its physicochemical properties. A central aspect in the study of lamotrigine's structure has been its tautomerism. Both theoretical and experimental studies have demonstrated that lamotrigine predominantly exists in the diamino tautomeric form, which is thermodynamically favoured over alternative forms. Comparative studies of lamotrigine and its analogs have emphasized the importance of substituent effects on both the aromatic ring and the 1,2,4-triazine core. The 1,2,4-triazine core serves as the binding center for ion channels. Diamino groups at positions 3 and 5 enhance water solubility and participate in hydrogen bonding with biological targets. The substitution of the amino groups results in reduced anticonvulsant activity. The 2,3-dichlorophenyl group at position 6 significantly increases lipophilicity and facilitates blood-brain barrier (BBB) penetration. Variations in chlorine substitution aimed at further improving lipophilicity generally have little impact on overall efficacy. Replacing chlorine atoms with other halogens or methyl groups at specific positions of the dichlorophenyl ring yields derivatives with improved metabolic stability and altered affinity for ion channels. The formation of fluorinated lamotrigine analogs has also been associated with anti-inflammatory activity. Structural modification of lamotrigine through transformation of the 1,2,4-triazine ring into a 1,4-pyrazine ring and the introduction of an additional chlorine atom into the phenyl moiety led to the discovery of a new effective antiepileptic candidate, JZP-4 [38, 41, 46, 88–90]
Topiramate (N03A X)  Blocks calcium and sodium channels (NaV), potentiates GABA-A receptors, inhibits carbonic anhydrase [91], inhibits MPA/KA-type glutamate receptors [46]	The initial goal was to develop new carbonic anhydrase inhibitors based on saccharide structures. Topiramate became the first drug structurally related to monosaccharides, whereas most antiepileptics are lipophilic aromatic compounds. The fructopyranose ring provides high solubility and bioavailability. Isopropylidene groups enhance lipophilicity. The sulfamate group is a key inhibitory fragment for carbonic anhydrase and also modulates the drug's effects on ion channels. Even minor modifications to the fructopyranose scaffold or the sulfamate group can significantly influence both the inhibitory potential against carbonic anhydrase and the anticonvulsant efficacy. Removal of the sulfamate group from the molecule leads to a loss of carbonic anhydrase inhibition and anticonvulsant activity. Changes in the linker length between the sulfamate group and the pyran ring, as well as alterations in the steric substituents around the ring oxygen atoms, correlate with changes in the inhibition of constant values toward various human carbonic anhydrase isoforms. One of the key strategies for topiramate modification involved the synthesis of cyclic sulfur-containing derivatives, such as the cyclic candidate RWJ-37947. Derivatives in which the sulfamate group was replaced by tetrazole or oxadiazole rings retained hydrogen bonding capacity but exhibited altered affinity toward carbonic anhydrase [38, 41, 46, 92–97]

5. Discussion

The summarized results regarding the key structural fragments of antiepileptic active pharmaceutical ingredients (APIs) and their target interactions indicate significant diversity in molecular features and mechanisms of action. Gabapentin and pregabalin, both characterized by aliphatic backbones with $-CH_2NH_2$ and -COOH functional groups, act primarily through modulation of voltage-gated calcium channels (CaV). Vigabatrin, which contains unsaturated $-CH = CH_2$, $-CH_2NH_2$, and COOH moieties, uniquely targets GABA metabolism by inhibiting GABA transaminase (GABA-T). Levetiracetam, distinguished by its pyrrolidone ring and $CONH_2$ group, interacts with CaV channels and the synaptic vesicle glycoprotein SV2A, in-

dicating a dual mechanism. Lamotrigine possesses a 1,2,4-triazine core with a chlorinated phenyl ring and amino group (-NH_2), exhibiting activity on sodium channels (NaV) and the SV2A system. Topiramate, a structurally complex molecule containing a fructopyranose ring, sulfonamide (-SO_2NH_2), and gem-dimethyl substituents, shows the broadest pharmacodynamic spectrum – modulating NaV and CaV channels, potentiating GABA-A receptors, and inhibiting carbonic anhydrase (CA-II). Valproic acid, with its branched aliphatic structure and carboxylic group, exhibits threefold activity: on NaV and CaV channels and inhibition of GABA-T. The carboxamide derivatives-carbamazepine, oxcarbazepine, and eslicarbazepine-share a common dibenzazepine core, with variations in functional groups (-$CONH_2$, -C = O, -OH), and act primarily on NaV channels; oxcarbazepine and eslicarbazepine additionally affect CaV channels. Clonazepam, as a benzodiazepine, features a fused diazepine ring, chlorinated phenyl group, and nitro functionality, and selectively enhances GABA-A receptor activity. Barbiturates like phenobarbital and benzobarbital contain barbituric or barbiturate rings, with ethyl or phenyl substituents, and also target GABA-A receptors. Benzobarbital includes an additional N-benzoyl fragment that may contribute to its pharmacological behaviour. Phenytoin, defined by its hydantoin ring and two phenyl groups, acts primarily on NaV channels. Zonisamide, combining a benzoxazole core and sulfonamide group, targets both NaV and CaV channels and inhibits carbonic anhydrase. Lacosamide, structurally unique with its (R)-$CH(NHCOCH_3)$-CH_2-OCH_3 backbone and NHAc side chains, also modulates NaV channels. As evident from the presented data, among the established mechanisms of antiepileptic action, the most prevalent are the effects on voltage-gated sodium channels (NaV) and calcium channels (CaV), each observed in 8 active pharmaceutical ingredients (APIs). Notably, five APIs – topiramate, valproic acid, oxcarbazepine, eslicarbazepine, and zonisamide – exhibit both mechanisms simultaneously. In addition, six APIs were found to modulate GABAergic neurotransmission through interaction with GABA-A receptors or inhibition of GABA transaminase (GABA-T). Topiramate demonstrates the broadest pharmacodynamic profile, with four identified mechanisms of antiepileptic action: modulation of sodium and calcium channels, GABA-A receptor potentiation, and inhibition of carbonic anhydrase. It is followed by zonisamide and valproic acid, each exhibiting three distinct mechanisms of action.

As a continuation of the study, a fragment-based analysis was carried out to determine structural similarities among the 16 investigated APIs and to identify the most frequently occurring structural fragments and functional groups within their molecular frameworks. This included clustering of the molecular structures based on structural similarity, classification by functional group content, generation of a structural similarity matrix (heatmap), and visualization of clustering using the Bemis-Murcko framework. Furthermore, the compounds were assessed for their ADME-related physicochemical properties, including molecular weight, partition coefficient (LogP), topological polar surface area (TPSA), number of hydrogen bond donors and acceptors, number of rotatable bonds, and the fraction of sp^3-hybridized carbon atoms (Fraction CSP3). SMILES notations for the 16 APIs studied were used as input data for this analytical stage, serving as the basis for structural analysis and fragment similarity assessment of antiepileptic active pharmaceutical ingredients (APIs) present on the Ukrainian pharmaceutical market. These linear representations allowed computational modelling, molecular fingerprinting, and clustering procedures essential to fragment-based drug design [98–101].

Structural similarity of the studied compounds was analyzed and visualized using Python tools (Fig. 2–5), with Fig. 2 showing 2D clustering of molecular fingerprints into four KMeans-based groups reflecting structural and partial pharmacological classes (Table 2).

Fig. 3 presents the results of an analysis of the frequency of occurrence of key pharmacophoric groups within the structures of 16 antiepileptic compounds, aimed at identifying the most prevalent ones. The functional group analysis revealed the dominance of pharmacophores such as carbonyl, amide, amino groups, and benzene rings. These fragments are critical for binding to protein targets, forming hydrogen bonds, stabilizing the ligand within the active site, and mediating hydrophobic interactions.

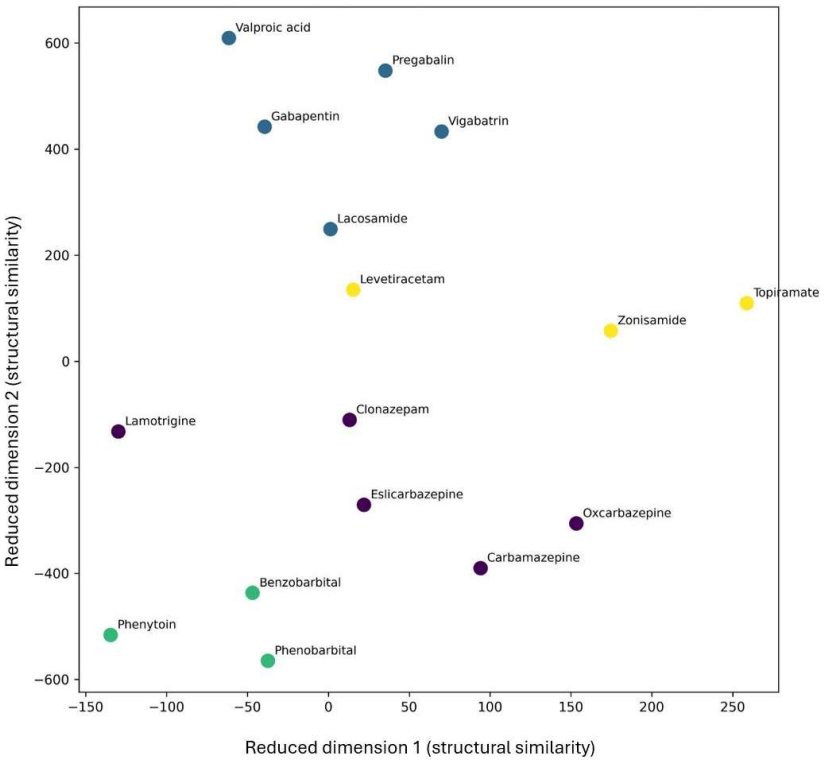


Fig. 2. 2D visualization of clustering of 16 antiepileptic APIs based on their structural similarity

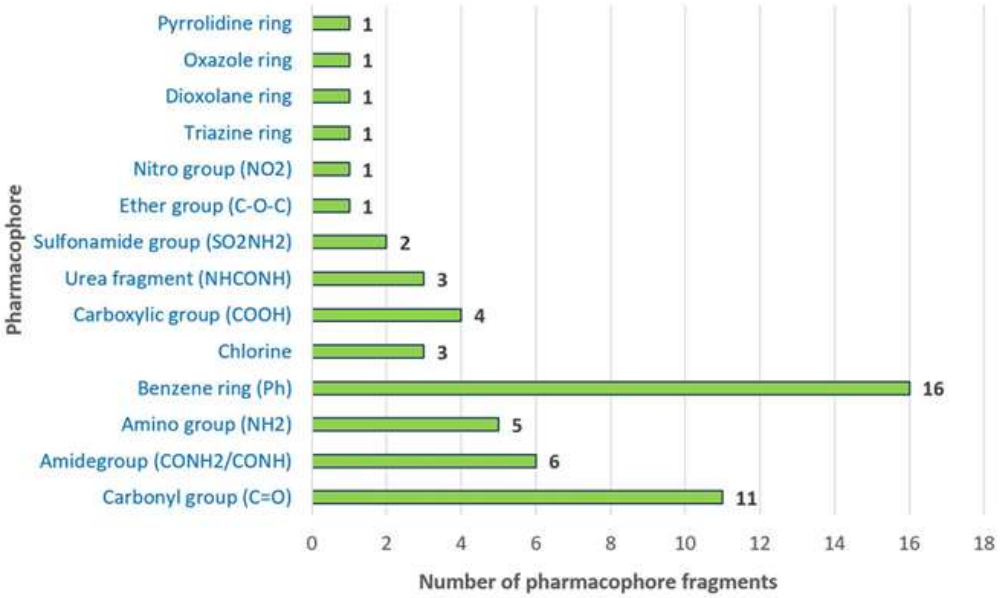


Fig. 3. Distribution of pharmacophoric fragments among 16 antiepileptic APIs

Table 2

Clustering of antiepileptic APIs based on structural similarity

Cluster	Cluster color	APIs grouped into a cluster	Chemical characteristic by which APIs are grouped into a cluster
1		Carbamazepine, Oxcarbazepine, Eslicarbazepine, Clonazepam, Lamotrigine	Aromatic structures with heterocycles, mainly NaV blockers or GABA-A modulators
2		Phenytoin, Phenobarbital, Benzobarbital	Barbiturates/hydantoins with a similar pharmacophore – two carbonyl groups in the cyclic nucleus
3		Gabapentin, Pregabalin, Vigabatrin, Lacosamide, Valproic acid	GABA mimetics or amino acid derivatives – contain a primary amino group and a carboxyl group
4		Levetiracetam, Zonisamide, Topiramate	Pharmacophorically complex molecules with sulfonamide, lactam residues, etc. with unique mechanisms of action (e.g., SV2A modulation)

The most frequently occurring functional group was the carbonyl group, represented in ketones (19.64%), carboxylic acids (7.34%), amides (10.71%), and within barbituric, hydantoin, and pyrrolidinone scaffolds. The high frequency of amino (8.93%) and amide (10.71%) groups reflects the role of these functionalities in modulating the GABAergic system or amino acid transporters. A significant proportion of benzene rings (28.57%) aligns with mechanisms of action involving interactions with NaV channels or the SV2A receptor.

Fig. 4 visualizes the results of a comparative structural similarity analysis of the 16 antiepileptic APIs through pairwise Tanimoto coefficient calculations based on ECFP4 fingerprints.

The resulting Tanimoto similarity heatmap revealed distinct clusters of compounds sharing common structural fragments. For example, high similarity levels (up to 0.88) were observed between barbiturates and hydantoins (phenytoin, phenobarbital), indicating a shared pharmacophore. Likewise, a strong similarity (0.86) was found among the dibenzazepine derivatives (carbamazepine, oxcarbazepine). In contrast, some molecules (e.g., valproic acid, topiramate, zonisamide) exhibited minimal overlap in structural fragments with other APIs, which correspond to their unique mechanisms of action and pharmacophoric profiles.

Additionally, the basic pharmacokinetic parameters of the investigated API structures were evaluated, including molecular weight, lipophilicity, polarity, hydrogen-bonding capacity, and molecular flexibility. The relationships between structural similarity and ADME characteristics were analyzed (Fig. 5). The results revealed substantial structural diversity, while also confirming structure-function correlations. For instance, high lipophilicity is characteristic of benzodiazepine and barbiturate derivatives (e.g., clonazepam, benzobarbital). Molecules such as gabapentin, lacosamide, and valproic acid demonstrate favourable bioavailability and good permeability. A low TPSA value (<90 Å^2) in all compounds indicates potentially good oral absorption. Structurally rigid molecules, such as phenytoin and carbamazepine, may benefit from more stable binding to NaV channels. Topiramate has the highest number of hydrogen bond acceptors (8), though it lacks donors. In contrast, gabapentin and pregabalin possess highly donor-acceptor-rich structures, contributing to effective protein interactions. The evaluation of drug-likeness criteria highlighted structure-property correlations, confirming that most compounds align with established rules, which serves to map the “chemical space” for fragment-based optimization rather than mere compliance verification. Overall, the ADME profiles align well with the structural clustering of the antiepileptic APIs.

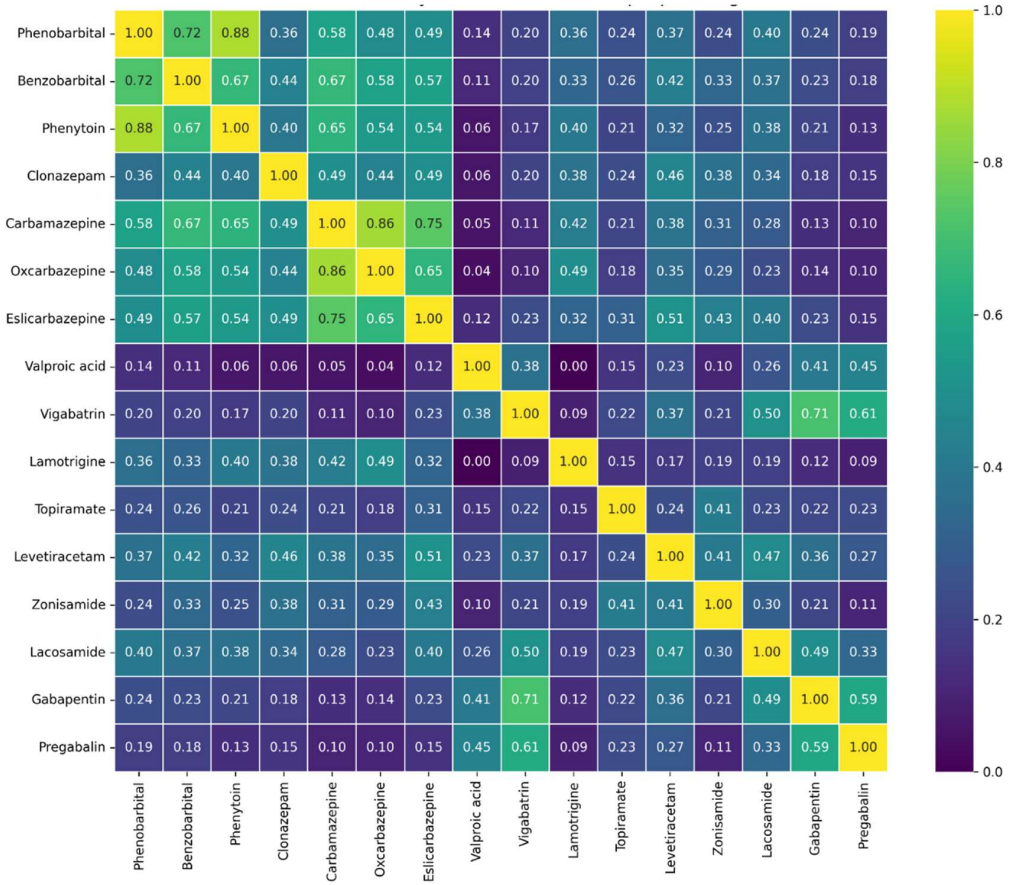


Fig. 4. Heatmap of structural similarity among 16 antiepileptic APIs (value 1.00 – identical or nearly identical structures, 0.00 – no shared fragments at all)

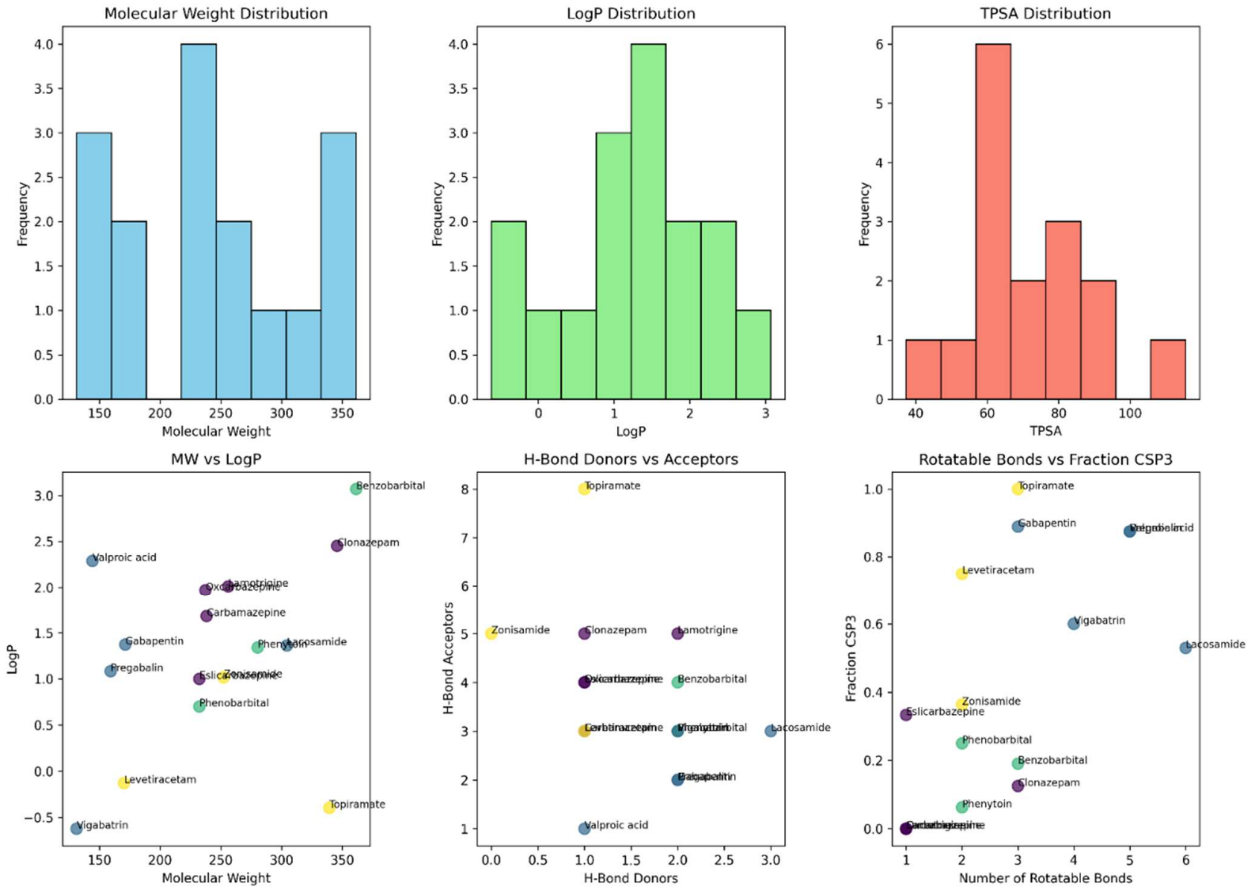


Fig. 5. Calculated ADME parameters for 16 antiepileptic APIs and their correlation relationships

Practical relevance. The structural-fragment analysis of 16 APIs can guide fragment-based design of new anticonvulsants, inform creation of fragment libraries for in silico screening, and support selection of alternative drugs in cases of intolerance or resistance. By linking common fragments with mechanisms of action and ADME profiles, the study provides a foundation for virtual screening, hybrid molecule synthesis, and broader pharmaceutical innovation.

Research limitations. The analysis covers only the structures of 16 antiepileptic APIs available on the pharmaceutical market of Ukraine, which limits the possibility of extrapolating the results to structural classes of other known antiepileptic compounds present on the global or other national markets.

Prospects for further research. The obtained results can be used for the design and synthesis of new antiepileptic compounds by combining the identified privileged fragments and applying bioisosteric replacements.

6. Conclusions

As a result of the fragment-based analysis of 16 active pharmaceutical ingredients (APIs) of antiepileptic drugs presented on the Ukrainian pharmaceutical market (ATC group N03A), it was established that despite their significant structural diversity, these compounds exhibit convergent spatial organization of key pharmacophoric elements that ensure effective binding to biological targets – ion channels (NaV, CaV), receptors (GABA-A, SV2A), and enzymes (GABA-T, CA-II). The analysis of functional fragments identified a number of recurring pharmacophoric groups, including carbonyl, amino, amide, and carboxyl groups, as well as aromatic rings, which are critical for hydrogen bonding, hydrophobic interactions, and proper positioning within the active site of the target protein. At the same time, unique pharmacophoric configurations were discovered (e.g., sulfonamide group in zonisamide, pyrrolidone in levetiracetam, and fructofuranose scaffold in topiramate), which are not shared with other structures but provide distinct mechanisms of action and open new therapeutic targets. Structural clustering confirmed that even chemically distinct molecules can achieve antiepileptic activity through similar spatial arrangements of critical pharmacophores, suggesting common principles of molecular recognition by biological targets. The identified correlations between structural fragments and ADME properties, including drug-likeness patterns, provide a foundation for pharmacophore modelling and fragment-library development, enabling the rational design of novel anticonvulsants with optimized pharmacokinetic profiles. Thus, the study not only confirms the importance of recurring pharmacophoric fragments but also emphasizes the role of the three-dimensional molecular configuration in mediating biological activity. The identified structure-activity-property correlations provide a scientifically grounded platform for the rational design of novel antiepileptic agents capable of overcoming current limitations in pharmacotherapy, including drug resistance observed in a subset of patients. These findings may also be applied to the construction of pharmacophore models and fragment libraries aimed at identifying new ligands with selective activity toward key targets involved in epileptogenesis. In summary, the further search for new anticonvulsants should leverage the identified key pharmacophoric elements fragments as building blocks and combine them rationally to generate multitarget molecules capable of modulating the relevant targets. In designing new compounds, candidates should be kept within a CNS-oriented ADME-properties window. In candidates with high lipophilicity (like barbiturates), introduce polar groups (hydroxyl) to improve absorption. Preference should be given to enantiopure (S)-configurations (as in pregabalin and levetiracetam) to enhance activity, solubility and BBB penetration, and avoid (R)-enantiomers to reduce toxicity.

Conflict of interest

The authors declare that they have no conflicts of interest concerning this research, whether financial, personal, or authorship-related, that could affect the research and its results presented in this article.

Funding

The study was carried out within the framework of the research project " Search for novel potential anticonvulsant agents for the treatment of post-traumatic epilepsy in military personnel and the civilian population", funded by the Ministry of Education and Science of Ukraine (Project registration number: 0125U001794).

Data availability

The manuscript has no associated data.

Use of artificial intelligence

The authors have used artificial intelligence technologies within acceptable limits to provide their own verified data, which is described in the research methodology section.

References

1. Epilepsy (2024). World Health Organization. Available at: https://www.who.int/news-room/fact-sheets/detail/epilepsy

2. Sinha, S., Dubey, M., Misal, S., Alavala, R. R., Ramaa, C. S.; Rao G., S. K., Alavala, R. R. (Eds.) (2025). Computational Analyses of the Mechanism of Action of Antiepileptic Agents. Applications of Computational Tools in Drug Design and Development. Singapore: Springer, 885–933. https://doi.org/10.1007/978-981-96-4154-3_24

3. Wu, Z., Chen, S., Wang, Y., Li, F., Xu, H., Li, M. et al. (2024). Current perspectives and trend of computer-aided drug design: a review and bibliometric analysis. International Journal of Surgery, 110 (6), 3848–3878. https://doi.org/10.1097/js9.0000000000001289

4. Karaküçük-İyidoğan, A., Başaran, E., Tatar-Yılmaz, G., Oruç-Emre, E. E. (2024). Development of new chiral 1,2,4-triazole-3-thiones and 1,3,4-thiadiazoles with promising in vivo anticonvulsant activity targeting GABAergic system and voltage-gated sodium channels (VGSCs). Bioorganic Chemistry, 151, 107662. https://doi.org/10.1016/j.bioorg.2024.107662

5. State Register of Medicinal Products of Ukraine. Available at: http://www.drlz.com.ua

6. Compendium. Available at: https://compendium.com.ua

7. Tsyvunin, V., Shtrygol', S., Havrylov, I., Shtrygol', D. (2021). Low-dose digoxin enhances the anticonvulsive potential of carbamazepine and lamotrigine in chemo-induced seizures with different neurochemical mechanisms. ScienceRise: Pharmaceutical Science, 6 (34), 58–65. https://doi.org/10.15587/2519-4852.2021.249375

8. Tsyvunin, V., Shtrygol', S., Prokopenko, Y., Georgiyants, V., Blyznyuk, N. (2016). Influence of dry herbal extracts on pentylenetetrazole-induced seizures in mice: screening results and relationship "chemical composition – pharmacological effect." ScienceRise: Pharmaceutical Science, 1 (1), 18–28. https://doi.org/10.15587/2519-4852.2016.71518

9. Tsyvunin, V., Shtrygol', S., Havrylov, I., Shtrygol', D., Reus, A. (2022). SGLT-2 inhibitors as potential anticonvulsants: empagliflozin, but not dapagliflozin, renders a pronounced effect and potentiates the sodium valproate activity in pentylenetetrazole-induced seizures. ScienceRise: Pharmaceutical Science, 5 (39), 83–90. https://doi.org/10.15587/2519-4852.2022.266065

10. Kamiński, K., Zagaja, M., Łuszczki, J. J., Rapacz, A., Andres-Mach, M., Latacz, G., Kieć-Kononowicz, K. (2015). Design, Synthesis, and Anticonvulsant Activity of New Hybrid Compounds Derived from 2-(2,5-Dioxopyrrolidin-1-yl)propanamides and 2-(2,5-Dioxopyrrolidin-1-yl)butanamides. Journal of Medicinal Chemistry, 58 (13), 5274–5286. https://doi.org/10.1021/acs.jmedchem.5b00578

11. Nath Pandeya, S. (2012). Semicarbazone – a versatile therapeutic pharmacophore for fragment based anticonvulsant drug design. Acta Pharmaceutica, 62 (3), 263–286. https://doi.org/10.2478/v10007-012-0030-1

12. Krasowski, M. D., McMillin, G. A. (2014). Advances in anti-epileptic drug testing. Clinica Chimica Acta, 436, 224–236. https://doi.org/10.1016/j.cca.2014.06.002

13. Serdaroğlu, G., Ortiz, J. V. (2016). Ab Initio Calculations on some Antiepileptic Drugs such as Phenytoin, Phenbarbital, Ethosuximide and Carbamazepine. Structural Chemistry, 28 (4), 957–964. https://doi.org/10.1007/s11224-016-0898-3

14. Ugale, V. G., Bari, S. B., Khadse, S. C., Reddy, P. N., Bonde, C. G., Chaudhari, P. J. (2020). Exploring Quinazolinones as Anticonvulsants by Molecular Fragmentation Approach: Structural Optimization, Synthesis and Pharmacological Evaluation Studies. ChemistrySelect, 5 (10), 2902–2912. https://doi.org/10.1002/slct.201904776

15. Abram, M., Jakubiec, M., Kamiński, K. (2019). Chirality as an Important Factor for the Development of New Antiepileptic Drugs. ChemMedChem, 14 (20), 1744–1761. https://doi.org/10.1002/cmdc.201900367

16. Kwan, P., Brodie, M. J. (2004). Phenobarbital for the Treatment of Epilepsy in the 21st Century: A Critical Review. Epilepsia, 45 (9), 1141–1149. https://doi.org/10.1111/j.0013-9580.2004.12704.x

17. Cozanitis, D. A. (2004). One Hundred Years of Barbiturates and Their Saint. Journal of the Royal Society of Medicine, 97 (12), 594–598. https://doi.org/10.1177/014107680409701214

18. Bialer, M. (2012). How did phenobarbital's chemical structure affect the development of subsequent antiepileptic drugs (AEDs)? Epilepsia, 53 (s8), 3–11. https://doi.org/10.1111/epi.12024

19. Murayama, N., Shimada, M., Yamazoe, Y., Sogawa, K., Nakayama, K., Fujii-Kuriyama, Y., Kato, R. (1996). Distinct Effects of Phenobarbital and Its N-Methylated Derivative on Liver Cytochrome P450 Induction. Archives of Biochemistry and Biophysics, 328 (1), 184–192. https://doi.org/10.1006/abbi.1996.0159

20. Bush, M. T., Sanders, E. (1967). Metabolic Fate of Drugs: Barbiturates and Closely Related Compounds. Annual Review of Pharmacology, 7 (1), 57–76. https://doi.org/10.1146/annurev.pa.07.040167.000421

21. SanMartin, R., Churruc, F. (2011). Drug Discovery in Epilepsy: A Synthetic Review. Novel Treatment of Epilepsy. https://doi.org/10.5772/24991

22. Rowe, E. J., Weinswig, M. H. (1964). Synthesis of N-Substituted and N,N′-Disubstituted Benzyl Derivatives of 5,5-Disubstituted Barbiturates. Journal of Pharmaceutical Sciences, 53 (2), 226–227. https://doi.org/10.1002/jps.2600530229

23. Nims, R. W., Syi, J. L., Wink, D. A., Nelson, V. C., Thomas, P. E., Jones, C. R. et al. (1993). Hepatic cytochrome P450 2B-type induction by ethyl/phenyl-substituted congeners of phenobarbital in the rat. Chemical Research in Toxicology, 6 (2), 180–187. https://doi.org/10.1021/tx00032a007

24. Vida, J. A., Hooker, M. L., Samour, C. M., Reinhard, J. F. (1973). Anticonvulsants. 4. Metharbital and phenobarbital derivatives. Journal of Medicinal Chemistry, 16 (12), 1378–1381. https://doi.org/10.1021/jm00270a013

25. Ernst, B., Clark, G., Grundmann, O. (2015). The Physicochemical and Pharmacokinetic Relationships of Barbiturates – From the Past to the Future. Current Pharmaceutical Design, 21 (25), 3681–3691. https://doi.org/10.2174/1381612821666150331131009

26. Ho, I. K., Harris, R. A. (1981). Mechanism of Action of Barbiturates. Annual Review of Pharmacology and Toxicology, 21 (1), 83–111. https://doi.org/10.1146/annurev.pa.21.040181.000503

27. Leeb-Lundberg, F., Olsen, R. W. (1982). Interactions of barbiturates of various pharmacological categories with benzodiazepine receptors. Molecular Pharmacology, 21 (2), 320–328. https://doi.org/10.1016/s0026-895x(25)14607-5

28. Vieira, A. A., Gomes, N. M., Matheus, M. E., Fernandes, P. D., Figueroa-Villar, J. D. (2011). Synthesis and in vivo evaluation of 5-chloro-5-benzobarbiturates as new central nervous system depressants. Journal of the Brazilian Chemical Society, 22 (2), 364–371. https://doi.org/10.1590/s0103-50532011000200024

29. Jursic, B. S., Neumann, D. M., Bowdy, K. L., Stevens, E. D. (2004). Simple, efficient, high yield syntheses of substituted and unsubstituted 5-benzoylbarbituric acids, and their corresponding schiff base phenylhydrazones. Journal of Heterocyclic Chemistry, 41 (2), 233–246. https://doi.org/10.1002/jhet.5570410214

30. Perekhoda, L. (2020). The application of PASS-computer program and molecular docking for the search of new anticonvulsants. Annals of Mechnikov's Institute, 4, 55–60. Available at: https://journals.uran.ua/ami/article/view/208223

31. Okujava, V. M., Chankvetadze, B. G., Rukhadze, M. D., Rogava, M. M., Tkesheliadze, N. B. (1991). Use of normal-phase microcolumn high-performance liquid chromatography for the study of hydrolytic stability, metabolic profiling and pharmacokinetics. Journal of Pharmaceutical and Biomedical Analysis, 9 (6), 465–473. https://doi.org/10.1016/0731-7085(91)80248-8

32. Patocka, J., Wu, Q., Nepovimova, E., Kuca, K. (2020). Phenytoin – An anti-seizure drug: Overview of its chemistry, pharmacology and toxicology. Food and Chemical Toxicology, 142, 111393. https://doi.org/10.1016/j.fct.2020.111393

33. Poupaert, J. H., Vandervorst, D., Guiot, P., Moustafa, M. M. M., Dumont, P. (1984). Structure-activity relationships of phenytoin-like anticonvulsant drugs. Journal of Medicinal Chemistry, 27 (1), 76–78. https://doi.org/10.1021/jm00367a015

34. Deodhar, M., Sable, P., Bhosale, A., Juvale, K., Dumbare, R., Sakpal, P. (2009). Synthesis and evaluation of phenytoin derivatives as anticonvulsant agents. Turkish Journal of Chemistry, 33 (3), 367–373. https://doi.org/10.3906/kim-0711-18

35. Henderson, J. D., Dayton, P. G., Israili, Z. H., Mandell, L. (1981). A nonmetabolized analog of phenytoin. Journal of Medicinal Chemistry, 24 (7), 843–847. https://doi.org/10.1021/jm00139a015

36. Philip, A. E., Poupaert, J. H., Chevé, G., Muccioli, G., Lambert, D., McCurdy, C. R. (2007). Structure-activity relationship of phenytoinergic antiepileptic drugs related to ameltolide. Medicinal Chemistry Research, 16 (3), 130–135. https://doi.org/10.1007/s00044-007-9016-9

37. Keppel Hesselink, J. M., Kopsky, D. J. (2017). Phenytoin: 80 years young, from epilepsy to breast cancer, a remarkable molecule with multiple modes of action. Journal of Neurology, 264 (8), 1617–1621. https://doi.org/10.1007/s00415-017-8391-5

38. Pal, R., Singh, K., Khan, S. A., Chawla, P., Kumar, B., Akhtar, M. J. (2021). Reactive metabolites of the anticonvulsant drugs and approaches to minimize the adverse drug reaction. European Journal of Medicinal Chemistry, 226, 113890. https://doi.org/10.1016/j.ejmech.2021.113890

39. Loscher, W. (2002). Basic Pharmacology of Valproate. CNS Drugs, 16 (10), 669–694. https://doi.org/10.2165/00023210-200216100-00003

40. Blaheta, R. A., Cinatl, J. (2002). Anti-tumor mechanisms of valproate: A novel role for an old drug. Medicinal Research Reviews, 22 (5), 492–511. https://doi.org/10.1002/med.10017

41. Landmark, C. J., Johannessen, S. I. (2008). Modifications of Antiepileptic Drugs for Improved Tolerability and Efficacy. Perspectives in Medicinal Chemistry, 2. https://doi.org/10.1177/1177391x0800200001

42. Mishra, M. K., Kukal, S., Paul, P. R., Bora, S., Singh, A., Kukreti, S. et al. (2021). Insights into Structural Modifications of Valproic Acid and Their Pharmacological Profile. Molecules, 27 (1), 104. https://doi.org/10.3390/molecules27010104

43. Acheampong, A. A. (1985). Quantitative structure-anticonvulsant activity studies of valproic acid analogues. [Doctoral dissertation, University of British Columbia]. Available at: https://doi.org/10.14288/1.0096534

44. Palaty, J. (1995). Unsaturated analogues of valproic acid: Structure activity relationships and interaction with GABA metabolism. [Doctoral Dissertation; University of British Columbia]. Available at: https://open.library.ubc.ca/collections/ubctheses/831/items/1.0088895

45. Shields, W. D., Pellock, J. M. (2011). Vigabatrin 35 years later – from mechanism of action to benefit-risk considerations. Acta Neurologica Scandinavica, 124, 1–4. https://doi.org/10.1111/j.1600-0404.2011.01606.x

46. Zhao, L.-X., Park, J. G., Moon, Y.-S., Basnet, A., Choi, J., Kim, E. et al. (2004). Design, synthesis and anticonvulsive activity of analogs of γ-vinyl GABA. Il Farmaco, 59 (5), 381–388. https://doi.org/10.1016/j.farmac.2004.01.011

47. Michael, K. B. (2022). Study of long-term visual function and plasma biomarkers in patients with epilepsy receiving Vigabatrin. [Doctoral Dissertation; University of Glasgow]. Available at: https://theses.gla.ac.uk/82953/

48. Tong, X. (2007). The pharmacokinetics and neuropharmacological action of the new antiepileptic drugs vigabatrin and levetiracetam. [Doctoral Thesis; University of London]. Available at: https://discovery.ucl.ac.uk/id/eprint/1445126/

49. Guberman, A. (1996). Vigabatrin. Canadian Journal of Neurological Sciences / Journal Canadien Des Sciences Neurologiques, 23 (S2), S13–S17. https://doi.org/10.1017/s0317167100020928

50. Alrashood, S. T. (2016). Carbamazepine. Profiles of Drug Substances, Excipients and Related Methodology, 133–321. https://doi.org/10.1016/bs.podrm.2015.11.001

51. McLean, M. J., Schmutz, M., Wamil, A. W., Olpe, H. -R., Portet, C., Feldmann, K. F. (1994). Oxcarbazepine: Mechanisms of Action. Epilepsia, 35 (s3), S5–S9. https://doi.org/10.1111/j.1528-1157.1994.tb05949.x

52. Almeida, L., Soares-da-Silva, P. (2007). Eslicarbazepine Acetate (BIA 2-093). Neurotherapeutics, 4 (1), 88–96. https://doi.org/10.1016/j.nurt.2006.10.005

53. Gerlach, A. C., Krajewski, J. L. (2010). Antiepileptic Drug Discovery and Development: What Have We Learned and Where Are We Going? Pharmaceuticals, 3 (9), 2884–2899. https://doi.org/10.3390/ph3092884

54. Das, N., Dhanawat, M., Shrivastava, S. K. (2012). An overview on antiepileptic drugs. Drug discoveries & therapeutics, 6 (4), 178–193. https://doi.org/10.5582/ddt.2012.v6.4.178

55. Chung, S. S., Kelly, K., Schusse, C. (2011). New and Emerging Treatments for Epilepsy: Review of Clinical Studies of Lacosamide, Eslicarbazepine Acetate, Ezogabine, Rufinamide, Perampanel, and Electrical Stimulation Therapy. Journal of Epilepsy Research, 1 (2), 35–46. https://doi.org/10.14581/jer.11008

56. Rocamora, R. (2015). A review of the efficacy and safety of eslicarbazepine acetate in the management of partial-onset seizures. Therapeutic Advances in Neurological Disorders, 8 (4), 178–186. https://doi.org/10.1177/1756285615589711

57. Arzimanoglou, A., Ben-Menachem, E., Cramer, J., Glauser, T., Seeruthun, R., Harrison, M. (2010). The evolution of antiepileptic drug development and regulation. Epileptic Disorders, 12 (1), 3–15. https://doi.org/10.1684/epd.2010.0303

58. Macdonald, R. L. (1989). Antiepileptic Drug Actions. Epilepsia, 30 (s1), S19–S28. https://doi.org/10.1111/j.1528-1157.1989.tb05810.x

59. Wilde, M., Auwärter, V., Moosmann, B. (2021). New psychoactive substances – Designer benzodiazepines. WIREs Forensic Science, 3 (6). https://doi.org/10.1002/wfs2.1416

60. Batlle Rocafort, E. (2018). Benzodiazepines and derivatives. Overview, analysis and synthesis. Available at: https://core.ac.uk/outputs/158608492/?source = 4

61. Arora, N., Dhiman, P., Kumar, S., Singh, G., Monga, V. (2020). Recent advances in synthesis and medicinal chemistry of benzodiazepines. Bioorganic Chemistry, 97, 103668. https://doi.org/10.1016/j.bioorg.2020.103668

62. Teli, S., Teli, P., Soni, S., Sahiba, N., Agarwal, S. (2023). Synthetic aspects of 1,4- and 1,5-benzodiazepines usingo-phenylenediamine: a study of past quinquennial. RSC Advances, 13 (6), 3694–3714. https://doi.org/10.1039/d2ra06045k

63. Leppik, I. E. (2004). Zonisamide: chemistry, mechanism of action, and pharmacokinetics. Seizure, 13, S5–S9. https://doi.org/10.1016/j.seizure.2004.04.016

64. Shimizu, M., Uno, H., Ito, T., Masuda, Y., Kurokawa, M. (1996). Research and Development of Zonisamide, a New Type of Antiepileptic Drug. Yakugaku Zasshi, 116 (7), 533–547. https://doi.org/10.1248/yakushi1947.116.7_533

65. Gidal, B. E., Resnick, T., Smith, M. C., Wheless, J. W. (2024). Zonisamide: A Comprehensive, Updated Review for the Clinician. Neurology. Neurology Clinical Practice, 14 (1). https://doi.org/10.1212/cpj.0000000000200210

66. Travagin, F., Vladiskovic, C., Giovenzana, G. B., Mantegazza, S., Razzetti, G. (2024). Improving Zonisamide Manufacturing: Insights into Stereochemistry and Mechanisms for Continuous Optimization. European Journal of Organic Chemistry, 27 (41). https://doi.org/10.1002/ejoc.202400686

67. Malik, S., Ahuja, P., Sahu, K., Khan, S. A. (2014). Design and synthesis of new of 3-(benzo[d]isoxazol-3-yl)-1-substituted pyrrolidine-2, 5-dione derivatives as anticonvulsants. European Journal of Medicinal Chemistry, 84, 42–50. https://doi.org/10.1016/j.ejmech.2014.07.016

68. Aratikatla, E. K., Bhattacharya, A. K. (2019). A Short Review of Synthetic Routes for the Antiepileptic Drug (R)-Lacosamide. Organic Process Research & Development, 24 (1), 17–24. https://doi.org/10.1021/acs.oprd.9b00373

69. Salomé, C., Salomé-Grosjean, E., Park, K. D., Morieux, P., Swendiman, R., DeMarco, E. et al. (2009). Synthesis and Anticonvulsant Activities of (R)-N-(4′-Substituted)benzyl 2-Acetamido-3-methoxypropionamides. Journal of Medicinal Chemistry, 53 (3), 1288–1305. https://doi.org/10.1021/jm901563p

70. Morieux, P., Salomé, C., Park, K. D., Stables, J. P., Kohn, H. (2010). The Structure-Activity Relationship of the 3-Oxy Site in the Anticonvulsant (R)-N-Benzyl 2-Acetamido-3-methoxypropionamide. Journal of Medicinal Chemistry, 53 (15), 5716–5726. https://doi.org/10.1021/jm100508m

71. Morieux, P. P. (2010). A chemical biology approach to discover the biological targets of the antiepileptic drug lacosamide. [Doctoral dissertation, The University of North Carolina at Chapel Hill]. https://doi.org/10.17615/h062-c988

72. Zhan, K., Liu, Y., Chen, Q., Zhuang, C., Zheng, R. (2024). Advances in the chemoenzymatic synthesis of gamma-aminobutyric acid derivatives. Sheng wu gong cheng xue bao = Chinese journal of biotechnology, 40 (9), 2831–2845. https://doi.org/10.13345/j.cjb.240032

73. Papagiouvannis, G., Theodosis-Nobelos, P., Tziona, P., Gavalas, A., Kourounakis, P. N., Rekka, E. A. (2022). Gabapentin antioxidant derivatives with anti-inflammatory and neuroprotective potency. Letters in Drug Design & Discovery, 19 (7), 579–590. https://doi.org/10.2174/1570180818666211210161922

74. Shi, W., Liu, H., Zhang, Y., Zhong, B., Yang, H. (2005). Design, Synthesis, and Preliminary Evaluation of Gabapentin-Pregabalin Mutual Prodrugs in Relieving Neuropathic Pain. Archiv Der Pharmazie, 338 (8), 358–364. https://doi.org/10.1002/ardp.200400958

75. Barenie, R., Darrow, J., Avorn, J., Kesselheim, A. S. (2021). Discovery and Development of Pregabalin (Lyrica). Neurology, 97 (17). https://doi.org/10.1212/wnl.0000000000012730

76. Kavoussi, R. (2006). Pregabalin: From molecule to medicine. European Neuropsychopharmacology, 16, S128–S133. https://doi.org/10.1016/j.euroneuro.2006.04.005

77. Bryans, J. S., Wustrow, D. J. (1999). 3-Substituted GABA analogs with central nervous system activity: A review. Medicinal Research Reviews, 19 (2), 149–177. https://doi.org/10.1002/(sici)1098-1128(199903)19:2<149::aid-med3>3.0.co;2-b

78. Belliotti, T. R., Capiris, T., Ekhato, I. V., Kinsora, J. J., Field, M. J., Heffner, T. G. et al. (2005). Structure-Activity Relationships of Pregabalin and Analogues That Target the α2-δ Protein. Journal of Medicinal Chemistry, 48 (7), 2294–2307. https://doi.org/10.1021/jm049762l

79. Fijałkowski, Ł., Sałat, K., Podkowa, A., Zaręba, P., Nowaczyk, A. (2017). Potential role of selected antiepileptics used in neuropathic pain as human GABA transporter isoform 1 (GAT1) inhibitors – Molecular docking and pharmacodynamic studies. European Journal of Pharmaceutical Sciences, 96, 362–372. https://doi.org/10.1016/j.ejps.2016.10.004

80. Yuen, P. W. (2007). α2δ Ligands: Neurontin®(Gabapentin) and Lyrica®(Pregabalin). The Art of Drug Synthesis, 225–240. https://doi.org/10.1002/9780470134979.ch16

81. Taylor, C. P., Angelotti, T., Fauman, E. (2007). Pharmacology and mechanism of action of pregabalin: The calcium channel α2–δ (alpha2–delta) subunit as a target for antiepileptic drug discovery. Epilepsy Research, 73 (2), 137–150. https://doi.org/10.1016/j.eplepsyres.2006.09.008

82. Howard, P., Remi, J., Remi, C., Charlesworth, S., Whalley, H., Bhatia, R. et al. (2018). Levetiracetam. Journal of Pain and Symptom Management, 56 (4), 645–649. https://doi.org/10.1016/j.jpainsymman.2018.07.012

83. Klitgaard, H., Verdru, P. (2007). Levetiracetam: the first SV2A ligand for the treatment of epilepsy. Expert Opinion on Drug Discovery, 2 (11), 1537–1545. https://doi.org/10.1517/17460441.2.11.1537

84. Kenda, B. M., Matagne, A. C., Talaga, P. E., Pasau, P. M., Differding, E., Lallemand, B. I. et al. (2003). Discovery of 4-Substituted Pyrrolidone Butanamides as New Agents with Significant Antiepileptic Activity. Journal of Medicinal Chemistry, 47 (3), 530–549. https://doi.org/10.1021/jm030913e

85. Contreras-García, I. J., Cárdenas-Rodríguez, N., Romo-Mancillas, A., Bandala, C., Zamudio, S. R., Gómez-Manzo, S. et al. (2022). Levetiracetam Mechanisms of Action: From Molecules to Systems. Pharmaceuticals, 15 (4), 475. https://doi.org/10.3390/ph15040475

86. Matagne, A., Margineanu, D., Kenda, B., Michel, P., Klitgaard, H. (2008). Anti-convulsive and anti-epileptic properties of brivaracetam (ucb 34714), a high-affinity ligand for the synaptic vesicle protein, SV2A. British Journal of Pharmacology, 154 (8), 1662–1671. https://doi.org/10.1038/bjp.2008.198

87. Sills, G. J., Rogawski, M. A. (2020). Mechanisms of action of currently used antiseizure drugs. Neuropharmacology, 168, 107966. https://doi.org/10.1016/j.neuropharm.2020.107966

88. Makki, M., Bakhotmah, D. A., Abdel-Rahman, R. M., Aqlan, F. M. (2018). New Route to Synthesize Fluorine Substituted Lamotrigine Drug Analogues as an Anti-Inflammatory Agent. Current Organic Synthesis, 15 (1), 116–125. https://doi.org/10.2174/1570179414666170509151123

89. Alkorta, I., Elguero, J., Font, A., Galcera, J., Mata, I., Molins, E., Virgili, A. (2014). An experimental and theoretical study of the structure of Lamotrigine in its neutral and protonated forms: evidence of Lamotrigine enantiomers. Tetrahedron, 70 (17), 2784–2795. https://doi.org/10.1016/j.tet.2014.02.075

90. Saralaya, S. S., Hiriyalau, S. S. (2024). An overview of prior art disclosures about the synthesis of lamotrigine and a glimpse of its closely related compounds. Indian Journal of Pharmacy & Drug Studies, 3 (1), 8–15. Available at: https://mansapublishers.com/index.php/ijpds/article/view/4503

91. Pearl, N. Z., Babin, C. P., Catalano, N. T., Blake, J. C., Ahmadzadeh, S., Shekoohi, S., Kaye, A. D. (2023). Narrative Review of Topiramate: Clinical Uses and Pharmacological Considerations. Advances in Therapy, 40 (9), 3626–3638. https://doi.org/10.1007/s12325-023-02586-y

92. Casini, A., Antel, J., Abbate, F., Scozzafava, A., David, S., Waldeck, H., Schäfer, S., Supuran, C. T. (2003). Carbonic anhydrase inhibitors: SAR and X-ray crystallographic study for the interaction of sugar sulfamates/sulfamides with isozymes I, II and IV. Bioorganic & Medicinal Chemistry Letters, 13 (5), 841–845. https://doi.org/10.1016/s0960-894x(03)00029-5

93. Maryanoff, B. (2009). Sugar Sulfamates for Seizure Control: Discovery and Development of Topiramate, a Structurally Unique Antiepileptic Drug. Current Topics in Medicinal Chemistry, 9 (11), 1049–1062. https://doi.org/10.2174/156802609789630938

94. Maryanoff, B. E., McComsey, D. F., Costanzo, M. J., Hochman, C., Smith-Swintosky, V., Shank, R. P. (2004). Comparison of Sulfamate and Sulfamide Groups for the Inhibition of Carbonic Anhydrase-II by Using Topiramate as a Structural Platform. Journal of Medicinal Chemistry, 48 (6), 1941–1947. https://doi.org/10.1021/jm040124c

95. Moore, G. (2017). The design and synthesis of novel APIs based upon topiramate. [Doctoral Dissertation: Newcastle University]. Available at: https://theses.ncl.ac.uk/jspui/handle/10443/3828

96. Ghiasi, M., Kamalinahad, S., Arabieh, M., Zahedi, M. (2012). Carbonic anhydrase inhibitors: A quantum mechanical study of interaction between some antiepileptic drugs with active center of carbonic anhydrase enzyme. Computational and Theoretical Chemistry, 992, 59–69. https://doi.org/10.1016/j.comptc.2012.05.005

97. Saeidian, H., Abdoli, M. (2015). The first general protocol forN-monoalkylation of sulfamate esters: benign synthesis ofN-alkyl Topiramate (anticonvulsant drug) derivatives. Journal of Sulfur Chemistry, 36 (5), 463–470. https://doi.org/10.1080/17415993.2015.1069294

98. El Kayal, W., Severina, H., Tsyvunin, V., Zalevskyi, S., Shtrygol', S., Vlasov, S. et al. (2022). Synthesis and anticonvulsant activity evaluation of n-[(2,4-dichlorophenyl)methyl]-2-(2,4-dioxo-1h-quinazolin-3-yl)acetamide novel 1-benzylsubstituted derivatives. ScienceRise: Pharmaceutical Science, 1 (35), 58–69. https://doi.org/10.15587/2519-4852.2022.253554

99. Kushniruk, V. M., Kovalevska, I. V., Ruban, O. A., Harna, N. V., Georgiyants, V. A. (2016). (2016). Technology scaling for obtaining N,N –dibenzyl amide of malonic acid – a potential anticonvulsant – in industrial environments. ScienceRise: Pharmaceutical Science, 4 (4), 30–35. https://doi.org/10.15587/2519-4852.2016.87441

100. Kavraiskyi, D. P., Shtrygol, S. Yu., Georgiyants, V. A., Severina, H. I. (2016). Experimental study of new pyrazolo[3,4-D] pyrimidine-4-one derivatives for anticonvulsant activity spectrum. ScienceRise: Pharmaceutical Science, 1 (1), 10–17. https://doi.org/10.15587/2519-4852.2016.70528

101. Davydov, E., Hoidyk, M., Shtrygol', S., Karkhut, A., Polovkovych, S., Klyuchivska, O. et al. (2024). Evaluation of thiopyrano[2,3-d]thiazole derivatives as potential anticonvulsant agents. Archiv Der Pharmazie, 357 (10). https://doi.org/10.1002/ardp.202400357

Received 08.07.2025
Received in revised form 12.08.2025
Accepted 21.08.2025
Published 30.08.2025

Maryna Stasevych, Doctor of Chemical Sciences, Professor, Department of Technology of Biologically Active Substances, Pharmacy and Biotechnology, Lviv Polytechnic National University, Stepana Bandery str., 12, Lviv, Ukraine, 79013

Mykhailo Hoidyk, PhD Student, Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Halytsky Lviv National Medical University, Pekarska str., 69, Lviv, Ukraine, 79010

Olexandra Roman, PhD, Associate Professor, Department of General, Bioinorganic, Physicocolloid Chemistry, Danylo Halytsky Lviv National Medical University, Pekarska str., 69, Lviv, Ukraine, 79010

Roksolana Konechna, PhD, Associate Professor, Department of Technology of Biologically Active Substances, Pharmacy and Biotechnology, Lviv Polytechnic National University, Stepana Bandery str., 12, Lviv, Ukraine, 79013

Andriy Karkhut, PhD, Associate Professor, Department of Technology of Biologically Active Substances, Pharmacy and Biotechnology, Lviv Polytechnic National University, Stepana Bandery str., 12, Lviv, Ukraine, 79013

Andrii Lozynskyi, Doctor of Pharmaceutical Sciences, Professor, Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Halytsky Lviv National Medical University, Pekarska str., 69, Lviv, Ukraine, 79010

Sviatoslav Polovkovych, Doctor of Chemical Sciences, Professor, Department of Technology of Biologically Active Substances, Pharmacy and Biotechnology, Lviv Polytechnic National University, Stepana Bandery str., 12, Lviv, Ukraine, 79013

Roman Lesyk*, Doctor of Pharmaceutical Sciences, Professor, Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Halytsky Lviv National Medical University, Pekarska str., 69, Lviv, Ukraine, 79010

***Corresponding author:** *Roman Lesyk, e-mail: roman.lesyk@gmail.com*