

Synthesis and anticonvulsant activity of clubbed thiazolidinone–barbituric acid and thiazolidinone–triazole derivatives

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Abstract

A new series of clubbed thiazolidinone–barbituric acid and thiazolidinone–triazole derivatives was synthesized to study the effect of a hydrophobic unit, hydrogen bonding domain and electron-donor group on the compounds' anticonvulsant activity. The structures of the synthesized compounds were confirmed by their spectroscopic data and elemental analysis. All compounds were evaluated for their anticonvulsant activity in two animal models of seizures, viz. maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ). The compounds were also evaluated for neurotoxicity. Compounds **4g**, **4i**, **5g** and **5i** exhibited excellent anticonvulsant activity in both animal models of seizure.

Keywords: 1,2,4-Triazoles, pentylenetetrazole, maximal electroshock, anticonvulsant, neurotoxicity

Introduction

Epilepsy is a neurological disorder characterized by unprovoked seizures, and affects at least 50 million people worldwide. There is a continuing demand for new anticonvulsant agents as it has not been possible to control every kind of seizure with the currently available antiepileptic drugs. About one third of patients do not respond well to current multiple drugs therapy.^{1,2} Studies³ reveal that 63% of patients diagnosed and treated were seizure-free and more than 50% of epilepsy patients have experienced unwanted side effects.^{4–6} Phenobarbital^{7a} and mephobarbital^{7b} are well-known barbituric acid derivatives which are used for the treatment of epilepsy. These

drugs are very effective in controlling the seizures but they suffer from major side effects such as sedation, and hypnosis. Substituted heterocyclic/substituted aryl systematic variation at the 5-position of the barbituric⁸⁻¹⁰ or thiobarbituric¹¹⁻¹³ acids nucleus remarkably increases the antiepileptic activity. Furthermore, thiazolidinone derivatives¹⁴⁻¹⁷ are also well known for their pronounced anticonvulsant activity. Many compounds bearing the 1,2,4-triazole nucleus have been reported earlier to possess anticonvulsant properties in various animal seizures models, such as the maximal electroshock (MES), pentylenetetrazole-induced (PTZ), 3-mercaptopropionic acid (MP), bicuculline, and quinolinic acid-induced seizures models.¹⁸⁻²⁰ In continuation of our program on the pharmacological evaluation of clubbed triazoles²¹⁻²⁶ we discuss herein the synthesis and anticonvulsant activity of clubbed thiazolidinones, with an *in vivo* efficacy approach²⁷ to furnish drugs which are more potent and at the same time better tolerated than existing drugs.²⁸ We have selected three easy screening models, the MES seizure model, the PTZ seizure model, and the rotarod procedure to get a first hint for efficacy and safety.

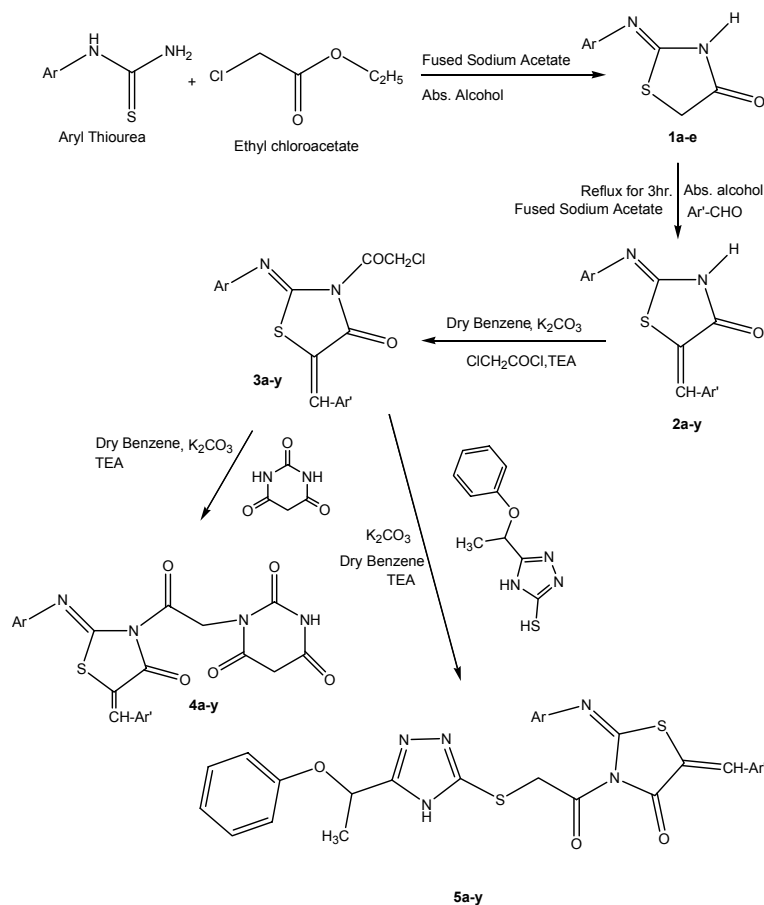
Results and Discussion

Chemistry

The target compounds were prepared by using the reaction sequence in Scheme 1. Various arylthioureas on treatment with ethyl chloroacetate gave the 2-arylimino-1,3-thiazolan-4-ones (**1a-e**), which on condensation with different aryl aldehydes in absolute alcohol furnished 2-arylimino-5-[(*Z*)-1-arylmethylidene]-1,3-thiazolan-4-ones (**2a-y**). The compounds **2a-y** on reacting with chloroacetyl chloride using triethylamine as a base afforded 3-(2-chloroacetyl)-2-arylimino-5-[(*Z*)-arylmethylidene]-1,3-thiazolan-4-ones (**3a-y**), thus providing a good leaving group, *i.e.*, chloride for different substitutions to be made. Using **3a-y** as intermediates, the first set of reactions with barbituric acid in triethylamine yielded the clubbed compounds (**4a-y**), while treatment with 5-(1-phenoxyethyl)-4H-1,2,4-triazole-3-thiol²⁹ in identical conditions provided us a set of bulkier derivatives (**5a-y**).

Pharmacology

All the newly synthesized compounds were tested *in vivo* in order to evaluate their anticonvulsant activity. The pharmacological data of all the compounds of this series are reported in Tables 5 and 6. The compounds **4a-4y**, substituted with different substituted phenyl thiazolidinonyl amino moieties at the 5- position of barbituric acid, show varying degrees of anticonvulsant activity. It was observed that compounds **4a-4e** exhibited a lower degree of anticonvulsant activity: however compounds **4f-4j** having 1-(2-2-[(2-hydroxyphenyl)imino]-5-[(*Z*)-1-arylmethylidene]-4-oxo-1,3-thiazolan-3-yl-2-oxoethyl)- substitution at the 5- position of barbituric acid have shown better response against MES, scPTZ and better neurotoxicity.



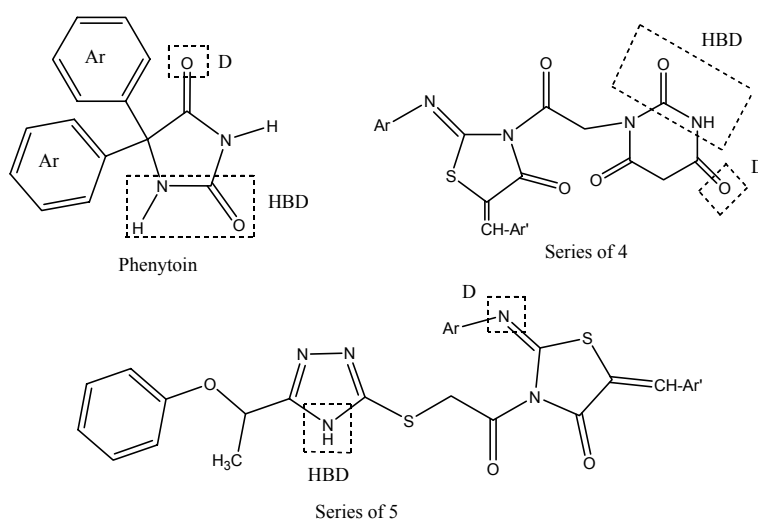
Scheme 1

Particularly, the compounds **4g** and **4i** have been found to be most potent in the series while from the rest of the compounds, **4l**, **4m**, **4o**, **4q** and **4s** have shown better activity compared to the other tested compounds

The next-stage compounds, *i.e.*, **5f–5j** characterized by the incorporation of an electron-donor hydroxyl group containing a 4-hydroxybenzylidenylimino group at the 2- position, while having the small hydrogen moiety at N-4 of the triazole ring at the 3rd position of the thiazolidinone. While evaluating the anticonvulsant activity, it was observed that compounds **5a–5e** exhibited a less- to moderate- degree of anticonvulsant activity, which suggested that we should go for different substitutions. The next step of modification provided us with the most potent group of compounds, *i.e.*, **5f–5j**. All these compounds showed potent anticonvulsant activity, however compounds **5f**, **5g** and **5i**, showed better response as anticonvulsant drugs, than the other substituted derivatives. Further, the next substitutions of this series could afford us **5l**, **5o**, and **5s**, which showed moderate anticonvulsant activity, while the rest were inactive.

The structural requirement for maintaining anticonvulsant activity was the presence of a hydroxyl –OH function at the 4- position of the phenyl ring, as seen with compounds **4f–4j** and **5f–5j**. This requirement was further evidenced by compounds **4k–4y** and **5k–5y** where the –OH

function was replaced by a -Cl, CH₃ or -NO₂ moiety. The complete loss of activity due to the disappearance of this function could be explained in terms of interaction at the binding site by the pharmacophoric models which were previously proposed³⁰⁻³³ (Scheme 2). In these models, it has been reported that the existence of a hydrophobic unit (Ar), an electron donor group (D) and hydrogen-bonding domain (HBD) was essential for anticonvulsant activity, as evidenced by the active drugs, such as carbamazepine or phenytoin, fulfilling these demands. As shown in Scheme 2, the replacement of the hydroxyl group responsible for hydrogen bonding in compounds **4f-4j** and **5f-5j** also resulted in the lack of a HBD leading to abolishment of the activity seen with compounds **4k-4y** and **5k-5y**. From the present study, four compounds (**4g**, **4i**, **5g** and **5i**) have emerged as the lead compounds. Further structural modifications of these molecules might lead to the discovery of more potent anticonvulsant agents with lower neurotoxicity.



Scheme 2. Structures of the synthesized compounds **4a-y** and **5a-y** and phenytoin, showing the general pharmacophore model for anticonvulsant activity.³⁰⁻³³ The essential structural requirements are indicated by dotted rectangles (Ar, hydrophobic unit; D, electron donor group; HBD, hydrogen-bonding domain).

Conclusions

The present study revealed that some of the thiazolidinone-barbituric acids and thiazolidinone-triazoles possessed a broad spectrum of anticonvulsant activity with less or no neurotoxicity. Ten compounds exhibited protection in the seizure models, *viz.*, MES, and scPTZ, and **4g**, **4i**, **5g** and **5i** have emerged as the most active compounds in these models with no neurotoxicity. We conclude that further structural modifications of these molecules might lead to the discovery of more potent anticonvulsant agents with still lower neurotoxicity.

Table 1. Physical and analytical data of compounds **4a–4y**

Comp	Ar	Ar'	Mol. formula	Mol. wt.	R S ^M	% Yield	M.P. (°C)	Elemental analysis		
								Calcd. (Found)		
								C	H	N
4a	-C ₆ H ₅	-C ₆ H ₅	C ₂₂ H ₁₆ N ₄ O ₅ S	448	IPA	51	279–283	58.92 (58.76)	3.60 (3.81)	12.49 (12.66)
4b	-C ₆ H ₅	-2-OHC ₆ H ₄	C ₂₂ H ₁₆ N ₄ O ₆ S	464	Ethanol/water (90:10)	87	175–179	56.89 (56.68)	3.47 (3.58)	12.06 (12.27)
4c	-C ₆ H ₅	-4-ClC ₆ H ₄	C ₂₂ H ₁₅ ClN ₄ O ₅ S	483	IPA	77	215–219	54.72 (54.61)	3.13 (3.34)	11.60 (11.84)
4d	-C ₆ H ₅	-4-CH ₃ C ₆ H ₄	C ₂₃ H ₁₈ N ₄ O ₅ S	462	IPA	80	234–237	59.73 (59.94)	3.92 (3.84)	12.11 (12.26)
4e	-C ₆ H ₅	-3-NO ₂ C ₆ H ₄	C ₂₂ H ₁₅ N ₄ O ₇ S	493	IPA	74	263–267	53.55 (53.37)	3.06 (3.18)	14.19 (14.34)
4f	-2-OHC ₆ H ₄	-C ₆ H ₅	C ₂₂ H ₁₆ N ₄ O ₆ S	464	IPA	59	175–179	56.89 (56.77)	3.47 (3.29)	12.06 (12.27)
4g	-2-OHC ₆ H ₄	-2-OHC ₆ H ₄	C ₂₂ H ₁₆ N ₄ O ₇ S	480	Methanol	70	248–252	55.00 (55.12)	3.36 (3.53)	11.66 (11.87)
4h	-2-OHC ₆ H ₄	-4-ClC ₆ H ₄	C ₂₂ H ₁₅ ClN ₄ O ₆ S	499	IPA	78	246–250	52.96 (52.87)	3.03 (3.21)	11.23 (11.45)
4i	-2-OHC ₆ H ₄	-4-CH ₃ C ₆ H ₄	C ₂₃ H ₁₈ N ₄ O ₆ S	478	IPA	71	216–220	57.73 (57.93)	3.79 (3.55)	11.71 (11.59)
4j	-2-OHC ₆ H ₄	-3-NO ₂ C ₆ H ₄	C ₂₂ H ₁₅ N ₅ O ₈ S	509	1,4-Dioxane	76	243–248	51.87 (51.68)	2.97 (2.71)	13.75 (13.69)
4k	-4-ClC ₆ H ₄	-C ₆ H ₅	C ₂₂ H ₁₅ ClN ₄ O ₅ S	483	Methanol	74	215–219	54.72 (54.57)	3.13 (3.39)	11.60 (11.44)
4l	-4-ClC ₆ H ₄	-2-OHC ₆ H ₄	C ₂₂ H ₁₅ ClN ₄ O ₆ S	499	Methanol	76	246–250	52.96 (52.84)	3.03 (3.11)	11.23 (11.37)
4m	-4-ClC ₆ H ₄	-4-ClC ₆ H ₄	C ₂₂ H ₁₄ Cl ₂ N ₄ O ₅ S	517	Methanol	80	214–218	51.08 (51.26)	2.73 (2.85)	10.83 (10.92)
4n	-4-ClC ₆ H ₄	-4-CH ₃ C ₆ H ₄	C ₂₃ H ₁₇ ClN ₄ O ₅ S	497	Methanol	69	223–228	55.59 (55.44)	3.45 (3.59)	11.27 (11.48)
4o	-4-ClC ₆ H ₄	-3-NO ₂ C ₆ H ₄	C ₂₂ H ₁₄ ClN ₅ O ₇ S	528	Methanol	72	220–224	50.05 (50.17)	2.67 (2.51)	13.27 (13.42)
4p	-4-CH ₃ C ₆ H ₄	-C ₆ H ₅	C ₂₃ H ₁₈ N ₄ O ₅ S	462	Methanol	76	234–237	59.73 (59.81)	3.92 (3.74)	12.11 (12.32)
4q	-4-CH ₃ C ₆ H ₄	-2-OHC ₆ H ₄	C ₂₃ H ₁₈ N ₄ O ₆ S	478	IPA	74	216–220	57.73 (57.57)	3.79 (3.93)	11.71 (11.62)
4r	-4-CH ₃ C ₆ H ₄	-4-ClC ₆ H ₄	C ₂₃ H ₁₇ ClN ₄ O ₅ S	497	IPA	81	223–228	55.59 (55.72)	3.45 (3.28)	11.27 (11.08)

4s	-4-CH ₃ C ₆ H ₄	-4-CH ₃ C ₆ H ₄	C ₂₄ H ₂₀ N ₄ O ₅ S	476	IPA	77	241–244	60.49 (60.38)	4.23 (4.41)	11.76 (11.54)
4t	-4-CH ₃ C ₆ H ₄	-3-NO ₂ C ₆ H ₄	C ₂₃ H ₁₇ N ₅ O ₇ S	507	IPA	78	240–244	54.44 (54.28)	3.38 (3.09)	13.80 (13.67)
4u	-3-NO ₂ C ₆ H ₄	-C ₆ H ₅	C ₂₂ H ₁₅ N ₄ O ₇ S	493	IPA	84	263–267	53.55 (53.36)	3.06 (3.22)	14.19 (14.52)
4v	-3-NO ₂ C ₆ H ₄	-2-OHC ₆ H ₄	C ₂₂ H ₁₅ N ₅ O ₈ S	509	IPA	70	243–248	51.87 (51.67)	2.97 (2.75)	13.75 (13.86)
4w	-3-NO ₂ C ₆ H ₄	-4-ClC ₆ H ₄	C ₂₂ H ₁₄ ClN ₅ O ₇ S	528	IPA	74	220–224	50.05 (50.19)	2.67 (2.84)	13.27 (13.48)
4x	-3-NO ₂ C ₆ H ₄	-4-CH ₃ C ₆ H ₄	C ₂₃ H ₁₇ N ₅ O ₇ S	507	IPA	78	240–244	54.44 (54.32)	3.38 (3.53)	13.80 (13.62)
4y	-3-NO ₂ C ₆ H ₄	-3-NO ₂ C ₆ H ₄	C ₂₂ H ₁₄ N ₆ O ₉ S	538	IPA	72	260–263	49.07 (49.24)	2.62 (2.71)	15.61 (15.78)

R S^M- Recrystallization Solvent

Table 2. Physical and analytical data of compounds **5a–5y**

Comp	Ar	Ar'	Mol. formula	Mol. wt.	R S ^M	% Yield	M.P. (°C)	Elemental analysis		
								Calcd. (Found)		
								C	H	N
5a	-C ₆ H ₅	-C ₆ H ₅	C ₂₈ H ₂₃ N ₅ O ₃ S ₂	542	EtOAc	68	178–	62.09	4.28	12.93
					/ benzene (extraction)		182	(62.24)	(4.42)	(12.88)
5b	-C ₆ H ₅	-2-OHC ₆ H ₄	C ₂₈ H ₂₃ N ₅ O ₄ S ₂	558	EtOAc	77	194–	60.31	4.16	12.56
					/ benzene (extraction)		198	(60.45)	(4.36)	(12.76)
5c	-C ₆ H ₅	-4-ClC ₆ H ₄	C ₂₈ H ₂₂ ClN ₅ O ₃ S ₂	576	EtOAc	72	188–	58.38	3.85	12.16
					/ benzene (extraction)		191	(58.61)	(3.77)	(12.34)
5d	-C ₆ H ₅	-4-CH ₃ C ₆ H ₄	C ₂₉ H ₂₅ N ₅ O ₃ S ₂	556	EtOAc	82	176–	62.68	4.53	12.60
					/ benzene (extraction)		180	(62.74)	(4.67)	(12.42)
5e	-C ₆ H ₅	-3-NO ₂ C ₆ H ₄	C ₂₈ H ₂₂ N ₆ O ₅ S ₂	587	EtOAc	71	164–	57.33	3.78	14.33
					/ benzene (extraction)		168	(57.57)	(3.89)	(14.48)
5f	-2-OHC ₆ H ₄	-C ₆ H ₅	C ₂₈ H ₂₃ N ₅ O ₄ S ₂	558	EtOAc	69	194–	60.31	4.16	12.56
					/ benzene (extraction)		198	(60.42)	(4.02)	(12.67)

5g	-2-OHC ₆ H ₄	-2-OHC ₆ H ₄	C ₂₈ H ₂₃ N ₅ O ₅ S ₂	574	EtOAc /1,4-dioxane (90:10)	48	187– 190	58.63 (58.77)	4.04 (4.25)	12.21 (12.37)
5h	-2-OHC ₆ H ₄	-4-ClC ₆ H ₄	C ₂₈ H ₂₂ ClN ₅ O ₄ S ₂	592	IPA	67	179– 183	56.80 (56.91)	3.75 (3.67)	11.83 (11.59)
5i	-2-OHC ₆ H ₄	-4-CH ₃ C ₆ H ₄	C ₂₉ H ₂₅ N ₅ O ₄ S ₂	572	IPA	68	182– 185	60.93 (60.87)	4.41 (4.26)	12.25 (12.47)
5j	-2-OHC ₆ H ₄	-3-NO ₂ C ₆ H ₄	C ₂₈ H ₂₂ N ₆ O ₆ S ₂	603	IPA	73	177– 180	55.80 (55.76)	3.68 (3.87)	13.95 (13.74)
5k	-4-ClC ₆ H ₄	-C ₆ H ₅	C ₂₈ H ₂₂ ClN ₅ O ₃ S ₂	576	IPA	78	188– 191	58.38 (58.24)	3.85 (3.73)	12.16 (12.42)
5l	-4-ClC ₆ H ₄	-2-OHC ₆ H ₄	C ₂₈ H ₂₂ ClN ₅ O ₄ S ₂	592	IPA	70	179– 183	56.80 (56.68)	3.75 (3.64)	11.83 (11.68)
5m	-4-ClC ₆ H ₄	-4-ClC ₆ H ₄	C ₂₈ H ₂₁ Cl ₂ N ₅ O ₃ S ₂	610	IPA	81	194– 198	55.08 (55.26)	3.47 (3.28)	11.47 (11.58)
5n	-4-ClC ₆ H ₄	-4-CH ₃ C ₆ H ₄	C ₂₉ H ₂₄ ClN ₅ O ₃ S ₂	590	IPA	80	197– 201	59.02 (59.16)	4.10 (4.34)	11.87 (11.73)
5o	-4-ClC ₆ H ₄	-3-NO ₂ C ₆ H ₄	C ₂₈ H ₂₁ ClN ₆ O ₅ S ₂	621	IPA	76	169– 173	54.15 (54.37)	3.41 (3.57)	13.53 (13.41)
5p	-4-CH ₃ C ₆ H ₄	-C ₆ H ₅	C ₂₉ H ₂₅ N ₅ O ₃ S ₂	556	EtOAc/CCl ₄ (extraction)	72	176– 180	62.68 (62.76)	4.53 (4.46)	12.60 (12.42)
5q	-4-CH ₃ C ₆ H ₄	-2-OHC ₆ H ₄	C ₂₉ H ₂₅ N ₅ O ₄ S ₂	572	EtOAc/CCl ₄ (extraction)	78	182– 185	60.93 (60.82)	4.41 (4.64)	12.25 (12.38)
5r	-4-CH ₃ C ₆ H ₄	-4-ClC ₆ H ₄	C ₂₉ H ₂₄ ClN ₅ O ₃ S ₂	590	EtOAc/CCl ₄ (extraction)	70	197– 201	59.02 (59.34)	4.10 (4.27)	11.87 (11.75)
5s	-4-CH ₃ C ₆ H ₄	-4-CH ₃ C ₆ H ₄	C ₃₀ H ₂₇ N ₅ O ₃ S ₂	570	EtOAc/CCl ₄ (extraction)	70	164– 167	63.25 (63.51)	4.78 (4.93)	12.29 (12.51)
5t	-4-CH ₃ C ₆ H ₄	-3-NO ₂ C ₆ H ₄	C ₂₉ H ₂₄ N ₆ O ₅ S ₂	601	EtOAc/CCl ₄ (extraction)	78	173– 176	57.99 (57.76)	4.03 (4.26)	13.99 (13.74)

5u	-3- NO ₂ C ₆ H ₄	-C ₆ H ₅	C ₂₈ H ₂₂ N ₆ O ₅ S ₂	587	EtOAc/CCl 4 (extraction)	76	164– 168	57.33 (57.46)	3.78 (3.49)	14.33 (14.56)
5v	-3- NO ₂ C ₆ H ₄	-2- OHC ₆ H ₄	C ₂₈ H ₂₂ N ₆ O ₆ S ₂	603	EtOAc/CCl 4 (extraction)	68	177– 180	55.80 (55.92)	3.68 (3.76)	13.95 (13.74)
5w	-3- NO ₂ C ₆ H ₄	-4- ClC ₆ H ₄	C ₂₈ H ₂₁ ClN ₆ O ₅ S ₂	621	EtOAc/CCl 4 (extraction)	72	169– 173	54.15 (54.34)	3.41 (3.50)	13.53 (13.65)
5x	-3- NO ₂ C ₆ H ₄	-4- CH ₃ C ₆ H 4	C ₂₉ H ₂₄ N ₆ O ₅ S ₂	601	IPA	70	173– 176	57.99 (57.85)	4.03 (4.18)	13.99 (13.76)
5y	-3- NO ₂ C ₆ H ₄	-3- NO ₂ C ₆ H 4	C ₂₈ H ₂₁ N ₇ O ₇ S ₂	632	IPA	78	178– 182	53.24 (53.35)	3.35 (3.19)	15.52 (15.66)

R S^M- Recrystallization Solvent**Table 3.** Physical and spectroscopic data of compounds **4a–4y**

Comp.	[M] ⁺ <i>m/z</i>	Nature of the crystals ^a	¹ H-NMR (δ ppm, DMSO-d ₆)
4a	449	Cream microcrystals	3.12 (s, 2H, CH ₂ of barbituric acid), 4.11 (s, 2H, CH ₂ CO), 7.12–7.42 (m, 10H, ArH), 7.62 (s, 1H, CH=C), 9.62 (s, 1H, NH).
4b	465	Cream microcrystals	3.07 (s, 2H, CH ₂ of barbituric acid), 4.05 (s, 2H, CH ₂ CO), 7.20–7.51 (m, 9H, ArH), 7.82 (s, 1H, CH=C), 8.75 (s, 1H, OH), 9.24 (s, 1H, NH).
4c	484	Yellow microcrystals	3.17 (s, 2H, CH ₂ of barbituric acid), 4.09 (s, 2H, CH ₂ CO), 7.19–7.37 (m, 9H, ArH), 7.54 (s, 1H, CH=C), 9.43 (s, 1H, NH).
4d	463	Cream microcrystals	2.33 (s, 3H, CH ₃), 3.13 (s, 2H, CH ₂ of barbituric acid), 4.13 (s, 2H, CH ₂ CO), 7.24–7.48 (m, 9H, ArH), 7.76 (s, 1H, CH=C), 9.26 (s, 1H, NH).
4e	494	Yellow microcrystals	3.11 (s, 2H, CH ₂ of barbituric acid), 4.21 (s, 2H, CH ₂ CO), 7.05–7.31 (m, 9H, ArH), 7.53 (s, 1H, CH=C), 9.35 (s, 1H, NH).
4f	465	Beige powder	3.03 (s, 2H, CH ₂ of barbituric acid), 4.16 (s, 2H, CH ₂ CO), 7.16–7.38 (m, 9H, ArH), 7.46 (s, 1H, CH=C), 9.44 (s, 1H, NH).
4g	481	Beige powder	3.24 (s, 2H, CH ₂ of barbituric acid), 4.26 (s, 2H, CH ₂ CO), 6.74–7.24 (m, 8H, ArH), 7.58 (s, 1H, CH=C), 8.24 (s, 2H, OH), 9.24 (s, 1H, NH).
4h	500	Beige powder	3.14 (s, 2H, CH ₂ of barbituric acid), 4.11 (s, 2H, CH ₂ CO), 6.79–7.31 (m, 8H, ArH), 7.55 (s, 1H, CH=C), 8.78 (s, 1H, OH), 9.56 (s, 1H, NH).
4i	479	Cream microcrystals	2.41 (s, 3H, CH ₃), 3.17 (s, 2H, CH ₂ of barbituric acid), 4.11 (s, 2H, CH ₂ CO), 6.64–6.94 (m, 8H, ArH), 7.52 (s, 1H, CH=C), 8.85 (s, 1H, OH), 9.48 (s, 1H, NH).
4j	510	Pale yellow	3.15 (s, 2H, CH ₂ of barbituric acid), 4.08 (s, 2H, CH ₂ CO), 6.70–7.07 (m, 8H, ArH), 7.81

		powder	(s, 1H, CH=C), 8.86 (s, 1H, OH), 9.76 (s, 1H, NH).
4k	484	Cream	3.17 (s, 2H, CH ₂ of barbituric acid), 4.11 (s, 2H, CH ₂ CO), 7.07–7.34 (m, 9H, ArH), 7.78
		microcrystals	(s, 1H, CH=C), 9.70 (s, 1H, NH).
4l	500	Cream	3.18 (s, 2H, CH ₂ of barbituric acid), 4.16 (s, 2H, CH ₂ CO), 6.78–7.21 (m, 8H, ArH), 7.56
		microcrystals	(s, 1H, CH=C), 8.76 (s, 1H, OH), 9.54 (s, 1H, NH).
4m	518	Cream	3.03 (s, 2H, CH ₂ of barbituric acid), 4.10 (s, 2H, CH ₂ CO), 6.81–7.34 (m, 8H, ArH), 7.64
		microcrystals	(s, 1H, CH=C), 9.57 (s, 1H, NH).
4n	498	Cream	2.23 (s, 3H, CH ₃), 3.10 (s, 2H, CH ₂ of barbituric acid), 4.13 (s, 2H, CH ₂ CO), 6.80–7.32
		microcrystals	(m, 8H, ArH), 7.84 (s, 1H, CH=C), 9.59 (s, 1H, NH).
4o	529	Brown powder	3.12 (s, 2H, CH ₂ of barbituric acid), 4.07 (s, 2H, CH ₂ CO), 6.79–7.31 (m, 8H, ArH), 7.60 (s, 1H, CH=C), 9.66 (s, 1H, NH).
4p	463	Yellow powder	2.29 (s, 3H, CH ₃), 3.18 (s, 2H, CH ₂ of barbituric acid), 4.15 (s, 2H, CH ₂ CO), 7.04–7.26 (m, 9H, ArH), 7.86 (s, 1H, CH=C), 9.52 (s, 1H, NH).
4q	479	Yellow powder	2.15 (s, 3H, CH ₃), 3.14 (s, 2H, CH ₂ of barbituric acid), 4.17 (s, 2H, CH ₂ CO), 6.76–7.35 (m, 8H, ArH), 7.66 (s, 1H, CH=C), 8.84 (s, 1H, OH), 9.68 (s, 1H, NH).
4r	498	Yellow powder	2.20 (s, 3H, CH ₃), 3.16 (s, 2H, CH ₂ of barbituric acid), 4.07 (s, 2H, CH ₂ CO), 6.85–7.37 (m, 8H, ArH), 7.70 (s, 1H, CH=C), 9.57 (s, 1H, NH).
4s	477	Yellow powder	2.39 (s, 6H, CH ₃), 3.08 (s, 2H, CH ₂ of barbituric acid), 4.16 (s, 2H, CH ₂ CO), 6.68–7.15 (m, 8H, ArH), 7.76 (s, 1H, CH=C), 9.63 (s, 1H, NH).
4t	508	Yellow powder	2.24 (s, 3H, CH ₃), 3.07 (s, 2H, CH ₂ of barbituric acid), 4.14 (s, 2H, CH ₂ CO), 6.87–7.33 (m, 8H, ArH), 7.74 (s, 1H, CH=C), 9.69 (s, 1H, NH).
4u	494	Yellow microcrystals	3.09 (s, 2H, CH ₂ of barbituric acid), 4.13 (s, 2H, CH ₂ CO), 7.08–7.36 (m, 9H, ArH), 7.55 (s, 1H, CH=C), 9.57 (s, 1H, NH).
4v	510	Yellow microcrystals	3.11 (s, 2H, CH ₂ of barbituric acid), 4.10 (s, 2H, CH ₂ CO), 6.75–7.34 (m, 8H, ArH), 7.58 (s, 1H, CH=C), 8.76 (s, 1H, OH), 9.51 (s, 1H, NH).
4w	529	Yellow microcrystals	3.16 (s, 2H, CH ₂ of barbituric acid), 4.13 (s, 2H, CH ₂ CO), 6.82–7.39 (m, 8H, ArH), 7.87 (s, 1H, CH=C), 9.653 (s, 1H, NH).
4x	508	Yellow microcrystals	2.17 (s, 3H, CH ₃), 3.15 (s, 2H, CH ₂ of barbituric acid), 4.17 (s, 2H, CH ₂ CO), 6.63–7.03 (m, 8H, ArH), 7.71 (s, 1H, CH=C), 9.67 (s, 1H, NH).
4y	539	Yellow powder	3.17 (s, 2H, CH ₂ of barbituric acid), 4.10 (s, 2H, CH ₂ CO), 6.88–7.34 (m, 8H, ArH), 7.76 (s, 1H, CH=C), 9.69 (s, 1H, NH).

^aAll the compounds are purified by column chromatography.

Experimental Section

General Procedures. The melting points were recorded on an Electrothermal apparatus and are uncorrected. The structures of synthesized compounds were assigned based on their analytical and spectroscopic properties. ¹H- NMR spectra were recorded on a Bruker Avance 300 MHz

instrument, using DMSO- d_6 as solvent and TMS as internal standard; the chemical shifts (δ) are reported in ppm and coupling constants (J) are given in Hz. Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), ds (double singlet), dd (double doublet), m (multiplet) and bs (broad singlet). Mass spectra were recorded on a Finnigan LCQ mass spectrometer. Elemental analyses were performed on a Heraeus CHN-Rapid Analyzer. Analytical figures were within $\pm 0.4\%$ of the theoretical values. The purity of the compounds was checked on Merck precoated silica gel 60 F-254.

General preparation of 2-arylimino-1,3-thiazolan-4-one (1).³⁴ The aryl thiourea (1 mmol) was dissolved in 25 mL absolute alcohol and refluxed with fused sodium acetate (1 mmole) and ethyl chloroacetate (1 mmole) for 3.5 h. The mixture was then poured into 250 mL of water. The product was then filtered, dried and recrystallized.

General preparation of 2-arylimino-5-(Z)-1-arylmethylidene-1,3-thiazolan-4-one (2). A mixture of the aromatic aldehyde (1 mmol), 2-arylimino-4-thiazolidenone (1 mmol) and fused sodium acetate (2 mmol) was taken in 15 mL of absolute alcohol and refluxed for 3 h. The hot mixture was then poured into 100 mL of water and kept overnight. The precipitate obtained was filtered and washed with water and then dried.

General preparation of 3-(2-chloroacetyl)-2-arylimino-5-(Z)-1-arylmethylidene-1,3-thiazolan-4-one (3). A solution of **2** (1 mmol) in 40 mL dry benzene was cooled to 0–5 °C. Chloroacetyl chloride (1 mmol) was added with vigorous stirring, followed by addition of triethylamine (1 mL) and potassium carbonate (1 mmol). The reaction mixture was then refluxed for 4–5 h. At the end of the 5th hour, the benzene was distilled off. The residue was washed with 5 mL of water. An oily product was obtained which was dissolved in a minimum quantity of acetone to obtain a precipitate which was filtered off, dried and crystallized.

General preparation of 1-(2-arylimino-5-(Z)-1-arylmethylidene-4-oxo-1,3-thiazolan-3-yl-2-oxoethyl)hexahydro-2,4,6-pyrimidinetriones (4). To a solution of barbituric acid (1 mmol) in 30 mL of dry benzene and (1 mmol) of **3**, triethylamine (0.4 mL) and potassium carbonate (1 mmol) was added. The mixture was refluxed for 4–5 h with constant stirring. The solvent was removed in *vacuo*. The residue obtained was treated with ice-cold water (5 mL), filtered, dried and crystallized.

General preparation of 2-[(substituted- phenyl)imino]-5-(Z)-1-arylmethylidene-3-(2-[5-(1-phenoxyethyl)-4H-1,2,4-triazol-3-yl]sulfanylacetyl)-1,3-thiazolan-4-one (5). 5-(1-Phenoxyethyl)-4H-1,2,4-triazole-3-thiol (1 mmol) in 30 mL of dry benzene was mixed with **3** (1 mmol). Anhydrous potassium carbonate and triethylamine 0.4 mL were added to the above mixture and stirred at room temperature for 6 h. The mixture was filtered and the filtrate evaporated to dryness. The residue was washed with water and recrystallized from ethanol.

Pharmacology

For the anticonvulsant studies, male albino mice (CF-1 strain, 18–25 g) and male albino rats (Sprague–Dawley, 100–150 g) were used as experimental animals. The animals were allowed to

adapt to the laboratory environment for one week before the experiments started. All experiments with drug injection were then carried out within one week to minimize the effect of increasing age on drug susceptibility. Each animal was used for only one experiment. Experimental animals were kept in groups of six in plastic cages at controlled temperature ($22 \pm 2^\circ\text{C}$) and humidity (about $55 \pm 15\%$) with a 12-h light cycle beginning at 6 a.m. They received standard laboratory rodent chow and tap water *ad libitum*.

Anticonvulsant screening

scPTZ test^{35,36}

Pentylenetetrazole (PTZ, Sigma Chemicals, USA) was used as convulsant. PTZ was dissolved in normal saline. The mice were divided into groups of six each, keeping the group weights as equal as possible. All the synthesized compounds **4a–y** and **5a–y** were suspended in 5% aqueous gum acacia to give a concentration of 1% (w/v). The test compounds were injected i.p. into each group. The control animals were injected with vehicle only. Thirty minutes later, for the administration of either vehicle or test compounds, the animals were injected with pentylenetetrazole (90 mg/kg, s.c.). This dose of pentylenetetrazole was shown to produce convulsions in all untreated mice and these animals exhibited 100% mortality during 24 h. The mice that survived after 24 h were considered to be protected. The number of protected animals in each group was recorded and the anticonvulsant activity of compounds **4a–y** and **5a–y** were represented as the percent protection.

MES test^{37,38}

Mice were divided into different groups with six mice in each group. Suspensions of the compounds/standard in 0.5% Tween-80 in saline were administered intraperitoneally (i.p.) at three dose levels (30, 100, 300 mg kg⁻¹). The untreated group was administered the same volume of the vehicle. A drop of 0.9% saline was instilled in each eye prior to the application of electrodes (Centroniks Electroconvulsimeter). The mice were subjected to electrical shock delivered through the corneal electrodes for 0.2 s (40 mA, 50 Hz, AC). Failure to extend the hind limbs to an angle with the trunk greater than 90° is defined as protection. The seizure pattern was recorded at 0.5- and 4 hours after administration of the dose (Tables 5 and 6).

Neurotoxicity screening³⁹

The Rotarod test has been performed to detect the motor deficit in mice. Animals were divided into the groups (each of six) and trained to stay on an accelerating rotarod that rotates at 10 revolutions per minute. The rod diameter was 3.2 cm. Trained animals (able to stay on the rotarod for at least two consecutive periods of 90 s) were given an i.p. injection of the test compounds in the doses of 30, 100 and 300 mg/kg. Neurological deficit was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the three trials. The dose at which animal fell off the rod, was determined, and the data are presented in Tables 5 and 6.

Table 4. Physical and spectral data of compounds **5a–5y**

Comp.	[M] ⁺ <i>m/z</i>	Nature of the crystals ^a	¹ H-NMR (δ ppm, DMSO-d ₆)
5a	543	Cream microcrystals	1.71 (d, 3H, <i>J</i> =6.4 Hz, -CH-CH ₃), 4.25 (s, 2H, S-CH ₂), 5.48 (q, 1H, <i>J</i> = 6.4 Hz, -CH-CH ₃), 6.77–7.45 (m, 15H, ArH), 7.56 (s, 1H, -CH), 12.25 (s, 1H, NH),
5b	559	Cream powder	1.56 (d, 3H, <i>J</i> =6.4 Hz, -CH-CH ₃), 4.17 (s, 2H, S-CH ₂), 5.42 (q, 1H, <i>J</i> = 6.4 Hz, -CH-CH ₃), 6.74–7.33 (m, 14H, ArH), 7.48 (s, 1H, -CH), 8.25 (s, 1H, OH), 12.34 (s, 1H, NH),
5c	577	Yellow microcrystals	1.84 (d, 3H, <i>J</i> =6.4 Hz, -CH-CH ₃), 4.14 (s, 2H, S-CH ₂), 5.46 (q, 1H, <i>J</i> = 6.4 Hz, -CH-CH ₃), 6.80–7.41 (m, 14H, ArH), 7.53 (s, 1H, -CH), 12.32 (s, 1H, NH),
5d	557	Cream powder	1.62 (d, 3H, <i>J</i> =6.4 Hz, -CH-CH ₃), 2.27 (s, 3H, CH ₃), 4.20 (s, 2H, S-CH ₂), 5.57 (q, 1H, <i>J</i> = 6.4 Hz, -CH-CH ₃), 6.81–7.37 (m, 14H, ArH), 7.51 (s, 1H, -CH), 12.30 (s, 1H, NH),
5e	588	Pale yellow powder	1.68 (d, 3H, <i>J</i> =6.4 Hz, -CH-CH ₃), 4.22 (s, 2H, S-CH ₂), 5.43 (q, 1H, <i>J</i> = 6.4 Hz, -CH-CH ₃), 6.70–7.29 (m, 14H, ArH), 7.55 (s, 1H, -CH), 12.25 (s, 1H, NH),
5f	559	Pale yellow powder	1.77 (d, 3H, <i>J</i> =6.4 Hz, -CH-CH ₃), 4.30 (s, 2H, S-CH ₂), 5.65 (q, 1H, <i>J</i> = 6.4 Hz, -CH-CH ₃), 6.79–7.28 (m, 14H, ArH), 7.40 (s, 1H, -CH), 8.31 (s, 1H, OH), 12.28 (s, 1H, NH),
5g	575	Pale yellow powder	1.80 (d, 3H, <i>J</i> =6.4 Hz, -CH-CH ₃), 4.31 (s, 2H, S-CH ₂), 5.66 (q, 1H, <i>J</i> = 6.4 Hz, -CH-CH ₃), 6.82–7.40 (m, 13H, ArH), 7.61 (s, 1H, -CH), 12.25 (s, 1H, NH),
5h	593	Pale yellow powder	1.75 (d, 3H, <i>J</i> =6.4 Hz, -CH-CH ₃), 4.22 (s, 2H, S-CH ₂), 5.52 (q, 1H, <i>J</i> = 6.4 Hz, -CH-CH ₃), 6.78–7.42 (m, 13H, ArH), 7.63 (s, 1H, -CH), 8.30 (s, 2H, OH), 12.41 (s, 1H, NH),
5i	573	Cream powder	1.68 (d, 3H, <i>J</i> =6.4 Hz, -CH-CH ₃), 2.31 (s, 3H, CH ₃), 4.18 (s, 2H, S-CH ₂), 5.45 (q, 1H, <i>J</i> = 6.4 Hz, -CH-CH ₃), 6.68–7.21 (m, 13H, ArH), 7.37 (s, 1H, -CH), 8.46 (s, 1H, OH), 12.25 (s, 1H, NH)
5j	604	Pale yellow powder	1.76 (d, 3H, <i>J</i> =6.4 Hz, -CH-CH ₃), 4.34 (s, 2H, S-CH ₂), 5.57 (q, 1H, <i>J</i> = 6.4 Hz, -CH-CH ₃), 6.69–7.33 (m, 13H, ArH), 7.52 (s, 1H, -CH), 8.41 (s, 2H, OH), 12.24 (s, 1H, NH),
5k	577	Cream microcrystals	1.69 (d, 3H, <i>J</i> =6.3 Hz, -CH-CH ₃), 4.40 (s, 2H, S-CH ₂), 5.51 (q, 1H, <i>J</i> = 6.3 Hz, -CH-CH ₃), 6.87–7.43 (m, 14H, ArH), 7.42 (s, 1H, -CH), 12.28 (s, 1H, NH),
5l	593	Cream microcrystals	1.77 (d, 3H, <i>J</i> =6.4 Hz, -CH-CH ₃), 4.28 (s, 2H, S-CH ₂), 5.47 (q, 1H, <i>J</i> = 6.4 Hz, -CH-CH ₃), 6.68–7.35 (m, 13H, ArH), 7.49 (s, 1H, -CH), 8.37 (s, 2H, OH), 12.34 (s, 1H, NH),
5m	611	Cream microcrystals	1.65(d, 3H, <i>J</i> =6.4 Hz, -CH-CH ₃), 4.21 (s, 2H, S-CH ₂), 5.43 (q, 1H, <i>J</i> = 6.4 Hz, -CH-CH ₃), 6.71–7.34 (m, 13H, ArH), 7.54 (s, 1H, -CH), 12.37 (s, 1H, NH),
5n	591	Cream microcrystals	1.82 (d, 3H, <i>J</i> =6.4 Hz, -CH-CH ₃), 2.29 (s, 3H, CH ₃), 4.35 (s, 2H, S-CH ₂), 5.48 (q, 1H, <i>J</i> = 6.4 Hz, -CH-CH ₃), 6.76–7.26 (m, 13H, ArH), 7.38 (s, 1H, -CH), 12.21 (s, 1H, NH),
5o	622	Cream powder	1.64 (d, 3H, <i>J</i> =6.3 Hz, -CH-CH ₃), 4.16 (s, 2H, S-CH ₂), 5.64 (q, 1H, <i>J</i> = 6.3 Hz, -CH-CH ₃), 6.84–7.37 (m, 13H, ArH), 7.52 (s, 1H, -CH), 12.23 (s, 1H, NH),
5p	557	Yellow powder	1.84 (d, 3H, <i>J</i> =6.3 Hz, -CH-CH ₃), 2.27 (s, 3H, CH ₃), 4.24 (s, 2H, S-CH ₂), 5.59 (q, 1H, <i>J</i> = 6.3 Hz, -CH-CH ₃), 6.87–7.46 (m, 14H, ArH), 7.64 (s, 1H, -CH), 12.38 (s, 1H, NH),
5q	573	Yellow microcrystals	1.67 (d, 3H, <i>J</i> =6.3 Hz, -CH-CH ₃), 2.23 (s, 3H, CH ₃), 4.23 (s, 2H, S-CH ₂), 5.62 (q, 1H, <i>J</i> = 6.3 Hz, -CH-CH ₃), 6.85–7.49 (m, 13H, ArH), 7.61 (s, 1H, -CH), 8.54 (s, 1H, OH), 12.22 (s, 1H, NH),

5r	591	Yellow microcrystals	1.63 (d, 3H, $J=6.4$ Hz, -CH-CH ₃), 2.37 (s, 3H, CH ₃), 4.14 (s, 2H, S-CH ₂), 5.49 (q, 1H, $J=6.4$ Hz, -CH-CH ₃), 6.81–7.39 (m, 13H, ArH), 7.66 (s, 1H, -CH), 12.27 (s, 1H, NH),
5s	571	Yellow microcrystals	1.78 (d, 3H, $J=6.3$ Hz, -CH-CH ₃), 2.40 (s, 6H, CH ₃), 4.20 (s, 2H, S-CH ₂), 5.56 (q, 1H, $J=6.3$ Hz, -CH-CH ₃), 6.74–7.42 (m, 13H, ArH), 7.58 (s, 1H, -CH), 12.30 (s, 1H, NH),
5t	602	Yellow microcrystals	1.76 (d, 3H, $J=6.4$ Hz, -CH-CH ₃), 2.41 (s, 3H, CH ₃), 4.23 (s, 2H, S-CH ₂), 5.51 (q, 1H, $J=6.4$ Hz, -CH-CH ₃), 6.80–7.37 (m, 13H, ArH), 7.64 (s, 1H, -CH), 12.37 (s, 1H, NH),
5u	588	Yellow powder	1.80 (d, 3H, $J=6.5$ Hz, -CH-CH ₃), 4.19 (s, 2H, S-CH ₂), 5.63 (q, 1H, $J=6.5$ Hz, -CH-CH ₃), 6.88–7.31 (m, 14H, ArH), 7.57 (s, 1H, -CH), 12.19 (s, 1H, NH),
5v	604	Yellow powder	1.81 (d, 3H, $J=6.3$ Hz, -CH-CH ₃), 4.24 (s, 2H, S-CH ₂), 5.60 (q, 1H, $J=6.3$ Hz, -CH-CH ₃), 6.74–7.34 (m, 13H, ArH), 7.56 (s, 1H, -CH), 8.44 (s, 2H, OH), 12.18 (s, 1H, NH),
5w	622	Yellow powder	1.63 (d, 3H, $J=6.3$ Hz, -CH-CH ₃), 4.26 (s, 2H, S-CH ₂), 5.55 (q, 1H, $J=6.3$ Hz, -CH-CH ₃), 6.83–7.45 (m, 13H, ArH), 7.63 (s, 1H, -CH), 12.31 (s, 1H, NH),
5x	602	Yellow powder	1.67 (d, 3H, $J=6.4$ Hz, -CH-CH ₃), 2.43 (s, 3H, CH ₃), 4.16 (s, 2H, S-CH ₂), 5.54 (q, 1H, $J=6.4$ Hz, -CH-CH ₃), 6.84–7.35 (m, 13H, ArH), 7.56 (s, 1H, -CH), 12.24 (s, 1H, NH),
5y	633	Yellow powder	1.69 (d, 3H, $J=6.4$ Hz, -CH-CH ₃), 4.14 (s, 2H, S-CH ₂), 5.48 (q, 1H, $J=6.4$ Hz, -CH-CH ₃), 6.70–7.33 (m, 13H, ArH), 7.51 (s, 1H, -CH), 12.21 (s, 1H, NH),

^aAll the compounds are purified by column chromatography.

Table 5. Anticonvulsant and neurotoxicity screening of synthesized compounds **4a–4y**

Compd.	Intraperitoneal injection in mice ^a						Acute toxicity ALD ₅₀ (mg kg ⁻¹ p.o.)
	MES		scPTZ		Neurotoxicity		
	screen		screen		screen		
	0.5h	4h	0.5h	4h	0.5h	4h	
4a	-	-	-	-	-	-	>1000
4b	300	-	-	-	300	-	>1000
4c	-	-	-	-	-	-	>1000
4d	300	300	-	-	-	-	>1000
4e	-	-	-	-	-	-	>2000
4f	100	300	300	-	300	-	>1000
4g	100	100	100	300	100	100	>1000
4h	100	300	300	-	-	-	>1000
4i	100	100	100	300	100	300	>2000
4j	100	-	300	-	300	300	>1000
4k	-	-	-	-	-	-	>1000
4l	300	-	300	-	-	-	>2000
4m	300	-	-	-	-	-	>1000
4n	-	-	-	-	-	-	>1000
4o	300	-	-	-	300	-	>1000
4p	-	-	-	-	-	-	>1000

4q	300	300	300	-	300	300	>1000
4r	-	-	-	-	-	-	>2000
4s	300	-	300	-	300	300	>1000
4t	-	-	-	-	-	-	>1000
4u	-	-	-	-	-	-	>1000
4v	-	-	-	-	-	-	>1000
4w	-	-	-	-	-	-	>1000
4x	-	-	-	-	-	-	>1000
4y	-	-	-	-	-	-	>1000
Phenytoin ^b	30	30	-	-	100	100	<i>NOT</i>
Carbamazepine ^b	30	100	100	300	100	300	<i>NOT</i>
Na Valproate ^b	300	-	300	-	-	-	<i>NOT</i>
Phenobarbital ^b	100	30	30	30	100	300	<i>NOT</i>

^a Doses of 30, 100 and 300 mg/kg were administered. The figures in the Table indicate the minimum dose whereby bioactivity was demonstrated in half or more of the mice. The animals were examined 0.5 and 4.0 h after injection were made. The dash (–) indicates the absence of activity at maximum dose administered (300 mg/kg). *NOT* indicates not calculated.

^b Data from Refs.^{40,41,42}

Table 6. Anticonvulsant and neurotoxicity screening of synthesized compounds **5a–5y**

Compd.	Intraperitoneal injection in mice ^a						Acute toxicity ALD ₅₀ (mg kg ⁻¹ p.o.)
	MES screen		scPTZ screen		Neurotoxicity screen		
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	
5a	-	-	-	-	-	-	>2000
5b	300	-	300	-	300	300	>1000
5c	300	-	-	-	-	-	>1000
5d	300	-	-	-	300	300	>1000
5e	-	-	-	-	-	-	>1000
5f	100	300	300	-	300	300	>2000
5g	100	100	100	300	100	-	>1000
5h	100	-	-	-	100	-	>1000
5i	100	300	100	300	100	100	>1000
5j	300	300	-	-	-	-	>500
5k	-	-	-	-	-	-	>1000
5l	300	-	300	300	-	-	>1000
5m	-	-	-	-	-	-	>1000
5n	-	-	-	-	-	-	>1000
5o	300	-	300	-	-	300	>1000

5p	-	-	-	-	-	-	>1000
5q	-	-	-	-	-	-	>1000
5r	-	-	-	-	-	-	>1000
5s	300	-	300	-	300	300	21000
5t	-	-	-	-	-	-	>1000
5u	-	-	-	-	-	-	>1000
5v	-	-	-	-	-	-	>1000
5w	-	-	-	-	-	-	>1000
5x	-	-	-	-	-	-	>1000
5y	-	-	-	-	-	-	>1000
Phenytoin ^b	30	30	-	-	100	100	NOT
Carbamazepine ^b	30	100	100	300	100	300	NOT
Na Valproate ^b	300	-	300	-	-	-	NOT
Phenobarbital ^b	100	30	30	30	100	300	NOT

^a Doses of 30, 100 and 300 mg/kg were administered. The figures in the Table indicate the minimum dose whereby bioactivity was demonstrated in half or more of the mice. The animals were examined 0.5 and 4.0 h after injection were made. The dash (–) indicates the absence of activity at maximum dose administered (300 mg/kg). *NOT* indicates not calculated.

^b Data from Refs. 40,41,42

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