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# 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

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**Abstract:** 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 (**6a-j**) were synthesized and evaluated for anticonvulsant activity and neurotoxicity. The structures of the synthesized compounds were confirmed on the basis of their spectral data and elemental analysis. A majority of the compounds was active in MES tests. Compound (**6e**) was found to be potent and had activity at lower dose of 30 mg/kg in MES-test. All the compounds were less toxic as compared with the standard drug phenytoin.

**Keywords:** coumarin, MES-test, 1,3,4-oxadiazole, Schiff bases

Epilepsy is one of the more common neurological disorders, affecting a large section of people. Many patients have seizures that are resistant to available medical therapies. Newer drugs have emerged as promising anticonvulsants. Despite introduction of these new drugs chronic patients face specific problems of neurotoxicity, symptoms of depression and CNS related ailments. All currently approved antiepileptic drugs have dose-related toxicity and idiosyncratic side effects. In response to the premise that major medical breakthroughs in non-pharmacological therapies for the treatment of epilepsy in the near future seem remote, the search for new antiepileptic drugs with lower toxicities and fewer side effects continues.

1,3,4-Oxadiazole derivatives are reported to show a broad spectrum of biological activities, which include antibacterial (1), anti-inflammatory (2), anticonvulsant (3, 4), CNS stimulant (5) and antihypertensive (6). Coumarins are also reported to possess important pharmacological activities like antitumor (7), antifungal (8), antihypertensive (9) and anti-inflammatory (10). This prompted us to synthesize and study anticonvulsant activity of compounds incorporating both these moieties i.e., 1,3,4-oxadiazole and coumarin. The compounds were evaluated for their antiepileptic and neurotoxic properties according to the protocols of Antiepileptic Drug Development (ADD) program developed by National Institute of Health (NIH).

## EXPERIMENTAL

All the solvents were of LR grade and were obtained from Merck, CDH and s. d. Fine Chemicals. Melting points were determined in open capillary tubes and are uncorrected. Thin layer chromatography was performed on silica gel G (Merck). The FT-IR spectra were recorded in KBr pellets on a (BIO-RAD FTS 135) WIN-IR spectrophotometer.

$^1$H-NMR spectra were recorded on a Bruker model DPX 300 FT NMR spectrometer in (DMSO-$d_6$) using tetramethylsilane ($Me_4Si$, TMS) as an internal standard. Mass spectra were recorded on a Jeol JMS-D instrument fitted with a JMS 2000 data system at 70 eV. The elemental analyses for C, H and N were within the limit of ±0.4% of the theoretical values. The physical constants of the synthesized compounds are given in Table 1.

### Anticonvulsant screening

In the preliminary screening, each compound was administered as i.p. injection at three dose levels (30, 100 and 300 mg/kg), the anticonvulsant activity was assessed after 30 min and 4 h intervals of administration. The anticonvulsant efficacy was evaluated by maximal electroshock-induced seizure

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(MES) using reported procedure (11) and the data are presented in Table-2.

Neurotoxicity screen

Minimal motor impairment was measured in mice by the rotarod test. The mice were trained to stay on an accelerating rotarod that rotates at 10 revolutions/min. The rod diameter was 3.2 cm. Trained animals were given i.p. injection of the test compounds 30, 100 and 300 mg/kg. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min. in each of the trials. All the animal experimental protocols have met with the approval of the Institutional Animal Ethics Committee (IAEC).

Synthesis of ethyl-2-oxo-2H-chromene-3-carboxylate (**3**)

Salicylaldehyde **(1)** (1.22 g, 0.01 mol) and diethylmalonate **(2)** (1.6 g, 0.01 mol) were dissolved in ethanol to give clear solution. Piperidine (2 mL) was added and the mixture was refluxed for 5 h. The content was concentrated to small volume. The product (**3)** was poured onto crushed ice, filtered out and crystallized from ethanol to give white shiny crystals, TLC pure (toluene: ethyl acetate: formic acid, TEF, 5:4:1, v/v/v). M.p. 120-122$^{o}$C; Yield: 90%; IR (KBr, cm$^{-1}$) $\nu_{max}$: 1710 (CO, coumarin), 1670 (C=O), 1750 (C=O, ester), 1200 (C-O); $^{1}$H-NMR (DMSO-$d_6$, 300 MHz, δ ppm): 7.5 (4H, m, Ar-H), 8.1 (1H, s, Ar-H, H-4), 1.83 (3H, t, $CH_3$), 3.20 (2H, q, $CH_2$). Mass m/z (%): 216 M$^{+}$.

Synthesis of 2-oxo-2H-chromene-3-carbohydrazide (12) (**4**)

Compound **(3)** (2.18 g, 0.01 mol) and hydrazine hydrate 99% (0.5 g, 0.01 mol) were dissolved in ethanol (50 mL) to give clear solution and refluxed for 10 h. The content was concentrated to half of the volume and allowed to cool. The solid mass of **(4)**, which separated out on cooling was retained by filtering and washed with small amount of ice-cooled ethanol (90%). M.p. 136-138$^{o}$C.

Synthesis of 2-oxo-N-[(1E)-1-phenylethylidene]-2H-chromene-3-carbohydrazide (**5a**)

A mixture of **(4)** (0.97 g, 0.005 mol) and acetophenone (0.6 g, 0.005 mol) in glacial acetic acid (10 mL) was refluxed for 1 h. The cooled reaction mixture was poured into ice-cold water and solid was filtered out. The dried solid was recrystallized from ethanol to give **(5a)**. M.p. 135-137$^{o}$C; yield 70%; IR (KBr, cm$^{-1}$) $\nu_{max}$: 1710 (CO, Coumarin), 1660 (C=O), 1610 -1500 (C=C). $^{1}$H-NMR (DMSO-$d_6$, 300 MHz, δ ppm): 1.2 (3H, s, $CH_3$), 6.8 (2H, m, Ar-H), 7.0 (5H, m, Ar-H), 7.2 (1H, m, Ar-H), 7.5 (1H, m, Ar-H), 8.1 (1H, s, Ar-H), 8.2 (1H, s, CONH). Mass m/z (%): 253 M$^{+}$.

Synthesis of 3-(4-acetyl-5-methyl-5-phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (**6a**)

A mixture of **(5a)** (0.59 g, 0.002 mol) and excessive acetic anhydride (10 mL) was refluxed for 1 h. The excessive acetic anhydride was distilled off

Table 1. Physical constants of the synthesized compounds (**6a-j**).

| Compound no. | $R_1$ | $R_2$ | M.p ($^{o}$C) | Yield (%) | Molecular formula | $R_f$[a] | $R_m$[b] | % N Found (Calc.) |
|---|---|---|---|---|---|---|---|---|
| **6a** | $CH_3$ | H | 150 | 70 | $C_{20}H_{16}O_4N_2$ | 0.73 | -0.13 | 8.07 (8.04) |
| **6b** | $CH_3$ | *p*-OH | 170 | 80 | $C_{20}H_{16}O_5N_2$ | 0.64 | -0.19 | 7.65 (7.68) |
| **6c** | $CH_3$ | *p*-$CH_3$ | 180 | 75 | $C_{21}H_{18}O_4N_2$ | 0.82 | -0.08 | 7.70 (7.73) |
| **6d** | $CH_3$ | *p*-$OCH_3$ | 175 | 63 | $C_{21}H_{18}O_5N_2$ | 0.76 | -0.11 | 7.42 (7.40) |
| **6e** | $CH_3$ | *p*-$NO_2$ | 190 | 67 | $C_{20}H_{16}O_6N_3$ | 0.79 | -0.10 | 10.61 (10.65) |
| **6f** | $CH_3$ | 2,3-$(OCH_3)_2$ | 220 | 82 | $C_{22}H_{20}O_6N_2$ | 0.74 | -0.13 | 7.15 (7.17) |
| **6g** | H | H | 200 | 69 | $C_{19}H_{14}O_4N_2$ | 0.76 | -0.11 | 8.43 (8.40) |
| **6h** | H | *m*-$NO_2$ | 240 | 58 | $C_{19}H_{13}O_6N_3$ | 0.83 | -0.08 | 11.03 (11.07) |
| **6i** | H | *p*-$NO_2$ | 270 | 72 | $C_{19}H_{13}O_6N_3$ | 0.71 | -0.14 | 11.11 (11.07) |
| **6j** | H | *o*-OH | 230 | 65 | $C_{19}H_{14}O_5N_2$ | 0.76 | -0.15 | 7.96 (7.99) |

[a] Eluents used in TLC were benzene: acetone (9 : 1, v/v) and toluene: ethyl acetate: formic acid (5 : 4 : 1, v/v/v)for all compounds. [b] $R_m$ = log (1-1/$R_f$).

Table 2. Anticonvulsant and neurotoxicity results of compounds **6a-j**.

| Compound no. | Intraperitonial injection in mice[a] | | | |
|---|---|---|---|---|
| | MES screen | | Toxicity screen | |
| | 0.5 h | 4 h | 0.5 h | 4 h |
| **6a** | 300 | - | - | - |
| **6b** | 300 | - | - | - |
| **6c** | 300 | 300 | - | 300 |
| **6d** | 300 | - | - | 300 |
| **6e** | - | 300 | - | 300 |
| **6f** | 300 | 300 | - | - |
| **6g** | - | - | - | - |
| **6h** | 100 | 300 | 300 | 300 |
| **6i** | 100 | 300 | 300 | 300 |
| **6j** | 300 | - | 300 | 300 |
| Phenytoin[b] | 30 | 30 | 100 | 100 |
| Carbamazepine[b] | 30 | 100 | 100 | 300 |
| Phenobarbital[b] | 100 | 30 | 100 | 300 |

[a] Doses of 30, 100 and 300 mg/kg were administered. The figure in the Table indicates the minimum dose whereby bioactivity was demonstrated in half or more of the animals. The animals were examined 0.5 and 4 h after administration. (-) indicates an absence of activity at the maximal dose administered (300 mg/kg).
[b] Data from Porter et al. (13).

at reduced pressure and residue was poured into ice cool water. The solid product was filtered and recrystallized from ethanol to give **(6a)**. M.p. 150-152°C ; yield 68%; IR (KBr, $cm^{-1}$) $\nu_{max}$: 1710 (CO, coumarin), 1524 (CN), 1670 (C=O), 1624, 1479, 1370, 1279, 1092, 1036, 1013 (oxadiazole nucleus); $^1$H-NMR (DMSO-$d_6$, 300 MHz, δ ppm): 2.36 (3H, s, $CH_3$), 2.5 (3H, s, $COCH_3$) , 7.14 (3H, bt, Ar-H), 7.27 (2H, d, *J* = 10 Hz, Ar-H ), 7.58 (2H, bt, Ar-H), 8.04 (2H, d, *J* = 9.5 Hz, Ar-H), 8.66 (1H, s, Ar-H). Mass m/z (%): 321 $M^+$. Similarly other compounds of the series were synthesized.

3-(4-Acetyl-5-methyl-5-p-hydroxyphenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (**6b**)

M.p. 170-172°C; yield 80%; IR (KBr, $cm^{-1}$) $\nu_{max}$: 1710 (CO, coumarin), 1564 (C=N), 1670 (C=O), 1601, 1369, 1173, 1097, 1014, (oxadiazole nucleus), 758 (substituted benzene); $^1$H-NMR (DMSO-$d_6$, 300 MHz, δ ppm): 2.50 (6H, s, $2CH_3$), 7.47 (4H, m, Ar-H), 7.76 (2H, m, Ar-H), 8.01 (2H, d, *J* = 10 Hz, Ar-H), 8.81 (1H, s, Ar-H), 10.64 (1H, s, OH). Mass m/z (%): 337 $M^+$.

3-(4-Acetyl-5-methyl-5-p-methylphenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H- chromen-2-one (**6c**)

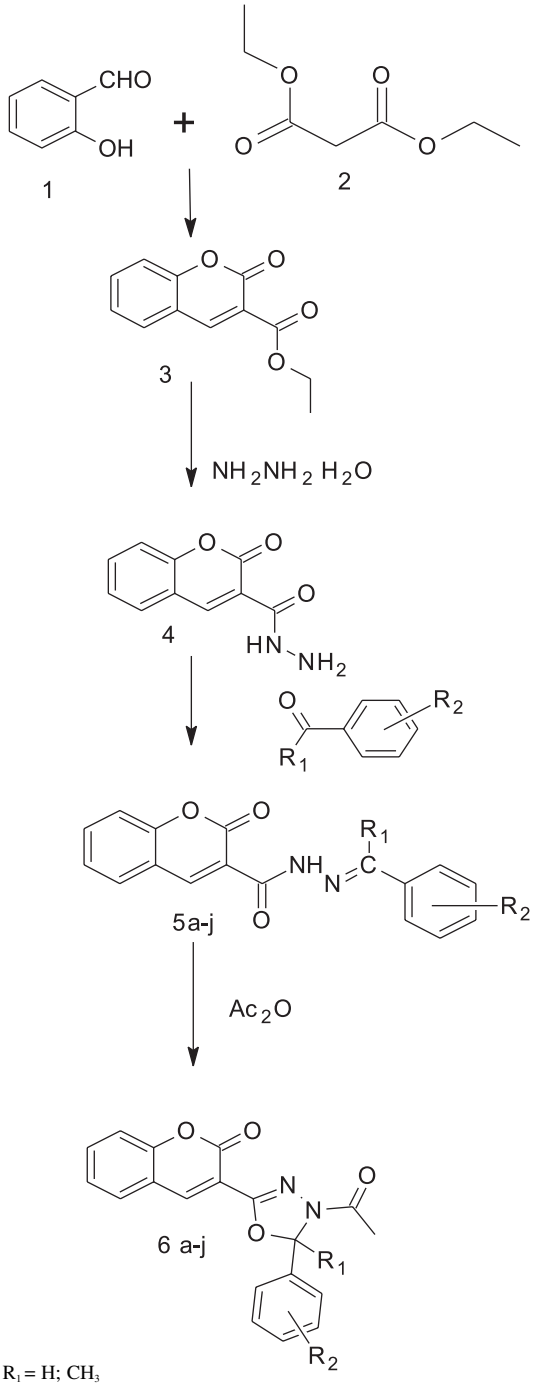
M.p. 180-182°C; yield 75%; IR (KBr, $cm^{-1}$) $\nu_{max}$: 1710 (CO, coumarin), 1564 (C=N), 1670 (C=O), 1369, 1173, 1097, 1014 (oxadiazole nucleus), 765 (substituted benzene); $^1$H-NMR (DMSO-$d_6$, 300 MHz, δ ppm): 2.36 (6H, s, $CH_3$), 2.50 (3H, s, $COCH_3$), 7.27 (2H, d, *J* = 10 Hz, Ar-H), 7.41 (2H, bt, Ar-H), 8.04 (2H, d, *J* = 10 Hz, Ar-H), 8.67 (1H, s, Ar-H). Mass m/z (%): 335$M^+$.

3-(4-Acetyl-5-methyl-5-p-methoxyphenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (**6d**)

M.p. 175-177°C; yield 63%; IR (KBr, $cm^{-1}$) $\nu_{max}$: 1716 (CO, coumarin), 1609 (C=N), 1690 (C=O), 1278, 1092, (oxadiazole nucleus), 751 (substituted benzene). $^1$H-NMR (DMSO-$d_6$, 300 MHz, δ ppm): 2.5 (3H, s, $CH_3$), 3.39 (3H, s, $COCH_3$), 3.49 (3H, s, $OCH_3$), 6.9 (4H, d, *J* = 10 Hz, Ar-H), 7.56 (2H, d, *J* = 10 Hz, Ar-H), 7. 40 (2H, t, Ar-H), 8.30 (1H, s, Ar-H). Mass m/z (%): 351 $M^+$.

3-(4-Acetyl-5-methyl-5-p-nitrophenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (**6e**)

M.p. 190-192°C; yield 67%; IR (KBr) $\nu_{max}$: 1710 (CO, coumarin), 1680 (C=O), 1520 (C=N), 1630, 1470, 1350, 1011 (oxadiazole nucleus), 750 (substituted benzene). $^1$H-NMR (DMSO-$d_6$, 300 MHz, δ ppm): 2.5 (6H s, $2CH_3$), 6.97 (4H, t, *J* = 6 Hz, Ar-H), 7.69 (2H, d, *J* = 10 Hz, Ar-H), 7.78 (1H, t, *J* = 6 Hz, Ar-H), 8.01 (1H, d, *J* = 10 Hz, Ar-H). Mass m/z (%): 366 $M^+$.




$R_1$ = H; $CH_3$
$R_2$ = H; OH; $CH_3$; $OCH_3$; 2,3-$(OCH_3)_2$; $NO_2$

Scheme 1. Synthetic pathways for compounds **6a-j**.

3-(4-Acetyl-5-methyl-5-o,m-dimethoxyphenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (**6f**)

M.p. 220-222°C; yield 82%; IR (KBr, $cm^{-1}$) $\nu_{max}$: 1718 (CO, coumarin), 1558 (C=N), 1684 (C=O), 158, 1521, 1456 (oxadiazole nucleus), 745 (substituted benzene). $^1$H NMR (DMSO-$d_6$, 300 MHz, δ ppm): 2.41 (3H, s, $CH_3$), 2.5 (3H, s, $COCH_3$), 3.74 (3H, s, $OCH_3$), 3.85 (3H, s, $OCH_3$), 6.95 (1H, d, *J* = 10 Hz, Ar-H), 7.19 (1H, d, *J* = 10 Hz, Ar-H), 7.43 (2H, m, Ar-H), 7.88 (2H, bt, Ar-H), 8.5 (1H, s, Ar-H), 8.96 (1H, s, Ar-H). Mass m/z (%): 381 $M^+$.

3-(4-Acetyl-5-H-5-phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (**6g**)

M.p. 200-202°C; yield 69%; IR (KBr, $cm^{-1}$) $\nu_{max}$: 1710 (CO, coumarin), 1530 (C=N), 1650 (C=O), 1510, 1354 (oxadiazole nucleus), 745 (substituted benzene). $^1$H-NMR (DMSO-$d_6$, 300 MHz, δ ppm): 2.50 (3H, s, $COCH_3$), 7.28 (1H, s, CH), 7.43 (4H, m, Ar-H), 7.5 (2H, d, *J* = 10 Hz, Ar-H), 7.7 (3H, bt, Ar-H), 8.4 (1H, s, Ar-H). Mass m/z (%): 307 $M^+$;

3-(4-Acetyl-5-H-5-m-nitropheny-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (**6h**)

M.p. 240-242°C; yield 50%; IR (KBr, $cm^{-1}$) $\nu_{max}$: 1710 (CO, coumarin), 1680 (C=O), 1530 (C=N), 1440, 1250, 1200, 1030 (oxadiazole nucleus), 691 (substituted benzene). $^1$H-NMR (DMSO-$d_6$, 300 MHz, δ ppm): 2.56 (3H, s, $COCH_3$), 7.32 (1H, t, *J* = 6 Hz, Ar-H), 7.74 (2H, m, Ar-H), 7.47 (4H, m, Ar-H), 8.21 (1H, dd, Ar-H), 8.53 (1H, s, Ar-H), 8.63 (1H, s, CH). Mass m/z (%): 352$M^+$.

3-(4-Acetyl-5-H-5-p-nitrophenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (**6i**)

M.p. 270-272°C; yield: 72%; IR (KBr, $cm^{-1}$) $\nu_{max}$: 1712 (CO, coumarin), 1682 (C=O), 1531 (C=N), 1440, 1277, 1208, 1033 (oxadiazole nucleus), 758 (substituted benzene). $^1$H-NMR (DMSO-$d_6$, 300 MHz, δ ppm ): 2.5 (3H, s, $COCH_3$), 7.48 (2H, m, Ar-H), 8.0 (2H, s, Ar-H), 8.15 (2H, d, *J* = 10 Hz, Ar-H), 8.49 (2H, d, *J* = 10 Hz, Ar-H), 8.6 (1H, dd, CH), 8.80 (1H, s, Ar-H). Mass m/z (%): 352 $M^+$.

3-(4-Acetyl-5-H-5-o-hydroxyphenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (**6j**)

M.p. 230-232°C; yield 65%; IR (KBr, $cm^{-1}$) $\nu_{max}$: 710 (CO, coumarin), 1525 (C=N), 1627 (C=O), 1439, 1428, 1365, 1074,1033 (oxadiazole nucleus), 3652 (Ar-OH). $^1$H-NMR (DMSO-$d_6$, 300 MHz, δ ppm): 2.5 (3H, s, $COCH_3$), 7.44 (4H, m, Ar-H), 7.51 (1H, d, *J* = 10 Hz, Ar-H), 7.87 (3H, bt, Ar-H), 8.87 (1H, s, CH), 8.50 (1H, s, Ar-H), 11.66 (1H, s, OH). Mass m/z (%): 232 $M^+$.

## RESULTS

Salicylaldehyde (**1**) and diethylmalonate (**2**) were reacted in the presence of piperidine in ethanol

to form ethyl-2-oxo-2*H*-chromene-3-carboxylate **(3)** which on treatment with hydrazine hydrate 99% resulted in 2-oxo-2*H*-chromonene-3-carbohydrazide **(4)** which further reacted with different aldehydes and ketones to form Schiff bases **(5a-j)** which on cyclization by refluxing in excessive acetic anhydride for 1 h resulted in 3-(4-acetyl-5*H*/methyl-5-substituted phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2*H*-chromen-2-ones **(6 a-j)**. Their $R_f$ values, melting points, elemental analysis, FT- IR, $^1$H-NMR and mass spectra characterized the synthesized compounds.

In the FT-IR spectra of the titled compounds, the carbonyl band of coumarin appears at 1710 $cm^{-1}$ and the carbonyl band of $COCH_3$ appears at 1670 $cm^{-1}$. The band at 1524 $cm^{-1}$ indicates the C=N stretching, other bands at 1479, 1370, 1279, 1092 $cm^{-1}$ correspond to the oxadiazole moiety. $^1$H-NMR spectra of the compounds **(6a-j)** showed a singlet of three acetyl protons at 2.5 ppm. The aromatic protons appeared at 7.02 – 8.04 ppm as a multiplet. A singlet appears at 8.66 for one (C- 4) aromatic proton.

The synthesized compounds **(6a-j)** were initially screened at 30, 100 and 300 mg/kg intraperitoneally in mice for anticonvulsant activity (Table 1). All the compounds except **(6g)** exhibit anticonvulsant activity. In the MES test compounds **(6h)** and **(6i)** with *m*-nitrophenyl and *p*-nitrophenyl substituents at position 5 of oxadiazole ring, respectively, showed activity at 100 mg/kg after 0.5 h. On the other hand, compounds **6a, 6b, 6c, 6d, 6f,** and **6j** showed protection in mice at the dose level of 300 mg/kg after 0.5 h. Some compounds like **6c, 6e, 6f, 6h** and **6i** were also active after 4 h extended period of time. Compound **(6e)** with *p*-nitrophenyl substitution at position 5 of oxadiazole ring was active at lower dose of 30 mg/kg after 4 h. Thus compound **(6e)** showing activity at lower dose of 30 mg/kg seems to be potent in anticonvulsant MES screening.

In the rotarod neurotoxicity screening compounds **6a, 6b, 6c, 6d, 6e, 6f** were devoid of toxicity at the dose of 300 mg/kg at 0.5 h. Compounds **6c, 6d** and **6e** were toxic at the dose of 300 mg/kg after 4 h. Compounds **6h, 6i** and **6j** were toxic after 0.5 h and 4 h. However, all the compounds were less toxic than phenytoin (100 mg/kg). It may be concluded that oxadiazole derivatives with coumarin moiety having nitrophenyl substitution at position 5 of oxadiazole ring were more potent than other compounds of the series.

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