Full Paper

Ultrasound-Assisted Synthesis, Anticonvulsant Activity, and Docking Study of Indole-Appended Thiazolidin-4-ones

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Two series of novel indolyl thiazolidin-4-one derivatives **4a–j** and **5a–j** were obtained by an ecofriendly synthetic protocol by treating a mixture of Schiff's bases (0.01 mol) with thioglycolic acid or thiolactic acid (0.01 mol) and anhydrous zinc chloride in catalytic amount in DMF as solvent under ultrasound irradiation, using an ultrasound synthesizer with a synthetic solid probe. The structures of the synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis. The anticonvulsant activity and neurotoxicity of the newly synthesized compounds were established by MES and sc-PTZ model and by rotarod test, respectively, *in vivo* using mouse models. The actophotometer was used for the screening of behavioral activity. The compounds exhibited promising anticonvulsant activity; especially, the compounds showed maximum protection in the MES model at a dose of 100 mg/kg. Further, docking studies of the synthesized compounds were performed against the sodium channel receptor and showed good binding interactions with the receptor. A computational study was carried out to highlight the pharmacophore distance mapping, log *p* determination, and pharmacokinetic parameters.

Keywords: Anticonvulsant activity / Computational study / Docking study / Indolyl thiazolidin-4-ones / Ultrasound irradiation

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Introduction

The characteristic event in epilepsy is the *seizure*, which is a condition that results from a temporary electrical disturbance in the brain due to an imbalance between excitatory and inhibitory neurotransmitters [1, 2]. According to an epidemiological survey, epilepsy affects more than 50 million people across the globe [3]. About one-third of the population develops refractory epilepsy to currently available antiepileptic drug therapy [4, 5]. The recent developments in antiepileptic agents have become more progressive and are affording many research opportunities in medicinal chemistry. The new drug development in AEDs is facilitated by the concept of "the new wave of research in the epileptics" [6].

The search for new antiepileptic drugs with one or more selective activity and low toxicity profile continues to be an area of investigation in medicinal chemistry. There are different pharmacophoric models that are applied for a rational drug design process for new anticonvulsant drugs [7–9]. Based on the above concept of drug design, we have designed and synthesized new 3-(substituted)-2-(1*H*-indol-3-yl)-thiazolidin-4-one by ultrasound irradiation.

Many researchers had investigated indole and thiazolidinone as potential anticonvulsant agents. Indole-containing compounds are known to have a wide range of pharmacological activities [10]. Researchers have reported that the indole derivatives can be used for the treatment of epilepsy [11–24]. Ralitoline (Fig. 1) is the compound which possesses a thiazolidinone moiety and is found to be effective in preclinical anticonvulsant evaluation. The available literature

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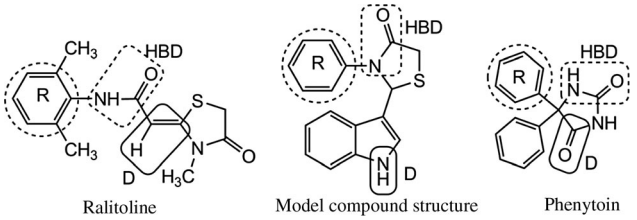


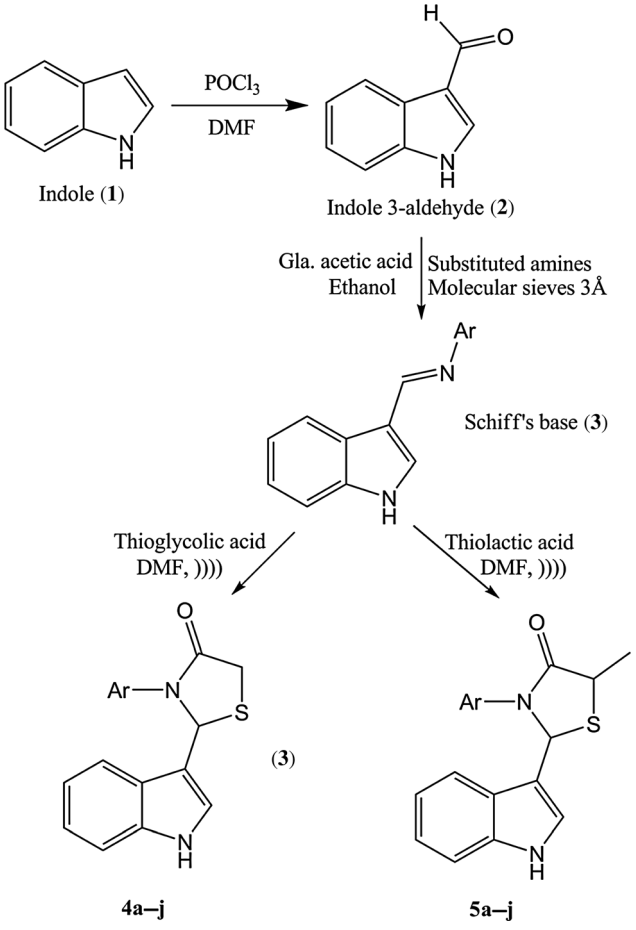
Figure 1. Pharmacophoric pattern of well-known anticonvulsants and model compound with essential structure elements.

reveals that the thiazolidinone nucleus is a good candidate for anticonvulsant activity. The mechanism involved in anticonvulsant activity of thiazolidinones is inhibition of oxidation of the substrates of the tricarboxylic acid cycle such as pyruvate, α-ketoglutarate, and citrate, and β-hydroxybutyrate [25–33]. Indole coupled with thiazolidinone derivatives has been previously synthesized by conventional methods and evaluated for anti-HIV, anticancer, and anti-tubercular activities [34]. However, to the best of our knowledge such compounds have never been synthesized by ultrasound irradiation and also have not been evaluated for anticonvulsant activity. Based on these reported literature and as a part of our continuous investigation in this area [35, 36] we thought to synthesize indole-appended phenylthiazolidin-4-one derivatives with enhanced CNS activities, which could be effectively used for the treatment of epilepsy. The ultrasound-promoted eco-friendly synthetic strategy was selected so as to get the desired products in better yield and in shorter reaction times [37]. All the synthesized compounds comprised essential pharmacophoric elements that were necessary for good anticonvulsant activity as suggested by Unverferth et al. [38] (Fig. 1). The computational studies such as molecular docking, log *p* determination, and pharmacokinetic parameters (ADME) were carried out and the results suggested that the compounds could be exploited as good anticonvulsant agents.

Results and discussion

Chemistry

The reaction sequence for the synthesis of the title compounds 3-(substituted)-2-(1*H*-indol-3-yl)thiazolidin-4-one **4a–j** and 3-(substituted)-2-(1*H*-indol-3-yl)methylthiazolidin-4-one **5a–j** is outlined in Scheme 1. 3-Formylindole **2** was synthesized by Vilsmeier–Haack reaction, and by refluxing **2** with various aromatic amines in ethanol indolyl Schiff's bases were obtained. In this reaction, activated molecular sieves 3 Å were used to obtain a better yield of the product and for the reaction rate enhancement. Finally, equimolar quantities of Schiff's bases and thioglycolic acid/thiolactic acid in DMF as solvent and catalytic amount of anhydrous zinc chloride,



Scheme 1. Scheme of synthesis.

were irradiated under ultrasound to afford corresponding coupled indolyl thiazolidin-4-one derivatives. The purity of the synthesized compounds was checked by thin-layer chromatography on silica gel G precoated plates (Merck) and visualization of the developed chromatogram was performed by staining with iodine and melting points were determined in open capillary tubes on a Buchi 530 melting point apparatus and are uncorrected. All the synthesized compounds were characterized by their physical data (Table 1) and spectral data.

The IR spectra of the Schiff's bases (C=N) showed stretching vibration in the region of 1620–1530 cm^{-1}. The absence of broad band of Schiff's bases (C=N) in the IR spectrum of indolyl thiazolidin-4-one confirms the formation of the title compounds. In ^{1}H NMR spectrum of series **4a–j**, the two protons of CH_2 of thiazolidinone ring (axial and equatorial) couple each other and split the signal in a double doublet in the region 3.90–4.00 δ ppm. In ^{1}H NMR, spectrum of series of derivatives **5a–j** exhibited quartet at (3.65 δ ppm) due to

Table 1. Physical data of final synthesized compounds.

Comp.	Ar	Mol. formula	Mol. wt	m.p. (°C)	Yield (%)
4a	Phenyl	$C_{17}H_{14}N_2OS$	294.37	220–222	65
4b*	4-Cl-Phenyl	$C_{17}H_{13}ClN_2OS$	328.81	188–190	52
4c*	3-Cl-Phenyl	$C_{17}H_{13}ClN_2OS$	328.81	125–127	60
4d	2,4-Cl-Phenyl	$C_{17}H_{12}Cl_2N_2OS$	363.26	229–230	56
4e*	4-Br-Phenyl	$C_{17}H_{13}BrN_2OS$	373.26	114–116	43
4f	4-CH_3-Phenyl	$C_{18}H_{16}N_2OS$	308.39	153–154	69
4g	2,4-CH_3-Phenyl	$C_{19}H_{18}N_2OS$	322.42	102–104	56
4h	4-OCH_3-Phenyl	$C_{18}H_{16}N_2O_2S$	324.39	201–202	49
4i	2-OH-Phenyl	$C_{17}H_{14}N_2O_2S$	310.37	133–135	58
4j	2-SH-Phenyl	$C_{17}H_{14}N_2OS_2$	326.43	98–100	62
5a	Phenyl	$C_{18}H_{16}N_2OS$	308.39	240–244	48
5b*	4-Cl-Phenyl	$C_{18}H_{15}ClN_2OS$	342.84	156–158	54
5c*	3-Cl-Phenyl	$C_{18}H_{15}ClN_2OS$	342.84	134–136	64
5d	2,4-Cl-Phenyl	$C_{18}H_{14}Cl_2N_2OS$	377.28	171–173	57
5e*	4-Br-Phenyl	$C_{18}H_{15}BrN_2OS$	387.29	229–231	62
5f	4-CH_3-Phenyl	$C_{19}H_{18}N_2OS$	322.42	126–128	59
5g	2,4-CH_3-Phenyl	$C_{20}H_{20}N_2OS$	336.45	193–195	56
5h	4-OCH_3-Phenyl	$C_{19}H_{18}N_2O_2S$	338.42	189–190	62
5i	2-OH-Phenyl	$C_{18}H_{16}N_2O_2S$	324.39	140–142	53
5j	2-SH-Phenyl	$C_{18}H_{16}N_2OS_2$	340.46	110–112	71

Ethanol is used for re-crystallization; mobile phase for TLC is ethylacetate/*n*-hexane (7:3) and benzene/methanol* (6:4).

neighboring methyl group on thiazolidinone ring and –CH of thiazolidinone ring splits the methyl protons in a doublet at 1.38 δ ppm, and in both the series, the presence of a sharp singlet at 6.44 δ ppm due to –CH of thiazolidinone ring confirms the formation of the title compounds.

The reactions were performed using ultrasound synthesizer with solid synthetic probe at a temperature of 90°C and at a frequency of 20 Hz. All the products were obtained in 60- to 90-min time, whereas the conventional synthesis of thiazolidinone using Dean-Stark apparatus requires 14–16 h for completion of reaction [39]. The conventional method suffers a major drawback as it involves use of benzene, which is a carcinogenic, harmful solvent. Therefore, the present methodology used for the synthesis of 3-(substituted)-2-(1*H*-indol-3-yl)thiazolidin-4-one **4a–j** and 3-(substituted)-2-(1*H*-indol-3-yl)-methylthiazolidin-4-one **5a–j** is very efficient, convenient, and ecofriendly.

Anticonvulsant activity

All the synthesized compounds were evaluated for their anticonvulsant activity by MES and sc-PTZ model and have shown best protection against MES test (Table 2). In MES test, the anticonvulsant activity of the newly synthesized compounds was carried out at 0.5 and 4 h at the dose of 100 mg/kg. The compounds **4c**, **4e**, and **4i** have shown best protection at both time intervals. In MES test, the compounds **4b**, **4c**, **4e**, **4f**, **4i**, and **4j** showed protection at 0.5 h, while compounds **4a**, **4c**, **4e**, **4g**, and **4i** showed protection at 4 h. In other series of **5a–j**, compounds **5f** and **5i** showed protection at both time intervals. The compounds **5a**, **5c**, **5e**, **5f**, **5h**, and **5i** showed protection at 0.5 h while compounds **5a**, **5d**, **5f**, **5g**, and **5i** showed protection at 4 h.

In sc-PTZ test (Table 2), among synthesized compounds in a first series, compounds **4c**, **4d**, **4f**, **4g**, **4i**, and **4j** showed protection at 0.5 h and **4f** and **4i** showed protection at 4 h and the dose 100 mg/kg. The compounds **4f** and **4i** showed protection in sc-PTZ test in both time intervals. Many compounds of the series **5a–j** were also found to be active in sc-PTZ test. The compounds **5b**, **5c**, **5e**, **5f**, and **5h** have shown protection at 0.5 h and compounds **5c**, **5e**, **5i**, and **5j** showed protection at 4 h. The compounds **5c** and **5e** have shown protection at both time intervals at the dose of 100 mg/kg.

Neurotoxicity screening

In neurotoxicity screening, the compounds **4c**, **4e**, and **4j** were found to be nontoxic at a dose of 100 mg/kg while compounds **4d**, **4f**, and **4h** were found to be toxic at the same dose after 4 h (Table 2). In the series of compounds **5a–j**, the compounds **5c**, **5f**, **5h**, and **5i** were non- toxic and the compounds **5b**, **5e**, and **5i** were found to be toxic at the dose of 100 mg/kg.

Behavioral activity

From the behavioral activity of synthesized compounds using actophotometer, the compounds **4a**, **4e**, **4f**, **4g**, **4h**, **4j**, and **5c**, **5d**, **5h**, **5i**, **5j** showed no behavioral despair effect when compared to diazepam at 0.5 h. The compounds **4a**, **4d** and **5c**, **5h**, and **5j** showed no behavioral despair effect when

Table 2. Anticonvulsant and neurotoxicity screening of compounds.

	MES screen		sc PTZ screen		Neurotoxicity screen
Comp.	0.5 h	4 h	0.5 h	4 h	4 h
4a	–	100	–	–	X
4b	100	–	–	–	X
4c	100	100	100	–	Nontoxic
4d	–	–	100	–	Toxic
4e	100	100		–	Nontoxic
4f	100	–	100	100	Toxic
4g	–	100	100	–	X
4h	–	–	–	–	Toxic
4i	100	100	100	100	Nontoxic
4j	100	–	100	–	X
5a	100	–	–	–	X
5b	–	100	100	–	Toxic
5c	100	–	100	100	Nontoxic
5d	–	100	–	–	X
5e	100	–	100	100	Toxic
5f	100	100	100	–	Nontoxic
5g	–	100	–	–	X
5h	100	–	100	–	Nontoxic
5i	100	100	–	100	Nontoxic
5j	–	–	–	100	Toxic
Phenytoin	100	100	X	X	X

Dose 100 mg/kg of the compound was administered and the protection and neurotoxicity were measured after 0.5 and 4 h. The figures indicate the minimal dose required to cause protection or neurotoxicity in 50% or more of the animals. The dash (–) indicates the absence of anticonvulsant activity or neurotoxicity. (X) denotes not tested.

Table 3. Behavioral study of compounds using actophotometer.

	Activity score	Post-treatment[a)]	
Comp.	Control (24 h before)	0.5 h	4 h
4a	178.41 ± 5.192	142.78 ± 3.852^{ns}	153.81 ± 6.094
4b	129.79 ± 4.294	39.80 ± 4.259	63.12 ± 2.835
4c	104.82 ± 3.942	41.39 ± 3.458	56.79 ± 4.042
4d	184.61 ± 10.628	68.58 ± 5.183	171.61 ± 3.473
4e	101.59 ± 6.547	97.32 ± 4.84^{ns}	85.59 ± 3.750
4f	117.44 ± 8.060	111.82 ± 4.663	62.42 ± 3.219
4g	123.22 ± 5.380	118.79 ± 4.176	78.02 ± 6.066
4h	127.63 ± 5.60	92.75 ± 4.913^{ns}	120.81 ± 5.152^{ns}
4i	150.60 ± 8.453	47.12 ± 1.789	63.09 ± 3.633
4j	115.18 ± 3.736	99.58 ± 5.662^{ns}	79.58 ± 4.517
5a	120.41 ± 2.731	84.40 ± 4.479^{ns}	116.14 ± 321
5b	102.63 ± 3.076	78.18 ± 2.596^{ns}	64.36 ± 2.182
5c	170.09 ± 4.722	133.78 ± 3.201	147.17 ± 4.283
5d	136.38 ± 5.409	110.34 ± 4.632	117.59 ± 2.874
5e	107.79 ± 8.285	83.12 ± 4.461	73.55 ± 3.544
5f	126.20 ± 4.259	78.40 ± 6.242^{ns}	101.02 ± 2.429
5g	103.07 ± 4.452	73.08 ± 4.069^{ns}	81.51 ± 3.458
5h	142.25 ± 8.381	121.60 ± 4.578	125.34 ± 3.487
5i	172.81 ± 3.216	144.01 ± 3.286	122.43 ± 3.400
5j	168.12 ± 7.087	132.11 ± 2.569	145.15 ± 2.267
Diazepam[b)]	214.60 ± 2.839	90.78 ± 3.942	122.72 ± 2.596

[a)] Each value represents the mean ± SEM significantly different from the control at $p < 0.05$; ns denotes not significant at $p < 0.05$ (Student's *t*-test); locomotor activity score was measured for 10 min.

[b)] The compound was tested at dose level of 4 mg/kg (i.p.).

compared to diazepam at 4 h (Table 3). All the other compounds were found to decrease behavioral activity of the animals at 100 mg/kg compared to diazepam.

Computational parameters

The docking study

In the present study, the synthesized derivatives were more effective in the MES model than in sc-PTZ model, and the MES test is known to be sensitive to sodium channel inhibitors, which suggests that the synthesized compounds might be inhibiting voltage-gated ion channels (particularly sodium channels). Based on these results, we docked the compounds against sodium channel receptor (PDB ID: 1BYY) [40] to understand the binding interactions. The docking calculation and hydrogen bond and hydrophobic bond interactions are presented in Table 4. The interaction energy of the compounds **4a–j** and **5a–j** and their anticonvulsant activity (MES test) showed the corresponding results. The docking results indicated that the thiazolidinone core of these compounds was held in the active pocket by combination of various hydrophobic and van der Waals interactions with the sodium channel receptor. The various hydrophobic interactions occurred between the thiazolidinone ring and active side chain of LYS1495, LYS1496, TYR1498, ASN1499, LYS1502, LYS1503, LEU1504, GLY1505, and SER1506. The amino acid residues such as LYS1495, GLY1505, and SER1506 had formed hydrogen bonds with –NH group of indole nucleus. The carbonyl group of thiazolidinone ring (**4b**, **4e**, **4f**, and **5e**) and sulfur atom of thiazolidinone ring (**4i** and **5j**) had formed the hydrogen bonding with SER1506. The substituents such as $-CH_3$ and $-OCH_3$ at 4th position of phenyl ring showed hyrdrophobic interactions with amino acid residues such as LYS1496, LYS1502, and LEU1504, thus suggesting that the introduction of these lipophilic groups at 4th position of phenyl ring would show good interactions with sodium channel receptors. The interactions of most active compounds **4e**, **4i**, **5e**, and **5f** from both the series are shown in Fig. 2 and revealed that the amino acids had formed good hydrophobic and van der Waals interactions. On the basis of this activity data (Table 2) and the docking results (Table 4), it was found that the synthesized derivatives of both the series **4a–j** and **5a–j** have potential to inhibit sodium channel receptors.

Table 4. Molecular docking statistics of indolyl-thiazolidinones.

Entry	Binding energy (kcal/mol)	Hydrogen bonds	Hydrophobic bonds
4a	−55.35	SER1506-NH of indole	ASN1499 and LEU1504-CH of thiazolidinone; LEU1504-CH_2 of thiazolidinone
4b	−54.39	SER1506-O=C of thiazolidinone	TYR1498, ASN1499, and LYS1502-CH of thiazolidinone; LYS1502-CH_2 of thiazolidinone
4c	−56.72	SER1506-NH of indole	TYR1498, ASN1499, and LYS1502-CH of thiazolidinone; LYS1502, LEU1504, GLY1505, and SER1506-CH_2 of thiazolidinone
4d	−55.20	LYS1495-NH of indole	ASN1499-CH of thiazolidinone; ASN1499, LYS1502, LEU1504, and SER1506-CH_2 of thiazolidinone
4e	−70.64	SER1506-O=C of thiazolidinone	TYR1498, ASN1499, and LYS1502-CH of thiazolidinone; TYR1498 and LYS1502-CH_2 of thiazolidinone
4f	−57.90	SER1506-O=C of thiazolidinone	TYR1498, ASN1499, and LYS1502-CH of thiazolidinone; LYS1502-CH_2 of thiazolidinone; ASN1499 and LYS1502-CH_3 of phenyl
4g	−58.18	SER1506-NH of indole	ASN1499 and LEU1504-CH of thiazolidinone; LEU1504-CH_2 of thiazolidinone
4h	−54.55	–	TYR1498, ASN1499, and LYS1502-CH of thiazolidinone; LYS1502, LEU1504, GLY1505, and SER1506-CH_2 of thiazolidinone; LYS1495 and LYS1496-CH_3O of phenyl
4i	−64.01	–	TYR1498 and SER1506-CH of thiazolidinone; TYR1498 and LYS1502-CH_2 of thiazolidinone
4j	−53.17	LYS1495-NH of indole	ASN1499-CH of thiazolidinone; ASN1499, LYS1502, LEU1504, GLY1505, SER1506-CH_2 of thiazolidinone
5a	−54.74	GLY1505, and SER1506-NH of indole	ASN1499 and LEU1505-CH of thiazolidinone; LEU1505-$CH(CH)_3$ of thiazolidinone; LEU1505-CH_3 of thiazolidinone
5b	−61.22	–	ASN1499-CH of thiazolidinone; ASN1499, LEU1504, and SER1506-$CH(CH)_3$ of thiazolidinone; ASN1499 and LEU1504-CH_3 of thiazolidinone
5c	−56.79	–	TYR1498 and SER1506-CH of thiazolidinone; TYR1498 and LYS1502-$CH(CH)_3$ of thiazolidinone; LYS1502-CH_3 of thiazolidinone
5d	−52.28	–	ASN1499 and LEU1504-$CH(CH)_3$ of thiazolidinone; LEU1504-CH_3 of thiazolidinone
5e	−65.95	SER1506-O=C of thiazolidinone	TYR1498, ASN1499, and LYS1502-CH of thiazolidinone; TYR1498 and LYS1502-$CH(CH)_3$ of thiazolidinone; LYS1502-CH_3 of thiazolidinone
5f	−75.70	SER1506-NH of indole	ASN1499 and LEU1504-CH of thiazolidinone; LEU1504-$CH(CH)_3$ of thiazolidinone; LEU1504-CH_3 of thiazolidinone
5g	−53.36	SER1506-NH of indole	ASN1499-CH of thiazolidinone; ASN1499 and LEU1504-CH_3 of phenyl
5h	−51.20	SER1506-NH of indole	ASN1499 and LEU1504-CH of thiazolidinone; ASN1499 and LEU1504-$CH(CH)_3$ of thiazolidinone; LEU1504-CH_3 of thiazolidinone
5i	−65.58	SER1506-S of thiazolidinone	TYR1498-CH of thiazolidinone; TYR1498 and LYS1502-$CH(CH)_3$ of thiazolidinone; LYS1502-CH_3 of thiazolidinone
5j	−47.62	SER1506-S of thiazolidinone	TYR1498, ASN1499, and LYS1502-CH of thiazolidinone; ASN1499, LYS1505, LYS1503, LEU1504, GLY1505, and SER1506-$CH(CH)_3$ of thiazolidinone; ASN1499, LYS1505, LYS1503, LEU1504, GLY1505, and SER1506-CH_3 of thiazolidinone

(−) Indicates no hydrogen bond interactions.

Distance mapping

The present work involves the correlation of the structural requirement of well-known and structurally different anticonvulsant compounds with the title compounds. A hydrophobic unit (R), an electron donor (D) group, and a hydrogen donor/acceptor (HBD) unit are the essential structural requirements that could be responsible for an interaction with the active site of voltage-gated sodium channels. In this study, we selected well-known and structurally different compounds having anticonvulsant activity, i.e., phenytoin, carbamazepine, lamotrigine, and diazepam. The pharmacophore distance estimation was done by mechanics calculation with the force fields based on CHARMm force fields and MM3 parametrization. Table 5 shows the distances between the various groups that are essential for anticonvulsant activity. Herein, we evaluated the synthesized compounds whether they satisfy the required conditions of the derived pharmacophore model. Our analyses of distance relationship showed that the synthesized compounds fulfill the essential demands of pharmacophoric model when they are compared to the average distance requirement.

log p determination

The compounds with optimum lipophilicity, i.e., having log *p* values near 2.0, pass blood–brain barrier (BBB) and can have

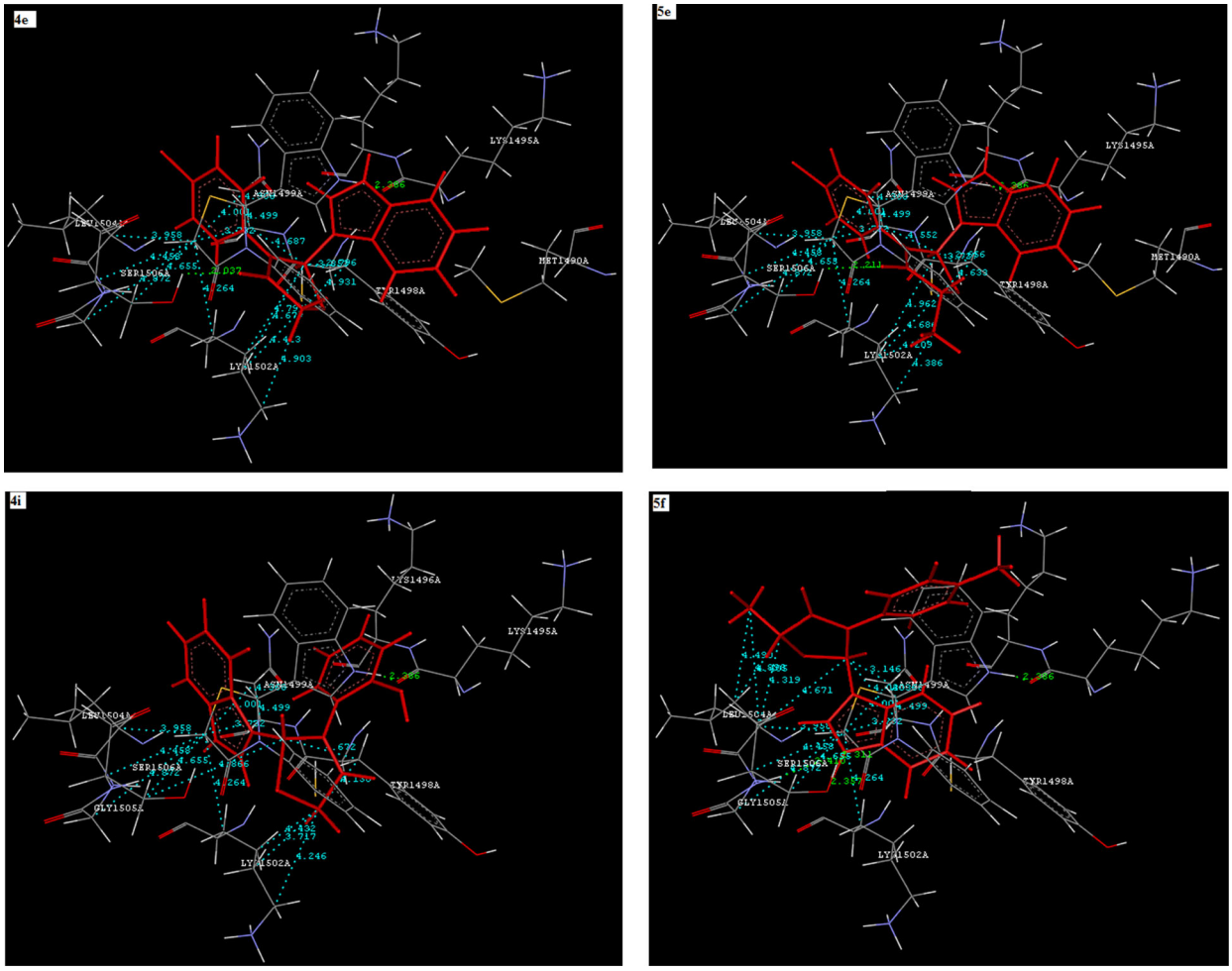


Figure 2. Docking images of compounds **4e**, **4i**, **5e**, and **5f**.

an effect on central nervous system. Here, we tried to correlate the anticonvulsant activity of synthesized compounds with calculated log *p*. The experimental log *p* values were determined by using octanol-phosphate buffer method. The data are presented in Table 6. As observed some of the experimental values were in good agreement with the theoretical values.

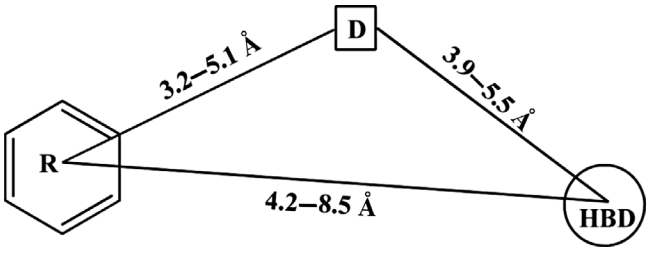
Prediction of ADME properties

A computational study for prediction of ADME properties of the title compounds was performed. Topological polar surface area (TPSA), i.e., surface belonging to polar atoms, is a descriptor that was shown to correlate well with passive molecular transport through membranes and, therefore, allows prediction of transport properties of drugs in the intestines and blood–brain barrier crossing. The percentage of absorption (% ABS) was calculated using TPSA. From all these parameters, it can be observed that all title compounds exhibited a great %ABS ranging from 89.56 to 96.54% (Table 7). From the synthesized compounds, only one compound **5d** violated only one of the Lipinski's parameters. None of the other compounds violated Lipinski's parameters, making them potentially promising agents for epilepsy therapy.

Structure–activity relationship (SAR)

In this study, two series of indolyl phenylthiazolidin-4-ones derivatives were investigated to determine the better activity of pharmacophoric groups. These pharmacophoric groups were selected from available literature and computational study. The compounds having electron-donating lipophilic groups such as $-CH_3$, $-OCH_3$, and polar –OH group at *para* position of the phenyl ring were found to be effective anticonvulsants. From the literature [41], bromide ion is found to show an inhibitory effect on CNS; among the

Table 5. Distance range between the essential structure elements R, D, and HBD.



Compounds	R–HBD	R–D	D–HBD
Phenytoin	3.58	3.77	2.21
Lamotrigine	6.44	3.41	4.45
Carbamazepine	5.09	4.87	4.06
Diazepam	4.79	4.82	1.49
Lead compounds	5.08	4.65	5.20

synthesized compounds, the derivative with *p*-bromo substituent has shown significant anticonvulsant activity and longest duration of action. MES test is known to be sensitive to sodium channel inhibitors; from the data analysis and docking study of the synthesized compounds, it was found that the compounds act by inhibiting the sodium channels.

Table 6. Experimental and theoretical log *p* values of compounds.

Compounds	Experimental log *p*	Theoretical log *p* (milog *p*[a)])
Rule	–	≤5
4a	3.12	3.467
4b	3.94	4.145
4c	3.84	4.121
4d	4.25	4.751
4e	4.01	4.276
4f	3.23	3.916
4g	3.75	4.292
4h	2.91	3.524
4i	2.85	3.2
4j	3.08	3.648
5a	3.15	3.830
5b	4.24	4.508
5c	3.89	4.484
5d	4.92	5.114
5e	4.48	4.639
5f	3.86	4.279
5g	3.81	4.655
5h	3.19	3.887
5i	3.65	3.563
5j	3.75	4.011

[a)] milog *p*, logarithm of compound partition coefficient between *n*-octanol and water calculated as per Molinspiration online property toolkit.

Conclusion

Two series of indole-appended thiazolidinones were designed and synthesized under ultrasound irradiation in good yield and at a faster reaction rate. The synthesized derivatives were evaluated for their anticonvulsant activity. The derivatives exhibited promising activity in MES and sc-PTZ test. The rotarod test was used for neurotoxicity evaluation and shows significant results. The various computational parameters studied include calculation of distance between pharmacophores, prediction of ADME properties; log *p* calculation, and docking studies. Among the two series of compounds synthesized, the compounds having electron-donating lipophilic groups such as $-CH_3$, OCH_3, and polar electron-donating –OH group exhibited significant anticonvulsant activity. The docking study reveals that the compounds have good binding interactions with the active site residues of sodium channel receptor. The docking results indicated that the thiazolidinone core of these compounds was held in the active pocket by combination of hydrogen bonding and various hydrophobic, van der Waals interactions with the sodium channel receptor.

Thus, the synthesized derivatives 3-(substituted)-2-(1*H*-indol-3-yl)thiazolidin-4-one **4a–j** and 3-(substituted)-2-(1*H*-indol-3-yl)-methylthiazolidin-4-one **5a–j** have been obtained in good yield in an eco-friendly synthetic protocol, have exhibited potential anticonvulsant activity, and can be developed as a lead molecule.

Experimental

Chemistry

All reagents and solvents were used as obtained from the supplier or recrystallized/redistilled unless otherwise noted. The ultrasound sonicator, Sonics Vibra-cell (Model No. VCX 500), with synthetic probe was used for synthesis of final title compounds. The progress of the reaction was monitored by TLC, silica gel-G (Merck) coated aluminum plates, visualized by iodine vapor. Infrared (IR) and nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra of the synthesized compounds were recorded on JASCO FTIR (PS 4000) using KBr pellets and Bruker Avance II (400 MHz) instruments, respectively. Chemical shifts are reported in parts per million (ppm), using TMS as an internal standard. Elemental analyses (C, H, and N) were undertaken with a Shimadzu FLASHEA112 analyzer and all analyses were consistent with theoretical values (within ±0.5%) unless indicated. The mass spectra were recorded on a Waters MicroMass ZQ 2000 spectrometer.

General procedure for the synthesis of Schiff's base

3-Formylindole **2** was synthesized from indole by Vilsmeier–Haack reaction [42] and indolyl Schiff's bases were obtained by refluxing compound **2** with various substituted aromatic amines in absolute ethanol as solvent [43]. Activated molecular sieves 3 Å were employed in this reaction for the removal of water formed in the reaction [44], which enhanced the yield and also enhanced the reaction rate.

Table 7. Pharmacokinetic parameters important for good oral bioavailability of the compounds.

Comp.	%ABS	TPSA (A^2)	*n*-ROTB	MW	MV	*n*-OHNH donors	*n*-ON acceptors	Lipinski's violations
Rule	–	–	–	<500	–	<5	<10	≤1
4a	96.54	36.1	2	294.37	257.11	1	3	0
4b	96.54	36.1	2	328.81	270.64	1	3	0
4c	96.54	36.1	2	328.81	270.64	1	3	0
4d	96.54	36.1	2	363.26	284.18	1	3	0
4e	96.54	36.1	2	373.26	274.99	1	3	0
4f	96.54	36.1	2	308.39	273.69	1	3	0
4g	96.54	36.1	2	322.42	290.23	1	3	0
4h	93.35	45.33	3	324.39	282.65	1	4	0
4i	89.56	56.32	2	310.37	265.13	2	4	0
4j	96.54	36.1	2	326.43	274.77	1	3	0
5a	96.54	36.1	2	308.39	273.70	1	3	0
5b	96.54	36.1	2	342.84	287.23	1	3	0
5c	96.54	36.1	2	342.84	287.23	1	3	0
5d	96.54	36.1	2	377.28	300.77	1	3	1
5e	96.54	36.1	2	387.29	291.58	1	3	0
5f	96.54	36.1	2	322.42	290.26	1	3	0
5g	96.54	36.1	2	336.45	306.46	1	3	0
5h	93.35	45.33	3	338.42	299.24	1	4	0
5i	89.56	56.32	2	324.39	281.71	2	4	0
5j	96.54	36.1	2	340.46	291.36	1	3	0

%ABS, percentage of absorption; TPSA, topological polar surface area; *n*-ROTB, number of rotatable bonds; MW, molecular weight; MV, molecular volume; *n*-OHNH, number of hydrogen bond donors; *n*-ON, number of hydrogen bond acceptors.

*General procedure for the synthesis of indolyl substituted thiazolidinones **4a–j** and **5a–j***

In an 25 mL beaker, the mixture of Schiff's bases (0.01 mol), thioglycolic acid or thiolactic acid (0.01 mol), and anhydrous zinc chloride in catalytic amount was taken in DMF (15 mL), as a solvent. The reaction mixture was sonicated for about 60–90 min at 90°C and at a frequency of 20 kHz using synthetic probe. Completion of the reaction was monitored by TLC. After completion of reaction, the mixture was poured into ice-cold water. The solid product formed was filtered, dried, and recrystallized from ethanol. The structures of the synthesized final compounds of the series **4a–j** and **5a–j** were confirmed by the spectral data and elemental analysis.

*2-(1H-Indol-3-yl)-3-phenylthiazolidin-4-one (**4a**)*

IR (KBr, ν_{max}, cm^{-1}): 3425–3279 (N–H indole), 3042 (C–H of aromatic ring), 1762 (C=O of thiazolidinone), 784 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 3.56–4.10 (dd, 2H, CH_2 of thiazolidinone), 6.01 (s, 1H, CH of thiazolidinone), 6.99–7.76 (m, 9H, Ar ring), 7.09 (s, 1H, C_2 of indole ring), 8.26 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 33.6, 70.8, 111.2, 112.2, 118.6, 119.8, 121.7, 123.8, 127.4, 127.6, 128.1, 128.9, 136.7, 141.7, 171.6, MS: $m/z = 294.2$ (M+). Anal. calcd. for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.35; H, 4.81; N, 9.49.

*3-(4-Chlorophenyl)-2-(1H-indol-3-yl)thiazolidin-4-one (**4b**)*

IR (KBr, ν_{max}, cm^{-1}): 3435–3262 (N–H indole), 3053 (C–H of aromatic ring), 1752 (C=O of thiazolidinone), 775 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 3.85–4.02 (dd, 2H, CH_2 of thiazolidinone), 6.24 (s, 1H, CH of thiazolidinone), 7.12–7.52 (m, 8H, Ar ring), 7.20 (s, 1H, C_2 of indole ring), 8.85 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 33.2, 70.2, 111.1, 112.7, 118.1, 119.4, 121.7, 123.1, 126.1, 126.4, 129.7, 129.9, 132.8, 137.7, 140.7, 171.1, MS: $m/z = 328.7$ (M+), 329.4 (M+1). Anal. calcd. for $C_{17}H_{13}ClN_2OS$: C, 62.10; H, 3.98; N, 8.52. Found: C, 62.13; H, 3.96; N, 8.50.

*3-(3-Chlorophenyl)-2-(1H-indol-3-yl)thiazolidin-4-one (**4c**)*

IR (KBr, ν_{max}, cm^{-1}): 3441–3285 (N–H indole), 3021 (C–H of aromatic ring), 1770 (C=O of thiazolidinone), 771 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 3.53–4.00 (dd, 2H, CH_2 of thiazolidinone), 6.13 (s, 1H, CH of thiazolidinone), 6.90 (s, 1H, C_2 of indole ring), 7.01–7.69 (m, 8H, Ar ring), 9.08 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 33.2, 70.1, 111.1, 112.5, 118.4, 119.8, 121.5, 123.1, 127.7, 130.6, 134.3, 135.6, 136.4, 144.6, 171.1, MS: $m/z = 328.7$ (M+), 329.4 (M+1). Anal. calcd. for $C_{17}H_{13}ClN_2OS$: C, 62.10; H, 3.98; N, 8.52. Found: C, 62.09; H, 3.99; N, 8.50.

*3-(2,4-Dichlorophenyl)-2-(1H-indol-3-yl)thiazolidin-4-one (**4d**)*

IR (KBr, ν_{max}, cm^{-1}): 3421–3265 (N–H indole), 3030 (C–H of aromatic ring), 1754 (C=O of thiazolidinone), 769 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 3.52–4.23 (dd, 2H, CH_2 of thiazolidinone), 5.96 (s, 1H, CH of thiazolidinone), 6.86 (s, 1H, C_2 of indole ring), 7.16–7.53 (m, 7H, Ar ring), 8.03 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 33.5, 70.8, 111.7, 112.2, 118.4, 119.3, 121.7, 123.5, 127.7, 131.4, 131.6, 136.6, 138.4, 144.6, 172.1, MS: $m/z = 363.3$ (M+1). Anal. calcd. for $C_{17}H_{12}Cl_2N_2OS$: C, 56.21; H, 3.33; N, 7.71. Found: C, 56.23; H, 3.32; N, 7.69.

*3-(4-Bromophenyl)-2-(1H-indol-3-yl)thiazolidin-4-one (**4e**)*

IR (KBr, ν_{max}, cm^{-1}): 3425–3252 (N–H indole), 3047 (C–H of aromatic ring), 1724 (C=O of thiazolidinone), 746 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 3.82–3.99 (dd, 2H, CH_2 of thiazolidinone), 6.18 (s, 1H, CH of thiazolidinone), 7.10 (s, 1H, C_2 of indole ring), 7.20–7.63 (m, 8H, Ar ring), 8.12 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 33.1, 70.9, 111.7, 112.1, 118.1, 119.2, 121.4, 123.5, 127.2, 131.4, 131.1, 136.2, 136.3, 140.4, 172.3, MS: $m/z = 373.6$ (M+1). Anal. calcd. for $C_{17}H_{13}BrN_2OS$: C, 54.70; H, 3.51; N, 7.50. Found: C, 54.72; H, 3.49; N, 7.51.

*2-(1H-Indol-3-yl)-3-p-tolylthiazolidin-4-one (**4f**)*

IR (KBr, ν_{max}, cm^{-1}): 3445–3285 (N–H indole), 3032 (C–H of aromatic ring), 1724 (C=O of thiazolidinone), 768 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.13 (s, 3H, methyl of Ar ring), 3.85–4.02 (dd, 2H, CH_2 of thiazolidinone), 6.43 (s, 1H, CH of thiazolidinone), 7.11–7.72 (m, 8H, Ar ring), 7.24 (s, 1H, C_2 of indole ring), 7.98 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 21.7, 33.7, 70.4, 111.1, 112.1, 118.4, 119.4, 121.4, 123.5, 127.2, 129.4, 133.1, 136.2, 138.3, 171.9, MS: $m/z = 308.6$ (M+1). Anal. calcd. for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08. Found: C, 70.13; H, 5.22; N, 9.10.

*3-(3,5-Dimethylphenyl)-2-(1H-indol-3-yl)thiazolidin-4-one (**4g**)*

IR (KBr, ν_{max}, cm^{-1}): 3421–3285 (N–H indole), 3025 (C–H of aromatic ring), 1758 (C=O of thiazolidinone), 785 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.29 (s, 6H, methyl of Ar ring), 3.42–4.10 (dd, 2H, CH_2 of thiazolidinone), 6.05 (s, 1H, CH of thiazolidinone), 7.25–7.86 (m, 7H, Ar ring), 7.42 (s, 1H, C_2 of indole ring), 8.23 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 21.2, 33.2, 70.4, 111.8, 112.3, 118.4, 118.6, 119.4, 121.5, 123, 126.2, 136.5, 138.1, 141.2, 171.2, MS: $m/z = 322.2$ (M+1). Anal. calcd. for $C_{19}H_{18}N_2OS$: C, 70.78; H, 5.63; N, 8.69. Found: C, 70.80; H, 5.61; N, 8.71.

*2-(1H-Indol-3-yl)-3-(4-methoxyphenyl)thiazolidin-4-one (**4h**)*

IR (KBr, ν_{max}, cm^{-1}): 3442–3290 (N–H indole), 3059 (C–H of aromatic ring), 1745 (C=O of thiazolidinone), 789 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.29 (s, 3H, methyl of Ar ring), 3.42–4.10 (dd, 2H, CH_2 of thiazolidinone), 6.05 (s, 1H, CH of thiazolidinone), 7.25–7.86 (m, 8H, Ar ring), 7.42 (s, 1H, C_2 of indole ring), 8.23 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 33.2, 55.6, 70, 111.5, 112.3, 114.6, 118.9, 119.4, 121.6, 123, 127.2, 134.5, 158.6, 171.2, MS: $m/z = 324.2$ (M+1). Anal. calcd. for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.64. Found: C, 66.62; H, 4.95; N, 8.66.

*3-(2-Hydroxyphenyl)-2-(1H-indol-3-yl)thiazolidin-4-one (**4i**)*

IR (KBr, ν_{max}, cm^{-1}): 3435–3275 (N–H indole), 3045 (C–H of aromatic ring), 1726 (C=O of thiazolidinone), 756 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 3.50–4.01 (dd, 2H, CH_2 of thiazolidinone), 4.89 (s, 1H, –OH), 5.91 (s, 1H, CH of thiazolidinone), 7.01–7.95 (m, 8H, Ar ring), 7.13 (s, 1H, C_2 of indole ring), 9.05 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 33.3, 71.5, 111.6, 112.5, 116.6, 118.9, 119.4, 121.4, 121.6, 123.5, 125.5, 127.2, 130.5, 136.6, 149.5, 171.2, MS: $m/z = 310.2$ (M+1). Anal. calcd. for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03. Found: C, 65.80; H, 4.56; N, 9.05.

*2-(1H-Indol-3-yl)-3-(2-mercaptophenyl)thiazolidin-4-one (**4j**)*

IR (KBr, ν_{max}, cm^{-1}): 3425–3279 (N–H indole), 3035 (C–H of aromatic ring), 1736 (C=O of thiazolidinone), 789 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 3.23–3.99 (dd, 2H, CH_2 of thiazolidinone), 3.51 (s, 1H, –SH), 5.99 (s, 1H, CH of thiazolidinone), 7.15–7.89 (m, 8H, Ar ring), 7.42 (s, 1H, C_2 of indole ring), 9.12 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 33.2, 70.5, 111.4, 112.8, 118.5, 119.8, 121.1, 123.5, 124.5, 124.8, 125.5, 125.8, 127.7, 136.5, 138.1, 171.7, MS: $m/z = 326.4$ (M+1). Anal. calcd. for $C_{17}H_{14}N_2OS_2$: C, 62.55; H, 4.32; N, 8.58. Found: C, 62.57; H, 4.35; N, 8.60.

*2-(1H-Indol-3-yl)-5-methyl-3-phenylthiazolidin-4-one (**5a**)*

IR (KBr, ν_{max}, cm^{-1}): 3430–3285 (N–H indole), 3039 (C–H of aromatic ring), 2950 (C–H of methyl), 1725 (C=O of thiazolidinone), 785 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.15 (d, 3H, methyl group attached to thiazolidinone), 3.78 (q, 1H, –CH– of thiazolidinone bearing methyl group), 6.32 (s, 1H, CH of thiazolidinone), 7.10–7.81 (m, 9H, Ar ring), 7.23 (s, 1H, =CH of indole ring), 9.02 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 20.2, 42.5, 68.5, 111.4, 112.8, 118.5, 119.8, 121.1, 123.5, 124.5, 124.8, 125.5, 125.8, 127.7, 136.5, 138.1, 171.7, MS: $m/z = 308.4$ (M+1). Anal. calcd. for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08. Found: C, 70.13; H, 5.25; N, 9.10.

*3-(4-Chlorophenyl)-2-(1H-indol-3-yl)-5-methylthiazolidin-4-one (**5b**)*

IR (KBr, ν_{max}, cm^{-1}): 3430–3285 (N–H indole), 3039 (C–H of aromatic ring), 2950 (C–H of methyl), 1725 (C=O of thiazolidinone), 785 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.53 (d, 3H, methyl group attached to thiazolidinone), 3.34 (q, 1H, –CH– of thiazolidinone bearing methyl group), 6.82 (s, 1H, CH of thiazolidinone), 7.13–7.53 (m, 8H, Ar ring), 7.15 (s, 1H, C_2 of indole ring), 9.23 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 20.3, 42.4, 68.8, 111.3, 112.7, 118.8, 119.1, 121, 123.2, 125.6, 127.5, 129.5, 133.5, 136.5, 139.8, 174.7, MS: $m/z = 342.5$ (M+1). Anal. calcd. for $C_{18}H_{15}ClN_2OS$, C, 63.06; H, 4.41; N, 8.17. Found: C, 63.08; H, 4.42; N, 8.15.

*3-(3-Chlorophenyl)-2-(1H-indol-3-yl)-5-methylthiazolidin-4-one (**5c**)*

IR (KBr, ν_{max}, cm^{-1}): 3441–3295 (N–H indole), 3030 (C–H of aromatic ring), 2950 (C–H of methyl), 1725 (C=O of thiazolidinone), 785 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.33 (d, 3H, methyl group attached to thiazolidinone), 3.53 (q, 1H, –CH– of thiazolidinone bearing methyl group), 6.02 (s, 1H, CH of thiazolidinone), 7.21–7.65 (m, 8H, Ar ring), 7.23 (s, 1H, C_2 of indole ring), 9.74 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 20.8, 42.5, 68.3, 111.4, 112.4, 118.8, 119.8, 121.4, 123.2, 125.4, 127.5, 130.5, 134.5, 135.5, 144.8, 174.1, MS: $m/z = 342.7$ (M+1). Anal. calcd. for $C_{18}H_{15}ClN_2OS$; C, 63.06; H, 4.41; N, 8.17. Found: C, 63.05; H, 4.43; N, 8.19.

*3-(2,4-Dichlorophenyl)-2-(1H-indol-3-yl)-5-methylthiazolidin-4-one (**5d**)*

IR (KBr, ν_{max}, cm^{-1}): 3420–3285 (N–H indole), 3032 (C–H of aromatic ring), 2950 (C–H of methyl), 1752 (C=O of thiazolidinone), 755 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.21 (d, 3H, methyl group attached to thiazolidinone), 3.46 (q, 1H,

–CH– of thiazolidinone bearing methyl group), 5.96 (s, 1H, CH of thiazolidinone), 7.34–7.62 (m, 7H, Ar ring), 7.13 (s, 1H, C_2 of indole ring), 9.13 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 20.1, 42.7, 67.2, 111.4, 112.4, 118, 119.8, 121.4, 123.2, 124.4, 126.5, 130.6, 136.5, 136.5, 138.8, 174.8, MS: $m/z = 377.1$ (M+1). Anal. calcd. for $C_{18}H_{14}Cl_2N_2OS$; C, 57.30; H, 3.74; N, 7.42. Found: C, 57.28; H, 3.73; N, 7.44.

*3-(4-Bromophenyl)-2-(1H-indol-3-yl)-5-methylthiazolidin-4-one (**5e**)*

IR (KBr, ν_{max}, cm^{-1}): 3445–3295 (N–H indole), 3056 (C–H of aromatic ring), 2950 (C–H of methyl), 1766 (C=O of thiazolidinone), 785 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.24 (d, 3H, methyl group attached to thiazolidinone), 3.41 (q, 1H, –CH– of thiazolidinone bearing methyl group), 5.96 (s, 1H, CH of thiazolidinone), 7.24 (s, 1H, C_2 of indole ring), 7.45–7.73 (m, 8H, Ar ring), 8.25 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 20.7, 42.8, 68.2, 111.4, 112.4, 118.7, 119, 121.3, 123, 127.5, 131.6, 136.8, 136.4, 140.8, 174, MS: $m/z = 386.1$ (M+1). Anal. calcd. for $C_{18}H_{15}BrN_2OS$; C, 55.82; H, 3.90; N, 7.23. Found: C, 55.84; H, 3.92; N, 7.25.

*2-(1H-Indol-3-yl)-5-methyl-3-p-tolylthiazolidin-4-one (**5f**)*

IR (KBr, ν_{max}, cm^{-1}): 3421–3255 (N–H indole), 3045 (C–H of aromatic ring), 2950 (C–H of methyl), 1736 (C=O of thiazolidinone), 756 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.26 (d, 3H, methyl group attached to thiazolidinone), 2.53 (s, 3H, methyl of Ar ring), 3.39 (q, 1H, –CH– of thiazolidinone bearing methyl group), 6.17 (s, 1H, CH of thiazolidinone), 7.29–7.52 (m, 8H, Ar ring), 7.35 (s, 1H, C_2 of indole ring), 9.51 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 20.2, 21.7, 42.6, 68.3, 111, 112.3, 118.4, 119.3, 121.6, 127.5, 129.6, 133.8, 136.4, 138.8, 174.4, MS: $m/z = 322.4$ (M+1). Anal. calcd. for $C_{19}H_{18}N_2OS$; C, 70.78; H, 5.63; N, 8.69. Found: C, 70.76; H, 5.65; N, 8.71.

*3-(3,5-Dimethylphenyl)-2-(1H-indol-3-yl)-5-methylthiazolidin-4-one (**5g**)*

IR (KBr, ν_{max}, cm^{-1}): 3452–3295 (N–H indole), 3056 (C–H of aromatic ring), 2950 (C–H of methyl), 1742 (C=O of thiazolidinone), 747 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.26 (d, 3H, methyl group attached to thiazolidinone), 2.43 (s, 6H, methyl of Ar ring), 3.47 (q, 1H, –CH– of thiazolidinone bearing methyl group), 6.28 (s, 1H, CH of thiazolidinone), 7.33–7.61 (m, 7H, Ar ring), 7.71 (s, 1H, C_2 of indole ring), 8.53 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 20.4, 21.5, 42.1, 68.4, 111.4, 112.7, 118.4, 118.5, 119.3, 121.6, 127.3, 136.4, 138.1, 174.5, MS: $m/z = 336.4$ (M+1). Anal. calcd. for $C_{20}H_{20}N_2OS$; C, 71.40; H, 5.99; N, 8.33. Found: C, 71.42; H, 5.98; N, 8.35.

*2-(1H-Indol-3-yl)-3-(4-methoxyphenyl)-5-methylthiazolidin-4-one (**5h**)*

IR (KBr, ν_{max}, cm^{-1}): 3445–3259 (N–H indole), 3033 (C–H of aromatic ring), 2950 (C–H of methyl), 1752 (C=O of thiazolidinone), 779 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.41 (d, 3H, methyl group attached to thiazolidinone), 3.52 (s, 3H, methoxy of Ar ring), 3.59 (q, 1H, –CH– of thiazolidinone bearing methyl group), 5.96 (s, 1H, CH of thiazolidinone), 7.24–7.56 (m, 8H, Ar ring), 7.49 (s, 1H, C_2 of indole ring), 9.13 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 20.1, 42.1, 55.4, 68.4, 111.7, 112.7, 114.5, 118.4, 119.3, 121.6, 122.3, 123.5, 127.8, 134.4, 136.1, 158.5, 174, MS: $m/z = 338.5$ (M+1). Anal. calcd. for $C_{19}H_{18}N_2O_2S$; C, 67.43; H, 5.36; N, 8.28. Found: C, 67.40; H, 5.34; N, 8.30.

*3-(2-Hydroxyphenyl)-2-(1H-indol-3-yl)-5-methylthiazolidin-4-one (**5i**)*

IR (KBr, ν_{max}, cm^{-1}): 3500 (O–H), 3456–3245 (N–H indole), 3057 (C–H of aromatic ring), 2950 (C–H of methyl), 1728 (C=O of thiazolidinone), 755 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.23 (d, 3H, methyl group attached to thiazolidinone), 3.14 (q, 1H, –CH– of thiazolidinone bearing methyl group), 5.15 (s, 1H, OH of Ar ring), 6.39 (s, 1H, CH of thiazolidinone), 7.13–7.64 (m, 8H, Ar ring), 7.22 (s, 1H, C_2 of indole ring), 8.53 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 20.3, 42.2, 68.8, 111.7, 112.7, 116.3, 117.8, 118.5, 119.5, 121.6, 123.5, 125.7, 127.8, 130.8, 136.1, 149.5, 174.7, MS: $m/z = 324.7$ (M+1). Anal. calcd. for $C_{18}H_{16}N_2O_2S$; C, 66.64; H, 4.97; N, 8.64. Found: C, 66.65; H, 4.99; N, 8.62.

*2-(1H-Indol-3-yl)-3-(2-mercaptophenyl)-5-methylthiazolidin-4-one (**5j**)*

IR (KBr, ν_{max}, cm^{-1}): 3445–3290 (N–H indole), 3045 (C–H of aromatic ring), 2950 (C–H of methyl), 1736 (C=O of thiazolidinone), 785 (C–S–C of thiazolidinone); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.57 (d, 3H, methyl group attached to thiazolidinone), 3.07 (s, 1H, SH of Ar ring), 3.24 (q, 1H, –CH– of thiazolidinone bearing methyl group), 6.23 (s, 1H, CH of thiazolidinone), 7.27–7.56 (m, 8H, Ar ring), 7.16 (s, 1H, C_2 of indole ring), 9.23 (s, 1H, NH of indole); ^{13}C NMR (100 MHz $CDCl_3$, ppm): 20.4, 42.7, 67.8, 111.7, 112.7, 118.5, 119.5, 121.6, 124.5, 125.5, 127.5, 129.4, 136.1, 138.5, 174.1, MS: $m/z = 340.7$ (M+1). Anal. calcd. for $C_{18}H_{16}N_2OS_2$; C, 63.50; H, 4.74; N, 8.23. Found: C, 63.52; H, 4.75; N, 8.24.

Pharmacology

The compounds 3-(substituted)-2-(1*H*-indol-3-yl)thiazolidin-4-one **4a–j** and 3-(substituted)-2-(1*H*-indol-3-yl)methylthiazolidin-4-one **5a–j** were evaluated for anticonvulsant activity according to anticonvulsant drug development (ADD) program protocol [45, 46]. All the synthesized compounds were evaluated for anticonvulsant activity using MES and sc-PTZ model and behavioral activity. Male Swiss albino mice (CF-1 strain, 20–30 g) were used as experimental animals. They were housed in groups of five and allowed free access to water and food. A 12 h:12 h light/dark cycle was maintained throughout the experimental studies. For MES and sc-PTZ models study, all the test compounds were administered in the form of suspension made up to 0.5% Tween 80 in 0.9% sodium chloride solutions. The approval of the Institutional Animal Ethics Committee (CPCSEA/IAEC/Pharm. Chem.-20/2012-2013/78) of Y.B. Chavan college of Pharmacy, Aurangabad (Maharashtra, India) was taken prior to the start of the experiments.

Anticonvulsant activity

All the test compounds were administered intra-peritoneally in a volume of 0.01 mL/g for mice at doses of 100 mg/kg. Anticonvulsant activity was assessed after 30 min and 4 h of drug administration. The preliminary anticonvulsants (MES and sc-PTZ) evaluations were done using reported procedures.

Neurotoxicity screening

Rotarod test was used to detect a neurological deficit inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the three trials. The dose at which the animal fell off the rod was determined. Animals were divided in groups of five and trained to stay on an accelerating rotarod that rotates at 10 rpm. The rod diameter was 3.2 cm. Trained animals (able to stay on the rotarod for at least two consecutive trials of 90 s each) were given an i.p. injection of the test compounds at doses of 100 mg/kg.

Behavioral activity

The activity was measured as digital score using actophotometer with the i.p. administration of drug (100 mg/kg) to mice. The mice were placed in the box and the behavior was noted for 10 min. Further, the animals were treated with the drug, and after 0.5 and 4 h drug administration the animal were re-tested. The activity score was noted, and based on these results, % decrease in locomotor activity was calculated.

Computational parameters

The docking study

Docking study of synthesized compounds was performed using VLife MDS 4.3 package. With this purpose, crystal structure of sodium channel receptor (PDB ID: 1BYY) was obtained from the Protein Data Bank in order to prepare protein for docking study. The standard operating procedure implemented in VLife MDS 4.3 package was followed for GRIP batch docking of synthesized compounds **4a–j** and **5a–j** against three-dimensional structure of sodium channel receptors [47].

Distance mapping

In conformational analysis of the clinically effective anticonvulsant drugs such as phenytoin, carbamazepine, lamotrigine, and diazepam, a molecular model was suggested on the basis of molecular dynamics distance estimations [48]. For the estimation of the molecular mechanics calculation of title compounds, the ACD/3D viewer 8.04 version program was used for employing the CHARMm force field.

log p determination

log *p* of all the synthesized compounds were determined by using partition coefficient between octanol and phosphate buffer. In a glass stoppered graduated tube, 10 mL of octanol and same volume of phosphate buffer with 5 mg of compound were taken. The mixture was then well mixed with the help of mechanical stirrer for 24 h and then allowed to separate the two phases for 6 h. The aqueous and octanol phase were separated and filtered through membrane filter, and drug content in aqueous phase was analyzed by UV spectroscopy [49].

Determination of physicochemical properties

The synthesized compounds were determined for prediction for ADME properties. The various ADME properties studied including polar surface area (TPSA), number of rotatable bonds, molecular volume, number of hydrogen donors, number of hydrogen acceptors, and violations of Lipinski rule were calculated by Molinspiration online property toolkit. %ABS was calculated by using formula: $\%ABS = 109 - (0.345 \times TPSA)$ [50].

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