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Research Article

Synthesis and Anticonvulsant Activity of Some Flavones Incorporated Hydrazide Derivatives

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ABSTRACT

A series of novel flavones incorporated hydrazide derivatives was synthesized and characterized by elemental and spectral studies. The newly synthesized flavones incorporated hydrazides were screened for anticonvulsant activity against maximal electroshock seizure (MES) model in male wistar rats and compared with the standard drug phenytoin**.** Compound *N'*-(2-(4-(dimethylamino)phenyl)chroman-4-ylidene)-2-phenoxybenzohydrazide **3g** was found to be most active compound as comparable to standard drug phenytoin. From the *in-silico* neurotoxicity study, the compound **3g** was found to lack of neurotoxicity.

Keywords Flavones, Hydrazones, Anticonvulsant, MES, *In silico* neurotoxicity, TPSA

INTRODUCTION

Epilepsy is a common neurological condition, affecting 60 million people worldwide according to epidemiological studies. In India, the prevalence rate of epilepsy varies from 1,710 to 9,780 cases per million populations[1]. However, all currently approved anticonvulsant agents have dose-related toxicity and idiosyncratic side effects. There is continuing demand for new anticonvulsant agents as it has not been possible to control every kind of seizure with existing antiepileptic drugs [2-3].

Hydrazones possessing an azomethine -NHN=CH- proton constitute an important class of compounds for new drug development. In the past decade, hydrazones have been designed as potential anticonvulsants that were structurally dissimilar from very common anticonvulsants containing the dicarboximide function (CONRCO), which may contribute to toxic side effects[4-7]. Bhat et al. (2008) 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[8].

In the present work, we planned to incorporate the substituted flavone moiety to phenoxy benzoic acid hydrazide and to screen for anticonvulsant activity. Adding the two active anticonvulsant pharmacophores were expected to have synergistic effect in dealing with anticonvulsant activity. This hydrazones based pharmacophoric model comprises following four essential binding sites:

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

The newly synthesized flavanone incorporated hydrazide derivatives were evaluated for anticonvulsant activity by the MES method by using phenytoin as standard. The development of anticonvulsant drug molecule must overcome the failure rate of poor absorption, distribution, metabolism, excretion (ADME) and toxicity (T) properties. Clinical failure of about 60% of the Investigational New Drug (IND) filing is attributed to their inadequate ADMET attributes. Among that 41% of compounds fail in drug development because of poor ADME and 22% of compounds fail in drug development because of toxicity[9]. To reduce the burden on experimental animals, *in-silico* neurotoxicity study of synthesized compounds was carried out.

MATERIALS AND METHODS

Chemistry

*Methyl-2-phenoxybenzoate (**1**)*

A solution of the appropriate phenoxybenzoic acid (10 mmol), absolute methanol (10 ml) and concentrated sulfuric acid (1 ml) was heated under reflux for the appropriate time 30-40 h. The solvent was evaporated under reduced pressure, the remaining contents cooled to room temperature, neutralized with a concentrated solution of sodium carbonate, then the aqueous solution extracted with ether. The combined ether extracts were dried, and the solvent is removed under reduced pressure to yield the corresponding ester [10].

Yield, 82 %; mp 90-92 °C. IR (KBr) υ_{max}/cm^{-1} 1593 (C=O), 1528, 1497 (Ar. C=C), 1362 (C-O-C). Anal. Calcd for $C_{14}H_{12}O_3$ (%): C, 73.67; H, 5.30. Found: C, 73.54; H, 5.37. Found: C, 73.51; H, 5.21.

*2-phenoxybenzohydrazide (**2**)*

A solution of hydrazine hydrate (99.9 %, 5 mmol) and Methyl 2-phenoxybenzoate **1** (1 mmol) was brought to a

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gentle reflux for the appropriate time 22 h, then cooled to room temperature. The solid formed was filtered (ice/water mixture was added in some cases to complete precipitation) and washed with several portions of cold water. The filtrate was dried by suction. Crystallization of crude product from EtOH afforded the corresponding 2-phenoxybenzohydrazide [10].

Yield, 82 %; mp 98-100 °C. IR (KBr) υ_{max}/cm^{-1} 3,320 (–NH-NH_2), 1621 (C=O), 1582 (C=N), 1562, 1472 (Ar. C=C), 1354 (C–O-C). Anal. Calcd for $C_{13}H_{12}N_2O_2$ (%): C, 68.41; H, 5.30; N, 12.27. Found: C, 68.36; H, 5.23; N, 12.33.

Compounds (**a-j**) were synthesized by as per reported in previous literature[11].

*N'-(2-(4-chlorophenyl)chroman-4-ylidene)-2-phenoxybenzohydrazide (**3a**)*

A mixture of 2-(2,3-dimethylphenylamino) benzohydrazide **2** (2.55 g, 0.01 mol) and 2-(4-Chlorophenyl)-2,3-dihydro-4*H*-chromen-4-one (2.58 g, 0.01 mol) in methanol was stirred at 60-70 °C for 6 h in the presence of 2-3 ml of glacial acetic acid. The reaction mixture was poured into a beaker containing crushed ice and allowed to stand for 2 h. The precipitate so formed was filtered and washed with ice cold water. The crude product was dried and recrystallized from chloroform. The completion of the reaction was monitored by running TLC.

Yield, 74 %; Mp 232-234 °C. IR (KBr) υ_{max}/cm^{-1} 3,480 (–NH), 1679 (C=O), 1603 (C=N), 1574, 1481, 1455 (Ar. C=C), 1366 (C–O-C), 837 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 9.86 (s, 1H, NH), 7.44-6.86 (m, 17H, Ar–H), 4.71 (t, 1H, CH), 2.91-2.72 (d, 2H, CH_2). LCMS *m/z*; 468.2, $[M+1]^+$. Anal. Calcd for $C_{28}H_{21}ClN_2O_3$ (%): C, 71.72; H, 4.51; N, 5.97 Found: C, 71.58; H, 4.58; N, 5.86.

The other compounds **3b** to **3j** were prepared by the same procedure using the corresponding flavones (**b-j**).

*N'-(2-(2-chlorophenyl)chroman-4-ylidene)-2-phenoxybenzohydrazide (**3b**)*

Yield, 62 %; Mp 254-256 °C. IR (KBr) υ_{max}/cm^{-1} 3,480 (–NH), 3186 (CH Str.), 1662 (C=O), 1602 (C=N), 1588, 1567, 1508 (Ar. C=C), 1336 (C–O-C), 812 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 9.40 (s, 1H, NH), 8.02-7.04 (m, 17H, Ar–H), 5.92-5.89 (t, 1H, CH), 2.99-2.87 (d, 2H, CH_2). LCMS *m/z*; 468.1, $[M]^+$. Anal. Calcd for $C_{28}H_{21}ClN_2O_3$ (%): C, 71.72; H, 4.51; N, 5.97 Found: C, 71.54; H, 4.43; N, 5.91.

*N'-(2-(2-nitrophenyl)chroman-4-ylidene)-2-phenoxybenzohydrazide (**3c**)*

Yield, 62 %; Mp 290-292 °C. IR (KBr) υ_{max}/cm^{-1} 3485 (–NH), 1,678 (C=O), 1602 (C=N), 1577, 1485, (Ar. C=C), 1,455 (C-NO_2), 1361 (C–O-C). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 9.54 (s, 1H, NH), 7.77-6.87 (m, 17H, Ar–H), 5.66 (t, 1H, CH), 2.66-2.98 (d, 2H, CH_2). LCMS *m/z*; 479.2, $[M+1]^+$. Anal. Calcd for $C_{28}H_{21}N_3O_5$ (%): C, 70.14; H, 4.41; N, 8.76. Found: C, 70.23; H, 4.47; N, 8.69.

*N'-(2-(3-nitrophenyl)chroman-4-ylidene)-2-phenoxybenzohydrazide (**3d**)*

Yield, 69 %; Mp 274-276 °C. IR (KBr) υ_{max}/cm^{-1} 3390 (–NH), 3064, 2972 (CH Str.), 1,695 (C=O), 1596 (C=N), 1583, 1492 (Ar. C=C), 1,454 (C-NO_2), 1311 (C–O-C). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 9.53 (s, 1H, NH), 8.13-6.90 (m, 17H, Ar–H), 5.57-5.55 (t, 1H, CH), 2.67-2.82 (d, 2H, CH_2). LCMS *m/z*; 479.2, $[M+1]^+$. Anal. Calcd for Anal. Calcd for $C_{28}H_{21}N_3O_5$ (%): C, 70.14; H, 4.41; N, 8.76. Found: C, 70.23; H, 4.49; N, 8.66.

N'-(2-(4-nitrophenyl)chroman-4-ylidene)-2-phenoxybenzohydrazide (**3e**)

Yield, 67 %; Mp 262-266 °C. IR (KBr) υ_{max}/cm^{-1} 3305 (–NH), 2910, 2855 (CH Str.), 1,644 (C=O), 1594 (C=N), 1573, 1501 (Ar. C=C), 1,469 (C-NO_2), 1335 (C–O-C). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 9.54 (s, 1H, NH), 7.73-6.91 (m, 17H, Ar–H), 5.62-5.60 (t, 1H, CH), 2.67-2.98 (d, 2H, CH_2). LCMS *m/z*; 479.2, $[M+1]^+$. Anal. Calcd for Anal. Calcd for $C_{28}H_{21}N_3O_5$ (%): C, 70.14; H, 4.41; N, 8.76. Found: C, 70.06; H, 4.32; N, 8.63.

*N'-(2-(4-hydroxyphenyl)chroman-4-ylidene)-2-phenoxybenzohydrazide (**3f**)*

Yield, 70 %; Mp 230-232 °C. IR (KBr) υ_{max}/cm^{-1} 3396 (–NH), 3293 (–OH), 2965, 2917 (CH Str.), 1,730 (C=O), 1,573 (C=N), 1,509, 1434 (Ar. C=C), 1,336 (C–OH), 1,319 (C–O-C). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 9.18 (s, 1H, NH), 8.50 (s, 1H, OH), 7.68-6.58 (m, 17H, Ar–H), 5.49 (t, 1H, CH), 2.61-2.84 (d, 2H, CH_2). LCMS *m/z*; 450.1, $[M+1]^+$. Anal. Calcd for $C_{28}H_{22}N_2O_4$ (%): C, 74.65; H, 4.92; N, 6.22. Found: C, 74.49; H, 4.81; N, 6.13.

*N'-(2-(4-(dimethylamino)phenyl)chroman-4-ylidene)-2-phenoxybenzohydrazide (**3g**)*

Yield, 64 %; Mp 248-250 °C. IR (KBr) υ_{max}/cm^{-1} 3389 (–NH), 3,064, 3031 (CH Str.), 1695 (C=O), 1,596 (C=N), 1583, 1454 (Ar. C=C), 1391 (C–N), 1310 (C–O-C). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 9.29 (s, 1H, NH), 7.51-7.07 (m, 17H, Ar–H), 5.74 (t, 1H, CH), 3.12-2.92 (d, 2H, CH_2), 2.86 (s, 6H, -N(CH_3)$_2$). LCMS *m/z*; 477.2, $[M+1]^+$. Anal. Calcd for $C_{30}H_{27}N_3O_3$ (%): C, 75.45; H, 5.70; N, 8.80. Found: C, 75.57; H, 5.63; N, 8.68.

*2-phenoxy-N'-(2-phenylchroman-4-ylidene)benzohydrazide (**3h**)*

Yield, 74 %; Mp 218-220 °C. IR (KBr) υ_{max}/cm^{-1} 3220 (–NH), 2921 (CH Str.), 1667 (C=O), 1604 (C=N), 1554, 1537 (Ar. C=C), 1285 (C–O-C). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 8.99 (s, 1H, NH), 7.54-6.76 (m, 18H, Ar–H), 5.49-5.45 (t, 1H, CH), 3.04-2.81 (d, 2H, CH_2). LCMS *m/z*; 434.2, $[M+1]^+$. Anal. Calcd for $C_{28}H_{22}N_2O_3$ (%): C, 77.40; H, 5.10; N, 6.45. Found: C, 77.29; H, 5.19; N, 6.53.

*N'-(2-(4-hydroxy-3-methoxyphenyl)chroman-4-ylidene)-2-phenoxybenzohydrazide (**3i**)*

Yield, 68 %; Mp 288-290 °C. IR (KBr) υ_{max}/cm^{-1} 3496 (–NH), 3278 (–OH), 2929 (CH Str.), 1649 (C=O), 1556 (C=N), 1540, 1505 (Ar. C=C), 1345 (C–OH), 1278 (C–O-C). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 9.64 (s, 1H, NH), 7.65-6.53 (m, 16H, Ar–H), 5.69-5.68 (t, 1H, CH), 4.40 (s, 1H, OH), 2.86 (s, 3H, -OCH_3), 2.99-2.59 (d, 2H, CH_2). LCMS *m/z*; 480.2, $[M+1]^+$. Anal. Calcd for $C_{29}H_{24}N_2O_5$ (%): C, 72.49; H, 5.03; N, 5.83. Found: C, 72.34; H, 5.11; N, 5.94.

*N'-(2-(2-hydroxyphenyl)chroman-4-ylidene)-2-phenoxybenzohydrazide (**3j**)*

Yield, 72 %; Mp 240-244 °C. IR (KBr) υ_{max}/cm^{-1} 3418 (–NH), 3244 (–OH), 3045, 2961 (CH Str.), 1666 (C=O), 1593 (C=N), 1497 (Ar. C=C), 1366 (C–OH), 1218 (C–O-

C). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 9.62 (s, 1H, NH), 8.16 (s, 1H, OH), 7.62-6.87 (m, 17H, Ar–H), 5.22 (t, 1H, CH), 3.18-2.92 (d, 2H, CH_2). LCMS *m/z*; 450.2, $[M+1]^+$. Anal. Calcd for $C_{28}H_{22}N_2O_4$ (%): C, 74.65; H, 4.92; N, 6.22. Found: C, 74.57; H, 4.81; N, 6.29.

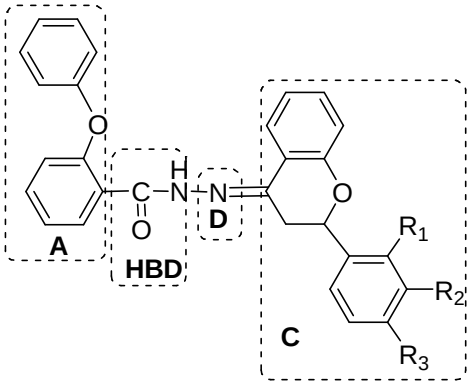


Figure 1 Structure of proposed general pharmacophore model of the synthesized compounds

Pharmacology

Animals: Male wistar rats procured from BN College of Pharmacy, Udaipur (150-200 g) were used in the present study. The animals were housed in colony cages, conditions of constant temperature (25±2 °C), relative humidity of 50 ± 5 %, a 12 h light/dark schedule and allowed free access to standard palletized laboratory animal and water except during the experiment. The animals were allowed to habituate to the laboratory environment for 24 h before the experiments were initiated. All the experimental procedures and protocols used in this study were reviewed and approved by the Institutional Animal Ethical Committee (IAEC), constituted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India. The protocol of the study was approved by Institutional Animal Ethical Committee (Ref. No. 99/LSC/BNCP-012/IAEC).

Acute Toxicity Study

Albino mice weighing 20-25 g and Wistar rats weighing 150-200 g were used for Acute toxicity study. The animals were housed in colony cages, conditions of constant temperature (22±2 °C), a 12 h light/dark schedule, and allowed free access to standard diet and tap water except during the experiment. The animals were allowed to habituate to the laboratory environment for 2 h before the experiments were initiated. The tested compounds were administered intraperitoneally at different dose levels in six groups, each group was consist of 10 animals. After 24 h of the drug administration the percent mortality in each group was observed, Approximate Lethal Dose was calculated by the Karbers Method (~400 mg/kg)[12].

Anticonvulsant activity

Maximal Electroshock Seizure Model (MES): Maximal electroshock seizure model was used in the present study to evaluate the anticonvulsant activity of the compounds on male wistar rats as per reported method. Seizures were induced in rats by delivering electroshock of 150 mA for 0.2 sec by means of an electro-convulsiometer through a pair of ear clip electrodes. The test compounds (30 mg/kg) were injected i.p. in the form of solution (The compounds were dissolved in 1% sodium carboxymethyl cellulose), 30 min before the maximal electroshock seizure (MES) test. Phenytoin (25 mg/kg) was used as a standard drug. The reduction in time or abolition of tonic extensor phase of MES- convulsions was noted [12-15]. The data are calculated & expressed as mean extensor phase duration in sec. followed by % protection and % potency in comparison with the standard as shown in Table 1 using the following formula:

% Protection = (MEPD*nc* – MEPD*sample*/ MEPD) X 100,

Where MEPDnc is the mean extensor phase duration of normal control in sec. and MEPD is the mean extensor phase duration of sample or standard in sec.

% Potency = (MEPDnc – MEPD/ MEPDnc –MEPDstd) X 100,

Where MEPDstd is the mean extensor phase duration of standard control in sec.

Statistical analysis

The results are expressed as the mean±SEM per group and the data were analyzed by one-way analysis of Variance (ANOVA) followed by Dunnett's test as post hoc test. *p* value <0.05 was considered statistically significant.

Computational Studies

Calculation of physicochemical parameters

In-silico study of synthesized compounds (3a-3j) was performed for the prediction of ADME properties. Polar surface area (TPSA)[16] was calculated using Molinspiration online property calculation toolkit (Molinspiration Cheminformatics, 2013)[17]. Absorption (%ABS) was calculated by: %ABS=109 -(0.345 × TPSA)[18].

In-silico neurotoxicity study

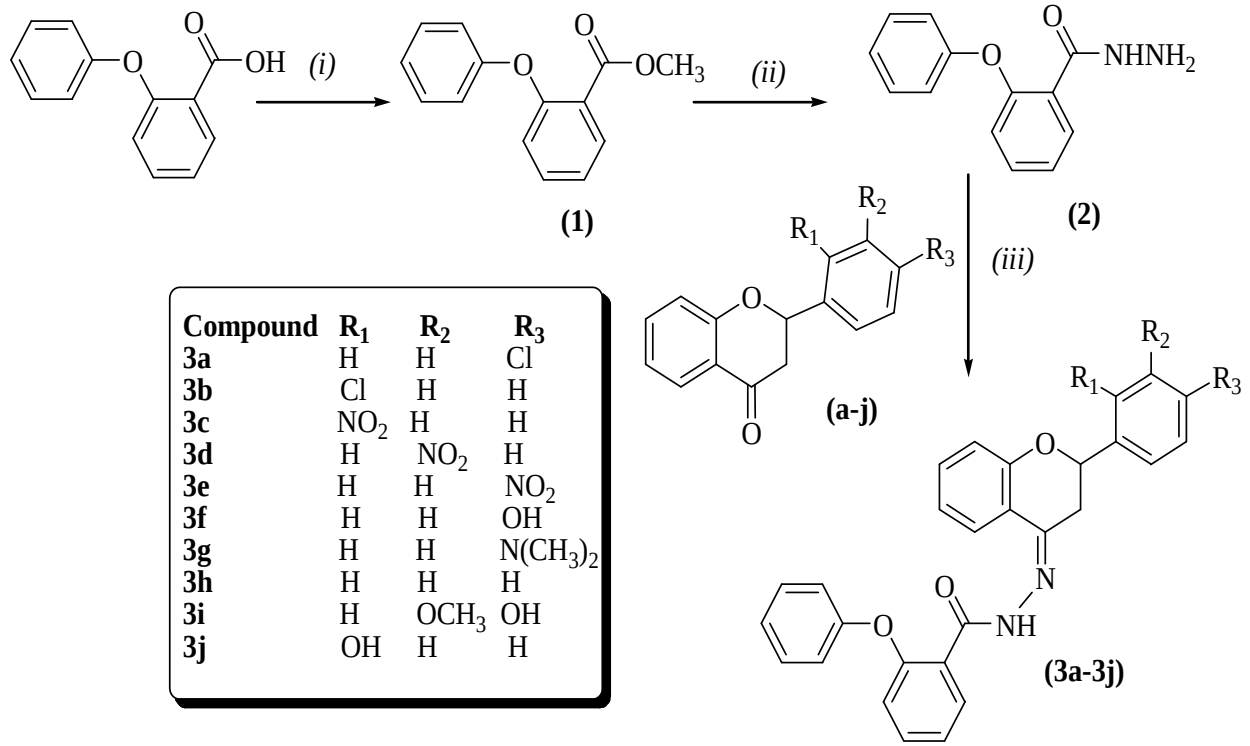
The Pentium IV work station and Pallas 6.1.1 software (Pallas, 2000)[19] were used to calculate and to predict the *in-silico* toxicity study of the molecules. Chem draw ultra software was used to draw the structure of the compounds to be analyzed and was saved as MDL file. The sketched molecules were calculated for the neurotoxicity[20-21].

RESULTS

Chemistry

The synthetic route used to synthesize title compounds is outlined in Figure 1 and structure of title compounds were confirmed by IR, ^{1}H NMR, LCMS and elemental analysis. Methyl 2-phenoxybenzoate (**1)**, the starting material, was prepared according to the method reported in the literature, using phenoxybenzoic acid. 2-phenoxybenzohydrazide (**2)** was prepared by esterification of phenoxybenzoic acid followed by treatment with hydrazine hydrate[10]. In the last step, flavones (a–j) were reacted with 2-phenoxybenzohydrazide (2) and gave flavones incorporated hydrazide derivatives of phenoxybenzoic acid (3a–3j).

The proposed structure of compounds 3a–3j was confirmed by elemental analysis and spectroscopic data (IR, ^{1}H NMR and LCMS). The IR spectra showed C=N absorption bands at 1604–1556 cm^{-1}. The ^{1}H NMR spectra of the compounds **3a–3j**, showed the one singlet of –NH–



Compound	R_1	R_2	R_3
3a	H	H	Cl
3b	Cl	H	H
3c	NO_2	H	H
3d	H	NO_2	H
3e	H	H	NO_2
3f	H	H	OH
3g	H	H	$N(CH_3)_2$
3h	H	H	H
3i	H	OCH_3	OH
3j	OH	H	H

Scheme 1: Synthesis of flavones incorporated hydrazides (i) CH_3OH, Conc H_2SO_4; (ii) $NH_2NH_2.H_2O$; (iii) CH_3OH; Glacial CH_3COOH

Table 1 Anticonvulsant activity of title compounds (3a-3j)

Compounds	Dose (mg/kg)	Extensor phase duration(Sec.)	Protection (%)	Potency (%)
Control	-	9.817±0.471	-	-
Phenytoin	25	2.050±0.547	79.12	100.00
3a	30	6.375±0.496**	35.06	44.31
3b	30	3.350±0.288**	65.87	83.26
3c	30	6.417±0.306**	34.63	43.78
3d	30	3.700±0.316**	62.31	78.76
3e	30	4.833±0.383**	50.76	64.16
3f	30	6.567±0.484**	33.11	41.85
3g	30	3.083±0.397**	68.59	86.70
3h	30	4.800±1.403**	51.10	64.59
3i	30	4.950±0.327**	49.58	62.66
3j	30	5.767±0.557**	41.26	52.15

Data analyzed by one way ANOVA followed by Dunnett's test, (n = 6), *P < 0.05, **P < 0.01 significant from control; ns, not significant.

N=C– at the region d = 9.86–8.99 ppm. For the compounds 3a–3j, the signals belonging to benzylidene group were observed at aromatic region, while the signals belonging to $–NHNH_2$ disappeared, indicating functionalization of hydrazide to hydrazone with substituted flavones. The remaining protons appeared at the expected chemical shifts. The physical data, IR, ^1H NMR and mass spectral data for all the synthesized compounds are reported in Materials and method section.

Anticonvulsant activity

The anticonvulsant activity was determined by MES method on wistar rats using phenytoin as standard drug (Table 1). In general, the results of the anticonvulsant activity are also encouraging as out of ten compounds tested, compounds 3b and 3g exhibited an anticonvulsant activity which is more potent than that of other compounds. The results of anticonvulsant activity showed that compound 3g, substituted with 4-dimethylamino, was found to be most active (showed 86.70 % potency) as comparable to standard phenytoin. Compound 3h without any substitution at phenyl ring showed 64.59 % potency as compared to phenytoin. Compounds substitution with 3-nitro (**3d**) showed moderate activity by 78.76 % potency, respectively, as compared to phenytoin. Compounds substituted with 4-chloro, 2-nitro, 2-hydroxy and 4-hydroxy did not show any marked protection against MES test.

CONCLUSION

In conclusion, we described analog-based design of

Table 2 *In-silico* prediction of pharmacokinetic parameters and neurotoxicity study

Compounds	MW	TPSA	*In-silico* % ABS	*In-silico* neurotoxicity (%)
Phenytoin	252.27	58.20	88.92	00
3a	468.94	59.93	88.32	00
3b	468.94	59.93	88.32	00
3c	479.49	105.75	72.52	00
3d	479.49	105.75	72.52	00
3e	479.49	105.75	72.52	00
3f	450.49	80.16	81.34	29
3g	477.56	63.17	87.21	00
3h	434.50	59.93	88.32	00
3i	480.52	89.39	78.16	29
3j	450.50	80.16	81.34	29

MW, molecular weight; %ABS, percentage of absorption; TPSA, topological polar surface area;

flavones-incorporated hydrazide derivatives of 2-phenoxybenzoic acid for *in vivo* anticonvulsant activity as flavones itself showed prominent anticonvulsant activity. Most of the compounds have displayed significant anticonvulsant activity as indicated by the protection against MES test in comparison with standard drug phenytoin (Table 1). From *in silico* neurotoxicity study, the most of the compounds were found free from neurotoxicity.

Compound *N'*-(2-(4-(dimethylamino)phenyl)chroman-4-ylidene)-2-phenoxybenzohydrazide 3g showed excellent anticonvulsant activity on MES model. Compounds substituted with 4-chloro, 2-nitro, 2-hydroxy and 4-hydroxy did not show any marked protection against MES test. Therefore, the nature of groups in flavone moiety is very important for anticonvulsant activity in MES model. These new findings might be beneficial in future research and development of hydrazones containing flavone nucleus as novel anticonvulsants.

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