Available online at www.ijpsdronline.com
International Journal of Pharmaceutical Sciences and Drug Research 2012; 4(3): 195-198

Research Article ISSN 0975-248X

Synthesis and Anticonvulsant Activity of Some Newer Semicarbazone Derivatives

Shahnawaz Sameem, Nitin Kumar, Devender Pathak*

Department of Pharmaceutical Chemistry, Rajiv Academy for Pharmacy, NH#2, Delhi-Mathura Highway, P.O. Chhatikara, Mathura-281 001, Uttar Pradesh, India

ABSTRACT

A series of 4-(3-Chlorophenyl)-1-(substituted acetophenone) semicarbazones **3(a-j)** was synthesized by starting with 3-chloroaniline which on reaction with sodium cyanate yielded 1-(3'-chlorophenyl) urea **(1)** followed by reaction with hydrazine hydrate in the presence of ethanol gave 4-(3'-chlorophenyl) semicarbazide **(2)**. Compound **(2)** on condensation with substituted acetophenone gets converted in to final compounds **3(a-j)**. The purity of the newer compounds was checked by m.p. and TLC analysis. The structures of the newly synthesized compounds were characterized by FTIR, ^{1}H NMR, EIMS-spectral data and elemental analysis. All the synthesized compounds were evaluated for their anticonvulsant activity by Maximal Electroshock (MES) method by using phenytoin as standard at a concentration of 30 mg/kg. The anticonvulsant effect of the newly synthesized compounds was assessed by absence or reduction of hind limb tonic extensor phase. Among the synthesized derivatives compounds **3e** and **3j** were found to be the most potent compounds in the series.

Keywords: Anticonvulsant, MES method, Semicarbazone.

INTRODUCTION

Epilepsy is a syndrome, not a disease characterized by paroxysmal, excessive and hypersynchronous discharges of large number of neurons. [1] Epilepsy is a common neurological disorder affecting a large section (0.5-1%) of the population throughout the world. [2-4] Currently available antiepileptic drugs (AEDs) are symptomatically effective in only 65-75% patients. [5-11] Recently drugs such as topiramate, zonisamide, vigabatrin etc. are used to in the treatment of epilepsy. In spite of the optimal use of available antiepileptic drugs (AEDs), lots of patients fail to control the seizure and other patients who experience the control in seizure occur with significant side effects which limit their use, and show the need for developing new anticonvulsant. [12-18]

From the previous studies it was shown that anticonvulsant properties have been shown by various amides (-$CONH_2$) and carbamides (NH-CO-NH) containing drugs. The prime requirement was to search the molecule that could have combination of both the structures. This event initiates the synthesis of semicarbazones as anticonvulsant agent. [19-20] These compounds were thought to be interacting with putative binding site. The pharmacophoric moiety was thought to be hydrogen bonding domain and aryl ring which is lipophilic. [21-22]

These semicarbazones do not contain dicarboximide group which is present in AEDs like phenobarbitone, phenytoin, iminostilbines etc. which may show the toxicity and side effects. [23] The present work highlights the synthesis of 4-(3-Chlorophenyl)-1-(substituted acetophenone) semicarbazones **3(a-j)** as shown in Scheme-1 and compare anticonvulsant activity with the standard drug.

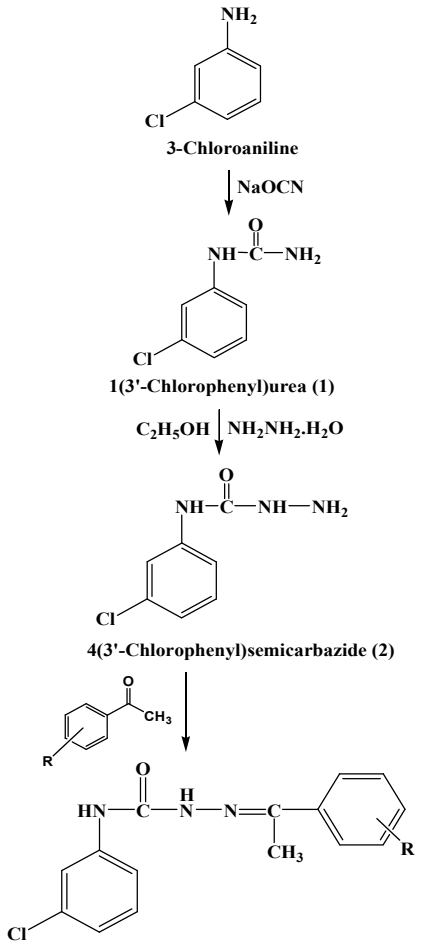
The newly synthesized semicarbazone derivatives were screened in vivo for their anticonvulsant activity by the maximal electroshock induced seizure (MES) method by using phenytoin as standard.

***Corresponding author: Prof. (Dr.) Devender Pathak,** Director, Rajiv Academy for Pharmacy, NH#2, Delhi-Mathura Highway, P.O. Chhatikara, Mathura-281 001, Uttar Pradesh, India; **Tel.:** +91-9897661620; **Fax:** +91-565-2825050; **E-mail:** dev_15@rediffmail.com

MATERIALS AND METHODS

All the chemicals used were procured from Qualigens® Fine Chemicals, Mumbai and CDH (P) Ltd., New Delhi. Melting point ranges of the newly synthesized compounds were determined by open capillary method and are uncorrected. Thin layer chromatography using Silica gel G (E. Merck) plates was used to access the reaction and purity of the synthesized compounds. Elemental analysis was obtained for all the newly synthesized compounds on Carlo Erba EA 1108 elemental analyser. The λ_{max} of the newly synthesized compounds were scanned on UV-Visible spectrophotometer Pharma spec-1700. IR spectrum of compounds in KBr pellets were recorded on a FTIR-8400S spectrophotometer (SHIMADZU) using KBr disc, ^{1}H NMR spectra were

recorded in DMSO on a Bruker Advance (400 MHz) NMR spectrophotometer using TMS as internal standard and mass spectra was taken by EIMS on SHIMADZU-2010 AT, software class VP.



Scheme 1: Synthesis of 4-(3-Chlorophenyl)-1-(substituted acetophenone) semicarbazones 3(a-j)

Synthesis of 1-(3-chlorophenyl) urea (1)

3-Chloroaniline (12.7 g, 0.1mol) was dissolved in a solution of glacial acetic acid (50 ml) and water (100 ml). To this a mixture of sodium cyanate (6.5 g, 0.1mol), glacial acetic acid (20 ml) and water (50 ml) was added with continuous stirring for 6-7 hours at room temperature. A solid product was obtained which was filtered, dried and recrystallized from ethanol to give compound **1. (Yield** 78.82%**; m.p.** 141-142ºC)

Synthesis of 4-(3-Chlorophenyl) semicarbazide (2)

Equimolar quantity of 1-(3-chlorophenyl) urea **(1)** (10.5 g, 0.06 mol) and hydrazine hydrate (12.6 g, 0.06 mol) was dissolved in ethanol (50 ml) and refluxed for 26 hrs. After this reaction mixture was poured to crushed ice. The solid obtained was filtered, dried and recrystallized from ethanol to give compound **2.** (**Yield** 74.65%**; m.p.** 138-139ºC)

General method for synthesis of 4-(3-Chlorophenyl)-1-(substitutedacetophenone) semicarbazones 3(a-j)

4-(3-Chlorophenyl) semicarbazide **(2)** (0.005 mol) and substituted acetophenone (0.005 mol) was dissolved in 30 ml of ethanol and refluxed for 13-14 hours. After this reaction mixture was poured to crushed ice. The solid obtained was filtered, dried and recrystallized from ethanol to give compound **3(a-j)**.

Spectral analysis

1-(Acetophenone)-4-(3-chlorophenyl) semicarbazone (3a)

UV (λ_{max}) (Ethanol): 269 nm**; FTIR (KBr):** 3352.69 (N-H str.), 3026.25 (Ar C-H str.), 1645.80 (C=O str.), 1580.80 **(**C=N str.), 1540.25 (Ar C=C str.), 1280.71 (C-N str.), 742.54 cm^{-1} (C-Cl str.)**; ^{1}H NMR (DMSO-d_6):** δ 1.84 (s, 3H, CH_3), 6.81-8.01 (m, 9H, Ar-H), 8.91 (s, 1H, Ar-NH, exchangeable with D_2O), 10.00 ppm (s, 1H, CONH, exchangeable with D_2O)**; EIMS: m/z (%)** 289.3 (31) $[M+2]^+$, 287.7 (100) $[M]^+$, 253.1 (28), 239.3 (56), 163.8 (69), 151.0 (19), 136.0 (26), 93.0 (55), 77.0 (34); **Elemental analysis:** Calcd for $C_{15}H_{14}ClN_3O$: C, 62.61; H, 4.90; N, 14.60% Found: C, 62.58; H, 4.87; N, 14.64%**.**

4-(3-Chlorophenyl)-1-(4'-hydroxyacetophenone) semicarbazone (3b)

UV (λ_{max}) (Ethanol): 278 nm**; FTIR (KBr):** 3592.20 (O-H str.), 3349.25 (N-H str.), 3023.65 (Ar C-H str.), 1642.48 (C=O str.), 1580.20 **(**C=N str.), 1536.09 (Ar C=C str.), 1209.28 (C-N str.), 688.39 cm^{-1} (C-Cl str.)**; ^{1}H NMR (DMSO-d_6):** δ 1.94 (s, 3H, CH_3), 6.85-8.01 (m, 8H, Ar-H), 8.94 (s, 1H, Ar-NH, exchangeable with D_2O), 9.74 (s, 1H, CONH, exchangeable with D_2O), 10.12 ppm (s, 1H, Ar-OH, exchangeable with D_2O)**; EIMS: m/z (%)** 305.0 (37) $[M+2]^+$, 305.0 (100) $[M]^+$, 269.1 (16), 239.0 (15), 163.8 (17), 151.1 (48), 136.0 (37), 93.0 (25), 75.0 (14)**; Elemental analysis:** Calcd for $C_{15}H_{14}ClN_3O_2$: C, 59.31; H, 4.65; N, 13.83% Found: C, 59.29; H, 4.61; N, 13.81%**.**

4-(3-Chlorophenyl)-1-(4'-methoxyacetophenone) semicarbazone (3c)

UV (λ_{max}) (Ethanol): 274 nm**; FTIR (KBr):** 3239.65 (N-H str.), 3052.62 (Ar C-H str.), 1654.71 (C=O str.), 1565.80 **(**C=N str.), 1542.20 (Ar C=C str.), 1280.71 (C-N str.), 1213.85 (C-O), 659.12 cm^{-1} (C-Cl str.)**; ^{1}H NMR (DMSO-d_6):** δ 1.93 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 6.83-8.01 (m, 8H, Ar-H), 8.99 (s, 1H, Ar-NH, exchangeable with D_2O), 10.17 ppm (s, 1H, CONH, exchangeable with D_2O)**; EIMS: m/z (%)** 319.03 (31) $[M+2]^+$, 317.74 (100) $[M]^+$, 283.33 (56), 239.03 (39), 163.08 (43), 151.01 (28), 136.02 (66), 93.08 (35), 77.08 (44); **Elemental analysis:** Calcd for $C_{16}H_{16}ClN_3O_2$: C, 60.47; H, 5.08; N, 13.22% Found: C, 60.43; H, 5.06; N, 13.20%**.**

1-(4'-Chloroacetophenone)-4-(3-chlorophenyl) semicarbazone (3d)

UV (λ_{max}) (Ethanol): 282 nm**; FTIR (KBr):** 3239.65 (N-H str.), 3052.62 (Ar C-H str.), 1655.71 (C=O str.), 1554.71 **(**C=N str.), 1535.20 (Ar C=C str.), 1280.71 (C-N str.), 659.12 cm^{-1} (C-Cl str.)**; ^{1}H NMR (DMSO-d_6):** δ 1.94 (s, 3H, CH_3), 7.26-8.21 (m, 8H, Ar-H), 9.19 (s, 1H, Ar-NH, exchangeable with D_2O), 10.19 ppm (s, 1H, CONH, exchangeable with D_2O)**; EIMS: m/z (%)** 323.03 (31) $[M+2]^+$, 321.14 (100) $[M]^+$, 253.01 (51), 239.03 (56), 163.08 (42), 151.01 (33), 136.02 (66), 93.08 (52), 77.08 (24); **Elemental analysis:** Calcd for $C_{15}H_{13}Cl_2N_3O$: C, 55.92; H, 4.07; N, 13.04% Found: C, 55.91; H, 4.05; N, 13.02%**.**

4-(3-Chlorophenyl)-1-(4'-fluoroacetophenone) semicarbazone (3e)

UV (λ_{max}) (Ethanol): 289 nm**; FTIR (KBr):** 3318.43 (N-H str.), 3072.39 (Ar C-H str.), 1657.41 (C=O str.), 1574.41 **(**C=N str.), 1535.71 (Ar C=C str.), 1242.07 (C-N str.), 1068.92 (C-F str.), 642.25 cm^{-1} (C-Cl str.)**; ^{1}H NMR (DMSO-d_6):** δ 1.96 (s, 3H, CH_3), 7.26-8.22 (m, 8H, Ar-H),

9.12 (s, 1H, Ar-NH, exchangeable with D_2O), 10.29 ppm (s, 1H, CONH, exchangeable with D_2O)**; EIMS: m/z (%)** 307.14 (31) $[M+2]^+$, 305.64 (100) $[M]^+$, 332.33 (55), 239.03 (45), 163.08 (69), 151.01 (39), 136.02 (66), 93.08 (50), 77.08 (54); **Elemental analysis:** Calcd for $C_{15}H_{13}ClFN_3O$: C, 58.93; H, 4.29; N, 13.74% Found: C, 58.92; H, 4.27; N, 13.72%**.**

1-(4'-Bromoacetophenone)-4-(3-chlorophenyl) semicarbazone (3f)

UV (λ_{max}) (Ethanol): 285 nm**; FTIR (KBr):** 3318.43 (N-H str.), 3084.37 (Ar C-H str.), 1657.07 (C=O str.), 1575.41 **(**C=N str.), 1540.87 (Ar C=C str.), 1242.07 (C-N str.), 642.26 (C-Cl str.), 547.75 cm^{-1} (C-Br str.)**; ^{1}H NMR (DMSO-d_6):** δ 2.06 (s, 3H, CH_3), 7.31-8.23 (m, 8H, Ar-H), 9.02 (s, 1H, Ar-NH, exchangeable with D_2O), 10.28 ppm (s, 1H, CONH, exchangeable with D_2O)**; EIMS: m/z (%)** 366.14 (32) $[M+2]^+$, 364.64 (100) $[M]^+$, 332.33 (44), 239.03 (62), 163.08 (56), 151.1 (69), 136.02 (76), 93.08 (55), 77.08 (44); **Elemental analysis:** Calcd for $C_{15}H_{13}BrClN_3O$: C, 49.14; H, 3.57; N, 11.46% Found: C, 49.10; H, 3.56; N, 11.44%**.**

4-(3-Chlorophenyl)-1-(4'-nitroacetophenone) semicarbazone (3g)

UV (λ_{max}) (Ethanol): 265 nm**; FTIR (KBr):** 3387.40 (N-H str.), 3044.40 (Ar C-H str.), 1645.40 (C=O str.), 1595.50 **(**C=N str.), 1547.00 (Ar C=C str.), 1515.00 (N=O str.) 1254.10 (C-N str.), 700.60 cm^{-1} (C-Cl str.)**; ^{1}H NMR (DMSO-δ_6):** δ 1.75 (s, 3H, CH_3), 7.30-8.67 (m, 8H, Ar-H), 8.91 (s, 1H, Ar-NH, exchangeable with D_2O), 9.91 ppm (s, 1H, CONH, exchangeable with D_2O)**; EIMS: m/z (%)** 334.44 (31) $[M+2]^+$, 332.64 (100) $[M]^+$, 298.13 (56), 239.3 (61), 163.8 (20), 151.1 (39), 136.02 (36), 93.08 (55), 77.08 (64); **Elemental analysis:** Calcd for $C_{15}H_{13}ClN_4O_3$: C, 54.14; H, 3.94; N, 16.84% Found: C, 54.11; H, 3.91; N, 16.82%**.**

1-(4'-Aminoacetophenone)-4-(3-chlorophenyl) semicarbazone (3h)

UV (λ_{max}) (Ethanol): 270 nm**; FTIR (KBr):** 3367.60 (N-H str.), 3040.60 (Ar C-H str.), 1645.50 (C=O str.), 1588.5 **(**C=N str.), 1545.00 (Ar C=C str.), 1250.90 (C-N str.), 750.90 cm^{-1} (C-Cl str.)**; ^{1}H NMR (DMSO-d_6):** δ 1.74 (s, 3H, CH_3), 3.92 (s, 2H, NH_2) 7.30-8.67 (m, 8H, Ar-H), 8.99 (s, 1H, Ar-NH, exchangeable with D_2O), 9.19 ppm (s, 1H, CONH, exchangeable with D_2O)**; EIMS: m/z (%)** 304.14 (31) $[M+2]^+$, 302.14 (100) $[M]^+$, 268.23 (56), 239.03 (50), 163.08 (49), 151.01 (38), 136.02 (26), 93.08 (35), 77.08 (24); **Elemental analysis:** Calcd for $C_{15}H_{15}ClN_4O$: C, 59.51; H, 4.99; N, 18.51% Found: C, 59.50; H, 4.97; N, 18.50%**.**

4-(3-Chlorophenyl)-1-(3'-nitroacetophenone) semicarbazone (3i)

UV (λ_{max}) (Ethanol): 268 nm**; FTIR (KBr):** 3344.80 (N-H str.), 3014.40 (Ar C-H str.), 1645.40 (C=O str.), 1588.00 **(**C=N str.), 1545.00 (Ar C=C str.), 1510.20 (N=O str.), 1254.10 (C-N str.), 668.60 cm^{-1} (C-Cl str.)**; ^{1}H NMR (DMSO-d_6):** δ 1.74 (s, 3H, CH_3), 7.30-8.67 (m, 8H, Ar-H), 8.89 (s, 1H, Ar-NH, exchangeable with D_2O), 9.91 ppm (s, 1H, CONH, exchangeable with D_2O)**; EIMS: m/z (%)** 334.44 (31) $[M+2]^+$, 332.64 (100) $[M]^+$, 298.13 (53), 239.3 (51), 163.8 (40), 152.1 (29), 136.02 (16), 90.08 (15), 75.08 (12); **Elemental analysis:** Calcd for $C_{15}H_{13}ClN_4O_3$: C, 54.13; H, 3.94; N, 16.84% Found: C, 54.10; H, 3.92; N, 16.81%**.**

1-(2'-Chloroacetophenone)-4-(3-chlorophenyl) semicarbazone (3j)

UV (λ_{max}) (Ethanol): 284 nm**; FTIR (KBr):** 3239.65 (N-H str.), 3052.62 (Ar C-H str.), 1654.71 (C=O str.), 1585.20 **(**C=N str.), 1542.71 (Ar C=C str.), 1280.71 (C-N str.), 659.71 cm^{-1} (C-Cl str.)**; ^{1}H NMR (DMSO-d_6):** δ 1.94 (s, 3H, CH_3), 7.26-8.21 (m, 8H, Ar-H), 9.19 (s, 1H, Ar-NH, exchangeable with D_2O), 10.19 ppm (s, 1H, CONH, exchangeable with D_2O); **EIMS: m/z (%)** 323.03 (31) $[M+2]^+$, 321.14 (100) $[M]^+$, 252.01 (51), 239.03 (60), 162.08 (52), 149.01 (18), 136.02 (26), 93.08 (45), 77.08 (34); **Elemental analysis:** Calcd for $C_{15}H_{13}Cl_2N_3O$: C, 55.92; H, 4.07; N, 13.04% Found: C, 55.91; H, 4.05; N, 13.02%**.**

Anticonvulsant activity

Anticonvulsant activity was performed by MES (maximal electroshock method)**.** This method has been approved by the Institutional Animal Ethical Committee at Rajiv Academy for Pharmacy, Mathura (Ref. No. IAEC/RAP/3055/2010). In the MES method, adult male and female Albino rats (Wistar strain) weighing 100-200 g were used. The animals were divided into three groups (control, standard and test) and each group comprising of three rats. The test compounds were suspended in 1% aqueous CMC suspension and were injected i.p. in doses ranging from 15, 30 and 60 mg/kg body weight. Phenytoin sodium was used as a standard drug which was given in the dose of 30 mg/kg by i.p. which was observed to protect 100% against the induced convulsions. The control group received only 1% aqueous CMC suspension. The seizures were induced by electroconvulsiometer (HICON®, Grover Ent., New Delhi).

The animals were subjected to electroshock by delivering the current of 150 mA through the corneal electrodes for a period of 0.2 seconds. The animals were observed for 30 min convulsive responses. Different stages of convulsions i.e. the tonic flexion (towards the upper extremities), tonic extensor phase (extension of the lower extremities), clonic convulsions (intermediate jerking of limbs), stupor (unconsciousness) and recovery or death were observed for each animal (data as shown in Table 2). The anticonvulsant effect of newly synthesized compounds was assessed by absence or reduction of hind limb tonic extensor phase.

Each value represents the mean SEM (standard error mean) of three rats significantly different from standard drug phenytoin ($t_{tab} < t_{cal}$, $P < 0.05$) (student's *t*-test)

RESULTS AND DISCUSSION

All newly synthesized compounds were characterized on the basis of their m.p, R_f value (data are shown in Table-1), FTIR, ^{1}H NMR, MASS spectra and elemental analysis.

Anticonvulsant activity of the compounds was performed using the maximal electroshock-induced seizure (MES) method in albino rats (Wistar strain) of either sex. This method claimed to detect compounds possessing activity against generalized tonic clonic (grandmal) seizures. The MES test is a measure of an anticonvulsant drug to abolish or reduce the time of the tonic extensor component of the hind limb in the maximal seizure pattern induced by 150 mA of current delivered for 0.2 seconds.

In the primary MES screening compound **3c**, **3e**, **3g** and **3j** afforded protection against seizures confirming their potential utility as prototypic molecules. The anticonvulsant activity data revealed that all the compounds showed remarkable reduction of hind limb tonic extensor phase when given in the dose of 30 mg/kg i.p. and compounds **3e** and **3j** were found to be the most potent compounds in the series. Moreover, anticonvulsant activity of the other tested

compounds was found to be much less effective than phenytoin used as standard anticonvulsant drug. According to the results obtained it seems that presence of chloro group, nitro group and hydroxy group attached on aryl ring increase the potency.

Table 1: Characterization data of the synthesized compounds 3(a-j)

Compound no.	R	m.p. (°C)	Yield (%)	*R_f Value
3a	4-H	108-109	62.05	0.72
3b	4-OH	143-144	54.25	0.63
3c	4-OCH_3	164-165	68.23	0.64
3d	4-Cl	158-159	70.23	0.70
3e	4-F	173-174	63.45	0.71
3f	4-Br	155-156	69.46	0.72
3g	4-NO_2	162-163	72.36	0.69
3h	4-NH_2	169-170	70.00	0.58
3i	3-NO_2	145-146	69.78	0.78
3j	2-Cl	172-173	61.23	0.66

Table 2: Anticonvulsant activity of titled compounds

Code of compounds	30 mg/kg (Dose)				
	Flexion (mean± SEM)	Extensor (mean±SEM)	Clonus (mean± SEM)	Stupor (mean±SEM)	Recovery/Death
3a	4.6±0.5	11.6±0.5	13.3±0.4	112.1±0.4	R
3b	5.1±0.4	7.2±0.2	11.8±0.6	110.7±0.4	R
3c	4.1±0.4	7.4±0.9	10.1±0.7	110.4±0.4	R
3d	4.9±0.2	8.4±0.6	12.3±0.9	114.1±0.6	R
3e	4.2±0.7	6.5±0.5	7.6±0.1	108.3±0.7	R
3f	5.1±0.9	8.8±0.4	12.8±0.4	112.5±0.2	R
3g	3.7±0.5	8.4±0.2	11.2±0.9	110.6±0.1	R
3h	5.3±0.5	9.1±0.3	10.8±0.4	118.6±0.7	R
3i	5.8±0.4	6.8±0.5	13.3±0.4	118.2±0.8	R
3j	3.6±0.4	6.2±0.9	7.2±0.4	106.1±0.9	R
Control	4.2±0.9	9.6±0.4	11.8±0.2	114.1±0.4	R
Phenytoin sodium	Absent	5.6±0.2	2.4±0.1	104.2±0.2	R

Phenytoin sodium (30 mg/kg i.p.)

ACKNOWLEDGEMENT

The authors are thankful to Department of Pharmaceutical Chemistry, Hamdard University, New Delhi for ^{1}H NMR spectral analysis and Central Drug Research Institute, Lucknow for Mass spectral analysis. Authors are also thankful to the management, Rajiv Academy for Pharmacy, Mathura for providing the facilities to carry out anticonvulsant activity.

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