ISSN 2063-5346

SYNTHESIS AND ANTICONVULSANT ACTIVITY OF SOME NOVEL FLAVANONE INCORPORATED SEMICARBAZIDES

Tripti Verma, Chandra Shekhar Sharma

Faculty of Pharmacy, Bhupal Nobles' University, Udaipur, Rajasthan, India-313001

Article History: **Received:** 01.02.2023 **Revised:** 07.03.2023 **Accepted:** 10.04.2023

Abstract

A series of novel flavone incorporated semicarbazides (**5a-5g**) was synthesized and characterized by elemental analyses, ^{1}H NMR, and mass spectral studies. The newly synthesized compounds were screened for their anticonvulsant activity against Pentylenetetrazole (PTZ)-induced Convulsions model in male wistar rats and compared with the standard drug phenytoin. Compound **5e** was found to be most active compound as comparable to standard drug phenytoin.

Keywords Flavones, Semicarbazide, Anticonvulsant, PTZ, NMR

Introduction

Epilepsy is defined as having two or more unprovoked seizures. There are 50 million persons with epilepsy globally, and half of them reside in developing nations [1-3]. Just 65-75% of individuals respond symptomatically to the antiepileptic medications (AEDs) that are currently on the market [4-5]. Around 20–30% of individuals experience seizures that are unresponsive to current medicinal treatments [6-7]. All currently approved antiepileptic drugs have dose-related toxicity and idiosyncratic side effects [8-9]. Despite improvements in the medication treatment of epilepsy, there are still a number of restrictions on antiepileptic drug therapy [10-11].

These facts warrant the search for new anticonvulsant drugs. From the previous reported studies, it was shown that anticonvulsant properties have been shown by various amides ($CONH_2$) and carbamides (NH–CO–NH) containing drugs. This study initiates the synthesis of semicarbazones as anticonvulsant agent. A series of aryl semicarbazones displayed excellent oral activity in the maximal electroshock (MES) screen in rats [12]. Aryl semicarbazides have been reported to show excellent anticonvulsant activity in rats and mice [13-15]. In recent years, aryl and heteroaryl semicarbazones have emerged as novel anticonvulsants [13, 15]. The semicarbazones do not contain dicarboximide group which is present in AEDs like phenobarbitone, phenytoin, iminostilbines, etc., which may show the toxicity and side effects [16]. Different aryl and heteroaryl moieties have been clubbed to the semicarbazone pharmacophore as hydrophobic domain which led to the increase in the activity significantly. Bhat et al. [17] synthesized a series of 3-(4-acetyl-5*H*/methyl-5-substituted phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2*H*-

chromene-2-ones (flavones) and evaluated for anticonvulsant activity and neurotoxicity. Some compounds were found to be potent in MES test. All the compounds were found to be less toxic as compared with the standard drug phenytoin.

In the present work, we intended to incorporate the modified flavone moiety with the semicarbazide since flavones alone shown strong anticonvulsant efficacy. Adding the two active anticonvulsant pharmacophores were expected to have synergistic effect in dealing with anticonvulsant activity. Based on these aspects some molecules are designed with potential anticonvulsant activity shown in Fig. 1. This semicarbazones based pharmacophoric model comprises following four essential binding sites:

1. An aryl hydrophobic binding site (A),
2. A hydrogen bonding domain (B),
3. An electron donor group (D), and
4. A hydrophobic–hydrophilic site (C).

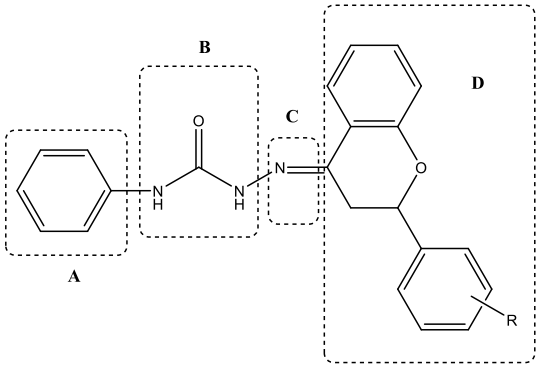
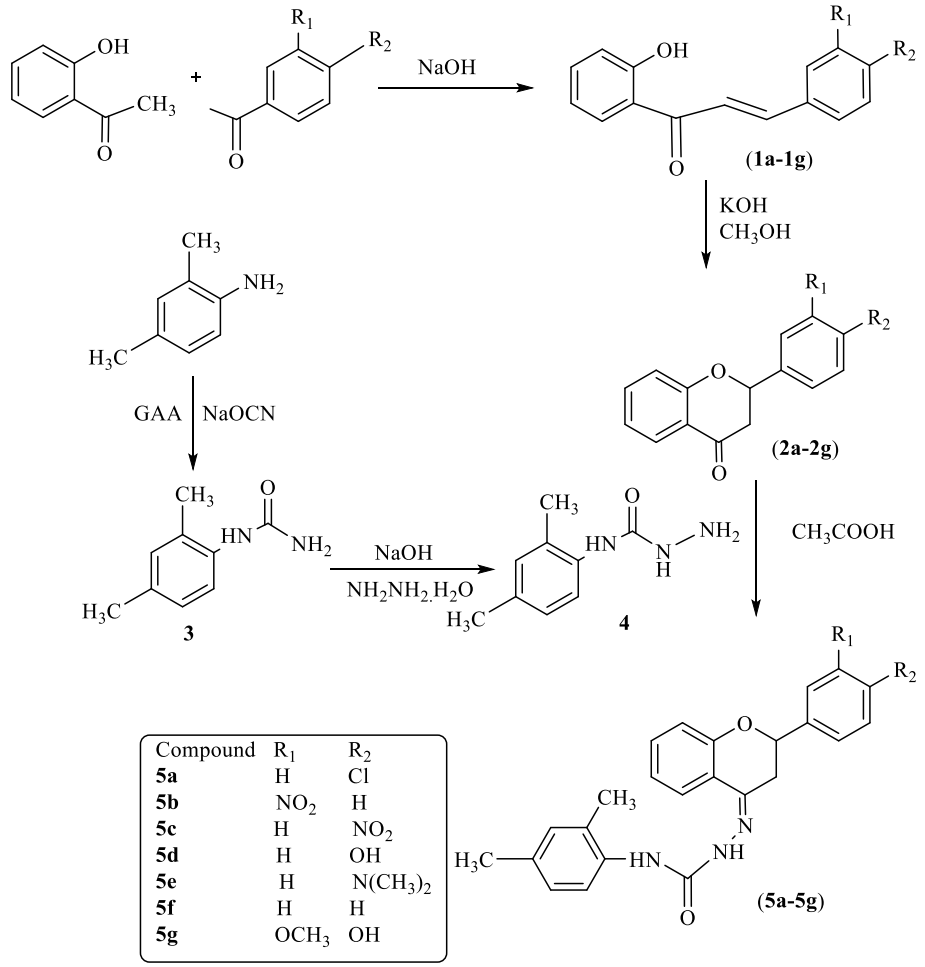


Figure 1: Structure of proposed general pharmacophore model of the synthesized compounds

The newly synthesized flavanone incorporated semicarbazide derivatives were evaluated for anticonvulsant activity by the PTZ method using phenytoin as standard.



Experimental Work

Melting points (°C) of the synthesized compounds were determined in open capillary tubes and are uncorrected. IR absorption spectra were recorded on Jasco FT/IR-470 PLUS, KBr diffuse reflectance (cm^{-1}), ^1H NMR spectra were recorded on the Bruker DPX-400 instrument at 400 respectively. The 1H chemical shifts are reported as parts per million (ppm) downfield from TMS (Me4Si). The LCMS of the compounds was recorded on Shimadzu 8201PC spectrometer. IR, ^1H NMR, and LCMS were consistent with the assigned structures. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapor. The elemental analysis (CHN analysis) was done on a CHN rapid analyzer. All the compounds gave satisfactory analysis within ±0.4 % of the theoretical values.

Synthesis of 3-(4-chlorophenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one (1a)

4-chloro benzaldehyde (0.012 mol) was added to a mixture of o-hydroxyacetophenone (0.01 mol) in 25 ml of ethanol in a 200 ml beaker. The content of the beaker were mixed well and to that 50 ml of 10% sodium hydroxide solution was added and stirred vigorously at 25 °C until the mixture was so thick that stirring was no longer effective (35 min.). After the completion of the stirring, the reaction mixture was kept in a refrigerator overnight. The reaction mixture was then diluted with ice cold water, acidified with 10% aqueous hydrochloric acid to precipitate the chalcone. The product was filtered with suction on a Buchner funnel, washed with cold water until the washings were neutral to litmus and then washed with ice-cold rectified spirit. The dried product was recrystallized from chloroformand dried at room temperature. The completion of reaction was monitored by running TLC.[125]

MP:110-112^{0}C; Mobile Phase: n-hexane: ethyl acetate (9.5:0.5); R_f value: 0.41; Yield: 75%.

The other compounds (**1b–1g**) were prepared by the same procedure using the corresponding aldehydes

1-(2-hydroxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-one (1b)

MP: 123-125^{0}C; Mobile Phase: n-hexane: ethyl acetate (9.5:0.5); R_f value: 0.72; Yield: 71%.

1-(2-hydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one (1c)

MP: 203-206^{0}C; Mobile Phase: n-hexane: ethyl acetate (7:3); R_f value: 0.47; Yield: 75%.

1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (1d)

MP: 135-137^{0}C; Mobile Phase: n-hexane:ethyl acetate (9.8:0.2); value: 0.74; Yield: 84%.

3-[4-(dimethylamino)phenyl]-1-(2-hydroxyphenyl)prop-2-en-1-one (1e)

MP: 128-130^{0}C; Mobile Phase: n-hexane: ethyl acetate (9:1); R_f value: 0.65; Yield: 78%.

1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (1f)

MP: 53-55^{0}C; Mobile Phase: n-hexane: ethyl acetate (9.5:0.5); R_f value: 0.50; Yield: 81%.

3-(4-hydroxy-3-methoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (1g)

MP: 122-124^{0}C; Mobile Phase: n-hexane:ethyl acetate (7:3); R_f value: 0.54; Yield: 79%.

2-(4-chlorophenyl)-2,3-dihydro-4*H*-chromen-4-one (2a)

3-(4-chlorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (0.001

mol) was dissolved in methanol in a 200 ml beaker. The resulting solution was made alkaline (pH 10.0) with potassium hydroxide pellets and was allowed to stand for 24 hr. at room temperature. The reaction mixture was then acidified (using 10% aqueous hydrochloric acid: ice-cold) to precipitate the flavanone. The product was filtered withsuction on a Buchner funnel, washed with cold water until the washings were neutral to litmus and then with ice-cold rectified spirit. The dried product was recrystallized from chloroform and dried at room temperature. The completion of reaction was monitored by running TLC.[125]

MP: 138-140^{0}C; Mobile Phase: n-hexane: ethyl acetate (9.5:0.5); R_f value: 0.48

Yield: 84%

The other compounds (**2b–2g**) were prepared by the same procedure using the corresponding chalcones.

2-(3-nitrophenyl)-2,3-dihydro-4*H*-chromen-4-one (2b)

MP: 270-272^{0}C; Mobile Phase: n-hexane: ethyl acetate (9.5:0.5); R_f value: 0.74; Yield: 88%

2-(4-nitrophenyl)-2,3-dihydro-4*H*-chromen-4-one (2c)

MP: 228-230^{0}C; Mobile Phase: n-hexane: ethyl acetate (7:3); R_f value: 0.50; Yield: 80%

2-(4-hydroxyphenyl)-2,3-dihydro-4*H*-chromen-4-one (2d)

Melting Point: 118-120^{0}C; Mobile Phase: n-hexane: ethyl acetate (9.8:0.2); R_f value: 0.71; Yield: 87%

2-[4-(dimethylamino)phenyl]-2,3-dihydro-4*H*-chromen-4-one (2e)

MP: 63-65^{0}C; Mobile Phase: n-hexane: ethyl acetate (9:1); R_f value: 0.70; Yield: 88%.

2-phenyl-2,3-dihydro-4*H*-chromen-4-one (2f)

MP: 100-102^{0}C; Mobile Phase: n-hexane: ethyl acetate (9.5:0.5); R_f value: 0.55; Yield: 86%

2-(4-hydroxy-3-methoxyphenyl)-2,3-dihydro-4*H*-chromen-4-one (2g)

MP: 268-270^{0}C; Mobile Phase: n-hexane: ethyl acetate (7:3); R_f value: 0.56; Yield: 91%

1-(2,4-dimethylphenyl)urea (3)

MP: 211-213^{0}C; Mobile Phase: Benzene: Acetone (9:1); R_f value: 0.69; Yield: 82%

4-(2,4-dimethylphenyl)semicarbazide (4)

MP: 265-267^{0}C; Mobile Phase: Benzene: Acetone (9:1); R_f value: 0.81; Yield: 92%

1-[2-(4-chlorophenyl)-2,3-dihydrochromen-4-ylidene]-4-(2,4-dimethylphenyl) semicarbazone (5a)

A mixture of 4-(2,4-dimethylphenyl)semicarbazide (0.01 mol) and 2-(4- chlorophenyl)-2,3-dihydro-4*H*-chromen-4-one (0.01 mol) in methanol, and catalytic amount of acetic acid were stirred at 60-70^{o}C for 3 hours. The reaction mixture was poured into a beaker containing crushed ice and allowed to stand for two hours. The precipitate so formed was filtered and washed with ice cold water. The crude product was dried and recrystallized from chloroform. The completion of reaction was monitored by running TLC.

MP: 104-106^{0}C; Mobile Phase: n-hexane:ethyl acetate (9.8:0.2); R_f value: 0.70; Yield: 90%.; Anal. Calcd. for $C_{24}H_{22}N_3O_2Cl$ (419.9): C, 68.65; H, 5.28; N, 10.01. Found: C, 68.67; H, 5.31; N, 9.98. IR (KBr) υ_{max}: 3340 (-NH), 3060, 3063, 3054, (CH Str.), 1668 (C=O), 1601 (C=N), 1530, 1461, 1440 (Ar. C=C), 1299

(C-O-C); ^{1}H NMR: 9.11(s, 1H, NH), 8.34 (s, 1H, NH), 7.75-7.81 (m, 4H, Ar-CH) 7.22-7.64 (m, 3H, Ar-CH) 6.65-7.08 (m, 4H, Ar-CH) 5.40-5.57 (m, 1H, O-CH), 3.60-3.64 (d, 1H, N=C-CH_2), 3.28-3.32 (d, 1H, N=C-CH_2), 2.33 (s, 3H, CH_3), 2.16 (s, 3H, CH_3); Mass (M/Z): 419.1 (M^+), 420.1 (M^{+1}).

The other compounds (**5b–5g**) were prepared by the same procedure using the corresponding flavones.

1-[2-(3-nitrophenyl)-2,3-dihydrochromen-4-ylidene]-4- (2,4-dimethylphenyl)semicarbazone (5b)

MP: 235-237^{0}C; Mobile Phase: n-hexane: ethyl acetate (9.5:0.5); R_f value: 0.72; Yield: 88%.

Anal. Calcd. for $C_{24}H_{22}N_4O_4$ (430.46): C, 66.97; H, 5.15; N, 13.02. Found: C, 66.93; H, 5.12; N, 12.98; IR (KBr) υ_{max}: 3648, 3565 (-NH), 2919, 2920, 3031(CH Str.), 1669 (C=O), 1594 (C=N), 1540, 1507, (Ar. C=C), 1471 (C-NO_2), 1231 (C-O-C); ^{1}H NMR: 9.29(s, 1H, NH), 8.16 (s, 1H, NH), 7.77-7.85 (m, 4H, Ar-CH) 7.23-7.55 (m, 3H, Ar-CH) 6.79-7.06 (m, 4H, Ar-CH) 5.31-5.38 (m, 1H, O-CH), 3.72-3.76 (d, 1H, N=C-CH_2), 3.34-3.39 (d, 1H, N=C-CH_2), 2.36 (s, 3H, CH_3), 2.19 (s, 3H, CH_3); Mass (M/Z): 430.3 (M^+).

1-[2-(4-nitrophenyl)-2,3-dihydrochromen-4-ylidene]-4- (2,4-dimethylphenyl)semicarbazone (5c)

MP: 120-122^{0}C; Mobile Phase: n-hexane: ethyl acetate (9.8:0.2); R_f value: 0.79; Yield: 94%; Anal. Calcd. for $C_{24}H_{22}N_4O_4$ (430.46): C, 66.97; H, 5.15; N, 13.02. Found: C, 66.93; H, 5.16; N, 12.96. IR (KBr) υ_{max}: 3648, 3566 (-NH), 3031 ,2920, 3042, (CH Str.), 1698 (C=O), 1557 (C=N), 1540, 1507, (Ar. C=C), 1473(C-NO_2), 1227 (C-O-C); ^{1}H NMR: 9.06 (s, 1H, NH), 8.42 (s, 1H, NH), 7.53-7.58 (m, 4H, Ar-CH) 6.86-7.03 (m, 3H, Ar-CH) 6.60-6.62 (m, 4H, Ar-CH) 5.34-5.40 (m, 1H, O-CH), 3.78-3.80 (d, 1H, N=C-CH_2), 3.45-3.48 (d, 1H, N=C-CH_2), 2.42 (s, 3H, CH_3), 2.28 (s, 3H, CH_3); Mass (M/Z): 430.2 (M^+).

1-[2-(4-hydroxyphenyl)-2,3-dihydrochromen-4-ylidene]- 4-(2,4-dimethylphenyl) semicarbazone (5d)

MP: 146-148^{0}C; Mobile Phase: n-hexane:ethyl acetate (9.5:0.5); R_f value: 0.62; Yield: 91%.

Anal. Calcd. for $C_{24}H_{23}N_3O_3$ (401.46): C, 71.80; H, 5.77; N, 10.47. Found: C, 71.78; H, 5.72; N, 10.48. IR (KBr) υ_{max}: 3648, 3566 (-NH), 3274 (-OH), 3031, 2919, 2920 (CH Str.), 1698 (C=O), 1557 (C=N), 1540, 1507, 1488 (Ar. C=C), 1261 (Ar-OH), 1229 (C-O-C); ^{1}H NMR: 9.18 (s, 1H, NH), 8.64 (s, 1H, NH), 8.34 (s, 1H, OH), 7.54-7.65 (m, 4H, Ar-CH) 7.26-7.32 (m, 3H, Ar-CH) 6.43- 6.64 (m, 4H, Ar-CH) 5.24-5.30 (m, 1H, O-CH), 3.98-3.91 (d, 1H, N=C-CH_2), 3.34-3.44 (d, 1H, N=C-CH_2), 2.34 (s, 3H, CH_3), 2.24 (s, 3H, CH_3); Mass (M/Z): 401.1 (M^+), 402.1 (M^{+1}).

1-[2-(4-(dimethylamino)phenyl)-2,3-dihydrochromen-4- ylidene]-4-(2,4-dimethylphenyl) semicarbazone (5e)

MP: 143-145^{0}C; Mobile Phase: n-hexane:ethyl acetate (9.5:0.5); R_f value: 0.63; Yield: 87%; Anal. Calcd. for $C_{26}H_{28}N_4O_2$ (428.53): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.82; H, 6.60; N, 13.08. IR (KBr) υ_{max}: 3648 (-NH), 3042, 3063, 3054 (CH Str.), 1733 (C=O), 1590 (C=N), 1540, 1507 (Ar. C=C), 1199(C-O-C); ^{1}H NMR: 9.25 (s, 1H, NH), 8.55 (s, 1H, NH), 7.80-7.87 (m, 4H, Ar-CH) 6.91-7.68 (m, 4H, Ar-CH) 6.87- 6.97 (m, 3H, Ar-CH) 5.23-5.28 (m, 1H, O-CH), 3.75-3.78 (d, 1H, N=C-CH_2), 3.39-3.48 (d, 1H, N=C-CH_2), 2.98 (s, 6H, CH_3), 2.45 (s, 3H, CH_3), 2.29 (s, 3H, CH_3); Mass (M/Z): 428.1 (M^+).

4-(2,4-dimethylphenyl)-1-(2-phenyl-2,3-dihydrochromen- 4-ylidene)semicarbazone (5f)

MP: 221-223^{0}C; Mobile Phase: n-hexane: ethyl acetate (9.8:0.2); R_f value: 0.83; Yield: 92%.

Anal. Calcd. for $C_{24}H_{23}N_3O_2$ (385.46): C, 74.78; H, 6.01; N, 10.90. Found: C, 74.75; H, 6.03; N, 10.88. IR (KBr) υ_{max}: 3648 (-NH), 3031, 3042, 3060 (CH Str.), 1682 (C=O), 1592 (C=N), 1540, 1447 (Ar. C=C), 1228(C-O-C); ^{1}H NMR: 9.08 (s, 1H, NH), 8.39 (s, 1H, NH), 7.51-7.56 (m, 5H, Ar-CH) 6.73-7.00 (m, 3H, Ar-CH) 6.49- 6.71 (m, 4H, Ar-CH) 5.28-5.39 (m, 1H, O-CH), 3.56-3.59 (d, 1H, N=C-CH_2), 3.41-3.44 (d, 1H, N=C-CH_2), 2.39 (s, 3H, CH_3), 2.23 (s, 3H, CH_3); Mass (M/Z): 385.1(M^+).

1-[2-(4-hydroxyl-3-methoxyphenyl)-2,3-dihydrochromen-4-ylidene]-4-(2,4-dimethylphenyl)semicarbazone (5g)

MP: 178-180^{0}C; Mobile Phase: n-hexane: ethyl acetate (9.5:0.5); R_f value: 0.61; Yield: 90%

Anal. Calcd. for $C_{25}H_{25}N_3O_4$ (431.48): C, 69.59; H, 5.84; N, 9.74. Found: C, 69.57; H, 5.81; N, 9.72. IR (KBr) υ_{max}: 3648 (-NH), 3277 (-OH), 2920, 2919 ,3031 (CH Str.), 1695 (C=O), 1560 (C=N), 1540, 1446 (Ar. C=C), 1267(Ar-OH), 1231 (C-O-C) ; ^{1}H NMR: 9.29 (s, 1H, NH), 8.42 (s, 1H, NH), 8.22 (s, 1H, OH), 7.72-7.78 (m, 4H, Ar-CH) 6.90-7.53 (m, 3H, Ar-CH) 6.74- 6.88 (m, 3H, Ar-CH) 5.09-5.15 (m, 1H, O-CH), 3.92 (s, 3H, CH_3), 3.61-3.68 (d, 1H, N=C-CH_2), 3.39-3.47 (d, 1H, N=C-CH_2), 2.44 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), Mass (M/Z): 431.2(M^+).

Anti-Convulsant Activity

Different type of epilepsies, *i.e.* grand mal, petit mal or psychomotor type, can be studied in laboratory animals. The maximal electro-shock (MES)-induced convulsions in animals represent grand mal type of epilepsy. Similarly, chemo-convulsions due to PTZ which produce clonic-type of convulsions resemble petit mal type of convulsions in man. These are the two procedures used to study convulsions, and to test anticonvulsant drugs in laboratory animals [18].

Pentylenetetrazole (PTZ)-induced Convulsions in Rats

Albino rats of 150-200 g body weight were divided into thirty seven groups of six animals each. The first group, receiving saline orally, served as control whereas the second group received 4mg/kg b.wt. of diazepam intraperitoneally (i.p) and all the other groups received a dose of 25 mg/kg b.wt. w.r.t. sample and presence or absence of clonic and/or tonic convulsions was noted for each animal. All the data were statistically analysed. Mean difference in Clonic/Tonic Convulsion was measured and percentage protection calculated by using formula

$$\% \text{ protection of Clonic/Tonic Convulsion} = (D_{test} / D_{std}) \times 100$$

where D_{test} and D_{std} are the mean Clonic/Tonic Convulsion of test group and std group, respectively [19].

Table 1: Clonic Convulsion Time duration (sec.)

Compound	Dose (mg/kg)	Mean(sec) ± SEM	% Protection
Control (Saline)	-	50.01±1.713	-
Standard (Diazepam)	4	0.4667±0.088***	100
5a	30	180.3±8.601 ns	-
5b	30	176.0±6.909 ns	-
5c	30	178.5±8.766 ns	-
5d	30	257.7±5.649 ns	-
5e	30	0.385±0.121***	82.49
5f	30	182.5±9.664 ns	-
5g	30	106.7±3.029 ns	-

Data were statistically analyzed by one-way analysis of Variance (ANOVA) followed by Dunnett's test as post hoc test. p value <0.001 was considered statistically significant as compared to Diazepam.

The number of animals in each group was 6 animals

**p<0.05, **p<0.01, ***p<0.001 and ns-no significance.*

Table 2: Tonic Convulsion Time duration (sec)

Compound	Dose (mg/kg)	Mean(sec) ± SEM	% Protection
Control (Saline)	-	360.0±5.791	-
Standard (Diazepam)	4	0.6333±0.123***	
5a	30	180.3±8.601 ns	-
5b	30	222.0±6.909 ns	-
5c	30	207.5±8.766 ns	-
5d	30	217.7±5.649 ns	-
5e	30	0.4843±0.102***	76.47
5f	30	137.5±9.664 ns	-
5g	30	186.7±3.029 ns	-

Data were statistically analyzed by one-way analysis of Variance (ANOVA) followed by Dunnett's test as post hoc test. p value <0.001 was considered statistically significant as compared to Diazepam.

The number of animals in each group was 6 animals

**p<0.05, **p<0.01, ***p<0.001 and ns-no significance.*

Results and Discussion

In this research work some novel flavanone incorporated semicarbazides were synthesized.

In the first step, chalcone (**1a-1g**) were synthesized by reaction of aromatic aldehyde and ketones. In second step, flavones (**2a-2g**) were synthesized by cyclization of chalones (**1a-1g**). On the other hand, the N-(2,4-dimethylphenyl)semicarbazide (**4**) was prepared in two steps *i.e.* (i) formation of 1-(2,4-dimethylphenyl)urea (**3**) from aromatic amines and (ii) preparation of N-(2,4-dimethylphenyl)semicarbazide (**4**) from substituted urea (**3**).

In the final step, flavanone incorporated semicarbazides (**5a-5g**) were synthesized by reaction of flavones (**2a-2g**) with N-(2,4-dimethylphenyl)semicarbazide (**4**).

All the synthesized title compounds (**5a-5g**) were screened for *in-vivo* anticonvulsant activity by PTZ induced convulsion method in rats using Diazepam (4mg/kg) as standard drug.

The compound (**5e**) showed potent anticonvulsant activity as compared to the standard Diazepam.

Conclusion

In summary, the present work concludes a simple and novel method for the synthesis of flavones incorporated semicarbazones compounds without using any costly chemicals and any drastic conditions. Most of the compounds have displayed considerable anticonvulsant activity as indicated by the protection against PTZ test in comparison with standard drug (Table 1 and 2). The compound (**5e**) showed potent anticonvulsant activity as compared to the standard Diazepam. Therefore, the nature of groups in flavone moiety is very important for anticonvulsant activity in PTZ model. Future studies and the creation of novel anticonvulsants with a flavone nucleus might benefit from these new discoveries.

References

[1]. Hauser, W. A., Annegers, J. F., & Kurland, L. T. (1993). Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia*, *34*(3), 453-458.

[2]. Jain, S. (2005). Priority of epilepsy research in Asia. *Epilepsia*, *46*, 46-47.

[3]. Garg, D. (2020). Specific considerations for epilepsy in India. *Current Medical Issues*, *18*(2), 105.

[4]. Elferink, J. A., & Van Zwieten-Boot, B. J. (1997). New antiepileptic drugs. Analysis based on number needed to treat shows differences between drugs studied. *BMJ: British Medical Journal*, *314*(7080), 603.

[5]. Craig, J. J., & Morrow, J. I. (1997). New antiepileptic drugs. Register of women who take the drugs during pregnancy has been set up. *BMJ: British Medical Journal*, *314*(7080), 603.

[6]. Löscher, W., Potschka, H., Sisodiya, S. M., & Vezzani, A. (2020). Drug resistance in epilepsy: clinical impact, potential mechanisms, and new innovative treatment options. *Pharmacological reviews*, *72*(3), 606-638.

[7]. Baker, G. A., Jacoby, A., Gorry, J., Doughty, J., Ellina, V., & SIGN Group. (2005). Quality of life of people with epilepsy in Iran, the Gulf, and Near East. *Epilepsia*, *46*(1), 132-140.

[8]. Cramer, J. A., Mintzer, S., Wheless, J., & Mattson, R. H. (2010). Adverse effects of antiepileptic drugs: a brief overview of important issues. *Expert review of neurotherapeutics*, *10*(6), 885-891.

[9]. Gates, J. R. (2000). Side effect profiles and behavioral consequences of antiepileptic medications. *Epilepsy & Behavior*, *1*(3), 153-159.

[10]. Wahab, A. (2010). Difficulties in treatment and management of epilepsy and challenges in new drug development. *Pharmaceuticals*, *3*(7), 2090-2110.

[11]. Mula, M., & Trimble, M. R. (2009). Antiepileptic drug-induced cognitive adverse effects: potential mechanisms and contributing factors. *CNS drugs*, *23*, 121-137.

[12]. Dimmock, J. R., Sidhu, K. K., Thayer, R. S., Mack, P., Duffy, M. J., Reid, R. S., Quail, J.W., Pugazhenthi, U. & Ong, A. (1993). Anticonvulsant activities of some arylsemicarbazones displaying potent oral activity in the maximal electroshock screen in rats accompanied by high protection indices. *Journal of medicinal chemistry*, *36*(16), 2243-2252.

[13]. Dimmock, J. R., Vashishtha, S. C., & Stables, J. P. (2000). Anticonvulsant properties of various acetylhydrazones, oxamoylhydrazones and semicarbazones derived from aromatic and unsaturated carbonyl compounds. *European journal of medicinal chemistry*, *35*(2), 241-248.

[14]. Andurkar, S. V., Béguin, C., Stables, J. P., & Kohn, H. (2001). Synthesis and structural studies of aza analogues of functionalized amino acids: new anticonvulsant agents. *Journal of medicinal chemistry*, *44*(9), 1475-1478.

[15]. Yogeeswari, P., Sriram, D., Jit, L. R. J. S., Kumar, S. S., & Stables, J. P. (2002). Anticonvulsant and neurotoxicity evaluation of some 6-chlorobenzothiazolyl-2-thiosemicarbazones. *European journal of medicinal chemistry*, *37*(3), 231-236.

[16]. Murti, Y., Agrawal, T., & Pathak, D. (2010). Synthesis and Anticonvulsant activity of substituted benzaldehyde-4-aryl-thiosemicarbazones. *Indian Drugs*, *47*(10), 19-27.

[17]. Bhat, M. A., Siddiqui, N., & Khan, S. A. (2008). Synthesis of novel 3-(4-acetyl-5H/methyl-5-substituted phenyl-4, 5-dihydro-1, 3, 4-oxadiazol-2-yl)-2H-chromen-2-ones as potential anticonvulsant agents. *Acta Pol Pharm*, *65*(2), 235-239.

[18]. Kulkarni, S. K. (1987). *Hand book of experimental pharmacology*. Vallabh Prakashan.

[19]. Tripathi, D. K., Ahmad, P., Sharma, S., Chauhan, D. K., & Dubey, N. K. (Eds.). (2017). Nanomaterials in Plants, Algae, and Microorganisms: Concepts and Controversies: Volume 1.