Synthesis of 6-Alkyloxyl-3,4-dihydro-2(1*H*)-quinoliones and Their Anticonvulsant Activities

Zhe-Shan Quan,[†] Jun-Min Wang,[†] Jung-Rae Rho,[‡] Kyung-Chell Kwak, Hee-Cheol Kang, Chang-Soo Jun, and Kyu-Yun Chai[*]

[†]College of Pharmacy, Yanbian University, Yanji, Jilin 133000, P.R. China
[‡]Department of Marine Information Science, Kunsan National University, Kunsan, Jeonbuk 573-701, Korea
Department of Bionanochemistry and Basic Sciences Research Institute, Wonkwang University / Medicinal Resources Research Center of Wonkwang University, Iksan, Jeonbuk 570-749, Korea. [*]E-mail: geuyoon@wonkwang.ac.kr
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A series of 6-alkyloxyl-3,4-dihydro-2(1*H*)-quinoliones (**5a-5n**) were synthesized through nitration, reduction, diazotization, hydrolysis and alkylation from 3,4-dihydro-2(1H)-quinolione. Their structures were characterized by IR, ^{1}H-NMR and MS. The anticonvulsant activity was evaluated by the Maximal electroshock test (MES) and the subcutaneous pentylenetetrazole (Metrazole) test (sc-Met). The neurotoxicity was measured by the Rotarod test (Tox). The result showed that 6-hexyloxy-3,4-dihydro-2 (1*H*)-quinolinone (**5c**) was potent in anti-MES and anti-scMet test with ED_{50} of 24.0 mg/kg and 21.2 mg/kg, respectively, albeit its TD_{50} (67.6 mg/kg) revealed the high neurotoxicity. 6-Benzyloxy-3,4-dihydro-2(1*H*)-quinolinone (**5f**) was less effective against MES induced seizure with ED_{50} of 29.6 mg/kg, but no neurotoxicity was observed even under 300 mg/kg. Its Protective index (PI) was greater than 10 preferable to Phenytoin, Carbamazepin, Phenobarbital and Valproate.

Key Words : [1,2,4]Triazolo[4,3-*a*]quinoline, Anticonvulsant, Maximal electroshock, Pentylenetetrazole, Neurotoxicity

Introduction

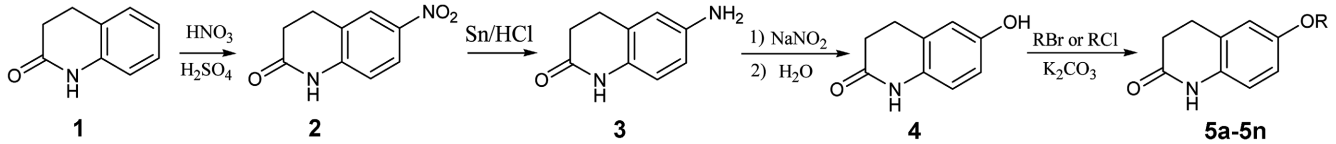
The derivatives of quinolinone have been known to possess various biological activities such as antitumor,[1] antimalarial,[2] antiplatelet,[3] antidepressant,[4] antiulcer,[5] neuroleptic,[6] and cardiac stimulant[7] activities. Their synthesis and anticonvulsant activities, however, have not been reported yet.

In previous search for the positive inotropic activity of quinolinones[8], 3,4-dihydro-2 (1*H*)-quinolione showed little anticonvulsant activity. The introduction of alkyloxyl into the phenyl ring, however, would increase its lipophilic property to enhance its anticonvulsant activity. Thus, we synthesized fourteen 6-alkyloxyl-3,4-dihydro-2(1*H*)–quinoliones. These new compounds were characterized by IR, ^{1}H-NMR, and MS. The anticonvulsant activity was evaluated by the Maximal eletroshock test (MES) and the subcutaneous pentylenetetrezole (Metrazole) test (sc-Met). The neurotoxicity was measured by the rotarod test (Tox).

Experimental Section

Chemistry. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded (KBr) on FT-IR1730. Nuclear magnetic resonance spectra (^{1}H) were measured on BRUKER-300 and all chemical shifts were given in ppm relative to tetramethylsilane. Mass spectra were measured at HP 1100 MSD.

According to the method described previously,[9] compound **4** was prepared from 3,4-dihydro-2 (1*H*)-quinolinone *via* nitration, reduction and diazotization which were all common reactions with high yields (Fig. 1). Then compound **5a-5n** were synthesized through the reaction of compound **4** with halogenated hydrocarbon in ethanol with K_2CO_3 as the



5a: R = n-C_3H_7 **5b**: R = n-C_4H_9 **5c**: R = n-C_6H_{13} **5d**: R = n-C_8H_{17} **5e**: R = n-$C_{12}H_{25}$ **5f**: R = $CH_2C_6H_5$ **5g**: R = $CH_2C_6H_4$(o-F) **5h**: R = $CH_2C_6H_4$(p-F) **5i**: R = $CH_2C_6H_3$(2,6-F_2) **5j**: R = $CH_2C_6H_4$(p-Cl) **5k**: R = $CH_2C_6H_3$(3,4-Cl_2) **5l**: R = $CH_2C_6H_4$(p-CH_3) **5m**: R = $CH_2C_6H_4$(p-OCH_3) **5n**: R = $CH_2C_6H_3$(3,4-OCH_2O)

Figure 1. The synthetic scheme of 6-alkyloxyl-3,4-dihydro-2(1H)-quinolines.

catalyst.

Synthesis of 6-Nitro-3,4-dihydro-2(1*H*)-quinolinone (2). To maintain the temperature between 0-5 °C, a three-necked round-bottomed flask containing 29.4 g(0.20 mol) of compound **1** and 60.8 mL of H_2SO_4 (78%) was placed in an ice-salt bath, in which a mixture of 60.8 mL of H_2SO_4 (78%) and 16.8 mL (0.37 mol) of HNO_3 (65%) was added with moderate speed to keep the temperature below 5 °C. After stirring for 3 hr, the mixture was poured into ice-water and filtered to give the crude product which was then recrystallized in acetone to yield light yellow solid **2** (35.2 g, yield 89%, mp 202-205 °C).

Synthesis of 6-Amino-3,4-dihydro-2(1H)-quinolinone (3). A mixture of 3.80 g (0.0320 mol) of Sn powder and 13 mL of hydrochloric acid (37%) was stirred until Sn was dissolved completely. Then 2.0 g of compound **1** (0.0104 mol) was added and the mixture was stirred in 95-100 °C for 2 hr. Precipitation occurred by the addition of 60 mL of ethanol into the cooled mixture. Dissolving the precipitate in water and adjusting its pH value to 8-9 using 25% NaOH resulted in precipitation of light yellow solid **3** (1.43 g, yield 85%, mp 174-176 °C).

Synthesis of 6-Hydroxy-3,4-dihydro-2(1*H*)-quinolinone (4). Compound **3** (6.0 g, 0.037 mol) was placed into a flask containing 13.4 mL of water and 8.2 mL of conc-H_2SO_4, and the mixture was put in an ice-salt bath to keep the temperature between 0-5 °C. $NaNO_2$ (2.76 g, 0.04 mol) dissolved in 7.50 mL of water was added slowly into the mixture to keep the temperature below 5 °C. Then the mixture was heated at reflux for 40 min, cooled and filtered after adding water (20 mL) to give a light yellow solid **4** (5.2 g, yield 86%, mp 235-236 °C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.42 (t, 2H, J = 7.2 Hz), 2.76 (t, 2H, J = 7.2 Hz), 6.53-6.67 (m, 3H), 8.94 (s, 1H), 9.73 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.67, 33.37, 114.57, 114.69, 125.63, 130.65, 150.97, 171.20.

General Procedure for the Synthesis of 6-Alkyloxyl-3,4-dihydro-2(1*H*)-quinolinone (5a-5n). K_2CO_3 (12.4 g, 0.09 mol), absolute ethanol (60 mL) and 6-hydroxy-3,4-dihydro-2(1*H*)-quinolinone (4.89 g, 0.03 mol) were added in a 100 mL round-bottomed flask equipped with reflux condenser. Alkyl bromide or benzyl chloride derivative (0.045 mol) was dropwise added into the mixture. The reaction mixture was heated at reflux for 2-24 hr and poured into 100 mL of ice-water. White solid (**5a-5n**) was obtained and recrystallized in EtOAc.

6-Propoxy-3,4-dihydro-2(1*H*)-quinolinone (5a). mp 131-133 °C; yield 61%; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.95 (t, J = 7.4 Hz, 3H), 1.62-1.74 (m, 2H), 2.39 (t, J = 7.5 Hz, 2H), 2.81 (t, J = 7.5 Hz, 2H), 3.84 (t, J = 6.5 Hz, 2H), 6.68-6.77 (m, 3H), 9.91 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 10.65, 23.35, 25.54, 32.81, 71.51, 113.17, 114.35, 127.82, 134.33, 153.78, 171.63. IR (KBr) cm^{-1}: 3429 (N-H), 1663 (C=O), 1243, 1021 (C-O-C); MS m/z 205 (M^+).

6-Butoxy-3,4-dihydro-2(1*H*)-quinolinone (5b). mp 102-105 °C; yield 68%; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.91 (t, J = 7.4 Hz, 3H), 1.34-1.47 (m, 2H), 1.60-1.69 (m, 2H), 2.38 (t, J = 7.5 Hz, 2H), 2.81 (t, J = 7.5 Hz, 2H), 3.88 (t, J = 6.4 Hz, 2H), 6.68-6.76 (m, 3H), 9.92 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 13.70, 18.80, 25.47, 30.51, 32.81, 67.39, 113.15, 113.91, 114.38, 127.80, 134.63, 154.09, 171.63. IR (KBr) cm^{-1}: 3436 (N-H), 1673 (C=O), 1244, 1030 (C-O-C); MS m/z 219 (M^+).

6-Hexyloxy-3,4-dihydro-2(1*H*)-quinolinone (5c). mp 94-96 °C; yield 67%; ^{1}H NMR (DMSO-d_6, 300MHz): δ0.86 (t, J = 6.5 Hz, 3H), 1.28-1.70 (m, 8H), 2.38 (t, J = 7.5 Hz, 2H), 2.81 (t, J = 7.5 Hz, 2H), 3.86 (t, J = 6.5 Hz, 2H), 6.67-6.76 (m, 3H), 9.92 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 13.10, 22.11, 24.73, 25.47, 28.09, 30.75, 32.81, 67.15, 113.15, 113.91, 114.38, 127.80, 134.63, 153.75, 171.63. IR (KBr) cm^{-1}: 3430 (N-H), 1677 (C=O), 1246, 1037 (C-O-C); MS m/z 247 (M^+).

6-Octyloxy-3,4-dihydro-2(1*H*)-quinolinone (5d). mp 91-93 °C; yield 64%; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.85 (t, J = 6.5 Hz, 3H), 1.25-1.68 (m, 12H), 2.37 (t, J = 7.5 Hz, 2H), 2.80 (t, J = 7.5 Hz, 2H), 3.86 (t, J = 6.5 Hz, 2H), 6.67-6.75 (m, 3H), 9.92 (s, 1H). IR (KBr) cm^{-1}: 3432 (N-H), 1677 (C=O), 1242, 1045 (C-O-C); MS m/z 375 (M^+).

6-Dodecyloxy-3,4-dihydro-2(1*H*)-quinolinone (5e). mp 84-86 °C; yield 60%; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.83 (t, J = 6.8 Hz, 3H), 1.23-1.65 (m, 20H), 2.38 (t, J = 7.5 Hz, 2H), 2.81 (t, J = 7.4 Hz, 2H), 3.86 (t, J = 6.3 Hz, 2H), 6.67-6.75 (m, 3H), 9.91 (s, 1H). IR (KBr) cm^{-1}: 3442 (N-H), 1674 (C=O), 1247, 1045 (C-O-C); MS m/z 331 (M^+).

6-Benzyloxy-3,4-dihydro-2(1*H*)-quinolinone (5f). mp 159-161 °C; yield 84%; ^{1}H NMR (DMSO-d_6, 300MHz): δ 2.39 (t, J = 7.4 Hz, 2H), 2.82 (t, J = 7.3 Hz, 2H), 5.02 (s, 2H), 6.75-6.87 (m, 3H), 7.31-7.43 (m, 5H), 9.94 (s, 1H). IR (KBr) cm^{-1}: 3432 (N-H), 1676 (C=O), 1239, 1013 (C-O-C); MS m/z 253 (M^+).

6-(2-Fluoro-benzyloxy)-3,4-dihydro-2(1*H*)-quinolinone (5g). mp 200-202 °C; yield 81%; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.39 (t, J = 7.4 Hz, 2H), 2.82 (t, J = 7.4 Hz, 2H), 5.06 (s, 2H), 6.76-6.88 (m, 3H), 7.21-7.56 (m, 4H), 9.97 (s, 1H). IR (KBr) cm^{-1}: 3433 (N-H), 1674 (C=O), 1239, 1012 (C-O-C); MS m/z 271 (M^+).

6-(4-Fluoro-benzyloxy)-3,4-dihydro-2(1*H*)-quinolinone (5h). mp 182-184 °C; yield 85%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 2.39 (t, J = 7.5 Hz, 2H), 2.82 (t, J = 7.5 Hz, 2H), 5.00 (s, 2H), 6.74-6.86 (m, 3H), 7.18-7.49 (m, 4H), 9.95 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ25.39, 32.81, 68.37, 113.27, 114.02, 114.60, 116.10, 127.90, 129.56, 133.35, 134.46, 154.59, 162.37, 171.63. IR (KBr) cm^{-1}: 3429 (N-H), 1661 (C=O), 1241, 1011 (C-O-C); MS m/z 271 (M^+).

6-(2,6-Difluoro-benzyloxy)-3,4-dihydro-2(1*H*)-quinolinone (5i). mp 244-246 °C; yield 87%; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.40 (t, J = 7.3 Hz, 2H), 2.83 (t, J = 7.3 Hz, 2H), 5.03 (s, 2H), 6.77-6.89 (m, 3H), 7.14-7.56 (m, 3H), 9.97 (s, 1H). IR (KBr) cm^{-1}: 3435 (N-H), 1672 (C=O), 1238, 1016 (C-O-C); MS m/z 298 (M^+).

6-(4-Chloro-benzyloxy)-3,4-dihydro-2(1*H*)-quinolinone (5j). mp 218-220 °C; yield 90%; ^{1}H NMR (DMSO-d_6, 300 MHz): δ2.39 (t, J = 7.4 Hz, 2H), 2.82 (t, J = 7.3 Hz, 2H), 5.02 (s, 2H), 6.77-7.44 (m, 7H), 9.96 (s, 1H). IR (KBr) cm^{-1}: 3438

(N-H), 1666 (C=O), 1242, 1014 (C-O-C); MS m/z 287 (M^+).

6-(3,4-Dichloro-benzyloxy)-3,4-dihydro-2(1*H*)-quinolinone (5k). mp 168-170 °C; yield 73%; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.39 (t, J = 7.5 Hz, 2H), 2.82 (t, J = 7.5 Hz, 2H), 5.05 (s, 2H), 6.74-6.88 (m, 3H), 7.40-7.69 (m, 3H), 9.96 (s, 1H). IR (KBr) cm^{-1}: 3428 (N-H), 1668 (C=O), 1245, 1029 (C-O-C); MS m/z 322 (M^+).

6-(4-Methyl-benzyloxy)-3,4-dihydro-2(1*H*)-quinolinone (5l). mp 169-171 °C; yield 91%; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.29 (s, 3H), 2.39 (t, J = 7.5 Hz, 2H), 2.81 (t, J = 7.5 Hz, 2H), 4.98 (s, 2H), 6.73-7.08 (m, 3H), 7.18 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 9.94 (s, 1H). IR (KBr) cm^{-1}: 3432 (N-H), 1669 (C=O), 1241, 1019 (C-O-C); MS m/z 271 (M^+).

6-(4-Methoxy-benzyloxy)-3,4-dihydro-2(1*H*)-quinolinone (5m). mp 170-172 °C; yield 85%; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.38 (t, J = 7.5 Hz, 2H), 2.81 (t, J = 7.5 Hz, 2H), 3.73 (s, 3H), 5.01 (s, 2H), 6.73-6.84 (m, 3H), 6.92 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 9.94 (s, 1H). IR (KBr) cm^{-1}: 3427 (N-H), 1702 (C=O), 1245, 1017 (C-O-C); MS m/z 283 (M^+).

6-(Benzo[1,3]dioxol-5-ylmethoxy)-3,4-dihydro-2(1*H*)-quinolinone (5n). mp 171-173 °C; yield 84%; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.39 (t, J = 7.4 Hz, 2H), 2.81 (t, J = 7.4 Hz, 2H), 4.90 (s, 2H), 6.01 (s, 2H), 6.57-6.98 (m, 7H), 9.89 (s, 1H). IR (KBr) cm^{-1}: 3431 (N-H), 1670 (C=O), 1246, 1044 (C-O-C); MS m/z 297 (M^+).

Pharmacology. Maximal electroshock (MES) test, subcutaneous pentylenetetrazole (scMet) test, and rotarod test were carried out by the Antiepileptic Drug Development Program (ADD), Epilepsy Branch, National Institutes of Health, Bethesda, MD.[10,11] All compositions were tested for anticonvulsant activity with C57B/6 mice in the 18-25 g weight range purchased from the Laboratory of Animal Research, college of pharmacy, Yanbian University. The tested compounds were dissolved in Polyethylene glycol-400.

In Phase I screening (Table 1) each compound was administered ip at three dose levels (30, 100 and 300 mg/kg, a total of 6 mice were used, two for each dose) with anticonvulsant activity and neurotoxicity assessed at 30 min and 4 hr intervals after administration. Anticonvulsant efficacy was measured by the maximal electroshock (MES) test and the subcutaneous pentylenetetrazol (scMet) test. In the MES test, seizures were elicited with a 60Hz alternating current of 50 mA intensity in mice. The current was applied *via* corneal electrodes for 0.2 s. Abolition of the hind-leg tonic-extensor component of the seizure indicated protection against the spread of MES-induced seizures. The scMet test involved subcutaneous injection of convulsant dose (CD_{97}) of pentylenetetrazol (85 mg/kg in mice). Elevation of the pentylenetrazol-induced seizure threshold was indicated by the absence of clonic spasms for at least 5 s duration over a 30 min period following administration of the test compound. Anticonvulsant drug-induced neurologic deficit was detected in mice by the rotarod ataxia test.

The pharmacological parameters estimated in phase I screening were quantified for compounds **5a**, **5b**, **5c** and **5f** in phase II screening (Table 2). Anticonvulsant activity was expressed in terms of the median effective dose (ED_{50}), and neurotoxicity was expressed as the median toxic dose (TD_{50}). For determination of the ED_{50} and TD_{50}, groups of 10 mice were given a range of ip doses of the test drug until at least three points were established in the range of 10-90% seizure protection or minimal observed neurotoxicity. From the plot of this data, the respective ED_{50}, TD_{50} values, 95% confidence intervals, slope of the regression line, and the standard error of the slope were calculated by means of a computer program written at National Institute of Neurological Disorders and Stroke (NINDS).

Result and Discussion

The compounds were tested for anticonvulsant activity using the procedures described previously.[10,11] The initial evaluation (phase I) of anticonvulsant activity of synthesized compounds is presented in Table 1. The compounds were administered intraperitoneally at three doses (30, 100, and 300 mg/kg). Three tests were performed for each compound: maximal electroshock (MES)-induced convulsions, subcutaneous metrazol (sc-Met)-induced convulsions and rotarod neurotoxicity test (Tox).

As a result of preliminary screening, compounds **5a**, **5b**, **5c** and **5f** were subjected to phase II trials for quantification of their anticonvulsant activity and neurotoxicity in mice. This phase provides an evaluation of the median effective dose (ED_{50}) and the median neurotoxic dose (TD_{50}). The 95% confidence interval, the slope of the regression line, and the SE of the slope were then calculated. These data are shown in Table 2 which also includes the comparison data with commercial antiepileptic drugs such as Phenytoin,

Table 1. Phase Anticonvulsant and Toxicity Data in Mice (i.p.)[a]

Compd	MES[b]		ScMet[c]		Rotarodtoxicity	
	0.5	4 h	0.5	4 h	0.5	4 h
1	300[d]	–[e]	300	–	300	–
5a	100	–	300	–	100	–
5b	100	–	100	–	100	–
5c	30	–	30	–	100	–
5d	–	–	–	–	–	–
5e	–	–	–	–	–	–
5f	30	–	300	–	–	–
5g	–	–	–	–	–	–
5h	–	–	–	–	–	–
5i	–	–	–	–	–	–
5j	–	–	–	–	–	–
5k	–	–	–	–	–	–
5l	–	–	–	–	–	–
5m	–	–	–	–	–	–
5n	–	–	–	–	–	–

[a]All of tested compounds were dissolved in Polyethylene giycol-400. [b]The maximal electroshock test was induced after 30 min post administration of the tested compounds. [c]Subcutaneous pentylenetetrazol (85 mg·kg^{-1}) 30 min after the tested compounds were administrated for 30 min. [d]Dose were denoted in mg·kg^{-1}. [e]– = no activity at 300 mg·kg^{-1}.

Table 2. Phase Quantitative Anticonvulsant Data in Mice (test drug administered ip)

	ED_{50}[a]			PI[b]	
	MES	scMet	Tox, TD_{50}[c]	MES	scMet
5a	78.9 (66.7-93.2)[e]	> 100	67.6 (56.1-81.5)	0.86	–
5b	28.9 (24.2-34.5)	51.4(43.40-60.68)	84.8 (70.7-101.6)	2.94	1.65
5c	24.0 (21.8-26.5)	21.2(17.70-25.43)	56.3 (46.9-67.8)	2.35	2.65
5f	29.6 (25.2-34.8)	> 100	> 300	> 10	–
Phenytoin[d]	9.5 (8.1-10.4)	> 300	65.5 (52.5-72.9)	6.9	< 0.22
Carbamazepin[d]	8.8 (5.5-14.1)	> 100	71.6 (45.9-135)	8.1	< 0.72
phenobarbital[d]	21.8 (21.8-25.5)	13.2 (5.8-15.9)	69 (62.8-72.9)	3.2	5.2
Valproate[d]	272 (247-338)	149 (123-177)	426 (369-450)	1.6	2.9

[a]the dose measured in $mg \cdot kg^{-1}$. [b]PI = TD_{50} / ED_{50}. [c]Minimal neurotoxicity was determined by the rotarod test after the tested compounds were administrated 30 min. [d]the data from Ucar *et al.*[12]) the 95% confidence limits.

Carbamazepine, Phenobarbital and Valproate. Some of these derivatives showed a high degree of protection against MES and scMet-induced seizures.

The result of the initial evaluation (phase I) indicates that only four compounds with substituted groups enhanced their anticonvulsant activities while the others showed a decrease of the activity after the introduction of alkoxy and benzyloxy derivatives in the 6th position of 3,4-dihydro-2(1*H*)-quinolinone (**1**). The lengthening of the alkyl chain resulted in a change in anticonvulsant activity of the 6-alkyloxyl derivatives. Compound **5c** with the *n*-hexyl substituted group was found to be the most active. Their activity disappeared, however, when the alkyl chain had more than 6 carbon numbers. Compound **5c** with ED_{50} of 24.0 mg/kg was better than Valproate and close to Phenobarbital in anti-MES activity. Also the quinolione with ED_{50} of 21.2 mg/kg in anti-scMet test was better than Valproate, Phenobarbital and Carbamazepin. However, its neurotoxicity (TD_{50} of 67.6 mg/kg) was measured to be higher than the others.

Among 6-substituted benzyloxyl derivatives, only compound **5f** which has no substituent in the phenyl ring exhibited high activity against seizure induced by MES and a little activity against scMet-induced seizure, while the compounds with substituents in the phenyl ring were inactive. No neurotoxicity was observed in compound **5f** as shown in Table 2 although, with ED_{50} of 29.6 mg/kg against MES, it was less effective than phenytoin, carbamazepin and Phenobarbital. Thus, the PI value of compound **5f** is greater than 10, which is considered to be superior to all the other drugs compared.

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