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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, biological evaluation and molecular docking studies of thiazole-based pyrrolidinones and isoindolinediones as anticonvulsant agents

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Abstract A series of new 1-(thiazol-2-yl)pyrrolidin-2-one **5a–m** and 2-(thiazol-2-yl)isoindoline-1,3-dione **6a–n** derivatives were synthesized and evaluated for anticonvulsant activity. The activity was established in three seizure models: PTZ, picrotoxin and MES. Selected compounds were elected for neurotoxicity by the rotarod test. The most active compound of the series was 1-(4-(naphthalen-2-yl)thiazol-2-yl)pyrrolidin-2-one (**5g**), showing a PTZ effect dose (ED_{50}) value of 18.4 mg/kg in mice. The median toxic dose (TD_{50}) was 170.2 mg/kg, which provided a protection index (PI = TD_{50}/ED_{50}) of 9.2. A computational study was also carried out, including prediction of pharmacokinetic properties and docking studies. The structural assignments of the newly synthesized compounds were elucidated on the basis of spectroscopic data and single-crystal X-ray crystallography.

Graphical Abstract A series of new thiazole-based pyrrolidinones **5a–m** and isoindolinediones **6a–l** were synthesized and tested as anticonvulsant. The most active compound was 1-(4-(naphthalen-2-yl)thiazol-2-yl)pyrrolidin-2-one (**5g**), showing ED_{50} value 18.4 mg/kg.

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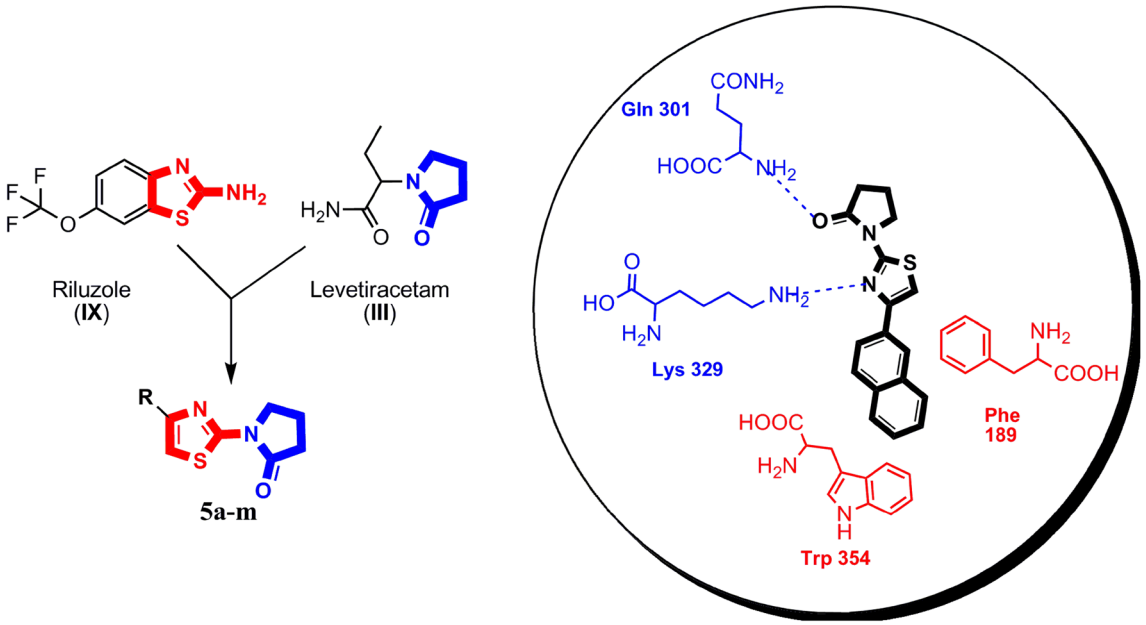


Keywords 2-Aminothiazole · Anticonvulsants · Neurotoxicity · Molecular docking · X-ray crystallography

Introduction

Epilepsy is a common disorder characterized by various forms of seizure and results from episodic neural discharges. Nearly all epileptic seizures are characterized by predominance of excitation over inhibition either simultaneously in many brain structures (primary, generalized convulsive seizures) or in a part of the brain (partial, focal seizures). Epilepsy affects 0.5–1 % of the population (Hemming *et al.*, 2008). Epilepsy is treated mainly by drugs, and in severe cases, brain surgery can be used. Current antiepileptic drugs (AEDs) are phenobarbital, phenytoin, carbamazepine, vigabatrin, valproate, felbamate and lamotrigine. They are effective in controlling seizures in about 70 % of the patients, but their use is often limited by side effects such as headache, nausea, anorexia, ataxia, hepatotoxicity, drowsiness, gastrointestinal disturbance, gingival hyperplasia and hirsutism (Brodie and Kwan, 2012; Johannessen and Landmark, 2010). Thus, there is an enormous need for the development of novel AEDs with fewer side effects and increased effectiveness.

Currently used AEDs can be classified into four main categories on the basis of molecular mechanisms of action. These categories are as follows: (1) modulation of voltage-dependent Na^+ and/or Ca^{2+} channels, (2) enhancement of the GABA-mediated effect or other effect on the GABA system, (3) inhibition of synaptic excitation mediated by ionotropic glutamate receptors and (4) modulation of synaptic release (Pollard and French, 2006). The incomplete information on the cellular mechanism of human epilepsy along with the complex mechanism of action of the majority of AEDs makes it difficult to use rational methodologies of discovery. Therefore, an alternative design of new anticonvulsants is based on the different pharmacophores that were established through the analysis of structural characteristics of clinically effective drugs as well as other anticonvulsant active compounds (Alam *et al.*, 2010; Deng *et al.*, 2010; Kaushik *et al.*, 2010a, b).

Structure–activity relationship (SAR) studies of some clinically available AEDs (e.g., phenytoin **I**, ethosuximide **II**, levetiracetam **III**, brivaracetam **IV**) and other anticonvulsant compounds **V**–**VII** (Fig. 1) revealed that many of these compounds possess five-membered cyclic imide moieties in their structures (Bialer *et al.*, 2007; Estrada and Pena, 2000; Kenda *et al.*, 2004; LeTiran *et al.*, 2001; Obniska *et al.*, 2002; Ragavendran *et al.*, 2007; Wong *et al.*, 1986). It is also well documented that nitrogen heteroatomic systems such as diazole, triazole, tetrazole, oxazole, oxadiazole, thiazole, thiadiazole or benzothiazole are one of the important core fragments that are incorporated in many anticonvulsant agents (Amir *et al.*, 2013; Kamboj *et al.*, 2015; Levandovskiy *et al.*, 2011; Manna *et al.*, 2014; VandeVrede *et al.*, 2014). Thiazole compounds are found in many drug developments as antitumor (Gursoy and Guzeldemirci, 2007; Wells *et al.*, 2003), anticonvulsant (Amin *et al.*, 2008; Dawood *et al.*, 2006; Koufaki *et al.*, 2007), anti-inflammatory (Rostom *et al.*, 2009), antihypertensive (Kashyap *et al.*, 2012), antimicrobial (Bondock *et al.*, 2007, 2010, 2013; Guzeldemirci and Kucukbasmaci, 2010; Shiradkar *et al.*, 2007), antioxidant (De *et al.*, 2008; Shih and Ke, 2004; Shih *et al.*, 2007), antifungal (Narayana

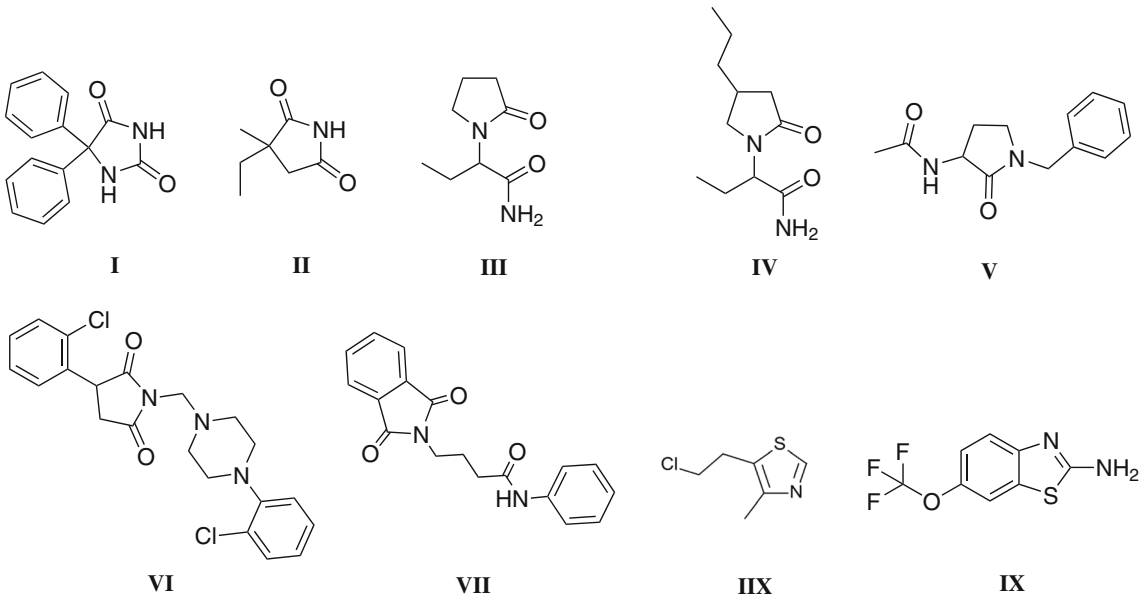


Fig. 1 Structures of some AEDs and anticonvulsant compounds incorporating a five-membered cyclic imide moiety

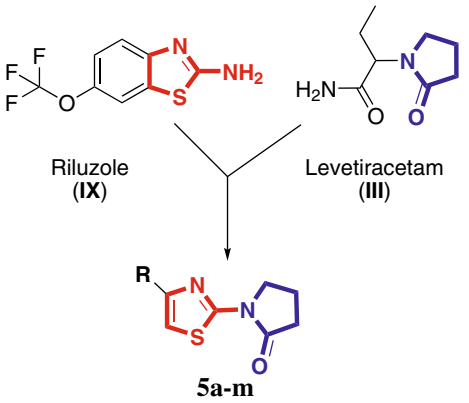


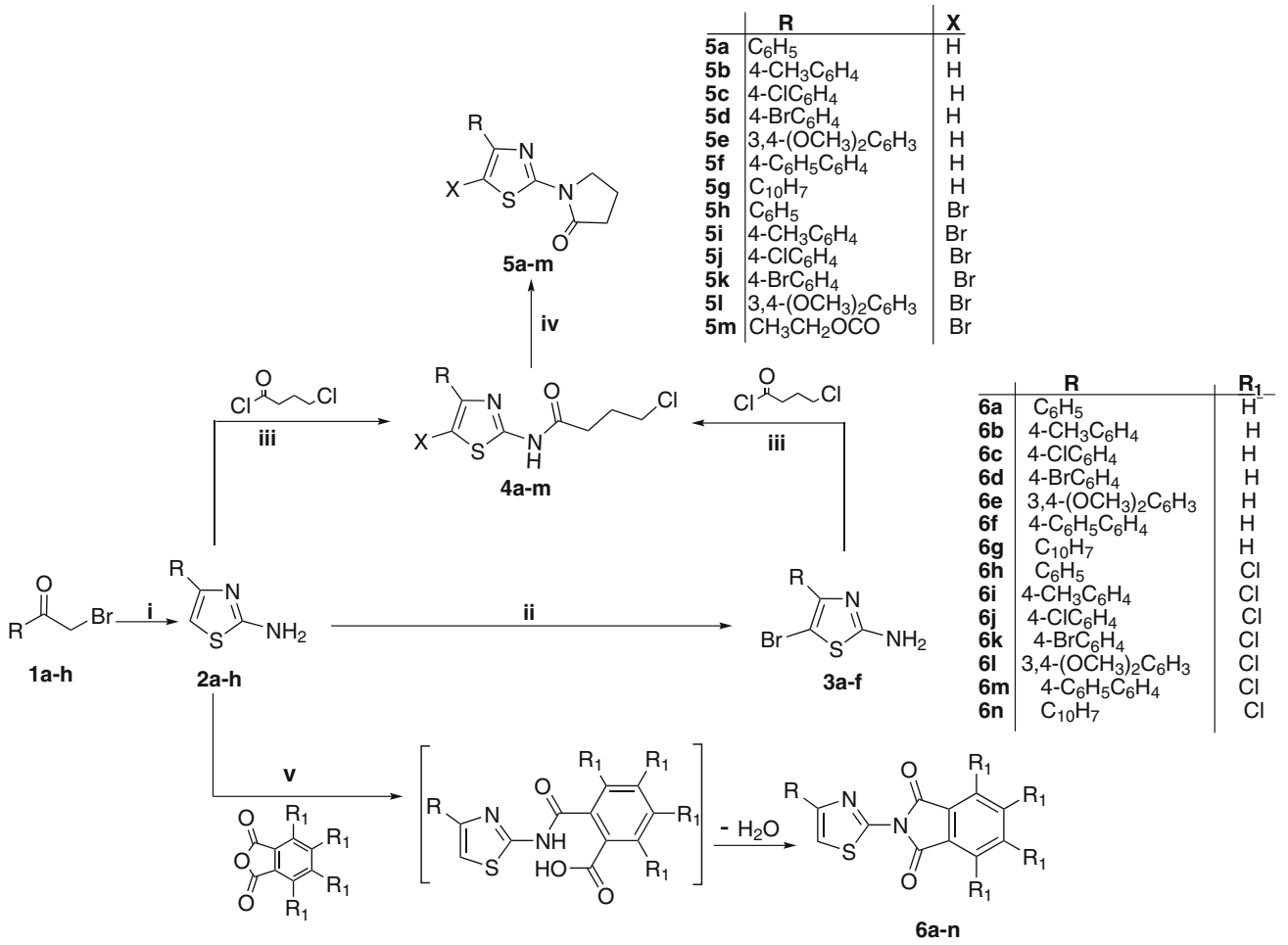
Fig. 2 Design of the titled compounds **5a**–**m** as anticonvulsants by molecular hybridization of five-membered cyclic imide moiety and thiazole ring

et al., 2004), antischizophrenic agents (Yurttas *et al.*, 2013), anti-HIV agents (Zia *et al.*, 2012), and also for the treatment of pain (Thore *et al.*, 2013) and as inhibitors of bacterial DNA gyrase (Gursoy and Guzeldemirci, 2007; Shiroya and Patel, 2013). For examples, chlormethiazole **IIX**, a thiazole derivative obtained from thiamine molecule, is used as a sedative or hypnotic and can also be used intravenously in treating status epilepticus (Nair *et al.*, 2011; Shorvon, 2013). Riluzole **IX** is a potent neuroprotective drug with additional anticonvulsant activity (Coleman *et al.*, 2015). Additionally, *N*-substituted phthalimides have important biological activities including anticonvulsant activities (Fhid *et al.*, 2014; Ragavendran *et al.*, 2007; Tiwari *et al.*, 2014; Yadav *et al.*, 2012).

The design and synthesis of the titled compounds were carried out with two objectives. The first was the molecular hybridization of the pyrrolidinone moiety and thiazoles (Fig. 2). The second was using different substitutions at positions 4 and 5 of the thiazole ring which may improve the anticonvulsant activity.

The present work comprises the synthesis and anticonvulsant activity of 1-(thiazol-2-yl)pyrrolidin-2-one derivatives **5a**–**m** (Fig. 2) and 2-(thiazol-2-yl)isoindoline-1,3-dione derivatives **6a**–**n** (Scheme 1). Their chemical structures were identified using IR, ^{1}H NMR, ^{13}C NMR, HRMS spectral analysis, molecular modeling studies and the prediction of ADME (absorption, distribution, metabolism and elimination) properties. In addition, a single-crystal X-ray crystallography technique was performed for compounds **5a** and **6e**.

As in many classes of drugs, the preclinical discovery and the development of a novel bioactive chemical entity for the treatment of epilepsy rely heavily on the use of predictable animal models. There are well documented in vivo animal models that are routinely used by most AEDs discovery programs. These include PTZ, picrotoxin (PIC) and MES. The PTZ- and MES-induced seizure models are recognized as the "gold standards" in the early stages of testing and are most widely used in the search for novel AEDs (White, 2003). These tests are designed to detect new bioactive chemical entities affording protection to generalized absence "petit mal" seizures and generalized tonic–clonic "grand mal" seizures (El-Behairy *et al.*, 2014). All the synthesized compounds **5a**–**m** and **6a**–**n** were evaluated for their initial anticonvulsant activity.



Scheme 1 Synthetic route of the target compounds. Reagents and conditions: *i* ethanol, reflux 30 h then stirring 12 h at RT, 68–90 %. *ii* Glacial acetic acid, heating 90 min at 80 °C, 65–79 %. *iii* K_2CO_3, $CHCl_3$, stirring 48 h at RT, 55–85 %. *iv* Piperidine, toluene, reflux 24 h, 59–81 %. *v* Glacial acetic acid, anhydrous sodium acetate, reflux 3 h, 74–90 % or fusion in oil bath for 2 h, 68–82 %

Results and discussion

Chemistry

The reaction sequence leading to the formation of the titled compounds, 1-(thiazol-2-yl)pyrrolidin-2-ones **5a**–**m** and 2-(thiazol-2-yl)isoindoline-1,3-diones **6a**–**n**, is shown in Scheme 1. The 2-aminothiazoles **2a**–**h** were obtained by reacting 2-bromo-1-arylethanones **1a**–**h** with thiourea in ethanol. The 5-bromothiazol-2-amine derivatives **3a**–**f** were prepared by bromination of 2-aminothiazoles **2a**–**f** in glacial acetic acid at room temperature. The *N*-(thiazol-2-yl)-4-chlorobutanamides **4a**–**m** were synthesized by reaction of 2-aminothiazoles **2a**–**h** and **3a**–**f** with 4-chlorobutyryl in chloroform. The *N*-(thiazol-2-yl)-4-chlorobutanamides **4a**–**m** were refluxed in toluene in the presence of piperidine to yield 1-(thiazol-2-yl)pyrrolidin-2-ones **5a**–**m**. 2-(Thiazol-2-yl)isoindoline-1,3-diones **6a**–**g** were obtained directly by heating phthalic anhydrides with 2-aminothiazoles **2a**–**g** in oil bath without solvent. Alternatively, refluxing 2-aminothiazoles **2a**–**g** with phthalic anhydrides and anhydrous sodium acetate in glacial acetic acid.

The structural assignments of the new compounds **5a** and **6e** were elucidated on the basis of IR, ^{1}H NMR, ^{13}C NMR, HRMS and single-crystal X-ray crystallography. The formation of 5-bromothiazol-2-amine derivatives **3a**–**f** was confirmed by the absence of the singlet at δ_H 7.1 ppm characterized for the thiazole H in ^{1}H NMR spectrum. The IR spectrum of the titled compound **5b** showed a band at 1681 cm^{-1} characterized for amide C=O and CH_3 band at 3099 cm^{-1}. Its ^{1}H NMR spectrum showed a multiplet at δ_H 2.18 ppm and two triplets at δ_H 2.64 and 4.14 ppm for the pyrrolidinone protons. In addition, the spectrum showed a singlet at δ_H 2.33 ppm for the CH_3 protons, another singlet at δ_H 7.63 ppm of the thiazol-H and two doublets at δ_H 7.24 and 7.83 ppm for the aromatic protons. Mass spectral data have further confirmed its purity and molecular weight.

Crystallography

The crystallographic structures of **5a** and **6e** are represented in Fig. 3. The single-crystal X-ray study on both derivatives unambiguously defines the exact structure. The bond lengths and angles are in normal ranges (Allen *et al.*, 1987).

Pharmacology

In this study, three seizure models were used for preliminary (phase I) screening of the synthesized compounds **5a–m** and **6a–l**, and the results are presented in Table 1. The PTZ screen showed that compounds **5b**, **5c**, **5e**, **5f**, **5g**, **5i**, **5j**, **5m**, **6a**, **6b**, **6g**, **6h**, **6i**, **6k** and **6l** were found to be active after 0.5 or/and 4.0 h, and the other derivatives were found to be devoid of anticonvulsant activity in the PTZ model under specified conditions. The most active compound was **5g**, characterized by a low ED_{50} and a high PI.

The same pattern of activity of the investigated compounds withdrawn from PTZ model was emphasized in the PIC model (Table 1). Compounds **5e**, **5h**, **5i**, **5l**, **5m**, **6f**, **6k** and **6l** proved to be the most active compounds in this study with remarkable protection against PIC-induced convulsions. This result suggests that the active compounds may act directly as $GABA_A$ receptor agonist. The suggested modes of action are either indirectly by increasing GABA synthesis or its release as a brain inhibitory neurotransmitter or that they may act by inhibiting the γ-amino butyrate aminotransferase (GABA-AT) enzyme. None of the tested compounds prevented the convulsions induced by maximal electric shock. In the neurotoxicity test, the percentage of mice that dropped from the rod within 3 min was calculated and converted into probit and plotted against the log dose. The dose of the compound that impaired the staying of the animals on the rod and impaired the motor coordination of the animals in the 50 % of tested animals was labeled TD_{50}. Potential compounds were also subjected to quantification studies, and the corresponding ED_{50}, TD_{50} and PI are reported in Table 1.

Molecular modeling study

Molecular docking is a very popular method employed to investigate molecular association. It is particularly useful in the drug discovery arena to study the binding of small molecules (ligands) to macromolecules (receptor or enzyme). Docking-based drug design by the use of structural biology remains one of the most logical and esthetically pleasing approaches in the drug discovery process. The structured knowledge of the binding capabilities of the active site residues to specific groups on the agonist or antagonist leads to various proposals for the synthesis of very specific agents with a high probability of biological action (Barril and Morley, 2005).

GABA is a predominant inhibitory neurotransmitter in mammalian central nervous system (CNS) modulating central inhibitory tone that acts via the activation of ionotropic $GABA_A$ and $GABA_C$ receptors and G-protein-coupled $GABA_B$ receptors (Osolodkin *et al.*, 2009). GABA-AT catalyzes the degradation of GABA to succinic semialdehyde. Depleted levels of GABA have been shown to cause convulsions (Bansal *et al.*, 2012). Raising GABA levels in the brain has an anticonvulsive effect (Madsen *et al.*, 2011). GABA-AT is a validated target for AEDs because its selective inhibition raises GABA concentration in the brain (Bansal *et al.*, 2013).

Docking with GABA-aminotransferase model

To compare the binding affinity of the newly synthesized compounds, they were docked in the empty binding site of GABA-AT (PDB entry 1OHV) (Storici *et al.*, 2004). Vigabatrin (standard drug) reveals MolDock score of −83.46 and forms three hydrogen bonds between its carboxylic moiety and Ser 137 with a bond distance of 2.99 Å and another two bonds with Thr 353 with bond distances of 2.91 and 3.02 Å (Fig. 4a). Compounds **5a–m** and **6a–n** exhibited binding scores ranging from −175.29 to −90.69. Compounds **5f** and

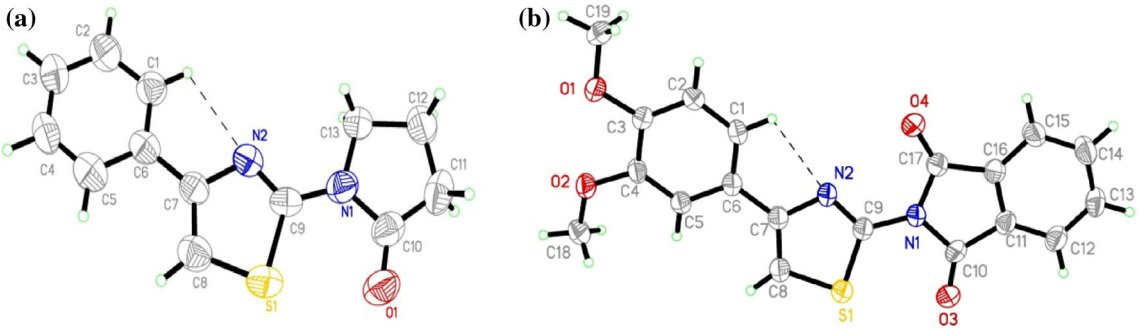


Fig. 3 ORTEP drawings with atomic numbering scheme of the asymmetric units of **5a** (*left*) and **6e** (*right*) with displacement ellipsoids 40 % probability level. The *dashed line* indicates intramolecular hydrogen bond between C1-H1A···N2

Table 1 Anticonvulsant activity of the tested compounds

Compounds	R	X	R_1	PTZ		Picrotoxin		ED_{50} (mg/kg)	TD_{50} (mg/kg)	PI
				0.5 h	4.0 h	0.5 h	4.0 h			
5a	C_6H_5	H		–	–	–	–	–	–	–
5b	4-$CH_3C_6H_4$	H		300	–	–	–	–	–	–
5c	4-ClC_6H_4	H		300	–	–	–	–	–	–
5d	4-BrC_6H_4	H		–	–	–	–	–	–	–
5e	3,4-$(OCH_3)_2C_6H_3$	H		300	300	300	–	108.5	227.8	2.1
5f	4-$C_6H_5C_6H_4$	H		200	300	–	–	56.9	185.6	3.2
5g	$C_{10}H_7$	H		200	300	–	–	18.4	170.2	9.2
5h	C_6H_5	Br		–	–	100	300	–	–	–
5i	4-$CH_3C_6H_4$	Br		300	–	300	–	–	–	–
5j	4-ClC_6H_4	Br		300	–	–	–	–	–	–
5k	4-BrC_6H_4	Br		–	–	–	–	–	–	–
5l	3,4-$(OCH_3)_2C_6H_3$	Br		–	–	100	300	–	–	–
5m	CH_3CH_2OCO	Br		300	–	300	–	129.6	259.2	2.0
6a	C_6H_5	H	H	300	300	–	–	110.2	209.4	1.9
6b	4-$CH_3C_6H_4$	H	H	300	300	–	–	90.2	279.6	3.1
6c	4-ClC_6H_4	H	H	–	–	–	–	–	–	–
6d	4-BrC_6H_4	H	H	–	–	–	–	–	–	–
6e	3,4-$(OCH_3)_2C_6H_3$	H	H	–	–	–	–	–	–	–
6f	4-$C_6H_5C_6H_4$	H	H	–	–	300	–	–	–	–
6g	$C_{10}H_7$	H	H	300	–	–	–	–	–	–
6h	C_6H_5	H	Cl	300	–	–	–	–	–	–
6i	4-$CH_3C_6H_4$	H	Cl	300	300	–	–	122.1	276.4	2.26
6j	4-ClC_6H_4	H	Cl	–	–	–	–	–	–	–
6k	4-BrC_6H_4	H	Cl	300	300	300	–	138.0	276.0	2.0
6l	3,4-$(OCH_3)_2C_6H_3$	H	Cl	300	–	100	300	111.3	189.2	1.7
6m	4-$C_6H_5C_6H_4$	H	Cl	–	–	–	–	–	–	–
6n	$C_{10}H_7$	H	Cl	–	–	300	–	–	–	–

Doses of 100, 200 and 300 mg/kg were administered. The numbers in the table indicate the minimum dose whereby bioactivity was demonstrated in half or more of the mice. The dash (–) indicates the absence of activity at maximum dose administered (300 mg/kg)

5g have good MolDock scores, −155.36 and −163.80, respectively, where they show the highest biological activities. Compound **5g** is the most active one among the series. It forms two hydrogen bonds. One hydrogen bond is between oxygen of pyrrolidin-2-one moiety with Glu 301 of distance 3.01 Å. The other hydrogen bond is between nitrogen of thiazole ring and Lys 329 with bond distance 2.85 Å and also the naphthyl moiety located in the hydrophobic pocket Trp 354 and Phe 189. The position of thiazole derivatives **5g** overlaps well with vigabatrin (standard drug) (Figs. 4b, 5). Lipophilicity appears to play crucial role in **5g** inhibitory activity, as naphthyl moiety is properly oriented to the more lipophilic area of GABA-AT binding site and forms CH–π interaction with Phe 189 and Trp 354.

Docking with human $GABA_A$ homology model

The $GABA_A$ receptor is a pentameric ligand-gated ion channel ($2\alpha_1$, $2\beta_2$, $1\gamma_2$). GABA binding site is the receptor located between α and β subunits, and the benzodiazepine (BDZ) binding site is located on the extracellular surface at the interface of the α and γ subunits (Fig. 6a) (Sigel, 2002). Although several studies have made significant strides in uncovering the specific amino acid residues that contribute to the binding of classical BDZ, complete descriptions of the residues that preferentially contribute to the binding of non-BZD ligands and the orientation of these ligands within the BZD site are relatively unknown (Sigel, 2002).

The results of docking studies of the reference drugs (diazepam, flunitrazepam, eszopiclone and zolpidem) and the tested compounds show good interactions with BZD

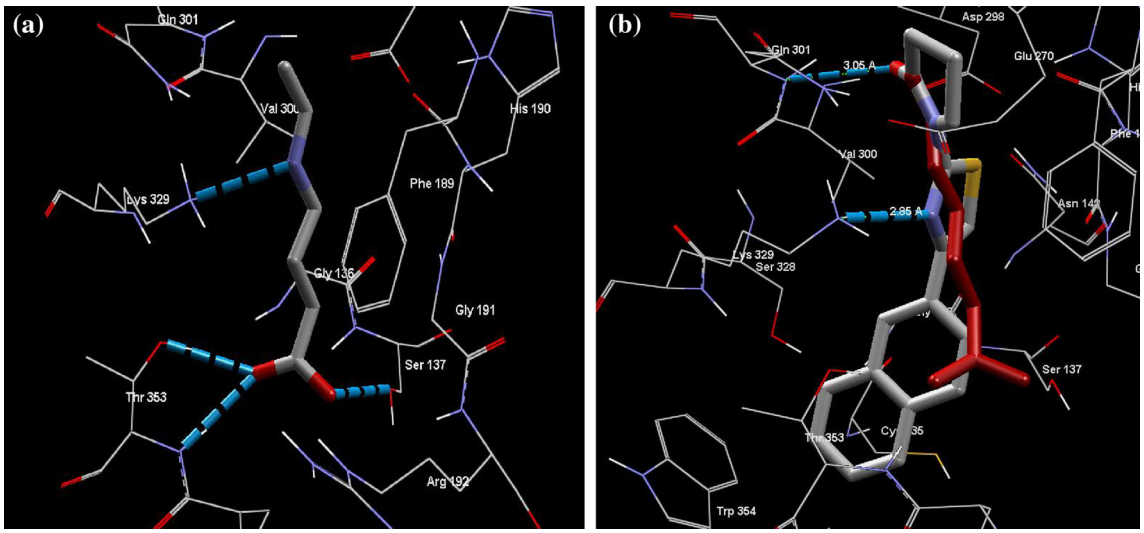


Fig. 4 **a** Vigabatrin with more hydrogen bonding to GABA-AT active site. **b** Interactions between compound **5g** and GABA-AT active site superimposed with standard inhibitor vigabatrin (*red* molecule) (Color figure online)

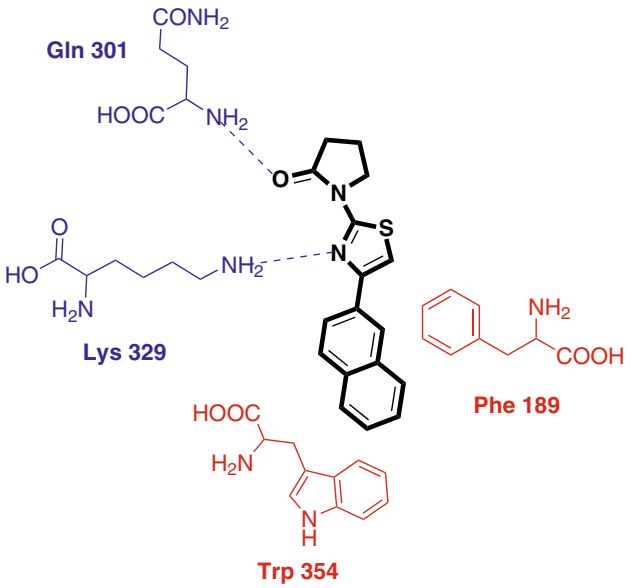


Fig. 5 Possible interactions between compound **5g** and the active site of GABA-AT enzyme

binding site residues. Eszopiclone makes nine hydrogen bonds with amino acid residues: Ser 61, His 101, Arg 144 and Tyr 199, and reveals MolDock score of −293.75 (Fig. 6b). Compounds **5a**–**m** have MolDock scores ranging from −211.30 to −305.27. This range increases in compounds **6a**–**g** from −271.82 to −298.37 and reaches the highest level in compounds **6h**–**n**, from −299.05 to −313.61. Compound **6l** which has the highest MolDock score in this experiment makes five hydrogen bonds with amino acid residues: Asn 60, Ser 61, Arg 144, Trp 196 and Trp 199 (Fig. 6c). Biologically, the most active compounds, **5f** and **5g**, show good MolDock score, −305.27 and −269.13, respectively. Taking into account the above results, differences in binding to the $GABA_A$ receptor within the two series **5a**–**m** and **6a**–**n** arise from the balancing of the H-bond network and internal energy which is a result of the different orientations of molecules into the same site of the receptor (Fig. 6d).

ADME properties

A computational study for the prediction of the ADME properties of the titled compounds was performed, and the results are presented in Table 2. Topological polar surface area (TPSA) is a descriptor that was shown to correlate well with passive molecular transport through membranes and, therefore, allows prediction of transport properties of the drugs in the intestines and blood brain barrier (BBB) crossing (Ertl *et al.*, 2000). The percentage of absorption (%ABS) was calculated using TPSA. The molecules have ideal ADME properties, showing high percentage of intestinal absorption. Log *P*, number of rotatable bonds (Veber *et al.*, 2002) and violations of Lipinski's rule of five were calculated by using Molinspiration online property calculation toolkit ("Molinspiration Cheminformatics: http://www.molinspiration.com/services/properties.html"). Calculated log *P* for synthesized compounds were then compared with the experimental capacity factor *K* data of these compounds.

From all these parameters, it can be observed that all the titled compounds exhibited a great %ABS ranging from 84.7 to 97.5 % (Table 2). Furthermore, compounds **6k**, **6l** and **6m** show violated two Lipinski's parameters. All the other compounds obey Lipinski's parameters, making them potentially promising agents for epilepsy therapy.

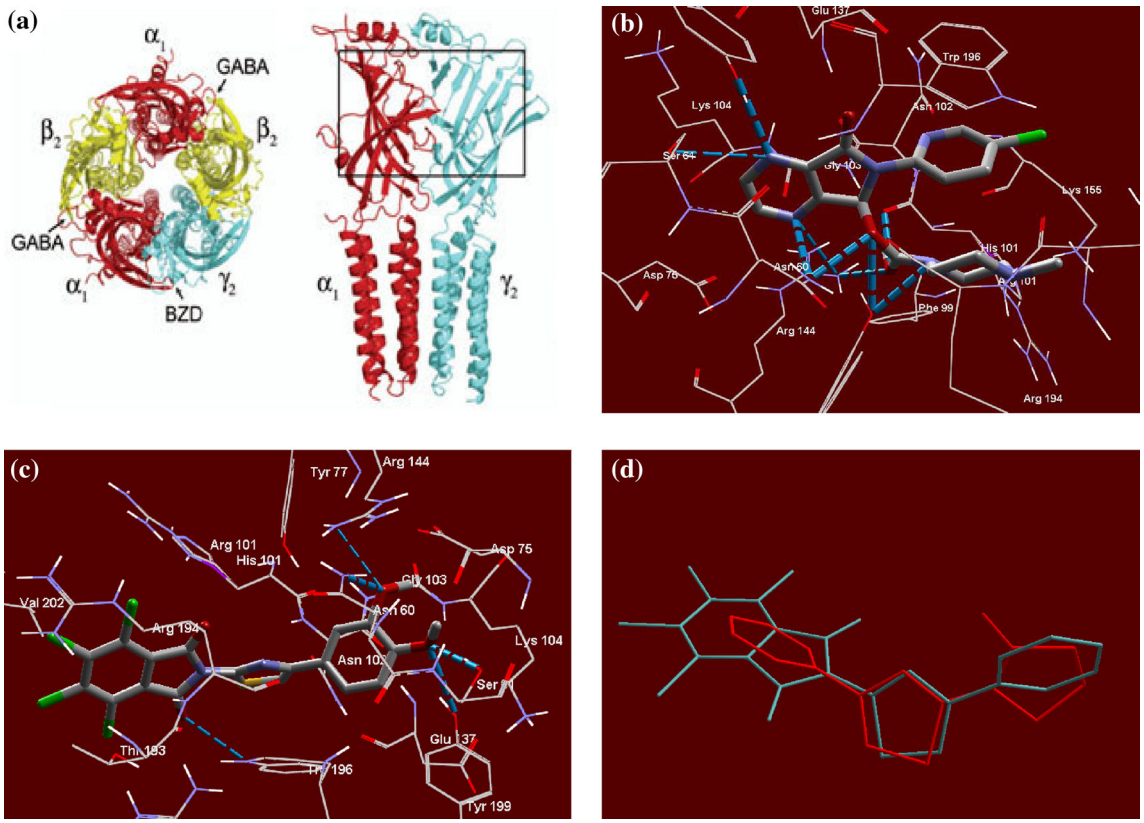


Fig. 6 **a** Homology model of the $\alpha1\beta2\gamma2$ $GABA_A$ receptor pentamer as seen from the extracellular membrane surface. *Arrows* indicate that GABA binds at the $\beta2/\alpha1$ interfaces, whereas benzodiazepines (BZDs) bind at the $\alpha1/\gamma2$ interface of the receptor. **b** Best pose of eszopiclone (*sticks*): *blue dashes* represent H-bonds. **c** Best pose of compound **6l** (*sticks*): *blue dashes* represent H-bonds. **d** Poses of **5a** (*red lines*) and **6h** (*gray lines*) in the BDZ binding site of $GABA_A$ receptor, showing the inversion of the whole molecule leads to a different binding mode (Color figure online)

Lipophilicity determination

The titled compounds showed dependence of biological activity on lipophilic character in a congeneric series. In particular, for drugs acting on central nervous system to be potent, they have to cross BBB. Thus, potency has been correlated with optimum lipophilicity (log *P*). The basic experimental method for the determination of lipophilicity is based on the partitioning of a molecule in a system of two immiscible phases (aqueous and lipophilic ones). Practically, this is performed using traditional shake-flask procedure with subsequent determination of the concentrations of the compound in both phases. Although different solvents were investigated for this purpose, octanol–water system remains the most popular model (Valko, 2004). Unfortunately, shake-flask method is extremely time-consuming and labor-intensive. It requires a high purity of the tested substances and often suffers from solubility and stability problems. Hence, nowadays this complicated approach was almost completely substituted by modern chromatographic techniques (Gocan *et al.*, 2006; Liu *et al.*, 2005). Among them, high-performance liquid chromatography (HPLC) is the leading and the most frequently used chromatographic method for the routine lipophilicity determination. It enables rapid, accurate and high-reproducibility analysis of relatively large sets of samples. These experiments are usually performed on reverse phase systems, where the chromatographic retention behavior of an analyte is directly related to its lipophilicity. The lipophilicity of the two series **5a–m** and **6a–n** of the anticonvulsant agents was determined using HPLC analyses on the modern C18-monolithic stationary phase which seems to be a reasonable alternative to the common stationary phase. Their higher permeability and higher stability resulted from the nature of monoliths enable the use of a fast flow. The experimental data (log *K*) and calculated *C*log *P* values by ChemBioDraw Ultra 11 software were compared and are shown in Table 2.

Conclusion

A series of 1-(thiazol-2-yl)pyrrolidin-2-one and 2-(thiazol-2-yl)isoindoline-1,3-dione derivatives were designed and synthesized. The anticonvulsant activity and the

Table 2 Pharmacokinetic parameters of the tested compounds

Compounds Rule	%ABS –	TPSA (A^2) –	*n*-ROTB –	MW <500	MV –	*n*-OHNH donors <5	*n*-ON acceptors <10	Lipinski's violations ≤1	Log *K*	*C*log
5a	97.5	33.20	2	244.31	213.33	0	3	0	2.02	2.54
5b	97.5	33.20	2	258.34	229.89	0	3	0	2.42	3.04
5c	97.5	33.20	2	278.76	226.87	0	3	0	2.69	3.26
5d	97.5	33.20	2	323.21	231.22	0	3	0	3.35	3.41
5e	91.1	51.66	4	304.37	264.43	0	5	0	1.89	2.27
5f	97.5	33.20	3	320.41	284.74	0	3	0	4.11	4.43
5g	97.5	33.20	2	294.37	257.33	0	3	0	3.26	3.71
5h	97.5	33.20	2	323.21	231.22	0	3	0	2.74	3.15
5i	97.5	33.20	2	337.24	247.78	0	3	0	358	3.65
5j	97.5	33.20	2	357.66	244.76	0	3	0	3.63	3.87
5k	97.5	33.20	2	402.11	249.10	0	3	0	3.86	4.02
5l	91.1	51.66	4	383.26	282.31	0	5	0	2.44	2.88
5m	88.4	59.50	4	319.18	221.14	0	5	0	0.89	1.10
6a	91.0	51.96	2	306.34	253.32	0	4	0	3.94	3.80
6b	91.0	51.96	2	320.37	269.88	0	4	0	4.39	4.30
6c	91.0	51.96	2	340.79	266.86	0	4	0	4.44	4.52
6d	91.0	51.96	2	385.24	271.21	0	4	0	4.70	4.67
6e	84.7	70.43	4	366.39	304.41	0	6	0	3.59	3.53
6f	91.0	51.96	3	382.44	324.73	0	4	1	4.92	5.69
6g	91.0	51.96	2	356.40	297.31	0	4	1	4.41	4.97
6h	91.0	51.96	2	444.12	307.46	0	4	1	6.01	6.31
6i	91.0	51.96	2	458.15	324.02	0	4	1	6.44	6.81
6j	91.0	51.96	2	478.57	321.00	0	4	1	6.61	7.02
6k	91.0	51.96	2	523.02	325.35	0	4	2	6.60	7.17
6 l	84.7	70.43	4	504.17	358.56	0	6	3	5.52	6.04
6m	91.0	51.96	3	520.22	378.87	0	4	2	7.24	8.19
6n	91.0	51.96	2	494.96	351.46	0	4	1	7.01	7.48

%ABS the percentage of absorption, *TPSA* (A^2) topological polar surface area, *n-ROTB* number of rotatable bonds, *MW* molecular wight, *MV* molecular volume, *log K* log capacity factor

neurotoxicity of the compounds were evaluated after intraperitoneal (i.p.) administration in three seizure models: the PTZ, the PIC and the MES models. Computational studies that cover prediction of the pharmacokinetic properties and docking studies were also performed. Compound **5g** displayed significant protection and emerged as the lead in this series. The results of the docking studies showed that the compounds exhibited good binding properties of $GABA_A$ to human homology model and GABA-AT enzyme. The data of docking studies strongly support the assumption that these receptors may be involved in observed anticonvulsant activity of 1-(thiazol-2-yl)pyrrolidin-2-one and 2-(thiazol-2-yl)isoindoline-1,3-dione derivatives. However, further studies need to be carried out to ascertain the precise mechanism of action of anticonvulsant activity of these molecules.

Experimental

Instrumentation and chemicals

Melting points (°C) were measured and uncorrected in open glass capillaries using Branstead 9001 electrothermal melting point apparatus. Infrared (IR) spectra were recorded in potassium bromide (KBr) disks using Shimadzu FT-IR spectrophotometer in the region 4000–400 cm^{-1}. ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra were obtained on Bruker AC 500 Ultra Shield spectrometer (Fällanden, Switzerland). High-resolution mass spectra (HRMS) were measured with JEOL the Tandem MStation JMS-700. X-ray data collection was carried out on Bruker SMART APEX II CCD diffractometer, cell refinement: SAINT; data reduction: SAINT; program used to solve structure: SHELXS; program

used to refine structure: SHELXL; molecular graphics: SHELXTL; software used to prepare material for publication: SHELXTL (Sheldrick, 2008) and PLATON (Spek, 2009).

Synthesis

General procedure of 2-aminothiazole derivatives ***2a–h***

2-Bromo-1-arylethanones (0.015 mol) were added to a solution of thiourea (1.5 g, 0.02 mol) in ethanol (50 mL). The mixture was reflux for 8 h and then cooled down to room temperature. The solvent was removed to half its volume in vacuum. The residue was brought to about pH 9 using ammonia. The mixture was extracted by EtOAc, and the extract was washed with saturated NaCl solution and dried over anhydrous Na_2SO_4. The solvent was removed in vacuum to give a precipitate which was crystallized from ethanol to afford the target compounds **2a–h**.

General procedure of 5-bromothiazol-2-amine derivatives ***3a–f***

2-Aminothiazoles (0.1 mol) were dissolved in the least amount of glacial acetic acid, and then bromine (0.11 mol) was added drop-wise with continuous stirring at room temperature. The mixture was heated at 80 °C for 90 min then stirred at room temperature for 12 h. The mixture was filtered and washed with water. The precipitate was heated in water, and the aqueous solution was alkalized by ammonia, filtered, washed with water and then dried. Crystals were formed from ethanol/water to give the 5-bromothiazol-2-amine compounds **3a–f**.

5-Bromo-4-phenylthiazol-2-amine (**3a**) (Sadigova, 2008) Mp: 155–156 °C, yield = 65 %. ^{1}H NMR (DMSO-d_6) δ: 7.76 (m, 5H, Ar-H), 13.2 (brs, 2H, NH_2). ^{13}C NMR (DMSO-d_6) δ: 87.6 (C-Br), 128.6, 129.2, 132.1, 135.1 145.8 (Ar-C), 166.0 (C-NH_2).

5-Bromo-4-p-tolylthiazol-2-amine (**3b**) (Nath *et al.*, 1981) Mp: 192–195 °C, yield = 75 %. ^{1}H NMR (DMSO-d_6) δ: 2.51 (s, 3H, CH_3), 7.37 (d, 2H, Ar-H, J = 8 Hz), 7.85 (d, 2H, Ar-H, J = 8 Hz), 12.8 (brs, 2H, NH_2). ^{13}C NMR (DMSO-d_6) δ: 20.3 (CH_3-C), 88.5 (C-Br), 126.2, 129.3, 130.7, 134.1 145.3 (Ar-C), 167.2 (C-NH_2).

5-Bromo-4-(4-chlorophenyl)thiazol-2-amine (**3c**) (Nath *et al.*, 1981) Mp: 157–159 °C, yield = 73 %. ^{1}H NMR (DMSO-d_6) δ: 4.54 (brs, 2H, NH_2), 7.41 (m, 2H, Ar-H), 7.64 (m, 2H, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 87.8 (C-Br), 128.2, 129.5, 132.1, 132.5 (Ar-C), 145.2 (thiazole C), 167.1 (C-NH_2).

5-Bromo-4-(4-bromophenyl)thiazol-2-amine (**3d**) (Nath *et al.*, 1981) Mp: 173–175 °C, yield = 67 %. ^{1}H NMR (DMSO-d_6) δ: 7.12 (brs, 2H, NH_2), 7.62 (m, 2H, Ar-H), 7.76 (m, 2H, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 87.7 (C-Br), 121.0, 129.8, 131.1, 132.8 (Ar-C), 145.8 (thiazole C), 167.0 (C-NH_2).

Bromo-4-(3,4-dimethoxyphenyl)thiazol-2-amine (**3e**) (Shetty *et al.*, 2010) Mp: 128–130 °C, yield = 65 %. FT-IR (KBr, cm^{-1}): 3386, 3274 (NH_2), 3110 (Ar CH). ^{1}H NMR (DMSO-d_6) δ: 3.72 (s, 6H, OCH_3), 6.84 (d, 1H, J = 8 Hz, Ar-H), 6.92 (d, 1H, J = 8 Hz, Ar-H), 7.2 (s, 2H, NH_2), 7.41 (s, 1H, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 63.4 (OCH_3), 101.2 (thiazole C-Br), 124.8, 125.2, 127.4, 127.9, 139.2, 139.8 (Ar-C), 147.1 (thiazole C), 168.8 (C-NH_2).

Ethyl 2-amino-5-bromothiazole-4-carboxylate (**3f**) Mp: 115–117 °C, yield = 79 %. ^{1}H NMR (DMSO-d_6) δ: 1.26 (t, 3H, J = 6 Hz, CH_3), 4.21 (q, 2H, J = 7 Hz, OCH_2), 7.46 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6) δ: 14.0 (CH_3), 60.4 (OCH_2), 101.3, 138.8 (thiazole C) 160.6 (C-NH_2), 166.7 (C=O).

General procedure of N-(thiazol-2-yl)-4-chlorobutanamide derivatives ***4a–m***

A mixture of 2-aminothiazole derivatives **2a–h** and **3a–e** (1.0 mmol) and K_2CO_3 (4.0 mmol) was stirred at room temperature with drop-wise addition of 4-chlorobutyryl chloride (4.0 mmol) in chloroform for 48 h. The reaction mixture was monitored by TLC (using chloroform/ethyl acetate 9:1). Ammoniated water was added, and the organic layer was separated and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuum. The resulting precipitate was crystallized from ethanol to give crystals of pure *N*-(thiazole-2-yl)-4-chlorobutanamide derivatives.

N-(4-phenylthiazol-2-yl)-4-chlorobutanamide (**4a**) Mp: 158–161 °C, yield = 55 %. FT-IR (KBr, cm^{-1}): 3434 (NH), 1683 (C=O). ^{1}H NMR (DMSO-d_6) δ: 2.01–2.12 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–Cl), 2.64 (t, 2H, J = 8 Hz, –$\underline{CH_2}$–CH_2–CH_2–Cl), 3.71 (t, 2H, J = 5.5 Hz, –CH_2–CH_2–$\underline{CH_2}$–Cl), 7.33 (d, 1H, J = 7 Hz, Ar-H), 7.43 (t, 2H, J = 6 Hz, Ar-H), 7.61 (s, 1H, thiazole H), 7.90 (d, 2H, J = 7 Hz, Ar-H), 12.32 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 27.4, 32.0, 44.7 (butamide C), 107.9 (thiazole C), 125.6, 127.7, 128.6, 134.2 (Ar-C), 148.7, 157.8 (thiazole C), 170.5 (C=O).

N-(4-p-tolylthiazol-2-yl)-4-chlorobutanamide (**4b**) Mp: 185–187 °C, yield = 67 %. ^{1}H NMR ($CDCl_3$) δ: 2.02–2.09 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–Cl), 2.25 (t, 2H, J = 7 Hz, –$\underline{CH_2}$–CH_2–CH_2–Cl), 2.53 (s, 3H, CH_3), 3.44 (t, 2H, J = 6.5 Hz, –CH_2–CH_2–$\underline{CH_2}$–Cl), 7.23 (s, 1H, thiazole H), 7.37 (d, 2H, J = 8 Hz, Ar-H), 7.85 (d, 2H, J = 8 Hz, Ar-H), 11.58 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 20.3 (CH_3-C), 26.4, 31.5, 42.7 (butamide C), 106.3

(thiazole C), 125.3, 128.7, 130.7, 137.4 (Ar-C), 148.7, 158.3 (thiazole C), 169.2 (C=O).

N-(4-(4-chlorophenyl)thiazol-2-yl)-4-chlorobutanamide (**4c**) Mp: 163–165 °C, yield = 85 %. FT-IR (KBr, cm^{-1}): 3253 (NH), 1672 (C=O). ^{1}H NMR (DMSO-d_6) δ: 2.05–2.14 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–Cl), 2.67 (t, 2H, J = 7.5 Hz, –$\underline{CH_2}$–CH_2–CH_2–Cl), 3.74 (t, 2H, J = 6.5 Hz, –CH_2–CH_2–$\underline{CH_2}$–Cl), 7.52 (d, 2H, J = 8.5 Hz, Ar-H), 7.70 (s, 1H, thiazole H), 7.94 (d, 2H, J = 8.5 Hz, Ar-H), 12.37 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 27.3, 32.0, 44.7 (butamide C), 108.6 (thiazole C), 127.3, 128.7, 132.1, 133.1(Ar-C), 147.4, 157.9 (thiazole C), 170.6 (C=O).

N-(4-(4-bromophenyl)thiazol-2-yl)-4-chlorobutanamide (**4d**) Mp: 157–159 °C, yield = 60 %. FT-IR (KBr, cm^{-1}): 3247 (NH), 1670 (C=O). ^{1}H NMR (DMSO-d_6) δ: 2.01–2.12 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–Cl), 2.63 (t, 2H, J = 7 Hz, –$\underline{CH_2}$–CH_2–CH_2–Cl), 3.70 (t, 2H, J = 6.5 Hz, –CH_2–CH_2–$\underline{CH_2}$–Cl), 7.62 (d, 2H, J = 8.5 Hz, Ar-H), 7.69 (s, 1H, thiazole H), 7.84 (d, 2H, J = 8.5 Hz, Ar-H), 12.34 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 27.3, 32.1, 44.1 (butamide C), 108.7 (thiazole C),120.7, 127.6, 131.6, 133.4(Ar-C), 147.5, 157.9 (thiazole C), 170.6 (C=O).

N-(4-(3,4-dimethoxyphenyl)thiazol-2-yl)-4-chlorobutanamide (**4e**) Mp: 132–135 °C, yield = 69 %. ^{1}H NMR (DMSO-d_6) δ: 2.04–2.15 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–Cl), 2.65 (t, 2H, J = 7 Hz, –$\underline{CH_2}$–CH_2–CH_2–Cl), 3.74 (t, 2H, J = 6.5 Hz, –CH_2–CH_2–$\underline{CH_2}$–Cl), 3.78 (s, 6H, OCH_3, 7.60 (d, 1H, J = 8.5 Hz, Ar-H), 7.67 (s, 1H, thiazole H), 7.84 (d, 1H, J = 8.5 Hz, Ar-H), 7.88 (s, 1H, Ar-H), 12.25 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 26.8, 31.7, 45.1(butamide C),62.7 (OCH_3),108.2 (thiazole C), 120.8, 127.1, 132.6, 133.4, 135.4 (Ar-C), 146.9, 157.2 (thiazole C), 170.1 (C=O).

N-(4-(biphenyl-4-yl)thiazol-2-yl)-4-chlorobutanamide (**4f**) Mp: 182–185 °C, yield = 71 %. FT-IR (KBr, cm^{-1}): 3369 (NH), 1658 (C=O). ^{1}H NMR (DMSO-d_6) δ: 2.02–2.11 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–Cl), 2.63 (m, 2H, –$\underline{CH_2}$–CH_2–CH_2–Cl), 3.70 (t, 2H, J = 6.5 Hz, –CH_2–CH_2–$\underline{CH_2}$–Cl), 7.38 (d, 1H, J = 7 Hz, Ar-H), 7.48 (m, 2H, Ar-H), 7.72 (m, 5H, Ar-H), 7.98 (d, 2H, J = 8 Hz, Ar-H), 12.35 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 27.2, 32.0, 44.7 (butamide C), 108.1 (thiazole C), 126.1, 126.4, 126.9, 127.4, 128.9, 139.2 (Ar-C), 148.3, 157.8 (thiazole C), 170.5 (C=O).

N-(4-(naphthalen-2-yl)thiazol-2-yl)-4-chlorobutanamide (**4g**) Mp: 175–177 °C, yield = 58 %. ^{1}H NMR (DMSO-d_6) δ: 2.00–2.10 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–Cl), 2.64 (t, 2H, J = 6.5 Hz, –$\underline{CH_2}$–CH_2–CH_2–Cl), 3.71 (t, 2H, J = 6.5 Hz, –CH_2–CH_2–$\underline{CH_2}$–Cl), 7.53 (d, 2H, J = 6.5 Hz, Ar-H), 7.76 (s, 1H, Ar-H), 7.94 (m, 3H, Ar-H), 8.04 (d, 1H, J = 8.5 Hz, Ar-H), 8.42 (s, 1H, thiazole H), 12.41 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 27.4, 32.0, 44.7 (butamide C), 108.6 (thiazole C), 123.9, 124.1, 126.1, 126.4, 127.5, 128.1, 128.2, 131.7, 132.4, 133.1 (Ar-C), 148.6, 157.9 (thiazole C), 170.6 (C=O).

N-(5-bromo-4-phenylthiazol-2-yl)-4-chlorobutanamide (**4h**) Mp: 147–149 °C, yield = 67 %. ^{1}H NMR (DMSO-d_6) δ: 2.04–2.12 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–Cl), 2.60 (t, 2H, J = 8 Hz, –$\underline{CH_2}$–CH_2–CH_2–Cl), 3.75 (t, 2H, J = 6.5 Hz, –CH_2–CH_2–$\underline{CH_2}$–Cl), 7.39 (d, 1H, J = 7 Hz, Ar-H), 7.44 (t, 2H, J = 6 Hz, Ar-H), 7.87 (d, 2H, J = 7 Hz, Ar-H), 12.31 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 27.3, 32.4, 44.1 (butamide C), 107.8 (thiazole C), 125.5, 128.1, 128.5, 134.2 (Ar-C), 148.8, 157.4 (thiazole C), 170.7 (C=O).

N-(5-bromo-4-p-tolylthiazol-2-yl)-4-chlorobutanamide (**4i**) Mp: 163–165 °C, yield = 74 %. FT-IR (KBr, cm^{-1}): 3224 (NH), 1649 (C=O). ^{1}H NMR (DMSO-d_6) δ: 2.03–2.12 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–Cl), 2.30 (s, 3H, CH_3), 2.60–2.68 (m, 2H, –$\underline{CH_2}$–CH_2–CH_2–Cl), 3.68 (t, 2H, J = 6 Hz, –CH_2–CH_2–$\underline{CH_2}$–Cl), 7.27 (d, 2H, Ar-H, J = 8 Hz), 7.75 (d, 2H, J = 8 Hz, Ar-H), 12.55 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 20.8 (CH_3 − C), 27.2, 31.8, 44.6 (butamide C), 96.2 (thiazole C), 127.7, 128.9, 130.4, 137.7 (Ar-C), 145.7, 156.7 (thiazole C), 171.0 (C=O).

N-(5-bromo-4-(4-chlorophenyl)thiazol-2-yl)-4-chlorobutanamide (**4j**) Mp: 166–168 °C, yield = 58 %. ^{1}H NMR (DMSO-d_6) δ: 2.03–2.09 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–Cl), 2.69 (t, 2H, –$\underline{CH_2}$–CH_2–CH_2–Cl), 3.72 (t, 2H, –CH_2–CH_2–$\underline{CH_2}$–Cl), 7.72 (d, 2H, J = 8.5 Hz, Ar-H), 7.84 (d, 2H, J = 8.5 Hz, Ar-H), 12.65 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 27.2, 31.9, 44.6 (butamide C), 97.0 (thiazole C), 122.0, 129.8, 131.4, 132.3 (Ar-C), 144.0, 157.0 (thiazole C), 171.2 (C=O).

N-(5-bromo-4-(4-bromophenyl)thiazol-2-yl)-4-chlorobutanamide (**4k**) Mp: 173–175 °C, yield = 63 %. FT-IR (KBr, cm^{-1}): 3226 (NH), 1652 (C=O). ^{1}H NMR (DMSO-d_6) δ: 2.02–2.10 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–Cl), 2.63 (t, 2H, –$\underline{CH_2}$–CH_2–CH_2–Cl), 3.70 (t, 2H, –CH_2–CH_2–$\underline{CH_2}$–Cl), 7.70 (d, 2H, Ar-H, J = 8.5 Hz), 7.82 (d, 2H, Ar-H, J = 8.5 Hz), 12.62 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 27.2, 31.9, 44.6 (butamide C), 97.0 (thiazole C), 122.0, 129.8, 131.4, 132.3 (Ar-C), 144.0, 157.0 (thiazole C), 171.2 (C=O).

N-(5-bromo-4-(3,4-dimethoxyphenyl)thiazol-2-yl)-4-chlorobutanamide (**4l**) Mp: 157–160 °C, yield = 52 %. ^{1}H NMR (DMSO-d_6) δ: 2.06–2.14 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–Cl), 2.61 (t, 2H, J = 7 Hz, –$\underline{CH_2}$–CH_2–CH_2–Cl), 3.71 (t, 2H, J = 6.5 Hz, –CH_2–CH_2–$\underline{CH_2}$–Cl), 3.77 (s, 6H, OCH_3, 7.60 (d, 1H, J = 8.5 Hz, Ar-H), 7.84 (d, 1H, J = 8.5 Hz, Ar-H), 7.88 (s, 1H, Ar-H), 12.48 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 26.9, 31.7, 45.5 (butamide C), 62.1 (OCH_3),

108.2 (thiazole C), 118.3, 127.7, 131.6, 132.5, 133.1, 135.4 (Ar-C), 146.9, 157.2 (thiazole C), 170.7 (C=O).

Ethyl 5-bromo-2-(4-chlorobutanamido)thiazole-4-carboxylate (**4m**) Mp: 177–179 °C, yield = 78 %. FT-IR (KBr, cm^{-1}): 3267 (NH), 1708 (ester C=O), 1689 (amide C=O). ^{1}H NMR ($CDCl_3$) δ: 1.34 (t, 3H, J = 7 Hz, CH3) 2.05–2.14 (m, 2H, –CH_2–CH_2–CH_2–Cl), 2.59 (t, 2H, J = 7 Hz, –CH_2–CH_2–CH_2–Cl), 3.56 (t, 2H, J = 6 Hz, –CH_2–CH_2–CH_2–Cl), 3.33 (q, 2H, J = 7 Hz, O–CH_2–CH_3), 10.1 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 14.2 (CH_3), 27.2, 32.5, 43.8 (butamide C),61.8 (OCH_2), 112.1, 137.7, 157.0 (thiazole C), 161.0 (O-C=O) 170.6 (N–C=O). HRMS *m/z*: Calcd. for $C_{10}H_{12}BrClN_2O_3S$: 353.9440; found, 353.9681.

General procedure of 1-(thiazol-2-yl)pyrrolidin-2-one derivatives ***5a–m***

A mixture of 4-chloro-*N*-(thiazol-2-yl)butanamide derivatives **4a**–**m** (4 mmol) and piperidine (0.8 mL, 8 mmol) in toluene (50 mL) was heated under reflux for 24 h. The reaction mixture was cooled, poured into ammoniated water and stirred. Toluene was then separated, dried over anhydrous Na_2SO_4 and finally evaporated to give a crude product. This product was purified by Chromatotron silica plate with 1 cm thickness using $CHCl_3$/EtOAc (95:5 v/v) as eluting system. The solid obtained was recrystallized to give the required products.

1-(4-Phenylthiazol-2-yl)pyrrolidin-2-one (**5a**) (Paul *et al.*, 1982) Mp: 163–164 °C, yield = 72 %. FT-IR (KBr, cm^{-1}): 3078 (Ar CH), 1697 (C=O). ^{1}H NMR (DMSO-d_6) δ: 2.01–2.12 (m, 2H, –CH_2–CH_2–CH_2–N), 2.64 (t, 2H, J = 8 Hz, –CH_2–CH_2–CH_2–N), 4.14 (t, 2H, J = 7 Hz, –CH_2–CH_2–CH_2–N), 7.30–7.38 (m, 1H, Ar-H), 7.41–7.49 (m, 2H, Ar-H), 7.71 (s, 1H, thiazole H), 7.94 (d, 2H, J = 7 Hz, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 17.5, 31.2, 47.7 (pyrrolidinone C), 108.3 (thiazole C), 125.7, 127.8, 128.6, 134.0(Ar-C), 148.5, 156.8 (thiazole C), 173.8 (C=O). HRMS *m/z*: Calcd. for $C_{13}H_{12}N_2OS$: 244.0670; found, 244.0639.

1-(4-p-Tolylthiazol-2-yl)pyrrolidin-2-one (**5b**) (Uehara *et al.*, 2013) Mp: 163–165 °C, yield = 75 %. FT-IR (KBr, cm^{-1}): 3099 (CH_3), 1681 (C=O). ^{1}H NMR (DMSO-d_6) δ: 2.11–2.20 (m, 2H, –CH_2–CH_2–CH_2–N), 2.33 (s, 3H, CH_3), 2.64 (t, 2H, J = 7.5 Hz, –CH_2–CH_2–CH_2–N), 4.14 (t, 2H, J = 7 Hz, –CH_2–CH_2–CH_2–N), 7.24 (d, 2H, J = 7.5 Hz, Ar-H), 7.63 (s, 1H, thiazole H), 7.83 (d, 2H, J = 8 Hz, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 17.6 (CH_3), 20.7, 31.2, 47.7 (pyrrolidinone C), 107.4 (thiazole C), 125.6, 129.2, 131.4, 137.1 (Ar-C), 148.6, 156.7 (thiazole C), 173.8(C=O). HRMS *m/z*: Calcd. for $C_{14}H_{14}N_2OS$: 258.0827; found, 258.0823.

1-(4-(4-Chlorophenyl)thiazol-2-yl)pyrrolidin-2-one (**5c**) (Uehara *et al.*, 2013) Mp: 205–208 °C, yield = 68 %. FT-IR (KBr, cm^{-1}): 3099 (Ar CH), 1691 (C=O). ^{1}H NMR (DMSO-d_6) δ: 2.11–2.20 (m, 2H, –CH_2–CH_2–CH_2–N), 2.65 (t, 2H, J = 8 Hz, –CH_2–CH_2–CH_2–N), 4.14 (t, 2H, J = 7 Hz, –CH_2–CH_2–CH_2–N), 7.50 (d, 2H, J = 8.5 Hz, Ar-H), 7.78 (s, 1H, thiazole H), 7.96 (d, 2H, J = 8.5 Hz, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 17.6, 31.2, 47.7 (pyrrolidinone C), 109.0 (thiazole C), 127.4, 128.6, 132.2, 132.9 (Ar-C), 147.3, 157.0 (thiazole C), 173.9 (C=O). HRMS *m/z*: Calcd. for $C_{13}H_{11}ClN_2OS$: 278.0281; found, 277.9900.

1-(4-(4-Bromophenyl)thiazol-2-yl)pyrrolidin-2-one (**5d**) Mp: 215–217 °C, yield = 71 %. ^{1}H NMR (DMSO-d_6) δ: 2.12–2.21 (m, 2H, –CH_2–CH_2–CH_2–N), 2.65 (t, 2H, J = 8 Hz, –CH_2–CH_2–CH_2–N), 4.13 (t, 2H, J = 7 Hz, –CH_2–CH_2–CH_2–N), 7.63 (d, 1H, J = 8.5 Hz, Ar-H), 7.80 (s, 1H, thiazole H), 7.90 (d, 2H, J = 7.5 Hz, Ar-H,). ^{13}C NMR (DMSO-d_6) δ: 17.6, 31.2, 47.7 (pyrrolidinone C), 109.0 (thiazole C), 120.8, 127.7, 131.6, 133.2 (Ar-C), 147.3, 157.0 (thiazole C), 173.9(C=O). HRMS *m/z*: Calcd. for $C_{13}H_{11}BrN_2OS$: 321.9775; found, 321.9917.

1-(4-(3,4-Dimethoxyphenyl)thiazol-2-yl)pyrrolidin-2-one (**5e**) Mp: 167–169 °C, yield = 65 %. ^{1}H NMR (DMSO-d_6) δ: 2.09–2.17 (m, 2H, –CH_2–CH_2–CH_2–N), 2.64 (t, 2H, J = 7 Hz, –CH_2–CH_2–CH_2–N), 4.11 (t, 2H, J = 6.5 Hz, –CH_2–CH_2–CH_2–N), 3.77 (s, 6H, OCH_3, 7.61 (d, 1H, J = 8.5 Hz, Ar-H), 7.65 (s, 1H, thiazole H), 7.88 (d, 1H, J = 8.5 Hz, Ar-H), 7.93 (s, 1H, Ar-H). ^{13}C NMR (DMSO-d_6) δ:21.8, 31.7, 47.1 (pyrrolidinone C),62.5 (OCH_3), 108.1 (thiazole C), 120.7, 127.3, 132.6, 132.9, 133.4, 135.4 (Ar-C), 146.9, 157.1 (thiazole C), 170.9 (C=O). HRMS *m/z*: Calcd. for $C_{15}H_{16}N_2O_3S$: 304.0882; found, 303.9683.

1-(4-(Biphenyl-4-yl)thiazol-2-yl)pyrrolidin-2-one (**5f**) Mp: 210–212 °C, yield = 77 %. FT-IR (KBr, cm^{-1}): 3109 (Ar CH), 1681 (C=O). ^{1}H NMR (DMSO-d_6) δ: 2.15–2.24 (m, 2H, –CH_2–CH_2–CH_2–N), 2.66 (t, 2H, J = 8 Hz, –CH_2–CH_2–CH_2–N), 4.11–4.20 (m, 2H, –CH_2–CH_2–CH_2–N), 7.39 (s, 1H, thiazole H), 7.44–7.51 (m, 2H, Ar-H), 7.71-.7.79 (m, 5H, Ar-H), 8.00–8.07 (m, 2H, Ar-H,). ^{13}C NMR (DMSO-d_6) δ: 21.5, 31.2, 47.4 (pyrrolidinone C), 107.0 (thiazole C), 126.3, 126.5, 126.9, 127.4, 128.9, 132.2, 132.9 (Ar-C), 141.2, 147.5 (thiazole C), 173.2 (C=O). HRMS *m/z*: Calcd. for $C_{19}H_{16}N_2OS$: 320.0983; found, 319.9664.

1-(4-(Naphthalen-2-yl)thiazol-2-yl)pyrrolidin-2-one (**5g**) Mp: 162–165 °C, yield = 72 %. ^{1}H NMR (DMSO-d_6) δ: 2.16–2.22 (m, 2H, J = 7 Hz, –CH_2–CH_2–CH_2-N), 2.67 (t, 2H, J = 7.5 Hz, –CH_2–CH_2–CH_2–N), 4.22 (t, 2H, J = 6.5 Hz, –CH_2–CH_2–CH_2–N), 7.49–7.54 (m, 2H, Ar-H), 7.87 (s, 1H, thiazole H), 7.92 (d, 1H, Ar-H, J = 7 Hz), 7.94–8.02 (m, 2H, J = 7 Hz, Ar-H), 8.08 (d, 1H,

J = 7 Hz, Ar-H) 8.48 (s, 1H, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 17.6, 31.2, 47.8 (pyrrolidinone C),109.0 (thiazole C), 124.0, 124.2, 126.1, 126.5, 127.5, 128.1, 128.2, 131.5, 132.5, 133.1 (Ar-C), 148.5, 157.0 (thiazole C), 173.9 (C=O). HRMS *m/z*: Calcd. for $C_{17}H_{14}N_2OS$: 294.0827; found, 293.9884.

1-(5-Bromo-4-phenylthiazol-2-yl)pyrrolidin-2-one (**5h**) Mp: 158–160 °C, yield = 75 %. FT-IR (KBr, cm^{-1}):1695 (C=O). ^{1}H NMR (DMSO-d_6) δ: 2.14–2.19 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–N), 2.65 (t, 2H, J = 7.5 Hz, –$\underline{CH_2}$–CH_2–CH_2–N), 4.06 (t, 2H, J = 7.0 Hz, –CH_2–CH_2–$\underline{CH_2}$–N), 7.44 (d, 1H, J = 7.5 Hz, Ar-H), 7.50 (t, 2H, J = 7.5 Hz, Ar-H), 7.90 (d, 2H, J = 7.0 Hz, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 17.6, 30.9, 47.1(pyrrolidinone C), 97.4 (thiazole C-Br), 127.9, 128.3, 128.4, 133.0 (Ar-C), 145.6, 155.6 (thiazole C), 174.5 (C=O). HRMS *m/z*: Calcd. for $C_{13}H_{11}BrN_2OS$: 321.9775; found, 321.9766.

1-(5-Bromo-4-p-tolylthiazol-2-yl)pyrrolidin-2-one (**5i**) Mp: 165–167 °C, yield = 59 %. ^{1}H NMR ($CDCl_3$) δ: 2.43 (s, 3H, CH_3), 2.75–2.81 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–N), 3.01 (t, 2H, J = 7.0 Hz, –$\underline{CH_2}$–CH_2–CH_2–N), 4.40 (t, 2H, J = 6.5 Hz, –CH_2–CH_2–$\underline{CH_2}$–N), 7.28 (s, 2H, Ar-H), 7.80 (s, 2H, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 17.2 (CH_3), 20.6, 30.1, 47.5 (pyrrolidinone C), 97.4 (thiazole C), 128.6, 129.2, 131.3, 137.5 (Ar-C), 147.6, 156.2 (thiazole C), 173.2(C=O). HRMS *m/z*: Calcd. for $C_{14}H_{13}BrN_2OS$: 335.9932; found, 336.0088.

1-(5-Bromo-4-(4-chlorophenyl)thiazol-2-yl)pyrrolidin-2-one (**5j**) Mp: 184–186 °C, yield = 64 %. FT-IR (KBr, cm^{-1}): 3098 (Ar CH), 1692 (C=O). ^{1}H NMR (DMSO-d_6) δ: 2.12–2.19 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–N), 2.67 (t, 2H, J = 8 Hz, –$\underline{CH_2}$–CH_2–CH_2–N), 4.12 (t, 2H, J = 7 Hz, –CH_2–CH_2–$\underline{CH_2}$–N), 7.52 (d, 2H, J = 8.5 Hz, Ar-H), 7.92 (d, 2H, J = 8.5 Hz, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 17.6, 31.2, 47.7 (pyrrolidinone C), 109.1 (thiazole C), 127.4, 128.6, 132.2, 132.9 (Ar-C), 147.3, 157.1 (thiazole C), 173.7(C=O). HRMS *m/z*: Calcd. for $C_{13}H_{10}BrClN_2OS$: 355.9386; found, 355.9301.

1-(5-Bromo-4-(4-bromophenyl)thiazol-2-yl)pyrrolidin-2-one (**5k**) Mp: 195–197 °C, yield = 70 %. ^{1}H NMR (DMSO-d_6) δ: 2.17–2.23 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–N), 2.67 (t, 2H, J = 8 Hz, –$\underline{CH_2}$–CH_2–CH_2–N), 4.19 (t, 2H, J = 7 Hz, –CH_2–CH_2–$\underline{CH_2}$–N), 7.66 (d, 1H, J = 8.5 Hz, Ar-H), 7.90 (d, 2H, J = 7.5 Hz, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 17.6, 31.2, 47.7 (pyrrolidinone C), 109.1 (thiazole C), 120.8, 127.7, 131.7, 133.2 (Ar-C), 147.3, 157.7 (thiazole C), 173.(C=O). HRMS *m/z*: Calcd. for $C_{13}H_{10}Br_2N_2OS$: 399.8881; found, 399.8867.

1-(5-Bromo-4-(3,4-dimethoxyphenyl)thiazol-2-yl)pyrrolidin-2-one (**5l**) Mp: 170–172 °C, yield = 71 %. ^{1}H NMR (DMSO-d_6) δ: 2.08–2.16 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–N), 2.71 (t, 2H, J = 7 Hz, –$\underline{CH_2}$–CH_2–CH_2–N), 4.21 (t, 2H, J = 6.5 Hz, –CH_2–CH_2–$\underline{CH_2}$–N), 3.79 (s, 6H, OCH_3, 7.62 (d, 1H, J = 8.5 Hz, Ar-H), 7.85 (d, 1H, J = 8.5 Hz, Ar-H), 7.91 (s, 1H, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 21.7, 31.6, 47.1 (pyrrolidinone C), 62.7 (OCH_3),108.4 (thiazole C), 121.5, 127.2, 132.3, 132.9, 133.1, 135.2 (Ar-C), 147.0, 157.2 (thiazole C), 170.8 (C=O). HRMS *m/z*: Calcd. for $C_{15}H_{15}BrN_2O_3S$: 381.9987; found, 381.9905.

Ethyl 5-bromo-2-(2-oxopyrrolidin-1-yl)thiazole-4-carboxylate (**5m**) Mp: 161–163 °C, yield = 61 %. FT-IR (KBr, cm^{-1}): 1706 (ester C=O), 1693 (amide C=O). ^{1}H NMR (DMSO-d_6) δ: 1.32 (t, 3H, J = 7 Hz, CH3) 2.11–2.20 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–N), 2.65 (t, 2H, J = 8 Hz, –$\underline{CH_2}$–$\underline{CH_2}$–C$\underline{H_2}$–N), 4.02 (t, 2H, J = 7.5 Hz, –C$\underline{H_2}$–CH_2–$\underline{CH_2}$–N), 4.32 (q, 2H, J = 7 Hz, O–C$\underline{H_2}$–CH_3). ^{13}C NMR (DMSO-d_6) δ: 14.0 (CH_3), 17.6, 30.8, 47.2 (pyrrolidinone C), 61.0 (OCH_2), 110.8, 137.6, 155.6 (thiazole C), 160.4 (O-C=O) 175.0 (N–C=O). HRMS *m/z*: Calcd. for $C_{10}H_{11}BrN_2O_3S$: 317.9674; found, 317.9789.

General procedure of 2-(thiazol-2-yl)isoindoline-1,3-dione derivatives ***6a–g***

2-Aminothiazole derivatives **2a–g** (0.01 mol) were triturated and mixed with phthalic anhydride (1.48 g, 0.01 mol). The mixture was heated on an oil bath with occasional stirring for 2 h. The crude product was dissolved in hot EtOAc and filtered to remove any undissolved particles, and the 2-(thiazole-2-yl)isoindoline-1,3-dione derivatives were precipitated by cooling.

2-(4-Phenylthiazol-2-yl)isoindoline-1,3-dione (**6a**) (Rajpurohit and Sah, 2005) Mp: 127–129 °C, yield = 68 %. FT-IR (KBr, cm^{-1}): 3093 (Ar CH), 1728, 1716 (2 C=O). ^{1}H NMR (DMSO-d_6) δ: 7.31–7.37 (m, 1H, Ar-H), 7.55 (d, 2H, J = 7.5 Hz, Ar-H), 7.92–7.97 (m, 2H, Ar-H), 8.02–8.07 (m, 4H, Ar-H), 8.22 (s, 1H, thiazole H). ^{13}C NMR (DMSO-d_6) δ: 114.0 (thiazole C), 123.9, 127.5, 128.8, 131.0, 132.5, 132.7, 135.3 (Ar-C), 149.5, 151.9 (thiazole C), 164.8 (C=O). HRMS *m/z*: Calcd. for $C_{17}H_{10}N_2O_2S$: 306.0463; found, 305.9941.

2-(4-p-Tolylthiazol-2-yl)isoindoline-1,3-dione (**6b**) Mp: 171–173 °C, yield = 79 %. FT-IR (KBr, cm^{-1}): 3107 (Ar CH), 1750, 1731 (2 C=O). ^{1}H NMR (DMSO-d_6) δ: 2.32 (s, 3H, CH_3), 7.29 (d, 2H, J = 7 Hz, Ar-H), 7.85–7.94 (m, 2H, Ar-H), 7.92 (s, 2H, Ar-H), 8.03 (s, 2H, Ar-H), 8.09 (s, 1H, thiazole H). ^{13}C NMR (DMSO-d_6) δ: 20.8 (CH_3), 112.7 (thiazole C), 123.9, 125.8, 129.3, 131.0, 131.1, 135.2, 137.6 (Ar-C), 150.9, 151.5 (thiazole C), 164.9 (C=O). HRMS *m/z*: Calcd. for $C_{17}H_{10}N_2O_2S$: 320.0619; found, 319.9996.

2-(4-(4-Chlorophenyl)thiazol-2-yl)isoindoline-1,3-dione (**6c**) Mp: 197–199 °C, yield = 81 %. FT-IR (KBr, cm^{-1}): 3095 (Ar CH), 1782, 1728 (2 C=O). ^{1}H NMR (DMSO-d_6) δ: 7.55 (d, 2H, J = 7.5 Hz, Ar-H), 7.92–7.98 (m, 2H, Ar-H), 8.02–8.10 (m, 4H, Ar-H), 8.22 (s, 1H, thiazole H). ^{13}C NMR (DMSO-*d6*) δ: 114.0 (thiazole C), 123.9, 127.5, 128.8, 131.0, 132.5, 132.7, 135.3 (Ar-C), 149.5, 151.9 (thiazole C), 164.8 (C=O). HRMS *m/z*: Calcd. for $C_{17}H_9ClN_2O_2S$: 340.0073; found, 339.9948.

2-(4-(4-Bromophenyl)thiazol-2-yl)isoindoline-1,3-dione (**6d**) Mp: 186–188 °C, yield = 82 %. FT-IR (KBr, cm^{-1}): 3120 (Ar CH), 1739, 1679 (2 C=O). ^{1}H NMR (DMSO-d_6) δ: 7.68 (d, 2H, J = 8.5 Hz, Ar-H), 7.84–7.89 (m, 6H, Ar-H), 8.23 (s, 1H, thiazole H). ^{13}C NMR (DMSO-d_6) δ: 114.1 (thiazole C), 121.3, 123.9, 127.8, 131.0, 131.7, 132.9, 135.3 (Ar-C), 149.5, 151.9 (thiazole C), 164.8 (C=O). HRMS *m/z*: Calcd. for $C_{17}H_9BrN_2O_2S$: 383.9568; found, 383.9553.

2-(4-(3,4-Dimethoxyphenyl)thiazol-2-yl)isoindoline-1,3-dione (**6e**) Mp: 195–198 °C, yield = 71 %. FT-IR (KBr, cm^{-1}): 3101 (Ar CH), 1758, 1728 (2 C=O). ^{1}H NMR (DMSO-d_6) δ: 3.81 (s, 6H, OCH_3), 7.06 (d, 1H, J = 8 Hz, Ar-H), 7.55 (d, 2H, J = 7.5 Hz, Ar-H), 7.96 (s, 2H, Ar-H), 8.03 (s, 2H, Ar-H), 8.07 (s, 1H, thiazole H). ^{13}C NMR (DMSO-d_6) δ: 55.5 (OCH_3), 109.4 (thiazole C), 111.8, 112.0, 118.5, 123.9, 126.7, 131.1, 135.2, 148.8, 148.9 (Ar-C), 151.0, 151.3 (thiazole C), 165.0 (C=O). HRMS *m/z*: Calcd. for $C_{19}H_{14}N_2O_4S$: 366.0674; found, 366.0632.

2-(4-(Biphenyl-4-yl)thiazol-2-yl)isoindoline-1,3-dione (**6f**) Mp: 202–205 °C, yield = 78 %. ^{1}H NMR (DMSO-d_6) δ: 7.55 (d, 2H, J = 7.5 Hz, Ar-H), 7.72–7.79 (m, 6H, Ar-H), 8.01–8.13 (m, 5H, Ar-H), 8.29 (s, 1H, thiazole H). ^{13}C NMR (DMSO-d_6) δ: 114.0 (thiazole C), 123.9, 127.5, 128.8, 131.0, 132.5, 132.7, 135.3, 137.2, 137.9 (Ar-C), 149.5, 151.7 (thiazole C), 164.7 (C=O). HRMS *m/z*: Calcd. for $C_{23}H_{14}N_2O_2S$: 382.0776; found, 381.9953.

2-(4-(Naphthalen-2-yl)thiazol-2-yl)isoindoline-1,3-dione (**6g**) Mp: 215–217 °C, yield = 69 %.^{1}H NMR (DMSO-d_6): δ 7.47–4.50 (m, 4H, Ar-H), 7.66–7.69 (m, 6H, Ar-H), 8.02 (s, 1H, thiazole H), 8.15 (s, 1H, Ar-H). ^{13}C NMR: δ 114.3 (thiazole C), 122.8, 127.0, 127.8, 128.7, 130.5, 132.4, 132.8, 134.3, 136.3, 137.9 (Ar-C), 149.9, 151.5 (thiazole C), 164.9 (C=O). HR-EI-MS *m/z*: 356.0622 (M^+), Calcd. for $C_{23}H_{14}N_2O_2S$: 356.0619.

General procedure of 2-(thiazol-2-yl)4,5,6,7-tetrachloroisoindoline-1,3-dione derivatives ***6h–n***

A mixture of 2-aminothiazole derivatives **2a–g** (0.01 mol), anhydrous sodium acetate (0.8 g, 0.01 mol) and 4,5,6,7-tetrachlorophthalic anhydride (2.8 g, 0.01 mol) was heated in glacial acetic acid (50 mL) under reflux for 3 h. On cooling, the separated solid was filtered, washed with water (20 mL), dried and crystallized from ethanol to yield the title compounds.

2-(4-Phenylthiazol-2-yl)4,5,6,7-tetrachloroisoindoline-1,3-dione (**6h**) Mp: 255–257 °C, yield = 85 %. ^{1}H NMR (DMSO-d_6) δ: 7.37–7.42 (m, 1H, Ar-H), 7.47–7.51 (m, 2H, Ar-H), 7.92–8.01 (m, 2H, Ar-H), 8.24 (s, 1H, thiazole H). ^{13}C NMR (DMSO-d_6) δ: 114.2 (thiazole C), 124.4, 126.3, 127.2, 127.5, 128.3, 128.7, 128.9, 131.5, 132.2, 133.8 (Ar-C), 149.5, 150.4 (thiazole C), 161.4 (C=O). HRMS *m/z*: Calcd. for $C_{17}H_6Cl_4N_2O_2S$: 441.8904; found, 441.8900.

2-(4-p-Tolylthiazol-2-yl)4,5,6,7-tetrachloroisoindoline-1,3-dione (**6i**) Mp: 266–268 °C, yield = 89 %. FT-IR (KBr, cm^{-1}): 3120 (Ar CH), 1795, 1731 (2 C=O). ^{1}H NMR (DMSO-d_6) δ: 2.5 (s, 3H, CH_3), 7.34 (d, 2H, J = 8 Hz, Ar-H), 7.88 (d, 2H, J = 8 Hz, Ar-H), 8.16 (s, 1H, thiazole H). ^{13}C NMR (DMSO-d_6) δ: 114.2 (thiazole C), 125.8, 128.0, 128.3, 128.7, 128.8, 138.8 (Ar-C), 149.5, 150.4 (thiazole C), 160.6 (C=O). HRMS *m/z*: Calcd. for $C_{18}H_8Cl_4N_2O_2S$: 455.9061; found, 455.9042.

2-(4-(4-Chlorophenyl)thiazol-2-yl)4,5,6,7-tetrachloroisoindoline-1,3-dione (**6j**) Mp: 294–296 °C, yield = 78 %. FT-IR (KBr, cm^{-1}): 3120 (Ar CH), 1793, 1728 (2 C=O). ^{1}H NMR (DMSO-d_6) δ: 7.56 (d, 2H, J = 8 Hz, Ar-H), 8.02 (d, 2H, J = 8 Hz, Ar-H), 8.29 (s, 1H, thiazole H). ^{13}C NMR (DMSO-d_6) δ: 114.2 (thiazole C), 126.7, 128.2, 128.4, 128.9, 129.5, 129.9, 131.5, 132.5, 132.7 (Ar-C), 149.1, 151.4 (thiazole C), 160.4 (C=O). HRMS *m/z*: Calcd. for $C_{17}H_5Cl_5N_2O_2S$: 475.8514; found, 475.8501.

2-(4-(4-Bromophenyl)thiazol-2-yl)-4,5,6,7-tetrachloroisoindoline-1,3-dione (**6k**) Mp: 276–278 °C, yield = 90 %. ^{1}H NMR (DMSO-d_6) δ: 7.69 (d, 2H, J = 8.5 Hz, Ar-H), 7.95 (d, 2H, J = 8 Hz, Ar-H), 8.30 (s, 1H, thiazole H). ^{13}C NMR (DMSO-d_6) δ: 114.4 (thiazole C), 126.4, 126.5, 127.2, 127.6, 128.0, 128.7, 128.9, 132.8, 133.4, 139.8 (Ar-C), 150.5, 150.8 (thiazole C), 161.5 (C=O). HRMS *m/z*: Calcd. for $C_{17}H_5BrCl_4N_2O_2S$: 519.8009; found, 519.5808.

2-(4-(3,4-Dimethoxyphenyl)thiazol-2-yl)4,5,6,7-tetrachloroisoindoline-1,3-dione (**6 l**) Mp: 265–268 °C, yield = 74 %. FT-IR (KBr, cm^{-1}): 3112 (Ar CH), 1797, 1726 (2 C=O). ^{1}H NMR (DMSO-d_6) δ: 1.9 (s, 6H, OCH_3), 7.06 (d, 1H, J = 7.5 Hz, Ar-H), 7.55 (d, 2H, J = 8.5 Hz, Ar-H), 8.14 (s, 1H, thiazole H). ^{13}C NMR (DMSO-d_6) δ: 61.2 (OCH_3), 114.2 (thiazole C), 124.5, 125.4, 126.5, 127.1, 127.6, 128.2, 128.7, 128.9, 132.8, 133.4 (Ar-C), 149.1, 150.3 (thiazole C), 161.7 (C=O). HRMS *m/z*: Calcd. for $C_{19}H_{10}Cl_4N_2O_4S$: 501.9115; found, 501.9719.

2-(4-(Biphenyl-4-yl)thiazol-2-yl)-4,5,6,7-tetrachloroisoindoline-1,3-dione (**6m**) Mp: 277–279 °C, yield = 80 %. ^{1}H NMR (DMSO-d_6) δ: 7.37–7.42 (m, 1H, Ar-H),

7.48–7.56 (m, 2H, Ar-H), 7.75 (d, 2H, $J = 7$ Hz, Ar-H), 7.81 (d, 2H, $J = 7.5$ Hz, Ar-H), 8.09 (d, 2H, $J = 8$ Hz, Ar-H), 8.29 (s, 1H, thiazole H). ^{13}C NMR (DMSO-d_6) δ: 114.2 (thiazole C), 125.5, 126.7, 127.4, 128.1, 128.5, 129.2, 129.9, 131.0, 132.3, 132.9 (Ar-C), 149.5, 151.6 (thiazole C), 163.4 (C=O). HRMS *m/z*: Calcd. for $C_{23}H_{10}Cl_4N_2O_2S$: 517.9217; found, 517.9846.

2-(4-(Naphthalen-2-yl)thiazol-2-yl)-4,5,6,7-tetrachloroisoindoline-1,3-dione (**6n**) Mp: 260–263 °C, yield = 75 %. ^{1}H NMR (DMSO-d_6): δ 7.50–7.58 (m, 6H, Ar-H), 7.81(s, 1H, thiazole H), 8.29 (s, 1H, Ar-H). ^{13}C NMR: δ 114.4 (thiazole C), 126.5, 126.9, 127.8, 129.2, 129.5, 129.9, 131.4, 132.6, 132.9 (Ar-C), 148.5, 151.8 (thiazole C), 164.2 (C=O). HR-EI-MS *m/z*: (M^+) 491.9088, ($M^+ + 2$) 493.9073, ($M^+ + 4$) 495.9114, ($M^+ + 6$) 497.9098, ($M^+ + 8$) 499.9174. Calcd. for $C_{23}H_{10}Cl_4N_2O_2S$: 491.9061.

Crystallography

Crystals of compounds **5a** and **6e** were obtained by slow evaporation from solutions of ethanol/DMF and ethanol, respectively. The measurements of the crystals were performed on a Bruker SMART APEX II CCD diffractometer with graphite-monochromated Cu *Kα* radiation ($\lambda = 1.54178$ Å) at room temperature. The structures were solved by direct method and refined with SHELXTL (Sheldrick, 2008). E-maps provided the positions of all the non-H-atoms. The full-matrix least-squares refinement was carried out on F^2 using anisotropic temperature factors for all non-*H*-atoms. Crystallographic data for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Center and allocated with the deposition numbers: CCDC 963827 and 945621 for compounds **5a** and **6e**, respectively. Copies of data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EW, UK (Fax: Int. code (1223) 336-033; E-mail: deposit@ccdc.cam.ac.uk).

Molecular modeling

All the modeling studies were carried out on a desktop PC, Intel® Core™ 2 Duo CPU E8200 @ 2.66 GHz, RAM 4 GB operating under Windows 7 professional. It consists of several steps. First, the 3D crystal structures of GABA-AT with PDB code 1OHV (Storici *et al.*, 2004) were downloaded from Brookhaven Protein Data Bank (PDB; http://www.rcsb.org/pdb) and human $GABA_A$ homology model (Berezhnoy *et al.*, 2009) loaded to Molegro Virtual Docker (MVD 2013.6.0.0 [Win32]) program fully functional free trial version with time limiting license ("Molegro Virtual Docker (MVD 2013.6.0.0), Molegro bioinformatics solutions, Danish, 2013 http://www.molegro.com"; Thomsen and Christensen, 2006). All the atom types, charges and bond hybridization were carefully checked. The MolDock score (GRID) and MolDock Optimizer routines as implemented in Molegro Virtual Docker (MVD version 2013.6.0.0). The non-bonded oxygen atoms of waters present in the crystal structure were removed. ChemBio3D Ultra 10 (Kerwin, 2010) was used to draw the 3D structures of different ligands. Ligands were further pre-optimized using free version of Marvinsketch 4.1.13 from Chemaxon Ltd ("Marvinsketch, version 6.1.0, Chemaxon company cheminformatics technology products services, 2013 http://www.chemaxon.com," 2013) with MM force field and saved in Tripos mol2 file format. MolDock score functions were used with a 0.3 Å grid resolution. Prior to the calculations of the subject compounds, the MVD software was benchmarked docking the vigabatrin in case of GABA-TA and eszopiclone, zolpidem, diazepam and flunitrazepam in the homology model of $GABA_A$ receptor (Hanson *et al.*, 2008).

Anticonvulsant activity

The anticonvulsant activity was carried out on Swiss albino mice (25–30 g) of both sexes as experimental animals. The animals were housed under standard conditions and allowed free access to standard pellet diet and water (ab libitum). The first group of animals were administered 0.5 % methyl cellulose/water mixture which served as negative control. The second group of animals were treated with phenytoin sodium (25 mg/kg, i.p.) which served as positive control. The tested compounds were suspended in 0.5 % methyl cellulose/water mixture. In the preliminary screening tests by MES, PTZ and PIC, each compound was administered as an i.p. injection at three dose levels (100, 200 and 300 mg/kg), and anticonvulsant and neurotoxic effects were assessed at 30-min and 4-h intervals after administration in mice.

Pentylenetetrazole-induced convulsion test in mice

Pentylenetetrazole dissolved in 0.9 % sodium chloride solution (80 mg/kg) was administered in the posterior midline of the mice, and the onset and severity of convulsion was noted for the control group. The test group was administered with the selected compounds 0.5, 4 h prior to the administration of PTZ. The animals are placed in isolation cage to minimize stress and observed for the next 30 min to see the absence of seizure. An episode of clonic spasms was approximately 3–5 s of the fore and/or hind limbs. Animals which did not meet this criterion were considered protected (Wang *et al.*, 2012).

Picrotoxin-induced convulsion test in mice

Tested compounds in different doses were i.p. injected to mice, 0.5, 4 h later, animals were injected i.p. with PIC

(10 mg/kg) and observed for 30 min, and the percentage of anticonvulsant activity of the tested compounds was calculated (Hasan *et al.*, 2014).

MES-induced convulsions in mice

The MES is one of the electrical tests used to evaluate anticonvulsant activity. In this test, MES that induced 100 % maximal seizures was found to be 50 mA alternating current of 60 Hz frequency for 0.2 s, using ECT UNIT (model number 7801, UGO Basile, Varese, Italy). 100, 200 mg/kg of the test compounds were injected i.p. Thirty minutes later, mice were restrained by hand and subjected to electric shock through their ears. They were released immediately following the electrical stimulation to permit observation of the maximal seizure. The maximal seizure typically consists of a short period of initial tonic flexion and a prolonged period of tonic extension (especially the hind limb). Protection was defined as complete absence of hind limb tonic extension (Lotarski *et al.*, 2014).

Neurotoxicity-minimal motor impairment (MMI)

The neurotoxicity of all the test compounds was evaluated using rotarod test. Mice were trained to balance on the rotating rod (2.5 cm diameter, 25 cm height) that rotates at 6 rpm. Trained animals were treated with the test compounds administered i.p. Neurotoxicity was determined by the inability of the animal to remain on the rod for 1 min. The results are represented as TD_{50} which are further used in the calculation of PI (TD_{50}/ED_{50}) (Zaidi *et al.*, 2013).

Calculation of drug-likeness and ADME properties

The molecular properties such as TPSA, *C*log *P*, number of rotatable bonds and violations of Lipinski's rule of five were calculated using Molinspiration online property calculator tool kit ("Molinspiration Cheminformatics, Web-enabled software for large-scale calculation of molecular properties and database searches, Free online molecular descriptor calculations (Last accessed on 22.6.13). Available from: http://www.molinspiration.com/services/properties.html"). Topological polar surface area was used to calculate the percentage of absorption (%ABS) according to the equation: $\%ABS = 109 - [0.345 \times TPSA]$ (Ahsan *et al.*, 2011).

Lipophilicity

Agilent 6320 Ion Trap LC/MS mass spectrometer instrument was used, equipped with a quaternary model pump and an automatic injector (Agilent Technologies, Germany). The Onyx™ monolithic chromatographic column RP C18, 100 mm × 4.6 mm (Phenomenex Inc., USA), was used in this experiment. The mixture of acetonitrile (HPLC grade) (60 %) and 5 mmol ammonium formate buffer (40 %) was used as a mobile phase. The total flow of the column was 0.9 mL/min, injection volume was 10 µL, and column temperature was 25 °C. The acetic acid solution was used for dead time (t_0) determination. Retention times (t_R) were measured in minutes. The capacity factors k were calculated according to the formula $k = (t_R - t_0)/t_0$, where t_R is for the solute and t_0 denotes the dead time obtained via an unretained analyte (Mrkvičková *et al.*, 2008). The log k values of the individual compounds are shown in Table 2.

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