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Discovery and characterization of phenoxyacetic acid derivatives as potential antiepileptic agents

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This study aimed to discover novel multifunctional anticonvulsant agents through the evaluation of a series of test compounds **5d–f**, **7b**, and **10c–f**, which were previously identified based on their potent anti-inflammatory activity in both *in vitro* and *in vivo* models in acute and chronic seizure models. Initial screening in the pentylenetetrazol (PTZ)-induced seizure model identified compounds **7b**, **5f**, **5e**, and **10c** as the most effective, with compound **7b** demonstrating complete seizure protection (100%) and zero mortality, outperforming the reference drug valproic acid **(VI)**. These four candidates were further assessed in the pilocarpine-induced temporal lobe epilepsy model. Compound **7b** again showed superior efficacy, significantly delaying seizure onset by 188.6%, reducing seizure severity at all time points, and ensuring 100% survival. Mechanistic studies revealed that **7b** markedly reduced hippocampal oxidative stress markers, including malondialdehyde by 67.2% and nitric oxide levels by 41.0%. It also suppressed the neuroinflammatory cytokines TNF-α and IL-6 by 56.9% and 63.0%, respectively. In addition, compound **7b** attenuated excitotoxic glutamate accumulation by 61.5% and downregulated glial activation markers GFAP and Iba-1 by 73.9% and 49.8%, respectively, consistently outperforming valproic acid. Importantly, safety evaluation confirmed that high-dose administration of **7b** did not induce hepatic, renal, or cardiac toxicity. Collectively, these findings establish compound **7b** as a potent, safe, and multifunction anti-inflammatory and antiepileptic candidate, warranting further pharmacological and mechanistic investigation.

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1 Introduction

Epilepsy is a chronic neurological disorder that affects over 50 million individuals globally, accounting for nearly 1% of the world's population.[1] It ranks among the most widespread brain disorders and is second only to stroke in terms of prevalence. Beyond its physical manifestations, epilepsy imposes a substantial health and socioeconomic burden, significantly contributing to the global burden of neurological diseases.[2] Although epilepsy has been recognized since ancient times, significant progress in its diagnosis and treatment has only occurred in recent decades. Today, a wide range of antiepileptic drugs (AEDs) are available to manage seizure activity. However, approximately 30% of patients remain resistant to current pharmacological therapies, continuing to experience uncontrolled seizures despite medication.[3]

Currently, the primary treatment options for epilepsy involve long-term pharmacotherapy, with surgical intervention reserved for select cases where medications fail to provide adequate seizure control.[4] Commonly prescribed AEDs include phenytoin **(I)**, carbamazepine **(II)**, and others, which act through various mechanisms to suppress neuronal excitability and prevent seizure recurrence. However, these treatments are often associated with limited efficacy in drug-resistant patients and may cause undesirable side effects, highlighting the ongoing need for more effective and targeted therapeutic strategies.[5,6] Sulfamate-substituted drugs such as topiramate (TPM) **(III)** have shown clinical effectiveness across various seizure types. While the introduction of newer antiepileptic

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agents including pregabalin (**IV**), gabapentin (v), valproic acid (**VI**), lacosamide, vigabatrin, levetiracetam, and lamotrigine has marked a significant advancement in epilepsy management, many of these medications are still associated with undesirable adverse effects, including hepatotoxicity, hirsutism, nausea, and weight gain 7. Nonetheless, drug resistance and neurotoxicity remain major limitations of available therapies.[8] As a result, there is a continual demand for the development of antiepileptic drugs that offer improved efficacy with fewer side effects. Current medicinal chemistry efforts are therefore focused on identifying novel compounds with higher target selectivity and better safety profiles. The pharmacological actions of AEDs typically involve enhancement of GABAergic inhibitory transmission, inhibition of glutamatergic excitatory signaling, or modulation of voltage-gated sodium and T-type calcium channels.[9]

Reports in the literature indicate that some existing antiepileptic drugs lack specific receptor–binding interactions, while others exert their effects through diverse and sometimes unclear mechanisms of action.[10,11] Consequently, the development of novel therapeutic agents with well-defined targets and reduced side effect profiles has become a key focus in contemporary medicinal chemistry research. Ongoing research efforts are focused on the development of novel anticonvulsant agents to improve seizure control and address the limitations of existing therapies in epilepsy.[12] Inflammation, a natural defense response to harmful stimuli such as trauma, infection, or irritants, plays a critical role in many pathological conditions, including epilepsy.[13] Clinically, inflammation is characterized by symptoms such as heat, swelling, redness, pain, and impaired function.[14] It involves the activation and migration of leukocytes, increased vascular permeability, and the release of pro-inflammatory mediators. Enzymes such as cyclooxygenases (COX) and lipoxygenases, along with the subsequent production of prostaglandins, leukotrienes, and reactive oxygen species (ROS), contribute significantly to the inflammatory cascade.[15]

The development of hybrid molecules, which incorporate multiple pharmacophoric units into a single chemical scaffold, has gained increasing attention in the field of drug discovery due to their potential for enhanced biological activity and multi-target interactions. Within this approach, hydrazone derivatives distinguished by the presence of an azomethine (–NHN=CH) functional group have emerged as a promising class of therapeutic candidates, owing to their synthetic accessibility and diverse pharmacological profiles.[16] Markedly, several compounds bearing distinct structural moieties (**VII–X**) have demonstrated potent anticonvulsant activity through various mechanisms of action, supporting their relevance in the ongoing search for novel antiepileptic agents.[17–20] (Fig. 1).

2 Rational and design

Building upon our previously reported data and relevant literature,[21–23] the present study is designed to investigate the anticonvulsant potential of a series of the most biologically active compounds exhibiting high potency and selectivity toward the cyclooxygenase-2 (COX-2) enzyme. Increasing evidence has established a strong association between neuroinflammation and seizure pathophysiology, where elevated COX-2 expression in neuronal tissues contributes to the initiation and progression of epileptic activity. Consequently, COX-2 inhibition has emerged as a promising therapeutic approach for the management of epilepsy and other seizure-related disorders. To address this, a fragment-merging design strategy was employed, which integrates the critical pharmacophoric features of previously reported antiepileptic agents into a single, optimized molecular framework.

By strategically linking the phenoxyacetic acid moiety, which enhances hydrogen-bonding affinity within the COX-2 active

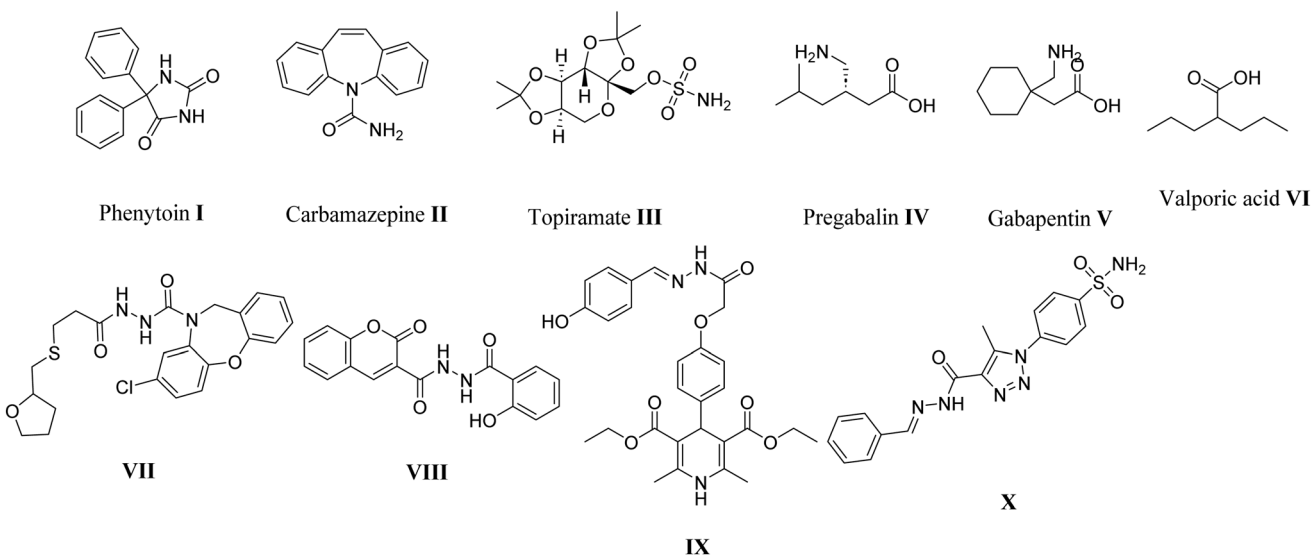


Fig. 1 Diagram of marketed I–VI and reported compounds VII–X that have been reports as anti-epileptic candidates.

site, with a hydrazide linker to ensure optimal accommodation within the binding pocket and facilitate additional hydrogen-bond interactions, the molecular framework was further optimized through the incorporation of an aromatic side arm designed to promote enhanced hydrophobic contacts.

At the core of this design lies the phenoxyacetic acid scaffold, a versatile pharmacophore widely recognized for its biological diversity and multifunctional therapeutic potential. Building upon this structural foundation, the resulting hybrid molecules were conceived to exhibit dual functionality:

1. Potent COX-2 inhibition, effectively reducing neuroinflammation and modulating inflammatory signaling cascades implicated in seizure onset and progression.

2. Significant anticonvulsant activity, facilitated by enhanced molecular recognition and improved interactions within the hydrophobic binding pocket of the COX-2 enzyme.

By adopting this rational drug design strategy, we aim to develop novel chemical entities with optimized pharmacological profiles, capable of exerting both anti-inflammatory and antiepileptic effects. This dual-action therapeutic approach has the potential to overcome the limitations of existing antiepileptic drugs by simultaneously targeting seizure activity and its underlying neuroinflammatory mechanisms, thereby paving the way for the development of next-generation antiepileptic agents with improved efficacy and safety profiles (Fig. 2).

3 Pathophysiology of neuroinflammation

The blood–brain barrier (BBB), formed by a selectively permeable monolayer of brain capillary endothelial cells, tightly regulates molecular trafficking between the bloodstream and the brain. Disruption of BBB integrity has been implicated in the pathogenesis and progression of several neurological disorders, including epilepsy.[24] Experimental evidence indicates that neuronal hyperexcitability, such as glutamate-mediated activation of NMDA receptors, compromises BBB function and permeability, while NMDA receptor antagonism prevents such breakdown. Seizure-induced BBB disruption facilitates leakage and alters the expression of ATP-binding cassette (ABC) transporters, notably P-glycoprotein (P-gp), which is strongly associated with antiepileptic drug (AED) resistance.[25] P-gp is upregulated in the brain and BBB following seizure activity, as demonstrated in both rodent models and

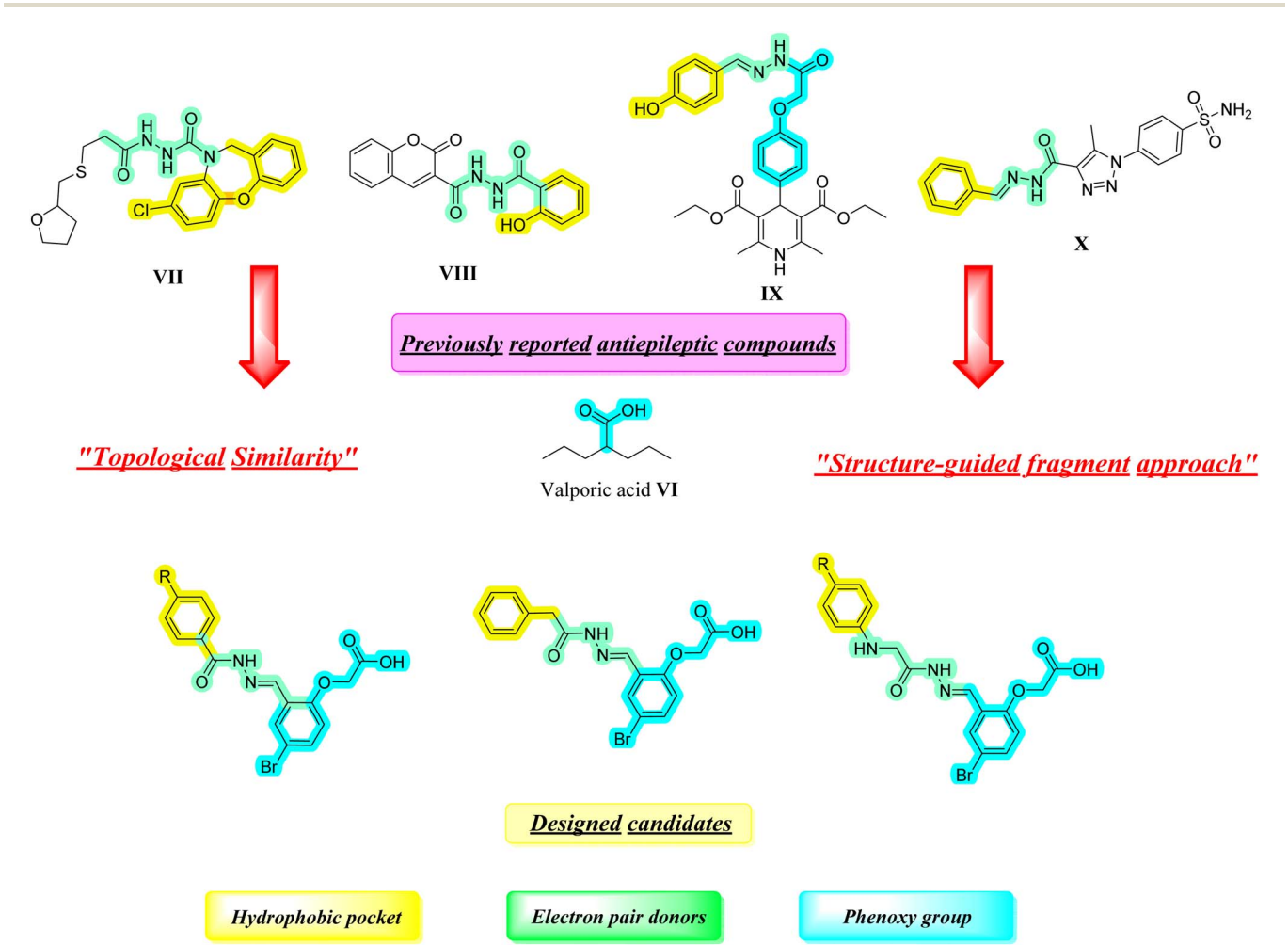


Fig. 2 Rationale and design for synthesis of designed compounds 5d–f, 7b, and 10c–f.

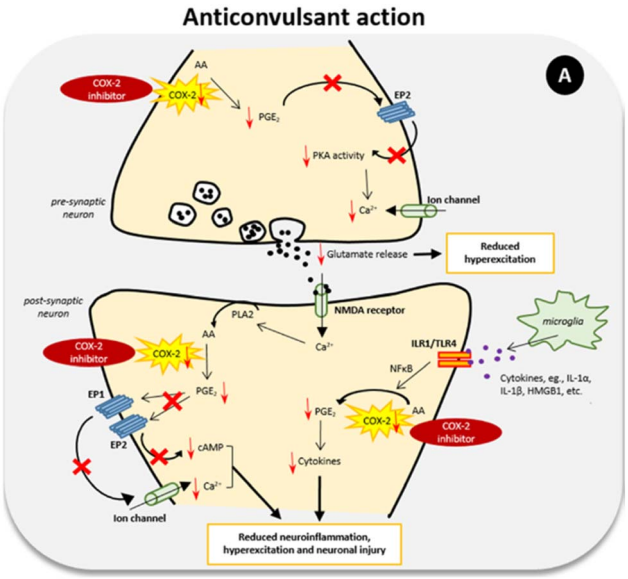


Fig. 3 Clinical role of COX-2 inhibitors in epilepsy management: (a) as anticonvulsants, COX-2 inhibitors reduce prostaglandin E_2 (PGE_2) production, thereby limiting activation of EP receptors. This leads to decreased calcium influx and glutamate release, effectively suppressing seizure activity. Additionally, they attenuate neuroinflammation by reducing cytokine production in brain cells.

patients with refractory epilepsy. This transporter actively effluxes AEDs from the brain back into circulation, reducing their therapeutic concentrations at neuronal targets and contributing to pharmacoresistance.[26] Markedly, glutamate-induced P-gp expression in brain capillary endothelial cells is mediated *via* NMDA receptor activation and has been shown to involve the cyclooxygenase-2 (COX-2) pathway.[27] Several *in vitro* and *in vivo* studies have demonstrated that COX-2 inhibition using agents such as celecoxib, indomethacin, SC-58236, and NS-398 attenuates seizure-induced P-gp upregulation in brain endothelial cells and limbic brain regions. Similarly, blockade of the EP1 receptor with SC-51089 also prevented P-gp overexpression, supporting the involvement of COX-2/EP1 signaling in this mechanism. These findings highlight COX-2 as a key upstream regulator of seizure-induced P-gp expression. While direct P-gp inhibition can increase AED brain levels, it may also lead to undesirable systemic effects.[28] (Fig. 3).

4 Neuroinflammatory cascade underlying convulsion pathophysiology

Seizure activity initiates a complex neuroinflammatory and oxidative cascade involving multiple molecular mediators that contribute to neuronal hyperexcitability and disease progression. Following an epileptogenic insult, excessive release of glutamate, the principal excitatory neurotransmitter, leads to overstimulation of NMDA receptors, resulting in calcium influx and the generation of reactive oxygen and nitrogen species (ROS/RNS), including nitric oxide (NO). Elevated NO contributes to oxidative stress, mitochondrial dysfunction, and blood–brain barrier (BBB) disruption. This excitotoxicity and oxidative stress promote the activation of microglia and astrocytes, indicated by increased expression of Iba1 and GFAP, respectively. Activated microglia release key pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which amplify the inflammatory response and further sensitize neurons by modulating glutamatergic signaling. TNF-α also increases glutamate release and decreases GABAergic inhibition, exacerbating excitability, while IL-6 contributes to BBB breakdown and influences the expression of efflux transporters like P-glycoprotein (P-gp), limiting the effectiveness of antiepileptic drugs (AEDs). Simultaneously, astrocytic activation (GFAP upregulation) impairs glutamate uptake, intensifying excitotoxicity. The resulting lipid peroxidation generates malondialdehyde (MDA), a biomarker of oxidative damage that further compromises membrane integrity and promotes neuronal injury. These interconnected

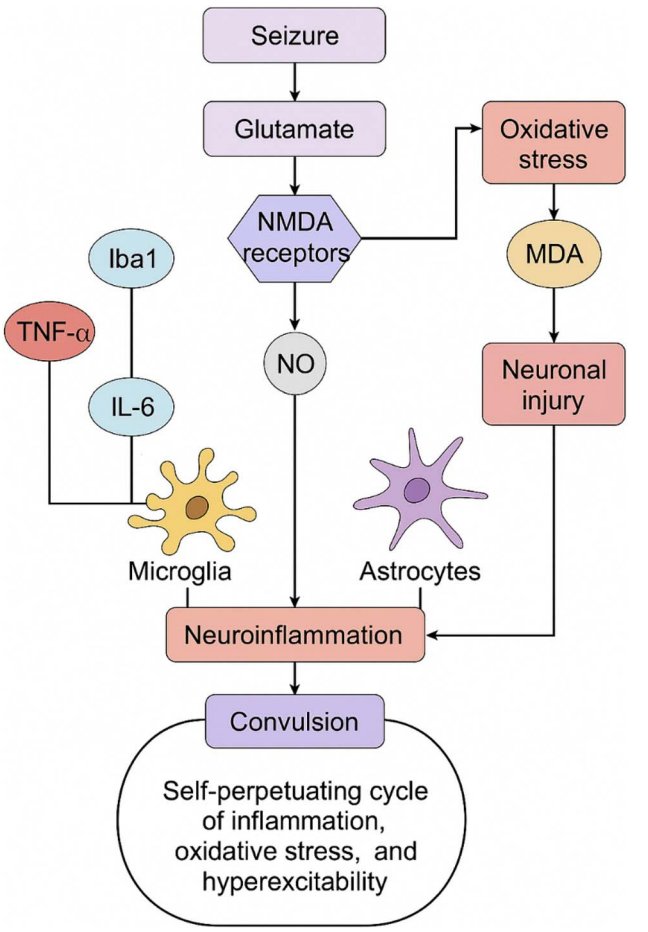


Fig. 4 Neuroinflammatory and oxidative stress cascade in epilepsy. The diagram illustrates the pathological interplay between glutamate excitotoxicity, oxidative stress (indicated by elevated NO and MDA), and neuroinflammatory mediators (TNF-α, IL-6). These factors activate microglia and astrocytes, reflected by increased Iba1 and GFAP expression, contributing to blood–brain barrier disruption, neuronal hyperexcitability, and reduced antiepileptic drug (AED) efficacy. This cycle perpetuates seizure activity and promotes pharmacoresistance.

processes create a self-perpetuating cycle of inflammation, oxidative stress, and hyperexcitability, ultimately lowering the seizure threshold, sustaining convulsive episodes, and contributing to the development of pharmacoresistance.[29–31] (Fig. 4).

5 Results and discussion

5.1 Chemistry[32]

The ^{1}H and ^{13}CNMR spectra confirmed the structures of hydrazones **5d–f** and **7b**. Compounds **5d–f** displayed characteristic signals for –CH_2–, –CH═N–, and –COOH protons, while **5e** showed additional methyl singlets. In **7b** compound, duplicated signals due to cis/trans isomerism were observed for methylene, imine, and carboxylic protons. The ^{13}CNMR spectra showed methylene carbon signals around 65.45 ppm and methyl carbons at approximate 21.53 ppm. Carbonyl and carboxylic carbon signals appeared between 163–173 ppm, consistent with the proposed structures and confirming successful hydrazone formation (Scheme 1).

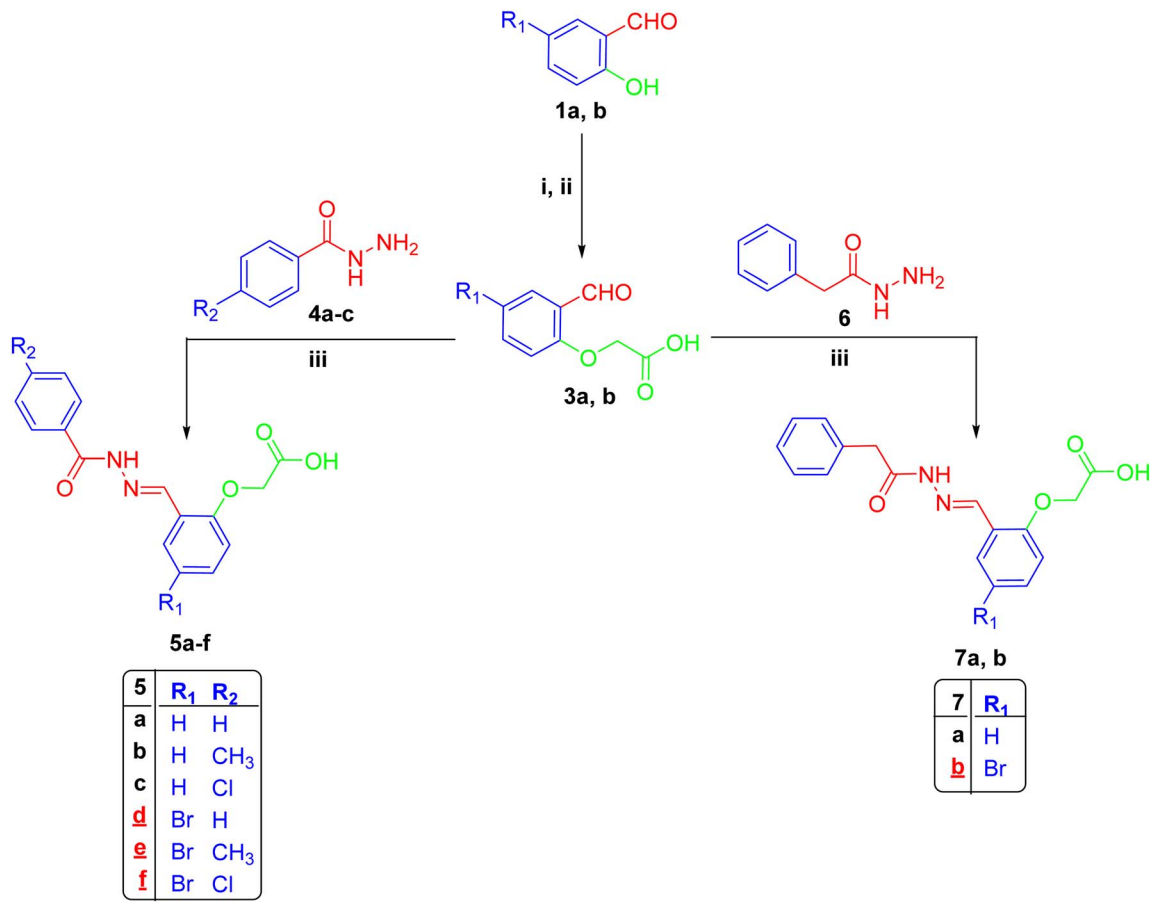
The ^{1}HNMR spectra of hydrazones **10c–e** displayed a characteristic methylene proton signal around 4.85 ppm. The presence of cis/trans isomers was evident from duplicated singlet signals for an additional imine proton around 8.39 and 8.59 ppm, and carboxylic proton approximately at 11.59 and 11.69 ppm. In the ^{13}CNMR spectra, duplicated methylene carbon signals appeared around 44.35/46.50 and 65.39/65.45 ppm, while carbonyl and carboxyl carbons were observed around 170.45 and 171.90 ppm, confirming the proposed structures and the existence of geometric isomerism (Scheme 2).

5.2 Biological study

Based on the aforementioned data illustrating the pathological cycle of inflammation, oxidative stress, and neuronal hyperexcitability in epilepsy, our design strategy focused on evaluating the most potent compounds **5d–f**, **7b** and **10c–f** exhibiting high COX-2 inhibitory activity. These compounds were further assessed for their anticonvulsant potential through targeting key sites implicated in seizure generation and propagation. The rationale is that COX-2 inhibition may interrupt the neuroinflammatory cascade modulating the release of pro-inflammatory cytokines, reducing oxidative burden, and restoring neuronal stability thereby offering a dual therapeutic action as both anti-inflammatory and antiepileptic agents.

5.3 Anti-inflammatory assay

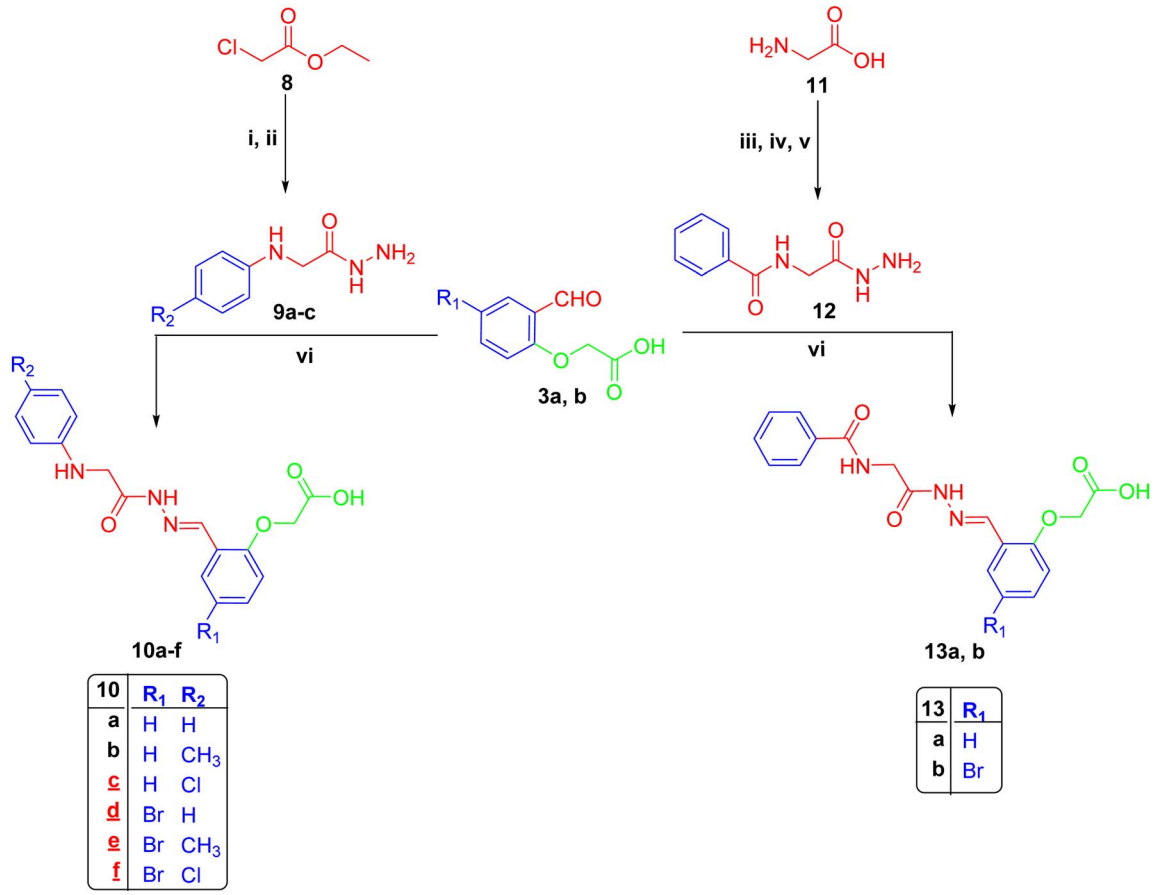
5.3.1 ***In-vitro*** **COX-2 assay.**[33] As reported in our previous study, compounds **5d–f**, **7b**, and **10c–f** demonstrated high



5	R_1	R_2
a	H	H
b	H	CH_3
c	H	Cl
d	Br	H
e	Br	CH_3
f	Br	Cl

7	R_1
a	H
b	Br

Scheme 1 (i) DMF/K_2CO_3, stir. 12 h; (ii) NaOH/MeOH, ref. 12 h; (iii) EtOH/AcOH, ref. 6 h.

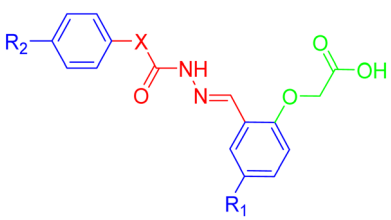


10	R_1	R_2
a	H	H
b	H	CH_3
c	H	Cl
d	Br	H
e	Br	CH_3
f	Br	Cl

13	R_1
a	H
b	Br

Scheme 2 (i) Ar-NH_2/DMF/K_2CO_3, stir. 12 h; (ii) $NHNH_2.H_2O$/MeOH, ref. 4 h; (iii) PhCOCl/NaOH, stir. at 0 °C 2 h; (iv) MeOH/H_2SO_4, ref. 6 h; (v) $NHNH_2$/MeOH, ref. 3 h; (vi) EtOH/AcOH, ref. 6 h.

Table 1 *In vitro* inhibitory activity of designed compounds **5d–f**, **7b** and **10c–f** toward COX-2 enzymes



Compounds	X	R_1	R_2	COX-1 IC_{50} (μM)	COX-2 IC_{50} (μM)
Celecoxib	—	—	—	14.93 ± 0.12	0.05 ± 0.02
5d	0	–Br	–H	9.03 ± 0.15	0.08 ± 0.01[a]
5e	0	–Br	$-CH_3$	7.00 ± 0.20	0.07 ± 0.01[a]
5f	0	–Br	–Cl	8.00 ± 0.20	0.06 ± 0.01[a]
7b	$-CH_2-$	–Br	–H	5.93 ± 0.12	0.06 ± 0.01[a]
10c	$-NH-CH_2-$	–H	–Cl	5.57 ± 0.12	0.07 ± 0.01[a]
10d	$-NH-CH_2-$	–Br	–H	7.00 ± 0.20	0.08 ± 0.01[a]
10e	$-NH-CH_2-$	–Br	$-CH_3$	4.07 ± 0.12	0.06 ± 0.01[a]
10f	$-NH-CH_2-$	–Br	–Cl	4.97 ± 0.06	0.09 ± 0.01[a]

[a] The data, which are shown as the mean ± SEM ($n = 3$), do not show any statistical significance when compared to celecoxib and mefenamic acid, with a p-value greater than 0.05 as determined by one-way ANOVA followed by Tukey and a post hoc test. With a red color scheme and strong lettering, the majority of active chemicals are shown.

potency and selective inhibitory activity against the COX-2 isozyme, exhibiting IC_{50} values in the range of 0.07–0.09 μM, which is comparable to or superior to the reference drug celecoxib (Table 1).

5.3.2 *In-vivo* assay of most potent compound 7b (ref. 34). Following alignment between the *in vitro* outcomes for the designed compounds, *in vivo* studies were conducted to further assess their anti-inflammatory potential. Carrageenan-induced paw edema in rats resulted in a significant increase in paw thickness and weight compared to the healthy control group, confirming the induction of acute inflammation. At the 5 hour mark, the carrageenan group exhibited a 94.04% ± 3.23 increase in paw weight. Treatment with the reference drug celecoxib led to a 41.65% reduction in paw thickness and a 68.15% weight gain, indicating significant anti-inflammatory effects.

Markedly, test compound **7b** demonstrated the highest inhibition of paw thickness (63.35%), outperforming celecoxib and indicating potent anti-inflammatory activity. These findings are consistent with previous reports[35,36] and affirm the reliability of the carrageenan model for evaluating acute inflammatory responses.[37,38] As summarized in Table 2, compound **7b** significantly reduced paw edema and showed efficacy comparable to standard drugs.

5.3.3 Anti-inflammatory scale of compound 7b (ref. 33). Compound **7b** demonstrated promising anti-inflammatory, analgesic, and safety profiles across multiple *in vivo* and *in vitro* studies:

Compound **7b** exhibited significant anti-inflammatory activity, demonstrating a marked reduction in inflammatory biomarkers. Specifically, **7b** decreased TNF-α levels by 64.88% and PGE_2 levels by 57.07%, showing comparable efficacy to the reference drug celecoxib.

Analgesic activity: using the hot plate latency test, **7b** demonstrated a progressive increase in latency time, reaching a 44.90% rise at 120 minutes, indicating strong central analgesic potential.

Histopathological findings: examination of paw tissues revealed that **7b** markedly reduced dermal inflammatory cell infiltration compared to the carrageenan group and reference drug, supporting its anti-inflammatory efficacy. Gastric histopathology further confirmed a favorable safety profile, with **7b** showing only minimal infiltration by a few mononuclear inflammatory cells and no significant ulcerogenic damage.

5.4 Anti-epileptic assay

Epilepsy is a complex and persistent neurological condition marked by spontaneous and recurrent seizures, often arising from disrupted neural homeostasis between excitatory and inhibitory pathways. This dysregulation frequently involves overactivation of excitatory glutamatergic signaling or diminished GABAergic inhibition, both of which contribute to enhanced neuronal excitability and seizure generation. Several interrelated pathophysiological processes, including oxidative damage, inflammatory signaling, and neurotransmitter

Table 2 Paw thickness difference at hourly intervals and the percentage of paw weight increase[a]

	Paw thickness difference at hourly intervals (mm) percentage of inhibition (%)					Paw weight increase (%)
	1st hour	2nd hour	3rd hour	4th hour	5th hour	
Control	0.04 ± 0.01	0.07 ± 0.02	0.08 ± 0.03	0.02 ± 0.01	0.00 ± 0.01	0.31 ± 2.33
Carrageenan	1.97 ± 0.38^{a}	3.29 ± 0.31^{a}	4.22 ± 0.29^{a}	5.05 ± 0.52^{a}	5.31 ± 0.52^{a}	94.04 ± 3.23^{a}
Celecoxib	1.4 ± 0.38^{ab} (29.31%)	2.36 ± 0.51^{ab} (28.34%)	2.83 ± 0.43^{ab} (33%)	3.01 ± 0.57^{ab} (40.39%)	3.10 ± 0.23^{ab} (41.65%)	29.95 ± 2.20^{ab}
7b	0.65 ± 0.16^{abc} (67.23%)	1.08 ± 0.21^{abcd} (67.11%)	1.64 ± 0.13^{abcd} (61.23%)	1.90 ± 0.19^{abcd} (62.42%)	1.95 ±± 0.19^{abcd} (63.35%)	33.07 ± 1.88^{ab}

[a] The data are presented as mean ± SD and were analyzed using two-way ANOVA (for paw thickness difference) or one-way ANOVA (for paw weight increase percentage), followed by Tukey's multiple comparisons test; $n = 6$. a: Significantly different from control group at $p < 0.05$, b: significantly different from carrageenan group at $p < 0.05$, c: significantly different from celecoxib group at $p < 0.05$, d: significantly different from mefenamic acid group at $p < 0.05$.

imbalances, are known to increase seizure vulnerability and drive epileptogenesis.[39,40]

The pentylenetetrazol (PTZ) seizure model remains a well-established tool in preclinical research for identifying compounds with anticonvulsant potential. As a GABA-A receptor antagonist, PTZ induces seizures by suppressing inhibitory neurotransmission, thereby provoking excessive neuronal firing and convulsive activity. This model is commonly used for the rapid screening of agents that may enhance inhibitory tone or reduce excitability.[41,42]

Complementing this, the pilocarpine-induced seizure model serves as a robust paradigm for investigating temporal lobe epilepsy (TLE) and status epilepticus (SE). Pilocarpine, a cholinergic muscarinic agonist, produces sustained neuronal hyperactivity through excessive excitation, triggering downstream events such as glutamate-induced excitotoxicity, oxidative stress, and cytokine-mediated neuroinflammation.[43,44] Given its clinical relevance to human TLE, this model is widely employed to assess the therapeutic efficacy of agents targeting multiple pathological pathways, including redox imbalance and neuroimmune activation. In the present study, test compounds were evaluated for anticonvulsant efficacy using both PTZ and pilocarpine models. Compounds demonstrating notable protection were subjected to further neurochemical assessments, including measurement of hippocampal glutamate, malondialdehyde (MDA), nitric oxide (NO), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and glial markers GFAP and Iba-1. This integrative approach was designed to clarify the molecular mechanisms by which these agents exert their protective effects and to identify potential candidates for further development in epilepsy therapy.

5.4.1 Assessment of seizure suppression potential in the pentylenetetrazol model. The anticonvulsant potential of compounds **5d–f**, **7b**, and **10c–f** was initially assessed using the pentylenetetrazol (PTZ) acute seizure model in mice. As summarized in Table 3, the PTZ control group exhibited no protection against seizure onset and a high mortality rate of 80% within 24 hours. In contrast, the standard antiepileptic drug, valproic acid **(VI)**, conferred 60% protection and reduced mortality to 30%.

Among the tested compounds, **7b** exhibited the most robust activity, achieving complete protection (100%) with no observed mortality. This was followed by compound **5f**, which provided 90% protection and a relative potency of 150% compared to valproic acid **(VI)**, with only 10% mortality. Both **5e** and **10c** showed comparable efficacy, each conferring 80% protection and a calculated potency of 133.33%, though their mortality rates differed slightly (10% and 20%, respectively). Compound **5d** also demonstrated notable effects with 60% protection and a relative potency equal to valproic acid (100%) (Table 3).

Table 3 Anticonvulsant activity of the tested compounds **5d–f**, **7b**, and **10c–f** in the PTZ-induced seizure model

	Protection (%)	Relative protection (%)	24 h mortality (%)
PTZ	0%	—	80%
VAL	60%	—	30%
5d	60%	100.00%	40%
5e	80%	133.33%	10%
5f	90%	150.00%	10%
7b	100%	166.67%	0%
10c	80%	133.33%	20%
10d	50%	83.33%	40%
10e	40%	66.67%	50%
10f	40%	66.67%	50%

On the other hand, compounds **10d**, **10e**, and **10f** exhibited modest activity. Compound **10d** provided only 50% protection, while **10e** and **10f** each showed 40% protection and shared the highest mortality rate among the test groups (50%). Overall, the PTZ model screening identified compounds **7b**, **5f**, **5e**, and **10c** as the most promising candidates, based on their superior seizure protection, enhanced relative potency, and lower mortality outcomes. These four compounds were consequently selected for further evaluation in the pilocarpine-induced temporal lobe epilepsy model (Fig. 5).

5.4.2 Analysis of seizure latency, progression, and survival in the pilocarpine-induced epilepsy model. To further validate the anticonvulsant efficacy of the most active candidates from the PTZ model, compounds **5e**, **5f**, **7b**, and **10c** were evaluated in the pilocarpine-induced seizure model, which mimics features of temporal lobe epilepsy. Key parameters analyzed included seizure onset (latency to forelimb clonus, stage 3), seizure severity over time, and 24 hour survival rates.

As shown in Table 4, untreated pilocarpine-exposed mice displayed rapid seizure onset (6.36 ± 0.58 min) and severe seizure activity, with Racine scores progressively escalating to stage 5 by 120 minutes, along with a survival rate of only 40%. Pre-treatment with valproic acid **(VI)** significantly delayed seizure onset (by 67.33%) and reduced final seizure severity (by 60%), improving survival to 60%.

Among the test groups, compound **7b** produced the most significant anticonvulsant effect, significantly prolonging latency to stage 3 seizures (by 188.58% and 72.46% compared to pilocarpine and valproic acid groups, respectively), while significantly attenuating seizure progression, culminating in a final Racine score of 0.9 ± 0.57 at 120 minutes and complete survival (100%) (Table 4).

Compound **5f** also showed strong activity, delaying seizure onset by 136.89% and reducing severity scores at all time points, with a 90% survival rate. Compound **5e** demonstrated intermediate efficacy with a 117.42% extended latency, a moderate reduction in seizure scores, and 70% survival. In contrast, compound **10c**, though delaying onset by 94.97%, exhibited less control over seizure severity and yielded a final survival rate of 70%, similar to **5e**.

Taken together, these results indicate that all tested compounds mitigated pilocarpine-induced seizure activity to varying degrees, with compound **7b** displaying the most potent and comprehensive neuroprotective profile, justifying its selection for further neurochemical and safety investigations.

5.4.3 Modulation of pilocarpine-induced hippocampal alterations by compound 7b. Oxidative damage and inflammation within the central nervous system are recognized as key contributors to seizure-induced neuropathology and the

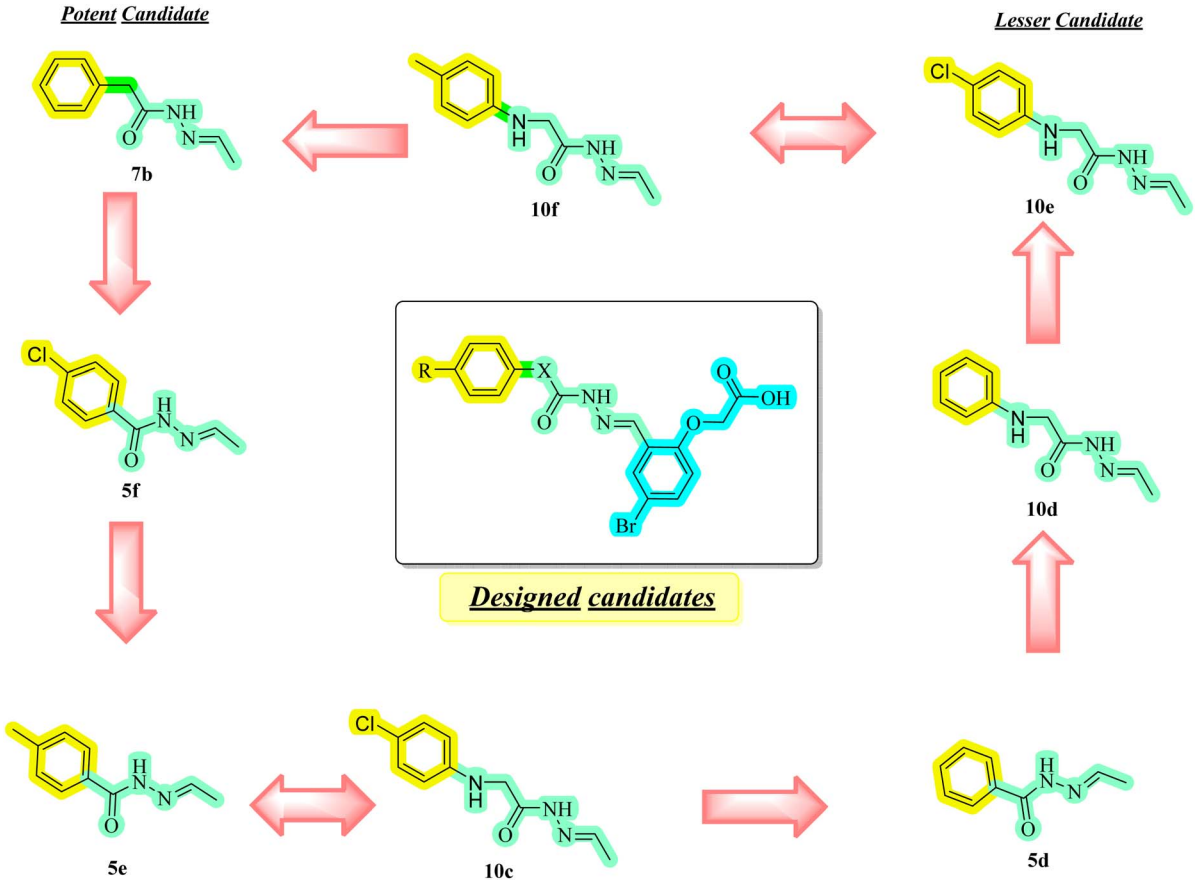


Fig. 5 SAR analysis of most designed compounds **5d–f**, **7b** and **10c–f** through *in vitro*-study of COX-2 isozyme.

Table 4 Effects of selected compounds on seizure onset, severity, and survival in the pilocarpine model[a]

		Seizure severity				
	Onset (mins)	30 min	60 min	90 min	120 min	24 h Survival (%)
Pilocarpine	6.36 ± 0.58	3.3 ± 0.48	4 ± 0.67	4.4 ± 0.52	4.75 ± 0.46	40%
Valproic acid **(VI)**	10.65 ± 0.52[a]	2.1 ± 0.57[a]	2.8 ± 0.63[a]	2.9 ± 0.57[a]	1.9 ± 0.57[a]	60%
5e	13.83 ± 0.49[ab]	2.8 ± 0.63	2.8 ± 0.63[a]	2.3 ± 0.48[a]	1.7 ± 0.48[a]	70%
5f	15.07 ± 0.43[ab]	2.5 ± 0.53	2.4 ± 0.52[a]	1.9 ± 0.32[ab]	1.3 ± 0.48[a]	90%
7b	18.36 ± 0.41[ab]	2.3 ± 0.48[a]	2.2 ± 0.42[a]	1.6 ± 0.7[ab]	0.9 ± 0.57[ab]	100%
10c	12.4 ± 0.34[ab]	3.3 ± 0.48[b]	3.2 ± 0.63	2.6 ± 0.52[a]	2.4 ± 0.52[a]	70%

[a] Results are presented as mean ± SD. Seizure onset data were analyzed using one-way ANOVA followed by Tukey's multiple comparisons test, while seizure severity over time was evaluated using two-way ANOVA with Tukey's post hoc test. Significance: a: $P < 0.05$ *vs.* pilocarpine group; b: $P < 0.05$ *vs.* valproic acid group.

development of epilepsy. Recurrent seizure activity enhances the generation of reactive oxygen and nitrogen intermediates, triggering peroxidative injury to membrane lipids, as indicated by increased malondialdehyde (MDA) levels, and the upregulation of nitric oxide (NO), which is associated with nitrosative stress. These processes compromise neuronal membrane integrity and accelerate cell death. In parallel, heightened glutamate release during seizures leads to excitotoxicity, mitochondrial dysfunction, and further oxidative imbalance.[45,46]

The inflammatory component of epilepsy is similarly prominent. Elevations in proinflammatory mediators, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), disrupt the blood–brain barrier, amplify neuronal excitability, and stimulate glial activation. Activated astrocytes and microglia, commonly indicated by increased expression of GFAP and Iba-1, respectively, sustain a chronic proinflammatory environment and play a crucial role in disease progression. Accordingly, therapeutic strategies aimed at suppressing oxidative stress, excitatory neurotransmitter dysregulation, and neuroinflammation offer significant promise for mitigating seizure severity and preventing neurodegeneration.[47,48]

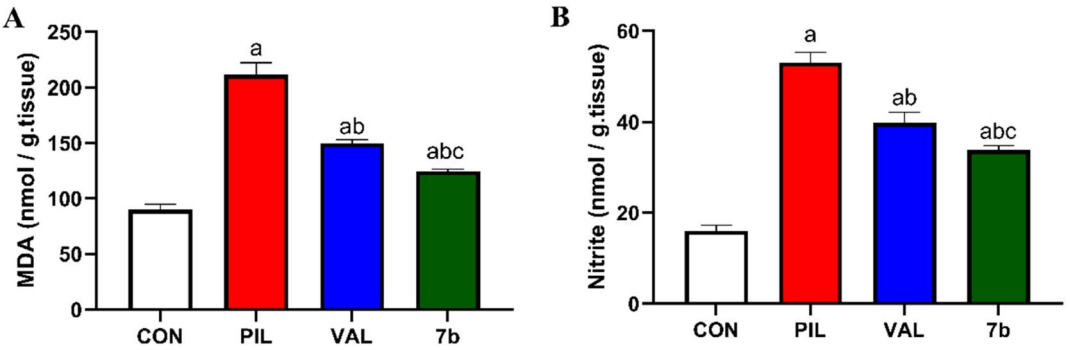


Fig. 6 Effect of compound **7b** on oxidative stress markers in hippocampal tissue. (A) malondialdehyde (MDA) and (B) nitric oxide (NO, as nitrite) levels in hippocampal tissue. Results are presented as mean ± SD. Data were analyzed using one-way ANOVA followed by Tukey's multiple comparisons test. Significance: a: $P < 0.05$ *vs.* normal control; b: $P < 0.05$ *vs.* pilocarpine group; c: $P < 0.05$ *vs.* valproic acid group. CON: normal control; PIL: pilocarpine group; VAL: valproic acid group.

As presented in Fig. 6, pilocarpine administration markedly elevated MDA and NO (measured as nitrite), indicating pronounced lipid peroxidation and nitrosative stress, with increases of 412.43% and 134.6%, respectively, compared to the normal control group. Treatment with compound **7b** significantly attenuated these oxidative changes, reducing MDA and nitrite levels by 67.15% and 41.01%, respectively, relative to the pilocarpine group, and performed better than valproic acid **(VI)**.

Neuroinflammatory mediators were also substantially elevated in the pilocarpine group, with TNF-α and IL-6 rising by 200.11% and 323.36%, respectively. Compound **7b** significantly reduced these cytokines by 56.95% (TNF-α) and 62.97% (IL-6), demonstrating potent anti-inflammatory activity, which exceeded that of valproic acid **(VI)** (Fig. 7).

Furthermore, compound **7b** effectively mitigated excitotoxicity, as indicated by a 61.5% reduction in hippocampal glutamate levels compared to the pilocarpine group. In terms of glial responses, **7b** downregulated GFAP and Iba-1 by 73.91% and 49.79%, respectively, relative to epileptic controls, with both values also significantly lower than those observed in valproic acid **(VI)** treated animals (Fig. 7). These data underscore the ability of compound **7b** to protect against pilocarpine-induced hippocampal injury through suppression of oxidative stress, proinflammatory signaling, and glial activation, alongside attenuation of excitotoxic neurotransmitter accumulation. Its

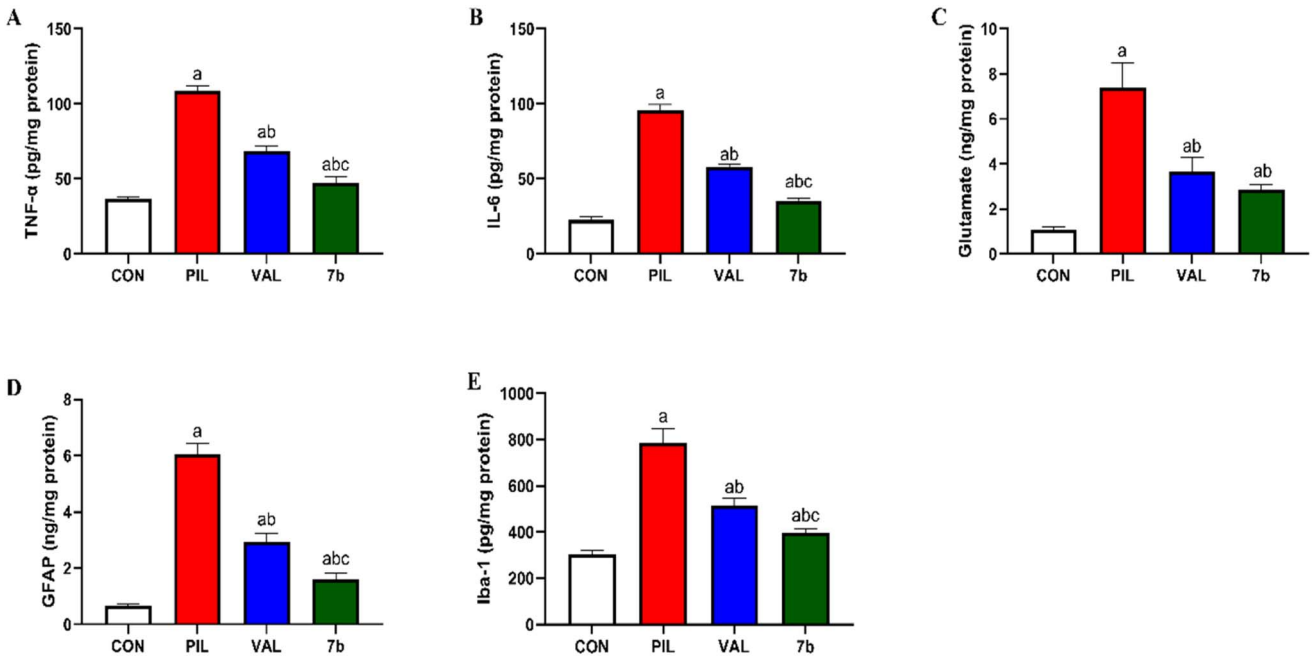


Fig. 7 Effect of compound **7b** on inflammatory, excitotoxic, and glial markers in the hippocampus. Hippocampal levels of (A) TNF-α, (B) IL-6, (C) glutamate, (D) GFAP, and (E) Iba-1. Results are presented as mean ± SD. Data were analyzed using one-way ANOVA followed by Tukey's multiple comparisons test. Significance: a: $P < 0.05$ *vs.* normal control; b: $P < 0.05$ *vs.* pilocarpine group; c: $P < 0.05$ *vs.* valproic acid group. CON: normal control; PIL: pilocarpine group; VAL: valproic acid group.

superior performance across all neurobiological markers further supports its potential as a multifunctional antiepileptic candidate.

Seizure episodes are closely associated with a cascade of neurochemical alterations, particularly those involving oxidative stress and nitrosative injury. In the present study, administration of pilocarpine led to a significant elevation in hippocampal MDA and NO levels, indicating extensive oxidative burden and lipid membrane disruption. The observed rise in MDA reflects increased lipid peroxidation, a consequence of reactive oxygen species attacking polyunsaturated fatty acids within neuronal membranes, ultimately compromising cellular structure. Concurrently, the surge in NO implies excessive production of reactive nitrogen species, which may combine with superoxide to generate peroxynitrite, a highly reactive compound known to trigger mitochondrial dysfunction and neuronal degeneration.[49,50]

Treatment with compound **7b** effectively counteracted these redox disturbances, as evidenced by its significant suppression of both MDA and NO levels compared to the epileptic control group. These findings highlight the potent antioxidant capacity of **7b**, which may underline its neuroprotective effect by stabilizing cellular membranes and mitigating oxidative insult within seizure-affected hippocampal regions.

The current results also emphasize the critical role of neuroinflammation in seizure-induced hippocampal injury, as evidenced by the marked elevation of tumor TNF-α and IL-6 levels following pilocarpine administration. These pro-inflammatory cytokines are well-established contributors to epileptogenesis, known to enhance synaptic transmission, disrupt blood–brain barrier integrity, and facilitate the activation of resident glial cells. Treatment with compound **7b** significantly attenuated the expression of both TNF-α and IL-6, suggesting an effective suppression of the inflammatory cascade. This anti-inflammatory action may play a pivotal role in the observed neuroprotection, reinforcing the therapeutic value of **7b** in mitigating seizure-related inflammatory damage.[51]

Elevated expression of glial markers in the pilocarpine group confirmed substantial activation of astrocytes and microglia, hallmarks of gliosis and persistent neuroinflammation. Specifically, the upregulation of GFAP and Iba-1 reflects the engagement of astrocytic and microglial populations in the epileptic hippocampus. Astrocytic activation impairs key homeostatic functions such as extracellular potassium buffering and glutamate reuptake, thereby intensifying neuronal excitability. Meanwhile, microglial activation facilitates the release of pro-inflammatory mediators and contributes to synaptic remodeling and neuronal injury.[52] Administration of compound **7b** led to a pronounced decrease in both GFAP and Iba-1 levels, suggesting effective attenuation of glial reactivity. Notably, this suppression exceeded the effects observed with valproic acid **(VI)**, indicating a strong glia-targeting capability that may underline the neuroprotective and anticonvulsant actions of **7b**.

5.4.4 Safety profile and systemic toxicity assessment of compound 7b. To ensure the safety of compound **7b** at doses exceeding the therapeutic range, a subacute toxicity assessment was conducted following oral administration of 100 mg kg^{-1}. Animals were observed over a 48 hour period for clinical signs of toxicity, abnormal behavior, or mortality. No adverse effects were noted in treated mice.[53] Biochemical evaluation of liver, kidney, and cardiac function was performed. As summarized in Table 5, there were no statistically significant differences between **7b**-treated mice and the control group in hepatic enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). Likewise, renal function remained unaffected, as reflected by normal serum urea and creatinine levels. Assessment of cardiac safety showed that creatine kinase-MB (CK-MB) levels remained within physiological limits, with no significant deviations from control values (Table 5).[54]

These biomarkers are widely accepted indicators of systemic organ function and are commonly employed to detect subclinical hepatic, renal, or myocardial toxicity. Specifically, ALT, AST, and ALP serve as sensitive markers of hepatocellular integrity and are frequently elevated in drug-induced liver injury. The stable levels observed in the current study suggest that compound **7b** does not induce hepatic damage. Similarly, serum urea and creatinine, which reflect renal excretory capacity and glomerular filtration, remained within physiological ranges, supporting the absence of nephrotoxic effects. The unchanged CK-MB concentrations further indicate a lack of cardiotoxicity, as this enzyme isoform is a reliable marker of myocardial injury.

Taken together, these findings confirm that compound **7b** exhibits a favorable systemic safety profile, with no evidence of hepatic, renal, or cardiac toxicity at supratherapeutic doses. (based on biochemical parameters following an acute supratherapeutic single dose). This aligns with its overall neuroprotective efficacy and reinforces its potential as a safe candidate for further antiepileptic drug development.[55]

Table 5 Evaluation of hepatic, renal, and cardiac safety of compound **7b**[a]

	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	Serum urea (mg dL^{-1})	Serum creatinine (mg dL^{-1})	CK-MB (U/L)
Control	32.01 ± 3.93	38.41 ± 3.83	129.99 ± 11.13	35.4 ± 3.58	0.64 ± 0.14	38.52 ± 5
7b	35.79 ± 6.22	36.38 ± 2.57	127.26 ± 11.78	37.81 ± 2.23	0.61 ± 0.12	42.65 ± 10.97

[a] Data are shown as mean ± SD. Unpaired *t*-test revealed no significant differences between groups. No significant alterations were observed, indicating preserved hepatic, renal, and cardiac function.

5.5 Toxicity impact

The oral toxicity of compound **7b** was evaluated using the Pro-Tox 3.0 *in silico* model. The compound was assigned to toxicity class 6, with a predicted median lethal dose (LD_{50}) of approximately 6500 mg kg^{-1}, indicating a relatively low acute toxicity and suggesting a favorable safety margin. Analysis of the toxicity radar chart and the active toxicity cluster further supported the low-risk profile of compound **7b**, showing no predicted toxicity toward the blood–brain barrier (BBB). However, the model identified a potential for nephrotoxicity, which may pose a limitation to its therapeutic application. These findings highlight the need for further structural refinement to minimize potential renal toxicity and improve the overall safety profile of the compound (Fig. 8, and 9, S1).

5.6 ADME study

The pharmacodynamic properties of compound **7b** were carefully evaluated to ensure its potency, selectivity, and efficient transport to the site of action at concentrations sufficient to exert a therapeutic effect. Considering the importance of molecular characteristics for human pharmacokinetics, the drug-likeness of **7b** was assessed using Lipinski's rule of five[56] and Veber's parameters.[57]

The SWISSADME predictions revealed that compound **7b** complies with both Lipinski's and Veber's criteria, indicating favorable drug-like properties. It also exhibited a high level of predicted human intestinal absorption (HIA), suggesting satisfactory oral bioavailability. Furthermore, **7b** was predicted not to be a substrate of P-glycoprotein (P-gp), which supports its good systemic availability. Importantly, the predicted blood–brain barrier (BBB) penetration for **7b** was low, indicating minimal potential for central nervous system (CNS) adverse effects. Collectively, these findings highlight compound **7b** as a promising candidate with favorable ADME characteristics and the potential for effective systemic exposure without significant CNS-related toxicity (Fig. 10 and Table 6).

5.7 Translational challenges

While compound **7b** exhibited superior anticonvulsant efficacy compared to valproic acid **(VI)** and demonstrated a favorable

Fig. 8 Toxicity radar chart showing the confidence of positive toxicity predictions for the compound relative to the average toxicity profile of its class.

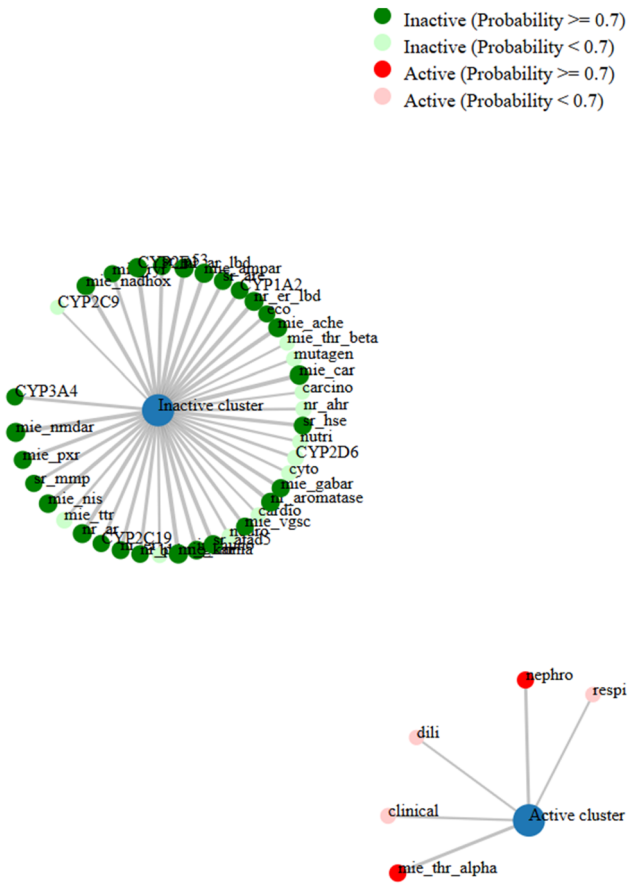


Fig. 9 Network chart illustrating the predicted associations between the selected compound and its potential biological activities.

multifunctional pharmacological profile, several translational challenges remain to be addressed before clinical advancement. Comprehensive pharmacokinetic (ADME) studies are required to elucidate its absorption, distribution, metabolism, and excretion characteristics, which are critical for ensuring consistent systemic exposure and therapeutic efficacy. Moreover, *in silico* predictions indicated limited blood–brain barrier (BBB) penetration, a factor that may restrict its effectiveness in certain central nervous system (CNS)-related pathologies. While this could be advantageous in reducing CNS-related adverse effects, its therapeutic relevance must be carefully evaluated depending on the intended clinical application (Table 7).

Additionally, the ProTox 3.0 analysis suggested a potential risk of nephrotoxicity, highlighting the need for structural refinement and early preclinical safety assessments to mitigate renal toxicity concerns. Addressing these aspects through rational optimization and comprehensive preclinical evaluation will be essential to enhance the drug-likeness, safety profile, and clinical translatability of compound **7b**.

5.8 Molecular docking study

Molecular docking studies were carried out to explore the binding interactions of the synthesized compounds within the active site of the voltage-gated calcium channels (VGCCs), which are known targets of the antiepileptic drug valproic acid **(VI)**. The analysis aimed to assess whether the designed compounds could mimic or enhance the binding behavior of valproic acid. This comparative docking analysis supports the proposed anticonvulsant potential of compound **7b** and provides mechanistic insight into its possible modulation of

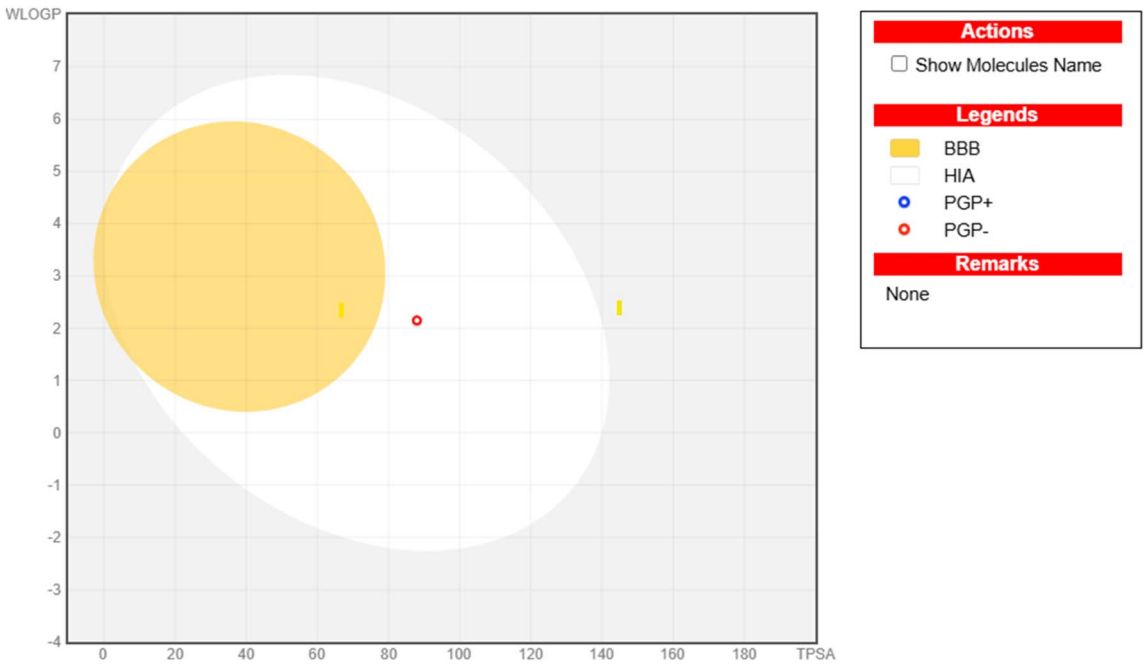


Fig. 10 Toxicity radar chart showing the confidence of positive toxicity predictions for the compound relative to the average toxicity profile of its class.

Table 6 The predicted ADME properties for the potent compound **7b**[a]

Compound	MW (g mol^{-1})	Rotatable bonds	H-bond acceptors	H-bond donors	Log *P*	TPSA (Å^2)	Gi absorption	Pgp substrate	Lipinski violations
7b	391.22	8	6	2	2.21	87.99	High	No	0

[a] MW: molecular weight; log *P*: lipophilicity; TPSA: topological polar surface area; P-gp: P-glycoprotein. All predictions were generated using the SwissADME web server.

Table 7 The predicted ADMET properties for the potent compound **7b**

Compound	BBB permeant	Bioavailability score	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
7b	No	0.56	Yes	Yes	No	No	No

calcium channel activity (the docing study of the anti-inflammatory for **7b** was mentioned in the supplementary material).

The reference drug valproic acid was found to form hydrogen bonds through its carboxylate group with key residues Thr29, Val289, and Arg119 within the active site of the VGSC. Similarly, the most potent compound, **7b**, exhibited comparable binding interactions. The carboxylate anion of compound **7b** formed hydrogen bonds with Thr29, Val289, and Arg119, consistent with the binding mode of valproic acid **(VI)**. Additionally, compound **7b** established a hydrogen bond between the oxygen atom of its phenoxy group and Thr333. Moreover, the carbonyl group of the hydrazone moiety formed a hydrogen bond with Thr193, further stabilizing the ligand within the binding pocket (Fig. 11, S3–S5 and Table 8).

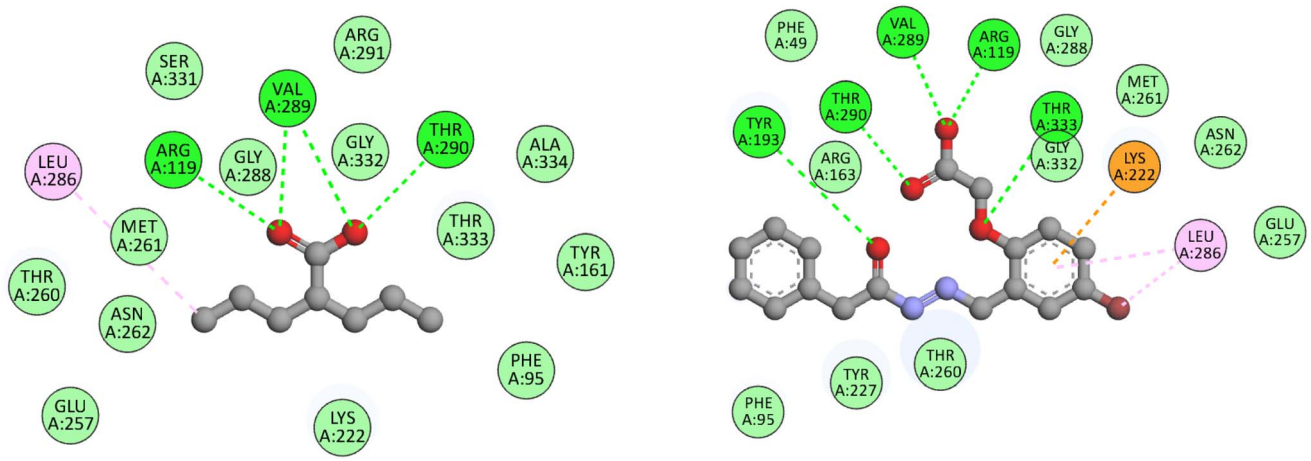


Fig. 11 2D schematic diagram of reference drug valproic acid (left) and potent **7b** (right) on the active site of VGCCs.

Table 8 The binding score, amino acid interactions, and bond lengths of compound **7b** within the active sites of VGCCs

Compound	Binding score (kcal mol^{-1})	Interaction	Bond length (Å)	Ligand atom	Residue
Valproic acid **(VI)**	−7.0	H. bond	3.02	Thr290	COO^-
		H. bond	3.03	Val289	COO^-
		H. bond	3.14	Arg119	COO^-
7b	−8.0	H. bond	2.30	Thr290	O of COO^-
		H. bond	2.02	Val289	CO of COO^-
		H. bond	2.08	Arg119	CO of COO^-
		H. bond	2.55	Thr333	O of phenoxy gp
		H. bond	2.95	Tyr193	C=O

6 Conclusion

This study provides compelling evidence for the anticonvulsant efficacy of selected test compounds specifically **5d–f**, **7b**, and **10c–f** evaluated in both PTZ- and pilocarpine-induced seizure paradigms. Among these, compound **7b** distinguished itself as the lead candidate, offering complete seizure protection in the PTZ model and significantly attenuating seizure onset, severity, and mortality in the pilocarpine model. Mechanistic insights revealed that **7b** effectively counteracts several hallmarks of epileptogenesis, including oxidative stress, neuroinflammation, excitotoxicity (as evidenced by reduced glutamate levels and improvement in seizure-related behavioral alterations in both models), and glial activation within the hippocampus. Moreover, systemic safety evaluations confirmed the absence of hepatotoxic, nephrotoxic, or cardiotoxic effects at higher doses. Future studies are warranted to explore dose–response relationships of **7b** to establish its therapeutic index and further characterize its pharmacological profile, including sub-chronic and chronic toxicity studies, histopathological evaluations, and validation in chronic seizure models such as kindling models. Taken together, these results position compound **7b** as a promising multifunctional agent for epilepsy management, meriting further exploration through advanced pharmacological and mechanistic studies to elucidate its full therapeutic potential.

7 Experimental

7.1 Synthesis of hydrazones 5d–f, 7b, and 10c–f

Equimolar amounts (2 mmol) of aldehydes **3a**, **3b** and hydrazides **4a–c**, **6**, or **9a–c** were refluxed in absolute EtOH (30 mL) with AcOH (0.3 mL) for 6 h. The resulting precipitate was filtered, dried, and recrystallized from EtOH/DMF to give the target hydrazones in good yield. (Fig. S6–S23)

The experimental procedures and spectral data for the synthesized compounds **5d–f**, **7b**, and **10c–f** are fully provided in the SI.

8 Material and methods

8.1 *In vitro* & *in vivo* anti-inflammatory assay[58–60]

Detailed descriptions of the procedures are included in the SI.

8.2 PTZ-induced convulsions[61–63]

Animals were randomly distributed into ten groups, each comprising ten mice (n = 10). The negative control group received an oral dose of 0.5% carboxymethyl cellulose (CMC), followed by an intraperitoneal injection of pentylenetetrazol (PTZ) at a convulsive dose of 85 mg kg^{-1} to induce seizures as documented in the supplementary file.

8.3 Pilocarpine-induced convulsions[64–66]

To further investigate the anticonvulsant efficacy of selected candidates, male mice (n = 10/group) were allocated into experimental groups based on prior outcomes from the PTZ model. The control group received an oral dose of 0.5% CMC without pilocarpine injection. Another group received the vehicle followed by intraperitoneal administration of pilocarpine (300 mg kg^{-1}) to induce status epilepticus. For the reference group, valproic acid **(VI)** (300 mg kg^{-1}, orally) was administered 30 minutes prior to pilocarpine as a standard antiepileptic comparator. The treatment groups received compounds **5e**, **5f**, **7b**, or **10c** (20 mg kg^{-1}, orally) 30 minutes before pilocarpine administration. These agents were selected based on their notable protective activity in the PTZ-induced seizure assay. To minimize peripheral muscarinic effects, hyoscine butylbromide (1 mg kg^{-1}, i.p.) was administered 20 minutes before pilocarpine injection then completed as displayed in the supplementary file.

8.4 Assessment of hippocampal biochemical alterations

8.4.1 Assessment of hippocampal oxidative markers. To evaluate oxidative damage in brain tissue, concentrations of malondialdehyde (MDA) and nitric oxide (NO, assessed as nitrite) were measured in hippocampal homogenates. Quantification was carried out using commercially available colorimetric assay kits (Biodiagnostics, Giza, Egypt), following the protocols provided by the manufacturer.

8.4.2 Evaluation of hippocampal inflammatory and neurochemical markers.[67] To investigate neuroinflammatory and excitotoxic changes following seizure induction, levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), glutamate, glial fibrillary acidic protein (GFAP), and ionized calcium-binding adapter molecule 1 (Iba-1) were measured in hippocampal samples as displayed in the supplementary file.

8.4.3 Evaluation of toxicity and safety.[68,69] To investigate the systemic safety of the most promising compound **7b**, mice were administered a higher oral dose (100 mg kg^{-1}), while control animals received 0.5% CMC as vehicle. Over a 48 hour observation period, animals were carefully monitored for any visible signs of toxicity, abnormal behaviors, or mortality as documented in the supplementary file.

8.5 *In silico* drug-likeness and ADME prediction

ADME study performed using the ProTox 3.0 server as displayed in the Supplementary file.

8.6 Molecular docking studies

Molecular docking was employed to as documented in the Supplementary file.

Ethical statement

All procedures involving animal handling and experimentation were conducted in accordance with the institutional ethical standards and were approved by the Ethics Committee of the Faculty of Pharmacy, Egyptian Russian University (Approval Code: ERUFP-PC-25-001).

Author contributions

Mohamed K. Elgohary: writing – original draft, investigation, methodology, conceptualization Mahmoud S. Elkotamy: writing – original draft, investigation, Mahmoud Abdelrahman Alkabbani: writing – original draft, methodology, Abdulrahman A. Almehizia: writing – original draft, funding acquisition, Ahmed M. Naglah, resources, writing – review & editing, funding acquisition, Mohammed H. Alqarni, writing – original draft, methodology, funding acquisition, Mohamed Fares, supervision, methodology, formal analysis, Wagdy M. Eldehna: supervision, project administration, methodology, formal analysis, Hatem A. Abdel-Aziz: supervision, project administration, methodology, formal analysis.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

AEDs	Antiepileptic drugs
BBB	Blood–brain barrier
GFAP	Glial fibrillary acidic protein
GABA	Gamma-aminobutyric acid
IL-6	Interleukin-6
Iba1	Ionized calcium-binding adapter molecule 1
MDA	Malondialdehyde
NMDA	*N*-Methyl-D-Aspartate
NO	Nitric oxide
P-gp	P-Glycoprotein
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
TNF-α	Tumor necrosis factor-alpha
VGSCs	Voltage-gated sodium channels
ABC	ATP-binding cassette
COX-2	Cyclooxygenase-2
EP1	Prostaglandin E2 Receptor 1

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: **https://doi.org/10.1039/d5ra05596b**.

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