Design and Synthesis of 3-Substituted-thiazolyl-2-iminothiazolidin-4-ones as a New Class of Anticonvulsants

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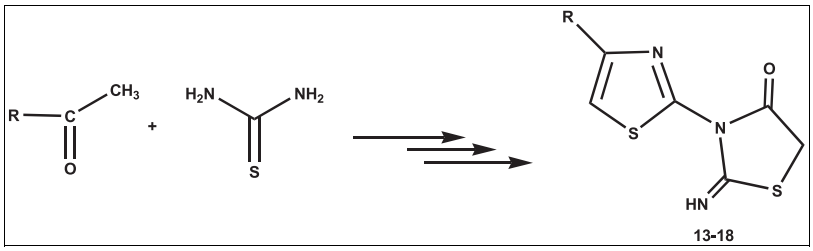

A new series of 3-substituted-thiazolyl-2-iminothiazolidin-4-ones were synthesized by nucleophilic substitution of *p*-substituted-thiazol-2-yl-chloroacetamides with potassium thiocyanide by cyclization. The starting material *p*-substituted-thiazol-2-yl-chloroacetamides were synthesized from *p*-substituted-thiazol-2-yl-amines with chloroacetyl chloride, which in turn was prepared from one pot reaction of substituted aryl acetophenone and amino group of thiourea. The title compounds were investigated for their anticonvulsant activity. Among the tested compounds, compound 3-(4-(4-fluorophenyl)thiazol-2-yl)-2-iminothiazolidin-4-one (**16**) emerged as the most active compound of the series, and it is moderately more potent than the reference standard diazepam.

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INTRODUCTION

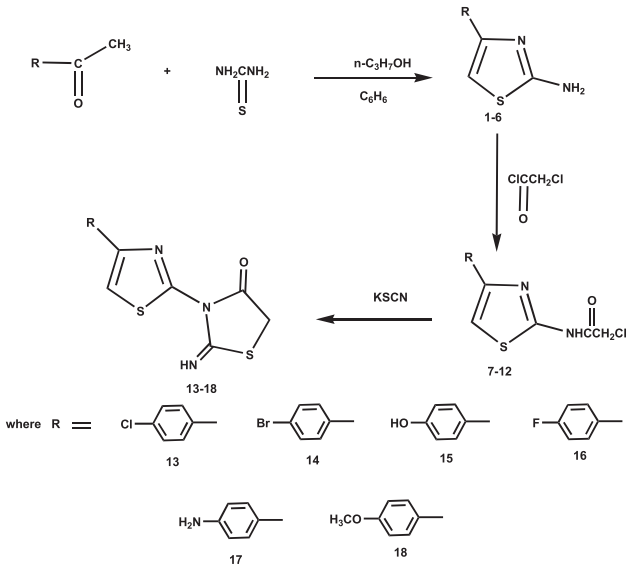
Epilepsy is a disorder characterized by paroxysmal, excessive, and hypersynchronous discharges of large numbers of neurons and affects at least 50 million people worldwide [1]. Epilepsy is the second most common chronic neurological condition reported by neurologists [2,3]. Despite the optimal use of available antiepileptic drugs (AEDs), many patients with epilepsy fail to experience seizure control and others do so only at the expense of significant toxic side effects [4]. The limitations with the conventional AEDs highlighted the need for developing newer agents for epilepsies, and therefore new, less toxic, and more effective drugs are required [5,6].

As a part of our ongoing new drug development program of AED, 3-substituted-2-iminothiazolidin-4-ones have been explored as possible anticonvulsant agents. Thiazolidin-4-ones belong to an important class of heterocyclic compound containing sulfur and nitrogen atom and received much attention of medicinal chemists because of their potential biological activities [7,8]. Thiazolidin-4-ones with 2,3-substitution are reported to possess significant hypoglycemic, anti-inflammatory, cholerectic, anti-HIV, diuretic, immunosuppresant, antipsychotic, and anticonvulsant activities [9–17]. Among the biological activities exhibited by thiazolidinones, the anticonvulsant activities of 3-substituted-2-iminothiazolidinones are interesting. Prompted by these reports of thiazolidinone derivatives as potent anticonvulsant agents, we aimed at preparing a series of 3-substituted thiazolyl-2-iminothiazolidin-4-one derivatives for their anticonvulsant potential.

RESULTS AND DISCUSSION

Chemistry. The synthetic route depicted in Scheme 1 outline the chemistry part of the present work. The key intermediate *p*-substituted-thiazol-2-amines **1–6** were obtained from the cyclocondensation of thiourea and *p*-substituted aryl acetophenones in the presence of *n*-propanol. The compounds **1–6** were then chlorinated by chloroacetyl chloride with vigorous shaking and refluxing to afford **7–12**. The compounds **7–12** were then reacted with potassium thiocyanide in acetone to afford the title compounds 3-substituted-thiazolyl-2-iminothiazolidin-4-ones **13–18**. The desired products were obtained in good and excellent yield and purity. The structures of all the new compounds were confirmed by IR spectra, which shows an intense peak in the region of 3600–3500 cm^{-1} for hydroxy (OH) stretching, intense peak in the region of 3400–3200 cm^{-1} for amino group (NH) stretching, 1690–1730 cm^{-1} for carbonyl group (CO), peaks in the region of 1150–1000 $cm^{-1}$for C—F stretching, 750–800 cm^{-1} for C—Br stretching, and 700–750 cm^{-1} for C—Cl stretching, respectively. The ^{1}H-NMR spectra of 3-substituted-thiazolyl-2-iminothiazolidin-4-ones (**1–18**)

Scheme 1. Synthesis of 3-substituted-thiazolyl-2-iminothiazolidin-4-ones.



show a multiplet in the range of δ 6.80–8.35 ppm owing to aromatic protons. A singlet shows at δ 2.30–2.80, 3.30–3.80, 4.00–5.00, and 9.90–11.0 ppm because of CH_2, CH_3, NH_2, and NH groups, respectively. Further elemental analysis and molecular ion recorded in the mass spectra confirmed the assigned structures and confirmed their purity.

Pharmacology. All the synthesized compounds were evaluated for their antiepileptic effects using male albino mice (Swiss, 18–25 g). The primary qualitative evaluations were performed in mice by maximal electroshock (MES) seizure test. Acute neurological toxicity induced by the compounds in mice was assessed through standardized rotorod test. In the initial screening, candidate compounds were screened for their antiepileptic potential through MES models in mice at a dose level of 20, 40, 60, 80, and 100 mg/kg by intraperitoneal route, and the groups of mice are tested at 1 h post administration of the test candidate. Compounds found to be active in these seizure challenges are generally regarded to be significantly useful candidates in treatment of partial, generalized, and even absence seizures. The data regarding the antiepileptic screening of all the compounds are reported in Table 1.

All the synthesized compounds were evaluated for anticonvulsant activity and have shown promising anticonvulsant activities. All the tested compounds showed protection against MES test indicative of their ability to inhibit the seizure spread. From the biological activity data reported in Table 1, it may be inferred that the anticonvulsant activity is strongly dependent on the nature of the substituent at *N*-3 of the thiazolidinone ring. Compounds **13**, **16**, **17**, and **18** showed significant protection against the MES models at 20 g/kg after 1 h. In particular, a high level of activity was observed for compounds (**13**, **16**, and **17)** possessing *para* chloro, fluoro, and amino phenyl moieties at *N*-3. When *para* chloro, fluoro, and amino phenyl moieties were replaced by bromo, hydroxyl, and methoxy phenyl substituents **14**, **15**, and **18**, the anticonvulsant activity was altered and has exhibited less significant effect. In addition, key intermediate *p*-substituted-thiazol-2-amines **1–6** were found to exhibit less anticonvulsant activity than the title compounds **13–18** and reference diazepam.

The anticonvulsion activity was enhanced by introducing *para* chloro, fluoro, and amino phenyl moieties (**13**, **16**, and **17**) at *N*-3 position. Among the test compounds, compound 3-(4-(4-fluorophenyl)-thiazol-2-yl)-2-iminothiazolidin-4-one **16** emerged as the most active compound (62.67%) of the series and moderately more potent than the reference standard diazepam.

Table 1

Anticonvulsant activity (duration in seconds) of compounds **1–6** and **13–18**.

Compound no.	Flexion	Extension	Convulsion	Stupor	Death	% Protection
Control	3.86 ± 0.30	22.16 ± 2.63	10.52 ± 1.04	87.07 ± 4.90	2/6	—
Standard	1.74 ± 0.25	2.23 ± 0.28	3.45 ± 0.61*	69.98 ± 5.32	0/6	57.91
1	2.92 ± 0.55*	5.23 ± 1.43*	9.25 ± 1.50*	68.20 ± 8.65 *	0/6	31.60
2	2.84 ± 0.58 **	5.41 ± 1.29*	9.15 ± 1.76*	68.53 ± 7.73 (ns)	0/6	31.82
3	2.95 ± 0.85*	4.61 ± 0.55*	7.53 ± 1.04*	73.20 ± 2.55**	0/6	34.34
4	2.86 ± 0.48**	3.51 ± 0.28**	4.85 ± 0.99**	70.37 ± 7.55**	0/6	44.22
5	2.88 ± 0.65*	3.78 ± 0.32**	4.86 ± 0.98**	72.37 ± 2.77**	0/6	43.20
6	2.59 ± 0.49*	2.26 ± 1.32**	8.12 ± 1.66*	71.17 ± 8.34 *	0/6	40.42
13	1.76 ± 0.25**	2.13 ± 0.12***	2.23 ± 0.26***	74.00 ± 6.71 ***	0/6	59.55
14	2.99 ± 0.33*	3.05 ± 0.32*	4.38 ± 0.45**	84.08 ± 3.92*	0/6	42.63
15	2.85 ± 0.38*	2.53 ± 0.39**	4.55 ± 0.38**	77.93 ± 3.49*	0/6	45.51
16	1.53 ± 0.28***	1.78 ± 0.23***	2.41 ± 0.49***	68.53 ± 5.29***	0/6	62.67
17	2.21 ± 0.24**	2.74 ± 0.45**	2.81 ± 0.42***	80.77 ± 3.44**	0/6	52.72
18	2.47 ± 0.25*	2.20 ± 0.32**	2.68 ± 0.64**	81.58 ± 4.47 *	0/6	51.72

All values are expressed as mean ± SEM ($n = 6$). ns indicates not significant; values are significantly different from the control group.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ versus control (one-way ANOVA followed by Dunnett's test).

CONCLUSION

In summary, synthesis of 3-substituted-thiazol-2-yl-2-iminothiazolidin-4-ones **1–18** by nucleophilic substitution of *p*-substituted-thiazol-2-yl-chloroacetamides with potassium thiocyanide has been described. All the compounds were tested for their anticonvulsant activity by MES method in mice. The title compounds have exhibited promising anticonvulsant activity. Among the series, compound 3-(4-(4-fluorophenyl) thiazol-2-yl)-2-iminothiazolidin-4-one (**16**) emerged as the most active compound of the series, and it was found moderately more potent than the reference compound diazepam.

EXPERIMENTAL

Chemistry. Melting points (mp) were taken in open capillaries on Thomas Hoover melting point apparatus (Thomas Hoover, Philadelphia, PA) and are uncorrected. The IR spectra were recorded in film or in potassium bromide disks on a Perkin-Elmer 398 spectrometer (Bio Engineering, Wald, Switzerland). The ^{1}H NMR spectra were recorded on a DPX-300 MHz Bruker FT-NMR spectrometer (Pacific Northwest, Richland, Washington, USA). The chemical shifts were reported as parts per million (δ ppm) tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a JEOL-SX-102 instrument (maspec, Tokyo, Japan) using fast atom bombardment (FAB positive). Elemental analysis was performed on a Perkin-Elmer 2400 CHN analyzer (Bio Engineering). and values were within the acceptable limits of the calculated values (± 0.4%). Spectral data (IR, NMR and mass spectra) confirmed the structures of the synthesized compounds; the purity of these compounds was ascertained by microanalysis. Elemental (C, H, N) analysis indicated that the calculated and observed values were within the acceptable limits (± 0.4%). The progress of the reaction was monitored on readymade silica gel plates (Merck Whitehouse Station, NJ) using chloroform/methanol (9:1) as a solvent system. Iodine was used as a developing agent. All chemicals and reagents used in the synthesis were obtained from Aldrich (Sigma-Aldrich, Spruce St. St. Louis, MO), or Spectrochem Pvt.Ltd (Mumbai, India) and were used without further purification.

General procedure for synthesis of 4-substituted-thiazol-2-amines (1–6). A solution of *p*-substituted acetophenone (0.01 mol) in *n*-propanol (35 mL) and appropriate amine (2.3 g, 0.01 mol) were taken in a 100-mL round bottom flask and refluxed for 2 h. The solution was added to pyridine (5 mL) drop by drop with vigorous stirring and refluxed for 5 h. The solution was evaporated to dryness and treated with 5% sodium bicarbonate solution. The solid obtained was filtered, washed with water, and dried. The residue was recrystallized with methanol.

Synthesis of 4-(4-chlorophenyl)-thiazol-2-amine (1). Yield 69%, mp 255–257°C; IR (KBr, cm^{-1}): 3358 (NH_2), 3082 (Ar—CH), 730 (C—Cl). ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.21 (s, 2H, NH_2), 6.61 (s, 1H, CH), 7.33–7.35 (d, J = 7.5 Hz, 2H, Ar—H), 7.53–7.55 (d, J = 8.0 Hz, 2H, Ar—H). MS (*m/z*): 210 [M$^+$]. *Anal*. Calcd for C_9H_7 ClN_2S: C, 51.31; H, 3.35; N, 13.29. Found: C, 51.51; H, 3.34; N, 13.24.

Synthesis of 4-(4-bromophenyl)-thiazol-2-amine (2). Yield 62%, mp 185–187°C; IR (KBr, cm^{-1}): 3386 (NH_2), 3068 (Ar—CH), 638 (C—Br). ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.42 (s, 2H, NH_2), 6.64 (s, 1H, CH), 7.37–7.39 (d, J = 7.5 Hz, 2H, Ar—H), 7.49–7.51 (d, J = 7.0 Hz, 2H, Ar—H). MS (*m/z*): 255 [M$^+$]. *Anal*. Calcd for C_9H_7 BrN_2S: C, 42.37; H, 2.77; N, 10.98. Found: C, 42.53; H, 2.76; N, 10.93

Synthesis of 4-(4-hydroxyphenyl)-thiazol-2-amine (3). Yield 70%, mp 172–174°C; IR (KBr, cm^{-1}): 3504 (OH), 3365 (NH_2), 3052 (Ar—CH). ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.16 (s, 2H, NH_2), 6.67 (s, 1H, CH), 6.79–6.81 (d, J = 8.0 Hz, 2H, Ar—H), 7.31–7.33 (d, J = 7.5 Hz, 2H, Ar—H), 11.21 (brs, 1H, OH). MS (*m/z*): 192 [M$^+$]. *Anal*. Calcd for C_9H_8 N_2 OS: C, 56.22; H, 4.19; N, 14.57. Found: C, 56.00; H, 4.20; N, 14.62.

Synthesis of 4-(4-fluorophenyl)-thiazol-2-amine (4). Yield 68%, mp 220–222°C; IR (KBr, cm^{-1}): 3383 (NH_2), 3084 (Ar—CH), 1045 (C—F). ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.32 (s, 2H, NH_2), 6.68 (s, 1H, CH), 7.03 (d, J = 7.5 Hz, 2H, Ar—H), 7.46 (d, J = 8.0 Hz, 2H, Ar—H); MS (*m/z*): 194 [M$^+$]. *Anal*. Calcd for C_9H_7 FN_2 S: C, 55.65; H, 3.63; N, 14.42. Found: C, 55.87; H, 3.62; N, 14.36.

Synthesis of 4-(4-aminophenyl)-thiazol-2-amine (5). Yield 72%, mp 232–234°C; IR (KBr, cm^{-1}): 3256 and 3374 (NH_2), 3053 (Ar—CH). ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.14 (s, 2H, NH_2), 4.46 (s, 2H, NH_2), 6.62 (s, 1H, CH), 6.52 (d, J = 8.0 Hz, 2H, Ar—H), 7.23 (d, J = 7.5 Hz, 2H, Ar—H). MS (*m/z*): 191 [M$^+$]. *Anal*. Calcd for C_9H_9 N_3 S: C, 56.52; H, 4.74; N, 21.97. Found: C, 56.74; H, 4.72; N, 21.88.

Synthesis of 4-(4-methoxyphenyl)-thiazol-2-amine (6). Yield 62%, mp 248–250°C; IR (KBr, cm^{-1}): 3325 (NH_2), 3064 (Ar—CH), 2816 (OCH_3). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.73 (s, 3H, OCH_3), 4.46 (s, 2H, NH_2), 6.65 (s, 1H, CH), 6.83 (d, J = 7.5 Hz, 2H, Ar—H), 7.37 (d, J = 7.5 Hz, 2H, Ar—H). MS (*m/z*): 206 [M$^+$]. *Anal*. Calcd for $C_{10}H_{10}$ N_2 O S: C, 58.23; H, 4.89; N, 13.58. Found: C, 58.46; H, 4.87; N, 13.53.

General procedure for synthesis of 4-substituted-thiazol-2-yl-chloroacetamides (7–12). A solution of 4-substituted-thiazol-2-amines (**1–6**) (0.01 mol) in dry benzene (65 mL) and chloroacetylchloride (5 mL) (0.01 mol) were taken in a 100-mL round bottom flask. The solution was stirred vigorously and refluxed for 3 h. After completion of the reaction, the solution was evaporated to dryness. The solid obtained was treated with 5% sodium bicarbonate and washed with water. The residue obtained was filtered and dried. The solid mass was recrystallized with methanol.

Synthesis of N-4-(4-chlorophenyl)-thiazol-2-yl-chloroacetamide (7). Yield 65%, mp 204–206°C; IR (KBr, cm^{-1}): 3431 (NH), 3056 (Ar—CH), 2915 (CH_2), 1705 (C═O), 736 (CH_2—Cl). ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.27 (s, 2H, CH_2), 6.64 (s, 1H, CH), 7.33 (d, J = 7.5 Hz, 2H, Ar—H), 7.42 (d, J = 8.0 Hz, 2H, Ar—H), 8.20 (br s, 1H, NH). MS (*m/z*): 287 [M^+]. *Anal*. Calcd for $C_{11}H_8$ Cl_2N_2 OS: C, 46.01; H, 2.81; N, 9.76. Found: C, 46.19; H, 2.80; N, 9.72.

Synthesis of N-4-(4-bromophenyl)-thiazol-2-yl-chloroacetamide (8). Yield 58%, mp 178–180°C; IR (KBr, cm^{-1}): 3412 (NH), 3073 (Ar—CH), 2933 (CH_2), 1712 (C═O), 622 (C—Br), 745 (CH_2—Cl). ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.21 (s, 2H, CH_2), 6.60 (s, 1H, CH), 7.37 (d, J = 7.5 Hz, 2H, Ar—H), 7.49 (d, J = 8.0 Hz, 2H, Ar—H), 8.03 (br s, 1H, NH). MS (*m/z*): 331 [M^+]. *Anal*. Calcd for $C_{11}H_8$ BrClN$_2$OS: C, 39.84; H, 2.43; N, 8.45. Found: C, 39.68; H, 2.44; N, 8.48.

Synthesis of N-4-(4-hydroxyphenyl)-thiazol-2-yl-chloroacetamide (9). Yield 66%, mp 196–198°C; IR (KBr, cm^{-1}): 3510 (OH), 3423 (NH), 3073 (Ar—CH), 2953 (CH_2), 1708 (C═O), 728 (CH_2—Cl). ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.28 (s, 2H, CH_2), 5.02 (s, 1H, Ar—OH), 6.62 (s, 1H, CH), 6.79 (d, J = 7.5 Hz, 2H, Ar—H), 7.31 (d, J = 7.5 Hz, 2H, Ar—H), 8.16 (br s, 1H, NH). MS (*m/z*): 268 [M^+]. *Anal*. Calcd for $C_{11}H_9$ ClN$_2$O$_2$S: C, 49.17; H, 3.38; N, 10.42. Found: C, 49.36; H, 3.37; N, 10.38.

Synthesis of N-4-(4-fluorophenyl)-thiazol-2-yl-chloroacetamide (10). Yield 71%, mp 205–207°C; IR (KBr, cm^{-1}): 3419 (NH), 3056 (Ar—CH), 2912 (CH_2), 1708 (C═O), 1056 (C—F), 720 (CH_2—Cl). ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.25 (s, 2H, CH_2), 6.62 (s, 1H, CH), 7.03 (d, J = 8.0 Hz, 2H, Ar—H), 7.46 (d, J = 8.0 Hz, 2H, Ar—H), 8.06 (br s, 1H, NH). MS (*m/z*): 270 [M^+]. *Anal*. Calcd for $C_{11}H_8$ Cl FN_2 OS: C, 48.80; H, 2.98; N, 10.35. Found: C, 48.99; H, 2.97; N, 10.31.

Synthesis of N-4-(4-aminophenyl)-thiazol-2-yl-chloroacetamide (11). Yield 72%, mp 232–234°C; IR (KBr, cm^{-1}): 3416 (NH), 3248 (NH_2), 3052 (Ar—CH), 2920 (CH_2), 1710 (C═O), 722 (CH_2—Cl). ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.00 (s, 2H, NH_2), 4.27 (s, 2H, CH_2), 6.63 (s, 1H, CH), 6.52 (d, J = 7.5 Hz, 2H, Ar—H), 7.23 (d, J = 8.0 Hz, 2H, Ar—H), 8.06 (br s, 1H, NH). MS (*m/z*): 267 [M^+]. *Anal*. Calcd for $C_{11}H_{10}$ ClN$_3$O S: C, 49.35; H, 3.76; N, 15.69. Found: C, 49.15; H, 3.78; N, 15.75.

Synthesis of N-4-(4-methoxyphenyl)-thiazol-2-yl-chloroacetamide (12). Yield 69%, mp 212–214°C; IR (KBr, cm^{-1}): 3420 (NH), 3048 (Ar—CH), 2916 (CH_2), 2820 (OCH_3), 1706 (C═O), 730 (CH_2-Cl). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.73 (s, 3H, OCH_3), 4.27 (s, 2H, CH_2), 6.64 (s, 1H, CH), 6.83 (d, J = 7.5 Hz, 2H, Ar—H), 7.37 (d, J = 7.5 Hz, 2H, Ar—H), 8.04 (br s, 1H, NH). MS (*m/z*): 282 [M^+]. *Anal*. Calcd for $C_{12}H_{11}$ Cl N_2 O_2 S: C, 50.97; H, 3.92; N, 9.91. Found: C, 51.17; H, 3.90; N, 9.87.

General procedure for synthesis of 3-substituted-thiazolyl-2-iminothiazolidin-4-ones (13–18). A solution of 4-substituted-thiazol-2-yl-chloroacetamides (**7–12**) (0.01 mol) in acetone (50 mL) and potassium thiocyanide (0.6 g, 0.01 mol) were taken in a 100-mL round bottom flask. The solution was stirred vigorously and reflux for 3 h. After the completion of the reaction, the solution was evaporated to dryness. The solid obtained was washed with water and dried. The residue was recrystallized with methanol.

Synthesis of 3-(4-(4-chlorophenyl)-thiazol-2-yl)-2-iminothiazolidin-4-one (13). Yield 63%, mp 186–188°C; IR (KBr, cm^{-1}): 3425 (NH), 3057 (Ar—CH), 1626 (C═NH), 1715 (C═O), 735 (C—Cl). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.76 (s, 2H, CH_2), 6.65 (s, 2H, CH), 7.33–7.42 (d, 4H, Ar—H), 10.5 (br s, 1H, NH). MS (*m/z*): 309 [M^+]. *Anal*. Calcd for $C_{12}H_8$ ClN_3 OS_2: C, 46.52; H, 2.60; N, 13.56. Found: C, 46.70; H, 2.59; N, 13.51.

Synthesis of 3-(4-(4-bromophenyl)-thiazol-2-yl)-2-iminothiazolidin-4-one (14). Yield 70%, mp 153–155°C; IR (KBr, cm^{-1}): 3436 (NH), 3042 (Ar—CH), 1620 (C═NH), 1712 (C═O), 648 (C—Br). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.74 (s, 2H, CH_2), 6.62 (s, 1H, CH), 7.37 (d, J = 8.0 Hz, 2H, Ar—H), 7.49 (d, J = 8.0 Hz, 2H, Ar—H), 10.8 (br s, 1H, NH). MS (*m/z*): 354 [M^+]. *Anal*. Calcd for $C_{12}H_8$ BrN_3OS_2: C, 40.69; H, 2.28; N, 11.86. Found: C, 40.85; H, 2.27; N, 11.82.

Synthesis of 3-(4-(4-hydroxyphenyl)-thiazol-2-yl)-2-iminothiazolidin-4-one (15). Yield 72%, mp 166–168°C; IR (KBr, cm^{-1}): 3526(OH), 3412 (NH), 3053 (Ar—CH), 1612 (C═NH), 1696 (C═O). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.76 (s, 2H, CH_2), 5.08 (s, Ar—OH), 6.67 (s, 1H, CH), 6.79 (d, J = 7.0 Hz, 2H, Ar—H), 7.31 (d, J = 7.5 Hz, 2H, Ar—H), 10.8 (br s, 1H, NH). MS (*m/z*): 291 [M^+]. *Anal*. Calcd for $C_{12}H_9$ $N_3O_2S_2$: C, 49.47; H, 3.11; N, 14.42. Found: C, 49.27; H, 3.12; N, 14.48.

Synthesis of 3-(4-(4-fluorophenyl)-thiazol-2-yl)-2-iminothiazolidin-4-one (16). Yield 68%, mp 226–228°C; IR (KBr, cm^{-1}): 3432 (NH), 3062 (Ar—CH), 1619 (C═NH), 1705 (C═O), 1049 (C—F). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.75 (s, 2H, CH_2), 6.68 (s, 1H, CH), 7.03 (d, J = 7.5 Hz, 2H, Ar—H), 7.46 (d, J = 7.5 Hz, 2H, Ar—H), 11.0 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 24.51, 97.89, 114.58, 127.25, 128.53, 146.25, 159.53, 161.39, 170.89, 172.54; MS (*m/z*): 293 [M^+]. *Anal*. Calcd for $C_{12}H_8$ FN_3 OS_2: C, 49.13; H, 2.75; N, 14.32. Found: C, 49.32; H, 2.74; N, 14.26.

Synthesis of 3-(4-(4-aminophenyl)-thiazol-2-yl)-2-iminothiazolidin-4-one (17). Yield 70%, mp 257–259°C; IR (KBr, cm^{-1}): 3456 (NH), 3291 and 3246 (NH_2), 3042 (Ar—CH), 1614 (C═NH), 1710 (C═O), ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.78 (s, 2H, CH_2), 4.08 (s, 2H, NH_2), 6.65 (s, 1H, CH), 6.52 (d, J = 8.0 Hz, 2H, Ar—H), 7.23 (d, J = 8.0 Hz, 2H, Ar—H), 10.3 (br s, 1H, NH). MS (*m/z*): 267 [M^+]. *Anal*. Calcd for $C_{12}H_{10}$ N_4O S_2: C, 49.64; H, 3.47; N, 19.30. Found: C, 49.83; H, 3.46; N, 19.22.

Synthesis of 3-(4-(4-methoxyphenyl)-thiazol-2-yl)-2-iminothiazolidin-4-one (18). Yield 72%, mp 242–244°C; IR (KBr, cm^{-1}): 3422 (NH), 3052 (Ar—CH), 2818 (OCH_3), 1716 (C═O), 1616 (C═NH). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.73 (s, 3H, OCH_3), 3.76 (s, 2H, CH_2), 6.68 (s, 1H, CH), 6.83 (d, J = 8.0 Hz, 2H, Ar—H), 7.37 (d, J = 7.5 Hz, 2H, Ar—H), 10.6 (br s, 1H, NH). MS (*m/z*): 282 [M^+]. *Anal*. Calcd for

$C_{13}H_{11}N_3O_2S_2$: C, 51.13; H, 3.63; N, 13.76. Found: C, 50.92; H, 3.65; N, 13.82.

PHARMACOLOGICAL ACTIVITY

Acute toxicity studies. Acute toxicity study was performed for all the synthesized compounds to ascertain safe dose by acute oral toxic class method of Organization of Economic Co-operation and Development, as per 423 guidelines (OECD). All the compounds tested for acute toxicity studies were also observed for gross behavioral changes in mice, continuously for 5 h at 1-h interval after administration of the compounds. Thereafter, the observations were recorded intermittently for 24 h and compared with that of the control group. In the behavioral profile, the animals have been observed for changes in their awareness and mood.

Anticonvulsant activity. The newly synthesized compounds were screened for their anticonvulsant activity by the MES-induced seizures method [16,17], wherein electroshock was applied via earclip electrodes using diazepam as a reference drug. Albino mice (purchased from the Agricultural University, Manuthy, Kerala) weighing 20–25 g were kept under hygienic conditions and on standard laboratory diet, and water was provided *ad libitum*. Mice were divided into groups of six animals each. The test groups received the tested compounds intraperitoneally at a dose of 10 mg/kg body weight. The standard group received diazepam in a dose of 10 mg/kg. One hour after the injection, electroshock was applied via earclip electrodes and generated by a stimulator (Ugo Basile ECT Unit, Pulse generator 57800-001, delivering an alternating 50-Hz current); the stimulus duration was 0.2 s, and the end point was tonic hind limb extension. The maximum electroshock was determined. The % protection as well as % potency was calculated according to the following equations:

$$\%\,\text{Protection of a compound} = \frac{(\text{MCT of the compound} - \text{MCT of the control})}{\text{MCT of the control}} \times 100$$

$$\%\,\text{Protection of a compound} = \frac{\text{MCT of the compound}}{\text{MCT of the reference drug}} \times 100$$

where MCT is the mean convulsion threshold. The results are presented in Table 1, which show the mean convulsion threshold and percentage protection for both the newly synthesized compounds and standard Diazepam.

Statistical analysis. All values are expressed as mean ± SEM. Data were analyzed by nonparametric ANOVA followed by Dunnett's multiple comparison tests, and other data were evaluated using GraphPad PRISM software. A p-value <0.05 was considered significantly different.

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