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Synthesis and Evaluation of Anticonvulsant Activity of Some 5,5-Disubstituted-N^3-[(2-aryl thiazolidine-4-one-3-yl)amino]hydantoins

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According to the World Health Organization, the majority of people with epilepsy who live in developing countries do not have access to high-quality treatment. Modern anticonvulsants are in high demand since the unwanted effects of those compounds already in use make therapy difficult. The synthesis of derivatives of 5,5-disubstituted-N^3-[(2-aryl thiazolidine-4-one-3-yl)amino]hydantoins has been reported. The position N3 of the hydantoin nucleus was substituted with 4-thiazolidinone moiety containing aryl substituent at 2nd position with the goal of achieving the enhanced anticonvulsant effect. Compounds **5c**, **5d**, **5l**, **5r** showed significant activity among the evaluated compounds compared to control at dose of 45 mg/kg. The analysis of structural features revealed that the substitution of *p*-hydroxy phenyl and cinnamyl substituted at 2nd position of thiazolidinone ring in 5,5-diphenyl-2,4-imidazolidinedione and *p*-chloro phenyl, *p*-methoxy phenyl substituted at 2nd position of thiazolidinone ring in (5,5-dialkyl)/(5-alkyl-5-substitutedphenyl)-2,4-imidazolidinedione skeleton enhanced the anticonvulsant potentiality of the synthesized compounds.

Keywords: Hydantoins, Anticonvulsant activity, Thiazolidinone, Electroshock induced convulsions.

INTRODUCTION

A common nerve illness called epilepsy is characterized by recurrent seizures brought on by uncontrolled electrostatic initiation in a cluster of brain cells [1,2]. Around 80% of epilepsy sufferers, according to the World Health Organization, reside in underdeveloped nations and the majority of them lack access to quality medication [3]. Hydantoins are cyclic monoacylureas, which make them weaker organic acids than barbiturates as antiepileptic drugs [4]. Every clinically effective drug used to treat generalized tonic-clonic seizures has an aryl substitution at the fifth position [5]. Hydantoins with lower alkyl substituent have anti-absence activity [6]. The neuronal sodium channel blocking in hydantoins causes a decrease in presynaptic glutamic acid release, an increase in the excitability threshold of the motor cortex's neuronal membrane and a shortening of the after discharge period [3]. Additionally, because of their numerous biological functions, such as their anticonvulsant effect, 4-thiazolidinone derivatives have drawn interest over time [7-9].

A thiazolidinone containing drug, Ralitoline's anticonvulsant activity was examined in various animal models and the results supported the substance's strong anticonvulsant effects, particularly against generalized tonic-clonic and complex partial seizures [10-12]. The present course of treatment not only leaves some patients still experiencing seizure activity, but it also remains ineffective and has a long list of side effects including hypnosis, neurotoxicity, depression and tiredness. There is a great demand for cutting-edge anticonvulsants because the adverse side effects of currently utilized anticonvulsants make therapy challenging [13]. Thus, in this article, the synthesis of hydantoins substituted with 4-thiazolidinone at N^3 is carried out in order to produce a library of compounds which may serve as a 'lead' for the creation of anticonvulsant agents.

EXPERIMENTAL

All the chemicals were procured from industrial suppliers. The melting points were taken in one end sealed glass capillary using liquid paraffin in Thiele's tube and are uncorrected. The progress of the reactions were checked by TLC using Merck precoated silica gel 60 F_{254} plates containing *n*-hexane:ethyl acetate (7:3) solvent system. Visualization was done by using iodine chamber or observed under ultraviolet light. Infrared

spectra of compounds were recorded on Shimadzu 1000 FTIR spectrometer in the range of 4000-200 cm^{-1}. Proton and carbon nuclear magnetic resonance (^1H NMR and ^{13}C NMR) spectra were recorded in DMSO-d_6 using Bruker Advance (400 MHz) and chemical shifts were recorded in parts per million (ppm). Mass spectra were recorded on WATERS, Q-TOF MICROMAA. All microwave reactions were carried on a Catalyst System CATA 2R-Scientific Microwave Synthesizer.

Synthesis

Step-1: Synthesis of 3-bromo-5,5-disubstituted imidazolidine-2,4-dione (2a-e): 5,5-Disubstituted imidazolidine-2,4-dione (0.1 mol) (**1a-e**) was suspended in excess of glacial acetic acid followed by the addition of bromine (0.2 mol) dropwise. After the complete addition of bromine, the reaction mixture was irradiated under microwave at 280 Watt for 20 min and poured into ice-cold water and left overnight. The product was filtered and washed with water, dried and then recrystallized from ethanol.

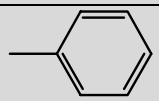
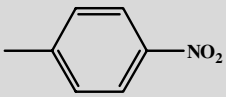
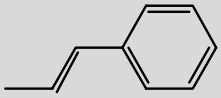
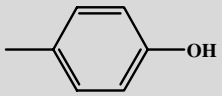
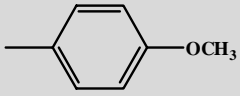
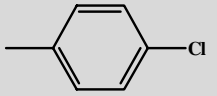
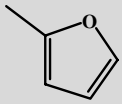
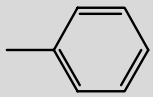
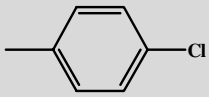
Step-2: Synthesis of 3-hydrazinyl-5,5-disubstituted-imidazolidine-2,4-dione (3a-e): 3-Bromo-5,5-disubstituted-imidazolidone-2,4-dione (0.1 mol) (**2a-e**) and hydrazine hydrate, 99% (0.2 mol) in methanol was irradiated under microwave at 420 Watt for 25 min. The excess of solvent was filtered off and poured into ice-cold water with vigorous stirring. The solid thus obtained was filtered and washed with water, dried and then recrystallized from ethanol.

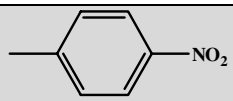
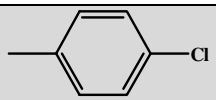
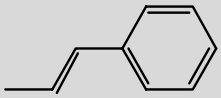
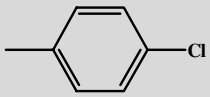
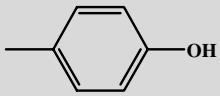
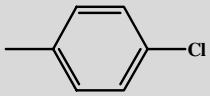
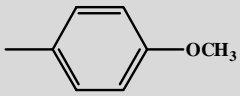
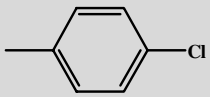
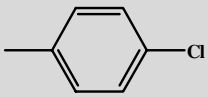
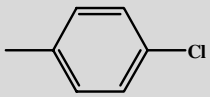
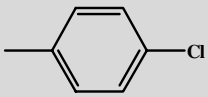
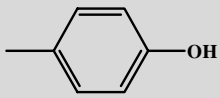
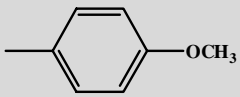
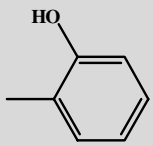
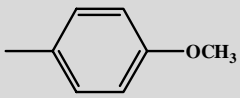
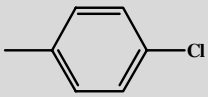
Step-3: Synthesis of 3-(2-(substituted benzylidine)-hydrazinyl)-5,5-disubstituted imidazolidine-2,4-dione derivatives (4a-r): An equimolar mixture of 3-hydrazinyl-5,5-disubstituted-imidazolidone-2,4-dione (**3a-e**), substituted aromatic aldehyde and few drops of glacial acetic acid in methanol was irradiated under microwave at 455 Watt for time as shown in Table-1. The mixture was then poured into ice-cold water with vigorous stirring. The solid thus obtained was filtered and washed with water, dried and recrystallized from ethanol (**Scheme-I**).

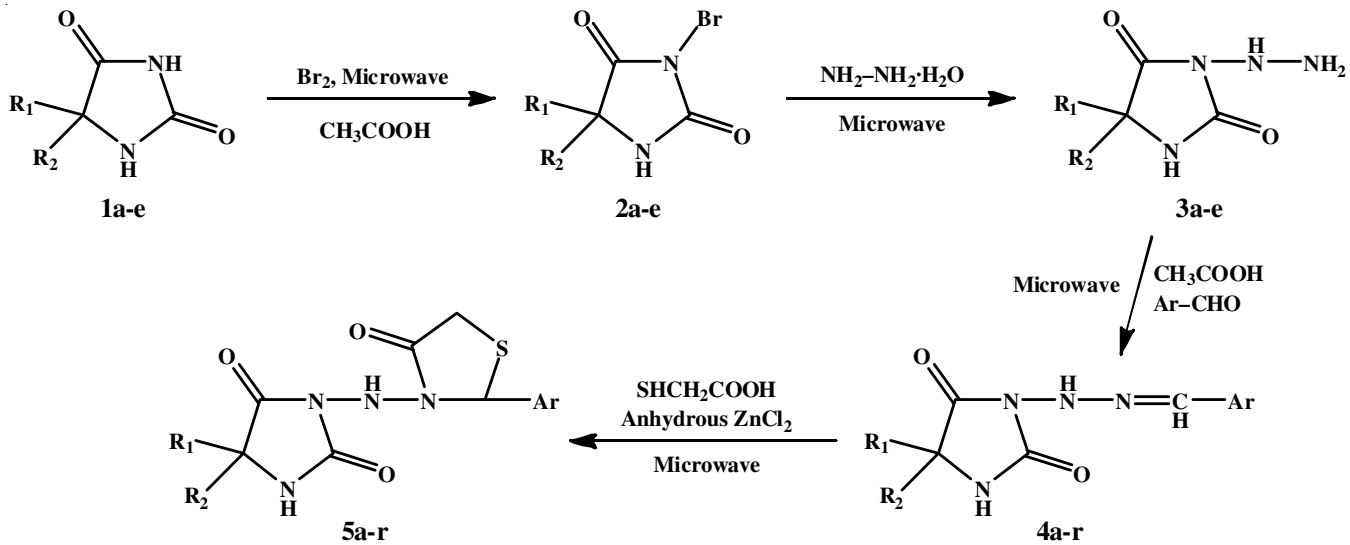
Step-4: Synthesis of 3-[(2-(substituted phenyl)thiazolidine-4-one-3-yl)amino]-5,5-disubstituted-imidazolidone-2,4-dione derivatives (5a-r): An equimolar mixture of 3-(2-(substituted benzylidine)hydrazinyl)-5,5-disubstituted imidazolidine-2,4-dione (**4a-r**), thioglycolic acid and pinch of anhydrous zinc chloride in methanol was irradiated under microwave at 455 Watt for time as shown in Table-1. The mixture was then poured into crushed ice with vigorous stirring. The solid thus obtained was filtered and washed with water, dried and recrystallized from ethanol (**Scheme-I**).

3-[(2-(Phenyl)-thiazolidine-4-one-3-yl)amino]-5,5-diphenylimidazolidine-2,4-dione (5a): White crystalline solid, yield: 67%, *m.f.*: $C_{24}H_{20}N_4O_3S$, *m.w.*: 444, m.p.: 244-246 ºC, R_f: 0.80. IR (KBr, ν_{max}, cm^{-1}): 3479 (-NH), 3072 (Ar-CH), 1660 (-CONH), 1598 (Ar-C=C), 1185 (C-N); ^1H NMR (400 MHz, δ ppm, DMSO-d_6): 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, $-CH_2$), 5.92 (s, 1H, -CH methine), 6.02 (s, 1H, -NH),

TABLE-1
DERIVATIVES OF 3-[(2-(SUBSTITUTED PHENYL)-THIAZOLIDINE-4-ONE-3-YL)AMINO]-5,5-DISUBSTITUTED-IMIDAZOIDONE-2,4-DIONE (**5a-r**)

Compound	Ar	R_1	R_2	Irradiation time (min)	
				Step 3	Step 4
5a		$-C_6H_5$	$-C_6H_5$	21	23
5b		$-C_6H_5$	$-C_6H_5$	25	26
5c		$-C_6H_5$	$-C_6H_5$	27	20
5d		$-C_6H_5$	$-C_6H_5$	20	25
5e		$-C_6H_5$	$-C_6H_5$	22	23
5f		$-C_6H_5$	$-C_6H_5$	25	20
5g		$-C_6H_5$	$-C_6H_5$	23	25
5h		$-CH_3$		22	24

5i		-CH_3		26	25
5j		-CH_3		25	24
5k		-CH_3		22	20
5l		-CH_3		25	28
5m		-CH_3		24	26
5n		-CH_3		25	20
5o		-CH_3	-CH_2CH_3	24	26
5p		-CH_3	-CH_2CH_3	22	24
5q		-CH_3	-CH_3	21	20
5r		-CH_3	-CH_3	22	20



Scheme-I: Synthesis of 3-[(2-(substituted phenyl)-thiazolidine-4-one-3-yl)amino]-5,5-disubstituted-imidazolidone-2,4-dione derivatives

7.06-7.14 (m, 15H, aromatic), ^{13}C NMR (δ_c ppm, DMSO-d_6): 35.7 (s, 1C, CH_2 carbon), 54.5 (s, 1C, CH carbon), 70.1 (s, 1C, C carbon), 126.3-139.9 (m, 18C, aromatic), 154.7 (s, 1C, urea), 168.8 (d, 2C, amide); MS (*m/z*): 445.13.

3-[(2-(4-Nitrophenyl)-thiazolidine-4-one-3-yl)amino]-5,5-diphenylimidazolidine-2,4-dione (5b): Yellow solid, yield: 65%, *m.f.*: $C_{24}H_{19}N_5O_5S$, *m.w.*: 489, m.p.: 182-184 ºC, R_f: 0.80. IR (KBr, ν_{max}, cm^{-1}): 3448 (-NH), 3194 (Ar-CH), 1610

(-CONH), 1570 (Ar-C=C), 1521 (N=O), 1155 (C-N); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, -CH_2), 5.92 (s, 1H, -CH methine), 6.02 (s, 1H, -NH), 7.06-7.32 & 8.07 (m, 14H, aromatic); ^{13}C NMR (δ_c ppm, DMSO-d_6): 35.7 (s, 1C, CH_2 carbon), 54.5 (s, 1C, CH carbon), 70.5 (s, 1C, C carbon), 121.0-146.8 (m, 18C, aromatic), 154.7 (s, 1C, urea), 168.8 (d, 2C, amide); MS (*m/z*): 490.11.

3-[(2-(Cinnamyl)-thiazolidine-4-one-3-yl)amino]-5,5-diphenylimidazolidine-2,4-dione (5c): White solid, yield: 76%, *m.f.*: $C_{27}H_{24}N_4O_3S$, *m.w.*: 484, m.p.: 140-142 ºC, R_f: 0.81. IR (KBr, ν_{max}, cm^{-1}): 3588 (-OH), 3275 (-NH), 3072 (Ar-CH), 1697 (-CONH), 1608 (Ar-C=C), 1195 (C-N); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 2.01 (s, 1H, -NH), 2.42 & 2.67 (m, 2H, -CH_2), 3.28-3.38 (m, 2H, -CH_2), 4.67 (s, 1H, -CH methine), 6.02 (s, 1H, -NH), 6.10 (m, 1H, CH ethylene), 6.41 (d, 1H, CH ethylene), 7.06-7.30 (m, 15H, aromatic); ^{13}C NMR (δ_c ppm, DMSO-d_6): 35.7 (s, 1C, CH_2 carbon), 38.1 (s, 1C, CH_2 carbon), 51.6 (s, 1C, CH carbon), 70.8 (s, 1C, C carbon), 122.5-139.9 (m, 20C, aromatic), 154.7 (s, 1C, urea), 168.5 (d, 1C, amide); MS (*m/z*): 485.16.

3-[(2-(4-Hydroxyphenyl)thiazolidine-4-one-3-yl)-amino]-5,5-diphenylimidazolidine-2,4-dione (5d): Off white solid, yield: 78%, *m.f.*: $C_{24}H_{20}N_4O_4S$, *m.w.*: 460, m.p.: 162-164 ºC, R_f: 0.84. IR (KBr, ν_{max}, cm^{-1}): 3269 (-NH), 3072 (Ar-CH), 1697 (-CONH), 1606 (Ar-C=C), 1238 (C-O), 1193 (C-N); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, -CH_2), 5.00 (s, 1H, -OH), 5.92 (s, 1H, -CH methine), 6.02 (s, 1H, -NH), 6.61-7.14 (m, 14H, aromatic); ^{13}C NMR (δ_c ppm, DMSO-d_6): 35.7 (s, 1C, CH_2 carbon), 54.5 (s, 1C, CH carbon), 70.8 (s, 1C, C carbon), 115.8-139.9 (m, 18C, aromatic), 154.7 (s, 1C, C urea), 168.8 (d, 2C, amide); MS (*m/z*): 461.14.

3-[(2-(4-Methoxyphenyl)thiazolidine-4-one-3-yl)-amino]-5,5-diphenylimidazolidine-2,4-dione (5e): White crystalline solid, yield: 81%, *m.f.*: $C_{25}H_{22}N_4O_4S$, *m.w.*: 474, m.p.: 186-188 ºC, R_f: 0.69. IR (KBr, ν_{max}, cm^{-1}): 3475 (-NH), 3068 (Ar-CH), 1660 (-CONH), 1625 (aliph. -C=C), 1597 (Ar-C=C), 1159 (C-N); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, -CH_2), 3.73 (s, 3H, -OCH_3), 5.92 (s, 1H, -CH methine), 6.02 (s, 1H, -NH), 6.65-7.14 (m, 14H, aromatic); ^{13}C NMR (δ_c ppm, DMSO-d_6): 35.7 (s, 1C, CH_2 carbon), 54.5 (s, 1C, CH carbon), 55.9 (s, 1C, OCH_3 carbon), 70.8 (s, 1C, C carbon), 114.2-159.1 (m, 18C, aromatic), 154.7 (s, 1C, urea), 168.8 (d, 2C, amide); MS (*m/z*): 475.14.

3-[(2-(4-Chlorophenyl)-thiazolidine-4-one-3-yl)amino]-5,5-diphenylimidazolidine-2,4-dione (5f): White solid, yield: 86%, *m.f.*: $C_{24}H_{19}N_4O_3SCl$, *m.w.*: 478, m.p.: 132-134 ºC, R_f: 0.70. IR (KBr, ν_{max}, cm^{-1}): 3444 (-NH), 3072 (Ar-CH), 1660 (-CONH), 1599 (Ar-C=C), 1244 (C-N), 723 (C-Cl); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, -CH_2), 5.92 (s, 1H, -CH methine), 6.02 (s, 1H, -NH), 7.00-7.15 (m, 14H, aromatic); ^{13}C NMR (δ_c ppm, DMSO-d_6): 35.7 (s, 1C, -CH_2), 54.5 (s, 1C,-CH), 70.8 (s, 1C, -C), 126.3-139.9 (m, 18C, aromatic), 154.7 (s, 1C, urea), 168.8 (d, 2C, amide); MS (*m/z*): 480.09.

3-[(2-(Furyl)-thiazolidine-4-one-3-yl)amino]-5,5-diphenylimidazolidine-2,4-dione (5g): Greyish solid, yield: 75%, *m.f.*: $C_{22}H_{18}N_4O_4S$, *m.w.*: 434, m.p.: 176-178 ºC, R_f: 0.77. IR (KBr, ν_{max}, cm^{-1}): 3273 (-NH), 3072 (Ar-CH), 1681 (-CONH), 1598 (Ar-C=C), 1359 (C-N), 1286 (C-O); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, -CH_2), 5.80 (s, 1H, -CH methine), 6.02 (s, 1H, -NH), 6.06-7.28 (m, 13H, aromatic); ^{13}C NMR (δ_c ppm, DMSO-d_6): 33.3 (s, 1C, -CH_2), 54.2 (s, 1C, -CH), 70.6 (s, 1C, -C), 106.7-151.6 (m, 18C, aromatic), 154.7 (s, 1C, urea), 168.8 (d, 2C, amide); MS (*m/z*): 435.10.

3-[(2-(Phenyl)-thiazolidine-4-one-3-yl)amino]-5-methyl-5-(4-chlorophenyl)imidazolidine-2,4-dione (5h): White solid, yield: 66%, *m.f.*: $C_{19}H_{17}N_4O_3SCl$, *m.w.*: 416, m.p.: 138-140 ºC, R_f: 0.81. IR (KBr, ν_{max}, cm^{-1}): 3207 (-NH), 3132 (Ar-CH), 1614 (-CONH), 1573 (Ar-C=C), 1371 (C-N), 650 (C-Cl); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 1.86 (s, 3H, -CH_3), 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, -CH_2), 5.92 (s, 1H, -CH methine), 6.02 (s, 1H, -NH), 7.06-7.22 (m, 9H, aromatic); ^{13}C NMR (δ_c ppm, DMSO-d_6): 25.9 (s, 1C, -CH_3), 35.7 (s, 1C,-CH_2), 54.5 (s, 1C, -CH), 66.3 (s, 1C,-C), 126.3-139.2 (m, 12C, aromatic), 154.7 (s, 1C, urea), 168.8 (s, 1C, amide), 172.8 (s, 1C, amide); MS (*m/z*): 418.07.

3-[(2-(4-Nitrophenyl)-thiazolidine-4-one-3-yl)amino]-5-methyl-5-(4-chlorophenyl)-imidazolidine-2,4-dione (5i): Yellow solid, yield: 68%, *m.f.*: $C_{19}H_{16}N_5O_5SCl$, *m.w.*: 461, m.p.: 124-126 ºC, R_f: 0.77. IR (KBr, ν_{max}, cm^{-1}): 3383 (-NH), 3068 (Ar-CH), 1614 (-CONH), 1573 (Ar-C=C), 1359 (N=O), 1230 (C-N), 766 (C-Cl); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 1.86 (s, 3H, -CH_3), 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, -CH_2), 5.92 (s, 1H, -CH methine), 6.02 (s, 1H, -NH), 7.06-8.07 (m, 8H, aromatic); ^{13}C NMR (δ_c ppm, DMSO-d_6): 25.9 (s, 1C, -CH_3), 35.7 (s, 1C,-CH_2), 54.5 (s, 1C, -CH), 66.3 (s, 1C, -C), 121.0-145.3 (m, 12C, aromatic), 154.7 (s, 1C, urea), 168.8 (s, 1C, amide), 172.8 (s, 1C, amide); MS (*m/z*): 463.05.

3-[(2-(Cinnamyl)-thiazolidine-4-one-3-yl)amino]-5-methyl-5-(4-chlorophenyl)-imidazolidine-2,4-dione (5j): off white solid, yield: 65%, *m.f.*: $C_{22}H_{21}N_4O_3SCl$, *m.w.*: 456, m.p.: 140-142 ºC, R_f: 0.77. IR (KBr, ν_{max}, cm^{-1}): 3479 (-NH), 3072 (Ar-CH), 1660 (-CONH), 1598 (Ar-C=C), 1185 (C-N); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 1.86 (s, 3H, -CH_3), 2.01 (s, 1H, -NH), 2.42 & 2.67 (m, 2H, -CH_2), 3.28-3.38 (m, 2H, -CH_2), 4.67 (s, 1H, -CH methine), 6.02 (s, 1H, -NH), 6.10 (m, 1H, -CH ethylene), 6.41 (d, 1H, -CH ethylene), 7.06-7.30 (m, 9H, arom.); ^{13}C NMR (δ_c ppm, DMSO-d_6): 25.9 (s, 1C, -CH_3), 36.2 (s, 1C, -CH_2), 38.1 (s, 1C, -CH_2) 51.5 (s, 1C, -CH), 66.3 (s, 1C,-C), 126.4-138.8 (m, 14C, aromatic), 154.7 (s, 1C, urea), 168.5 (s, 1C, amide), 172.8 (s, 1C, amide); MS (*m/z*): 458.10.

3-[(2-(4-Hydroxyphenyl)-thiazolidine-4-one-3-yl)-amino]-5-methyl-5-(4-chlorophenyl)-imidazolidine-2,4-dione (5k): White solid, yield: 76%, *m.f.*: $C_{19}H_{17}N_4O_4SCl$, *m.w.*: 432, m.p.: 80-82 ºC, R_f: 0.78. IR (KBr, ν_{max}, cm^{-1}): 3583 (-OH), 3417 (-NH), 3070 (Ar-CH), 2921 (aliph. -CH), 1606 (-CONH), 1573 (Ar-C=C), 1170 (C-N); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 1.86 (s, 3H, CH_3 protons), 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, -CH_2), 5.00 (s, 1H, -OH), 5.92 (s, 1H, -CH methine), 6.02 (s, 1H, -NH), 6.61-7.14 (m, 9H, aromatic); ^{13}C NMR (δ_c ppm, DMSO-d_6): 25.9 (s, 1C, -CH_3), 35.7 (s, 1C, -CH_2), 54.5 (s, 1C, -CH), 66.3 (s, 1C, -C), 115.8-156.9 (m, 12C, aromatic), 154.7 (s, 1C, urea), 168.8 (s, 1C, amide), 172.8 (s, 1C, amide); MS (*m/z*): 434.06.

3-[(2-(4-Methoxyphenyl)thiazolidine-4-one-3-yl)amino]-5-methyl-5-(4-chlorophenyl)imidazolidine-2,4-dione (5l): Off white, yield: 80%, *m.f.*: $C_{20}H_{19}N_4O_4SCl$, *m.w.*: 446, m.p. : 108-110 ºC, R_f: 0.79. IR (KBr, ν_{max}, cm^{-1}): 3477 (-NH), 3128 (Ar-CH), 1645 (-CONH), 1593 (Ar-C=C), 1251 (C-N); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 1.86 (s, 3H, -CH_3), 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, -CH_2), 3.73 (s, 3H, -OCH_3) 5.92 (s, 1H, -CH methine), 6.02 (s, 1H, -NH), 6.65-7.14 (m, 8H, arom.), ^{13}C NMR (δ_c ppm, DMSO-d_6): 25.9 (s, 1C, -CH_3), 35.7 (s, 1C, -CH_2), 54.5 (s, 1C, -CH), 55.9 (s, 1C, -CH_3), 66.3 (s, 1C, -C), 114.2-145.1 (m, 12C, aromatic), 154.7 (s, 1C, urea), 168.8 (s, 1C, amide), 172.8 (s, 1C, amide); MS (*m/z*): 448.07.

3-(2-(4-Chlorophenyl)thiazolidin-4-one-3-ylamino)-5-methyl-5-(4-chlorophenyl)imidzolidine-2,4-dione (5m): white crystalline, yield: 86%, *m.f.*: $C_{19}H_{16}N_4O_3SCl_2$, *m.w.*: 450, m.p.: 170-172 ºC, R_f: 0.80. IR (KBr, ν_{max}, cm^{-1}): 3207 (-NH), 3070 (Ar-CH), 2943 (aliph. CH), 1654 (-CONH), 1587 (Ar-C=C), 1168 (C-N), 650 (C-Cl); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 1.86 (s, 3H, CH_3 protons), 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, -CH_2), 5.92 (s, 1H, -CH methine), 6.02 (s, 1H, -NH), 7.00-7.22 (m, 8H, aromatic); ^{13}C NMR (δ_c ppm, DMSO-d_6): 25.9 (s, 1C, -CH_3), 35.7 (s, 1C,-CH_2), 54.5 (s, 1C, -CH), 66.3 (s, 1C,-C), 128.2-138.8 (m, 12C, aromatic), 154.7 (s, 1C, urea), 168.8 (s, 1C, amide), 172.8 (s, 1C, amide); MS (*m/z*): 452.03.

3-[(2-(4-Chlorophenyl)-thiazolidine-4-one-3-yl)amino]-5-methyl-5-(4-hydroxyphenyl)imidazolidine-2,4-dione (5n): White solid, yield: 64%, *m.f.*: $C_{19}H_{17}N_4O_4SCl$, *m.w.*: 432, m.p.: 272-274 ºC, R_f: 0.85. IR (KBr, ν_{max}, cm^{-1}): 3584 (-OH), 3520 (-NH), 3078 (Ar-CH), 1606 (-CONH), 1558 (Ar-C=C), 1172 (C-N), 738 (C-Cl); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 1.86 (s, 3H, -CH_3), 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, -CH_2), 5.00 (s, 1H, -OH), 5.92 (s, 1H, -CH methine), 6.02 (s, 1H, -NH), 6.68-7.15 (m, 8H, aromatic); ^{13}C NMR (δ_c ppm, DMSO-d_6): 25.9 (s, 1C, -CH_3), 35.7 (s, 1C, -CH_2), 54.5 (s, 1C, -CH), 66.3 (s, 1C, -C), 116.2-148.8 (m, 12C, aromatic), 154.7 (s, 1C, urea), 168.8 (s, 1C, amide), 172.8 (s, 1C, amide); MS (*m/z*): 434.06.

3-[(2-(4-Methoxyphenyl)thiazolidine-4-one-3-yl)amino]-5-ethyl-5-methyl-imidazolidine-2,4-dione (5o): White solid, yield: 68%, *m.f.*: $C_{16}H_{20}N_4O_4S$, *m.w.*: 364, m.p.: 152-154 ºC, R_f: 0.88. IR (KBr, ν_{max}, cm^{-1}): 3402 (-NH), 3062 (Ar-CH), 2972 (aliph. -CH), 1612 (-CONH), 1566 (Ar-C=C), 1180 (C-N), 1024 (C-O); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 0.96 (t, 3H, -CH_3), 1.58 (s, 3H, -CH_3), 1.79 (q, 2H, -CH_2), 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, -CH_2), 3.73 (s, 3H, -OCH_3), 5.92 (s, 1H, CH methine proton), 6.02 (s, 1H, NH proton), 6.65-6.95 (m, 4H, aromatic protons); ^{13}C NMR (δ_c ppm, DMSO-d_6): 16.4 (s, 1C, -CH_3), 23.9 (s, 1C, -CH_3), 30.0 (s, 1C, -CH_2), 35.7 (s, 1C, -CH_2), 54.5 (s, 1C, -CH), 55.9 (s, 1C, -CH_3), 66.3 (s, 1C, -C), 114.2-149.8 (m, 6C, aromatic), 154.7 (s, 1C, urea), 168.8 (s, 1C, amide), 175.2 (s, 1C, amide); MS (*m/z*): 365.12.

3-[(2-(2-Hydroxyphenyl)thiazolidine-4-one-3-yl)amino]-5-ethyl-5-methyl-imidazolidine-2,4-dione (5p): White, yield: 65%, *m.f.*: $C_{15}H_{18}N_4O_4S$, *m.w.*: 350, m.p.: 124-126 ºC, R_f: 0.92. IR (KBr, ν_{max}, cm^{-1}): 3643 (-OH), 3458 (-NH), 3097 (Ar-CH), 2978 (aliph. -CH), 1643 (-CONH), 1588 (Ar-C=C), 1195 (C-N); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 0.96 (t, 3H, -CH_3), 1.58 (s, 3H, -CH_3), 1.79 (q, 2H, -CH_2), 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, -CH_2), 5.00 (s, 1H, -OH), 5.92 (s, 1H, -CH methine), 6.02 (s, 1H, -NH), 6.61-6.90 (m, 4H, aromatic); ^{13}C NMR (δ_c ppm, DMSO-d_6): 15.5 (s, 1C, -CH_3), 23.8 (s, 1C, -CH_3), 31.5 (s, 1C, -CH_2), 35.7 (s, 1C, -CH_2), 44.3 (s, 1C,-CH), 57.6 (s, 1C, -C), 115.8-150.8 (m, 6C, aromatic), 154.7 (s, 1C, urea), 168.8 (s, 1C, amide), 175.2 (s, 1C, amide), MS (*m/z*): 351.11.

3-[(2-(4-Methoxyphenyl)thiazolidine-4-one-3-yl)amino]-5,5-dimethyl-imidazolidine-2,4-dione (5q): White, yield: 78%, *m.f.*: $C_{15}H_{18}N_4O_4S$, *m.w.*: 350, m.p.: 156-158 ºC, R_f: 0.84. IR (KBr, ν_{max}, cm^{-1}): 3481 (-NH), 3062 (Ar-CH), 2968 (aliph. -CH), 1602 (-CONH), 1560 (Ar-C=C), 1251 (C-O), 1180 (C-N); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 1.56 (s, 6H, CH_3 protons), 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, -CH_2), 3.73 (s, 3H, -OCH_3), 5.92 (s, 1H, -CH methine), 6.02 (s, 1H, -NH), 6.65-6.95 (m, 4H, aromatic); ^{13}C NMR (δ_c ppm, DMSO-d_6): 26.4 (s, 2C, -CH_3), 35.7 (s, 1C, -CH_2), 54.5 (s, 1C, -CH), 55.9 (s, 1C, -CH_3), 58.4 (s, 1C, -C), 114.2-131.8 (m, 6C, aromatic), 154.7 (s, 1C, urea), 168.8 (s, 1C, amide), 175.2 (s, 1C, amide); MS (*m/z*): 351.11.

3-[(2-(4-Chlorophenyl)-thiazolidine-4-one-3-yl)amino]-5,5-dimethyl-imidazolidine-2,4-dione (5r): Off white, yield: 85%, *m.f.*: $C_{14}H_{15}N_4O_3SCl$, *m.w.*: 354, m.p.: 128-130 ºC, R_f: 0.88. IR (KBr, ν_{max}, cm^{-1}): 3504 (-NH), 3049 (Ar-CH), 1624 (-CONH), 1595 (Ar-C=C), 1168 (C-N), 704 (C-Cl); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 1.53 (s, 6H, -CH_3), 2.01 (s, 1H, -NH), 3.28-3.38 (m, 2H, -CH_2), 5.92 (s, 1H, -CH methine), 6.02 (s, 1H, -NH proton), 7.00-7.15 (m, 4H, aromatic); ^{13}C NMR (δ_c ppm, DMSO-d_6): 26.4 (s, 2C, -CH_3), 35.7 (s, 1C, -CH_2), 54.5 (s, 1C, -CH), 57.4 (s, 1C, -C), 128.8-137.3 (m, 6C, aromatic), 154.7 (s, 1C, urea), 168.8 (s, 1C, amide), 175.2 (s, 1C, amide); MS (*m/z*): 356.01.

Animal ethics: The Institutional Animal Ethical Committee (IAEC) established under the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environments and Forests, Government of India, reviewed and approved all the procedures and protocols used in the animal experiments. Institutional Animal Ethical Committee (IAEC) Protocol approval No. MET/IOP/M. PHARM/2013-14/IAEC/01.

Acute toxicity studies: The OECD guidelines (no. 425) were followed for acute toxicity studies in mice to obtain median lethal dose (LD_{50}). Each animal was observed carefully for the signs of toxicity as well as for mortality in the first 30 min after dosing and then occasionally for further 4 h and daily thereafter for a period of 14 days. The number of mice dying during 48 h period was recorded.

Anticonvulsant activity: The anticonvulsant activity of the synthesized compounds was determined by evaluation of the ability of the compounds to protect mice against electroshock induced convulsions. These convulsions in animals represent grand mal type of epilepsy. In this model, electroshock (54 mA and 0.2 s) was applied through the corneal electrodes. For each compound, a group of six male Swiss Albino mice (22-30 g) were used. Phenytoin 25 mg/kg was considered as a reference for anticonvulsant effect. The synthesized compounds, phenytoin were administered 30 min before application of electroshock (54 mA and 0.2 s). The hind limb tonic extensions were observed during next 30 min.

RESULTS AND DISCUSSION

The synthesis of few 3-[(2-(substituted phenyl)thiazolidine-4-one-3-yl)amino]-5,5-disubstituted- imidazoidone-2,4-dione derivatives was accomplished through four steps starting from 5,5-disubstituted hydantoins, the N^3-H was replaced by bromine followed by hydrazinyl group. The hydrazinyl derivatives were converted into their Schiff bases with aromatic aldehydes and cyclized with thioglycolic acid. All reactions were carried out under microwave irradiation at 455 Watt (65% of total capacity of the oven) and the reactions were monitored by thin layer chromatography, the microwave irradiation was used as heating source for rapid and efficient reactions in shorter times; up to 20-28 min. The compounds were obtained in moderate to good yields ranging from 64-86%. The synthesized compounds were confirmed on the basis of IR, ^{1}H NMR wherein the characteristic δ value for C-H (methine) proton was observed within 4.67-5.92 ppm and ^{13}C NMR wherein the characteristic δ_c value for methane carbon was observed within 57.4-70.8 ppm.

Pharmacological evaluation of the synthesized compounds

Determination of LD_{50} (acute toxicity study): The LD_{50} for all the test compounds was calculated by using the software AOT425StatPgm an found to be 310.2 mg/kg. The actual doses taken for evaluation of activity of the synthesized compounds were Dose I: 30 mg/kg (approx. 1/10th that of LD_{50}) and Dose II: 45 mg/kg (approx.1.5 time of dose I).

Anticonvulsant activity: The anticonvulsant effect of some synthesized compounds was studied in mice by using MES-induced convulsions method. Table-2 depicts the comparison of the activity of synthesized compounds against control. The LD_{50} was found to be 310.2 mg/kg and the compounds were found to possess anticonvulsant activity. The maximal electroshock induced seizures is feasible animal model to evaluate the compound for potential as anticonvulsant activity.

TABLE-2
ANTICONVULSANT ACTIVITY STUDY OF SYNTHESIZED COMPOUNDS

Compound	Dose (mg/kg)	Duration (s) (Mean ± SEM)			Death/Recovery
		Tonic	Straub tail	Stupor	
Electroshock	54 mA for 0.2 s	7.6 ± 0.24	Present	193.4 ± 1.43	Recovery
Phenytoin	25	2.6 ± 0.27	Present	42.8 ± 1.28	Recovery
5a	30	6.7 ± 0.11	Present	67.1 ± 1.22	Recovery
	45	4.8 ± 0.13	Present	49.2 ± 1.02	Recovery
5b	30	5.1 ± 0.21	Present	75.1 ± 1.33	Recovery
	45	4.8 ± 0.12*	Present	91.2 ± 1.07	Recovery
5c	30	4.7 ± 0.16	Present	76.4 ± 1.20	Recovery
	45	4.1 ± 0.10**	Present	40.7 ± 1.19**	Recovery
5d	30	4.5 ± 0.14	Present	55.4 ± 1.35**	Death
	45	3.9 ± 0.09**	Present	51.4 ± 1.01**	Recovery
5e	30	6.1 ± 0.11	Present	74.1 ± 1.42	Recovery
	45	5.7 ± 0.19	Present	82.2 ± 1.32	Death
5f	30	6.6 ± 0.10	Present	66.2 ± 1.24*	Recovery
	45	4.4 ± 0.21*	Present	70.1 ± 1.14*	Recovery
5g	30	5.4 ± 0.34	Present	57.2 ± 1.09	Recovery
	45	5.0 ± 0.23	Present	64.8 ± 1.47*	Recovery
5h	30	6.3 ± 0.15	Present	70.1 ± 1.37	Recovery
	45	4.9 ± 0.20*	Present	77.8 ± 1.16	Recovery
5i	30	5.9 ± 0.41	Present	98.3 ± 1.24	Recovery
	45	4.3 ± 0.34**	Present	69.9 ± 1.35*	Recovery
5j	30	7.0 ± 0.18	Present	109.5 ± 1.42	Recovery
	45	6.4 ± 0.27	Present	89.1 ± 1.36	Recovery
5k	30	6.4 ± 0.44	Present	145.8 ± 1.06	Recovery
	45	3.6 ± 0.24**	Present	125.8 ± 1.20	Recovery
5l	30	7.6 ± 0.15	Present	170.8 ± 1.24	Recovery
	45	4.4 ± 0.07**	Present	59.6 ± 0.92**	Recovery
5m	30	6.4 ± 0.33	Present	53.8 ± 1.35**	Recovery
	45	5.4 ± 0.40*	Present	45.2 ± 1.28**	Recovery
5n	30	6.3 ± 0.41	Present	49.7 ± 1.11**	Recovery
	45	4.9 ± 0.23*	Present	62.2 ± 0.98**	Recovery
5o	30	4.7 ± 0.14**	Present	95.3 ± 1.38	Recovery
	45	4.5 ± 0.09**	Present	87.6 ± 1.29*	Recovery
5p	30	5.6 ± 0.37	Present	94.4 ± 1.51*	Recovery
	45	4.6 ± 0.28*	Present	101.2 ± 1.07	Recovery
5q	30	6.1 ± 0.22	Present	87.1 ± 1.48*	Recovery
	45	5.4 ± 0.39	Present	69.7 ± 1.00**	Recovery
5r	30	6.4 ± 0.27	Present	91.2 ± 1.56*	Death
	45	4.4 ± 0.20**	Present	44.0 ± 1.41**	Recovery

N = 6, in each group; *$p < 0.05$; **$p < 0.01$; NS: Non-significant; One Way ANOVA followed by Dunnett's test.

A 54 mA current applied through the ear pinna electrodes for 0.2 s was enough to cause the classic tonic clonic convulsions with the recognizable stupor phase and straub tail phases. Here, the absence of straub tail stages, the shortening of duration of these distinct phases and the recovery of animals were recorded. The duration of severe tonic phase was reduced up to 3.6 s and that of stupor phase was reduced up to 40.7 s compared to control. The analysis of structural features revealed that substitution of *p*-hydroxy phenyl and cinnamyl substituted at 2nd position of thiazolidinone ring in 5,5-diphenyl-2,4-imidazolidinedione and *p*-chloro phenyl, *p*-methoxy phenyl substituted at 2nd position of thiazolidinone ring in (5,5-dialkyl)/(5-alkyl-5-substituted phenyl)-2,4-imidazolidinedione skeleton enhanced the anticonvulsant potential of the synthesized compounds.

Conclusion

The synthesis of derivatives of 5,5-disubstituted N^3-[(2-aryl thiazolidine-4-one-3-yl)amino]hydantoins were carried using the microwave technology, which resulted in the drastically reduced reaction times and increased yields. The pharmacological evaluation of the compounds showed decrease in duration of tonic phase and decrease in the duration of stupor phase. Compounds **5c**, **5d**, **5l**, **5r** showed significant activity among the evaluated compounds compared to control at dose of 45 mg/kg.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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