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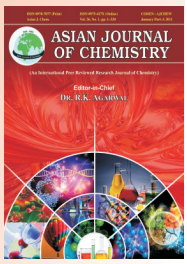

Synthesis and Anticonvulsant Activity Evaluation of 2-Phenyl-2*H*-benzo[*e*][1,3]oxazin-4(3*H*)-ones

LI-JING CUI[1], JUN GUO[2], GUO-HUA GONG[3,*] and ZHE-SHAN QUAN[2,*]

[1]Department of Pharmacy, Guangdong Food and Drug Vocational College, Guangzhou 510520, P.R. China
[2]College of Pharmacy, Yanbian University, Yanji 133002, Jilin Province, P.R. China
[3]Institute of Medicinal Chemistry, Inner Mongolia University for Nationalities, Tongliao 028002, Inner Mongolia Autonomous Region, P.R. China

*Corresponding authors: Fax: +86 433 2436020; E-mail: gongguohua0211@163.com; zsquan@ybu.edu.cn

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A series of new 2-phenyl-2*H*-benzo[*e*][1,3]oxazin-4(3*H*)-one derivatives **(1a-1t)** were designed based on the known anticonvulsant activity of quinolinone derivatives. All target compounds **1a-1t**, characterized by IR, ^{1}H NMR and MS, have been evaluated for their anticonvulsant activity against MES-induced seizures. The pharmacological results showed that all the compounds displayed some degree of anticonvulsant activity. Among them, 2-phenyl-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one **(1a)** and 2-(2-fluorophenyl)-2,3-dihydrobenzo-[*e*][1,3]oxazin-4-one **(1b)** were considerd more promising because of their lower ED_{50} (34.1 and 28.4 mg/kg) and higher protective index (11.1 and 8.0).

Keywords: Anticonvulsant, 1-Isoquinolinone, Benzo[*e*][1,3]oxazin-4(3*H*)-one, Maximal electroshock test, Neurotoxicity.

INTRODUCTION

Epilepsy, one of the most frequent neurological afflictions in men characterized by excessive temporary neuronal discharges resulting in uncontrolled convulsion, inflicts more than 60 million people worldwide[1, 2]. Despite the development of several new anticonvulsants, the treatment of epilepsy remains still inadequate. It is roughly estimated that up to 28-30 % of patients are poorly treated with the available antiepileptic drugs (AEDs)[3,4]. Moreover, many AEDs have serious side effects[5-10], and lifelong medication may be required. Therefore, there is a continuing demand for new anticonvulsant agents with more selectivity and lower toxicity.

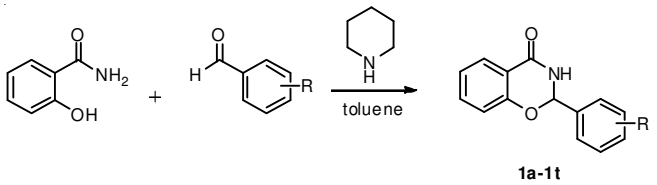
In the previous works, quinolinone derivatives were found to be active in anti-epileptic animal models and some of them showed better effect and lower toxicity than marketed drugs[11-15]. It is known that switch direction of the amide in quinolinone lead to 1-isoquinolinone, which possess the same moieties to the quinolinone. Based on the anticonvulsant profile of quinolinone derivatives, we speculated the 1-isoquinolinone nucleus incorporating some important elements required for anticonvulsant profile such as hydrophobic site and electron donor group would give some new anti-epileptic compounds. So in this study, we conducted the design and synthesis of a series of 1-isoquinolinone derivatives, 2-phenyl-2*H*-benzo[*e*]-[1,3]-oxazin-4(3*H*)-ones, which possessing the electron donor group-oxygen atom in first position and the hydrophobic site-phenyl group in second position.

The structures of all the target compounds were characterized using IR, ^{1}H NMR, MS and elemental analysis techniques. Their anticonvulsant activities was all evaluated by MES test in mice and their neurotoxicity was evaluated with the rotarod test.

EXPERIMENTAL

Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded (in KBr) on IRPrestige-21. ^{1}H NMR spectra were measured on an AV-300 (Bruker, Switzerland) and all chemical shifts were given in ppm relative to tetramethysilane. Mass spectra were measured on an HP1100LC (Agilent Technologies, USA). The ionization technique used for recording mass spectra was Atmospheric Pressure Chemical Ionization (APCI). Elemental analyses were performed on a 204Q CHN (Perkin-Elmer, USA). The chemicals were purchased from Aldrich Chemical Corporation.

General procedure for the synthesis of 2-phenyl-2,3-dihydrobenzo[*e*][1,3]oxazin-4-ones: To a round bottomed flask containing 50 mL of toluene, 2-hydroxybenzamide 1.37 g (0.01 mol) and substituted benzaldehyde (0.015 mol) were added followed by the catalytic amount of piperidine. The mixture was stirred for 22 h at 110 °C. After removing the solvent under reduced pressure, the residue was added 30 mL methanol and stirred to precipitation. The resulting precipitate was filtrated, washed with petroleum ether, then recrystallized by ethanol to afford compounds **1a-1t** (**Scheme-I**).



Scheme-I: Synthesis of title compounds **1a-1t**

2-Phenyl-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (1a): Yield: 84.5 %, m.p. 144-146 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.23 (s, 1H, -NH), 6.26 (s, 1H, -CH-), 7.02-8.02 (m, 9H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3188 ν(N-H), 1669 ν(C=O). MS *m/z* 226.3 (M+H). Anal. calcd. (%) for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.61; H, 4.82; N, 6.24.

2-(2-Fluorophenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (1b): Yield: 20.1 %, m.p. 154-156 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.24 (s, 1H, -NH), 6.62 (s, 1H, -CH-), 7.02-8.02 (m, 8H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3180 ν(N-H), 1690 ν(C=O). MS *m/z* 244.1 (M+H). Anal. calcd. (%) for $C_{14}H_{10}NO_2F$: C, 69.13; H, 4.14; N, 5.76. Found: C, 69.15; H, 4.24; N, 5.61.

2-(3-Fluorophenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (1c): Yield: 30.3 %, m.p. 136-138 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.25 (s, 1H, -CH-), 6.57 (s, 1H, -NH), 7.01-7.98 (m, 8H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3182 ν(N-H), 1687 ν(C=O). MS *m/z* 244.2 (M+H). Anal. calcd. (%) for $C_{14}H_{10}NO_2F$: C, 69.13; H, 4.14; N, 5.76. Found: C, 69.15; H, 4.24; N, 5.60.

2-(4-Fluorophenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (1d): Yield: 42.9 %, m.p. 169-172 °C. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 6.24 (s, 1H, -CH-), 6.55 (s, 1H, -NH), 6.99-8.00 (m, 8H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3179 ν(N-H), 1686 ν(C=O). MS *m/z* 244 (M+H). Anal. calcd. (%) for $C_{14}H_{10}NO_2F$: C, 69.13; H, 4.14; N, 7.76. Found: C, 69.15; H, 4.04; N, 7.81.

2-(2-Chlorophenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (1e): Yield: 17.1 %, m.p. 142-144 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.16 (s, 1H, -NH), 6.68 (s, 1H, -CH-), 7.04-8.03 (m, 8H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3172 ν(N-H), 1691 ν(C=O). MS *m/z* 260.4 (M+H). Anal. calcd. (%) for $C_{14}H_{10}NO_2Cl$: C, 64.75; H, 3.88; N, 5.39. Found: C, 63.76; H, 3.77; N, 5.49.

2-(3-Chlorophenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (1f): Yield: 31.3 %, m.p. 156-158 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.24 (s, 1H, -CH-), 6.67 (s, 1H, -NH), 7.01-7.99 (m, 8H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3175 ν(N-H), 1690 ν(C=O). MS *m/z* 260.1 (M+H). Anal. calcd. (%) for $C_{14}H_{10}NO_2Cl$: C, 64.75; H, 3.88; N, 5.39. Found: C, 64.74; H, 3.68; N, 5.39.

2-(4-Chlorophenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (1g): Yield: 35.3 %, m.p. 198-200 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.23 (s, 1H, -CH-), 6.47 (s, 1H, -NH), 6.99-7.99 (m, 8H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3176 ν(N-H), 1687 ν(C=O). MS *m/z* 260.0 (M+H). Anal. calcd. (%) for $C_{14}H_{10}NO_2Cl$: C, 64.75; H, 3.88; N, 5.39. Found: C, 64.78; H, 3.98; N, 5.26.

2-(2,4-Dichlorophenyl)-2,3-dihydrobenzo[*e*][1,3]-oxazin-4-one (1h): Yield: 35.8 %, m.p. 180-184 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.34 (s, 1H, -NH), 6.63 (s, 1H, -CH-), 7.03-8.00 (m, 7H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3174 ν(N-H), 1691 ν(C=O). MS *m/z* 294.0 (M+H). Anal. calcd. (%) for $C_{14}H_9NO_2Cl_2$: C, 57.17; H, 3.08; N, 4.76. Found: C, 57.09; H, 3.18; N, 4.66.

2-(3,4-Dichlorophenyl)-2,3-dihydrobenzo[*e*][1,3]-oxazin-4-one (1i): Yield: 34.2 %, m.p. 199-201 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.24 (s, 1H, -CH-), 6.82 (s, 1H, -NH), 7.00-7.97 (m, 7H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3175 ν(N-H), 1690 ν(C=O). MS *m/z* 294.1 (M+H). Anal. calcd. (%) for $C_{14}H_9NO_2Cl_2$: C, 57.17; H, 3.08; N, 4.76. Found: C, 57.05; H, 3.26; N, 4.56.

2-(2,6-Dichlorophenyl)-2,3-dihydrobenzo[*e*][1,3]-oxazin-4-one (1j): Yield: 35.4 %, m.p. 130-134 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.05 (s, 1H, -NH), 7.02 (s, 1H, -CH-), 7.04-8.03(m, 7H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3172 ν(N-H), 1693 ν(C=O). MS *m/z* 294.4 (M+H). Anal. calcd. (%) for $C_{14}H_9NO_2Cl_2$: C, 57.17; H, 3.08; N, 4.76. Found: C, 57.05; H, 3.20; N, 4.69.

2-(2-Bromophenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (1k): Yield: 18.3 %, m.p. 170-172 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.22 (s, 1H, -NH), 6.64 (s, 1H, -CH-), 7.04-8.02 (m, 8H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3182 ν(N-H), 1679 ν(C=O). MS *m/z* 304.0 (M+H). Anal. calcd. (%) for $C_{14}H_{10}NO_2Br$: C, 55.29; H, 3.31; N, 4.61. Found: C, 55.27; H, 3.13; N, 4.64.

2-(3-Bromophenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (1l): Yield: 18.7 %, m.p. 184-186 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.23 (s, 1H, -CH-), 6.41 (s, 1H, -NH), 7.01-8.01 (m, 8H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3181 ν(N-H), 1680 ν(C=O). MS *m/z* 304.1 (M+H). Anal. calcd. (%) for $C_{14}H_{10}NO_2Br$: C, 55.29; H, 3.31; N, 4.61. Found: C, 55.26; H, 3.44; N, 4.62.

2-(4-Bromophenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (1m): Yield: 24.2 %, m.p. 202-204 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.23 (s, 1H, -CH-), 6.56 (s, 1H, -NH), 6.99-7.98 (m, 8H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3187 ν(N-H), 1674 ν(C=O). MS *m/z* 304.1 (M+H). Anal. calcd. (%) for $C_{14}H_{10}NO_2Br$: C, 55.29; H, 3.31; N, 4.61. Found: C, 55.27; H, 3.13; N, 4.63.

2-(2-(Trifluoromethyl)phenyl)-2,3-dihydrobenzo-[*e*][1,3]oxazin-4-one (1n): Yield: 33.1 %, m.p. 158-161 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.23 (s, 1H, -NH), 6.67 (s, 1H, -CH-), 7.01-8.14 (m, 8H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3190 ν(N-H), 1667 ν(C=O). MS *m/z* 294.3 (M+H). Anal. calcd. (%) for $C_{15}H_{10}NO_2F_3$: C, 61.44; H, 3.44; N, 4.78. Found: C, 61.46; H, 3.66; N, 4.74.

2-(4-(Trifluoromethyl)phenyl)-2,3-dihydrobenzo-[*e*][1,3]oxazin-4-one (1o): Yield: 30.6 %, m.p. 212-215 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.35 (s, 1H, -CH-), 6.67 (s, 1H, -NH), 7.01-7.99 (m, 8H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3191 ν(N-H), 1662 ν(C=O). MS *m/z* 294.6 (M+H). Anal. calcd. (%) for $C_{15}H_{10}NO_2F_3$: C, 61.44; H, 3.44; N, 4.78. Found: C, 61.40; H, 3.58; N, 4.76.

2-(3-Nitrophenyl)-2,3-dihydrobenzo[e][1,3]oxazin-4-one (1p) Yield: 37.7 %, m.p. 204-206 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.41 (s, 1H, -CH-), 7.02-8.35 (m, 8H, Ar-H), 8.53 (s, 1H, -NH). IR (KBr, ν_{max}, cm^{-1}): 3197 (N-H), 1685 (C=O). MS *m/z* 270.4 (M+H). Anal. calcd. (%) for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.24; H, 3.61; N, 10.58.

2-*p*-Tolyl-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (1q): Yield: 39.1 %, m.p. 158-162 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.42 (s, 3H, -CH_3), 6.16 (s, 1H, -NH), 6.21 (s, 1H, -CH-), 6.99-8.01 (m, 8H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3185 ν(N-H), 1688 ν(C=O). MS *m/z* 240.5 (M+H). Anal. calcd. (%) for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.33; H, 5.55; N, 5.94.

2-(4-Methoxyphenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (1r): Yield: 22.3 %, m.p. 179-182 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.87 (s, 3H, -OCH_3), 6.19 (s, 1H, -CH-), 6.23 (s, 1H, -NH), 6.96-7.99 (m, 8H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3187 ν(N-H), 1689 ν(C=O). MS *m/z* 256.3 (M+H). Anal. calcd. (%) for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.47; H, 5.03; N, 5.29.

2-(3,4-Dimethoxyphenyl)-2,3-dihydrobenzo[*e*][1,3]-oxazin-4-one (1s): Yield: 16.8 %, m.p. 146-150 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.92-3.94 (m, 6H, -OCH_3), 6.20 (s, 1H, -CH-), 6.39 (s, 1H, -NH), 6.91-8.00 (m, 7H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3191 ν(N-H), 1689 ν(C=O). MS *m/z* 286.1 (M+H). Anal. calcd. (%) for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.34; H, 5.42; N, 4.83.

2-(3,4,5-Trimethoxyphenyl)-2,3-dihydrobenzo[*e*][1,3]-oxazin-4-one (1t): Yield: 32.1 %, m.p. 166-169 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.88-3.90 (m, 9H, -OCH_3), 6.17 (s, 1H, -CH-), 6.54 (s, 1H, -NH), 6.83-8.00 (m, 6H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3194 ν(N-H), 1694 ν(C=O). MS *m/z* 316.5 (M+H). Anal. calcd. (%) for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.70; H, 5.28; N, 4.56.

Maximal electroshock test (MES): The maximal electroshock seizure test was carried out according to the standard protocol[16,17]. KunMing mice were stimulated through corneal electrodes to 50 mA current at a pulse of 60 Hz applied for 0.2 s. Animals were previously administered with the test drug i.p. Abolition of hind limb tonic extension spasm was recorded as the anticonvulsant activity. The test compounds were dissolved in DMSO. In the preliminary screening, each compound was administered as an i.p. injection at three dose levels (30, 100 and 300 mg/kg) and the anticonvulsant activity assessed after 0.5 h and 4.0 h intervals of administration.

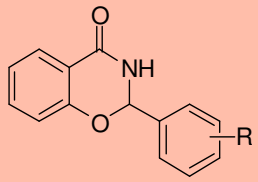
Neurotoxicity (NT) screening[16,17]: The neurotoxicity of the compounds were measured in mice by the rotarod test. The mice were trained to stay on an accelerating rotarod of diameter 3.2 cm that rotates at 10 rpm. Trained animals were given i.p. injection of the test compounds. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the trials.

RESULTS AND DISCUSSION

In this paper, the target compounds 2-phenyl-2*H*-benzo[*e*][1,3]oxazin-4(3*H*)-ones **(1a-1t)**, were prepared according to a reported procedure[18]. Briefly, they were obtained by cyclization of 2-hydrozybenzamide and substituted benzaldehyde in the presence of piperidine at 110 °C in toluene. All compounds were identified by the spectral data. In general, IR spectra showed the C=O peak at 1694-1662 cm^{-1}, the NH stretching vibrations at 3197-3172 cm^{-1}. In the nuclear magnetic resonance spectra (^{1}H NMR), the signals of the respective protons of the synthesized compounds were verified on the basis of their chemical shifts, mutiplicitiesand coupling constants. The spectra showed the amide (NH) proton as a blunt singlet at 6.05-6.82 ppm and the methenyl group (CH) at 6.17-7.02 ppm.

Anticonvulsant activity: The pharmacological testing of all the target compounds were performed according to the standard protocol given by epilepsy branch of the National Institute of Neurological Disorders and Stroke (NINDS) and adopted by the Antiepileptic Drug Development (ADD) program[19]. Their anticonvulsant activity was assessed by the most adopted animal model electroshock (MES) test. All the synthesized compounds were administered intraperitoneally into mice using doses of 30, 100 and 300 mg/kg and the observations were taken at two different time intervals (0.5 h and 4.0 h). Neurological impairment was evaluated by rotarod method and the data are presented in Table-1.

TABLE-1
PHASE-I EVALUATION OF ANTICONVULSANT ACTIVITY IN MICE (i.p.)



Compd.	R	MES[a] (mg/kg) 0.5 h			MES (mg/kg) 4 h		
		300	100	30	300	100	30
1a	-H	3/3	3/3[b]	2/3	-[c]	2/3	-
1b	*o*-F	3/3	3/3	1/3	-	2/3	-
1c	*m*-F	3/3	3/3	1/3	-	3/3	-
1d	*p*-F	3/3	3/3	2/3	-	3/3	-
1e	*o*-Cl	3/3	2/3	1/3	-	2/3	-
1f	*m*-Cl	3/3	2/3	1/3	-	1/3	-
1g	*p*-Cl	1/3	0/3	0/3	-	2/3	-
1h	2,4-Cl	1/3	0/3	0/3	-	1/3	-
1i	3,4-Cl	1/3	0/3	0/3	-	1/3	-
1j	2,6-Cl	1/3	0/3	0/3	-	0/3	-
1k	*o*-Br	2/3	1/3	0/3	-	2/3	-
1l	*m*-Br	2/3	0/3	0/3	-	0/3	-
1m	*p*-Br	1/3	0/3	0/3	-	0/3	-
1n	*o*-CF_3	2/3	1/3	0/3	-	1/3	-
1o	*p*-CF_3	1/3	0/3	0/3	-	0/3	-
1p	*m*-NO_2	1/3	0/3	0/3	-	0/3	-
1q	*p*-CH_3	3/3	2/3	1/3	-	2/3	-
1r	*p*-OCH_3	1/3	0/3	0/3	-	0/3	-
1s	3,4-$(OCH_3)_2$	1/3	0/3	0/3	-	0/3	-
1t	3,4,5-$(OCH_3)_3$	3/3	2/3	0/3	-	1/3	-

[a]Maximal electroshock: doses of 30, 100 and 300 mg/kg were administrated intraperitoneally in mice; The animals were examined 0.5 h after administration.
[b]The figures n_1/n_2: the animals protected/the animals tested.
[c]The dash (-) : not tested.

In the phase I preliminary anticonvulsant screening, all the compounds showed some degree of protection in MES screen which was the indicative of the good ability of these compounds to prevent the seizure spread. Half of the compounds were active at a dose of 100 mg/kg after 0.5 h. These include compounds **1a-1f**, **1k**, **1n**, **1q** and **1t**. Compounds **1a-1f** and **1q** showed protection from seizure at the dose 30 mg/kg after 0.5 h. At 4 h interval, compounds **1a-1i**, **1k**, **1n**, **1q** and

1t showed activity at dose of 100 mg/kg. Compounds **1a**-**1f**, **1k**, **1n**, **1q** and **1t** have shown activity at dose of 100 mg/kg at 0.5 h and 4 h indicating that these compounds having quick onset and long duration of action. From these data, we can see that compounds with non-substituted or F-substituted phenyl group showed better activity. The effect of electron withdrawing groups or electron releasing groups were found to be uncertain on the anticonvulsant activity such as **1n** (*o*-CF_3), **1o** (*p*-CF_3), **1p** (*m*-NO_2), **1q** (*p*-CH_3), **1r** (*p*-OCH_3), **1s** (3,4-$(OCH_3)_2$), **1t** (3,4,5-$(OCH_3)_3$).

On the basis of the considerable anticonvulsant promise suggested in phase I testing, compounds **1a**-**1c** and **1e** were subjected to phase II trials for quantification of their anticonvulsant activity (indicated by ED_{50}) and neurotoxicity (indicated by TD_{50}) in mice. Results of the quantitative test for selected compounds, along with the data on the standard drug carbamazepine and valproate, are reported in Table-2. All the compounds showed weaker anticonvulsant activity compared to currently used antiepileptic drugs carbamazepine but better than valproate. Addtion, all the tested compounds showed the safer profile than carbamazepine and valproate with the higher protective index. 2-Phenyl-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (**1a**) and 2-(2-fluorophenyl)-2,3-dihydrobenzo[*e*][1,3] oxazin-4-one (**1b**) were considerd more promising in these compounds because of their lower ED_{50} (34.1 and 28.4 mg/kg) and higher protective index (11.1 and 8.0).

TABLE-2
PHASE II QUANTITATIVE ANTICONVULSANT DATA IN MICE (I.P.)

Compounds	ED_{50} mg/kg MES	TD_{50} mg/kg Rotarod	PI TD_{50}/ED_{50}
1e	45.6 (34.5-60.4)	353.5 (239.4-521.7)	7.7
1c	35.3 (23.9-52.2)	235.7 (159.6-347.8)	6.6
1b	28.4 (18.1-44.6)	227.2 (144.7-356.5)	8.0
1a	34.1 (21.7-53.5)	380.2 (283.1-510.6)	11.1
Carbamazepine	9.8 (8.9-10.8)	44.0 (40.2-48.1)	4.5
Valproate	272 (247-338)	426 (369-450)	1.6

In conclusion, a series of new 2-phenyl-2*H*-benzo[*e*][1,3]-oxazin-4(3*H*)-one derivatives were designed based on the known anticonvulsant activity of quinolinone derivatives. All target compounds **1a-1t** displayed some degree of anticonvulsant activity in mice. Among them, 2-phenyl-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (**1a**) and 2-(2-fluorophenyl)-2,3-dihydrobenzo[*e*][1,3]oxazin-4-one (**1b**) were considered more promising because of their lower ED_{50} (34.1 and 28.4 mg/kg) and higher protective index (11.1 and 8.0). The obtained results showed that certain compounds could be useful as a template for future design, modification and investigation to produce more active and lower toxic analogues.

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