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Synthesis of 8-Alkoxy-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-ones and Evaluation of their Anticonvulsant Properties

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A series of 8-alkoxy-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one derivatives were synthesized using 7-hydroxy-3,4-dihydro-2(1*H*)-quinolone as the starting material. Their anticonvulsant activities were evaluated by the maximal electroshock test (MES) and the subcutaneous pentylenetetrazole test (sc-PTZ), and their neurotoxicities were measured by the rotarod neurotoxicity test (Tox). The tests demonstrated that 8-hexyloxy-4,5-dihydro-[1.2.4]triazole[4.3-*a*]quinoline-1-one (**4e**) and 8-heptyloxy-4,5-dihydro-[1,2,4] triazole[4,3-*a*]quinoline-1-one (**4f**) were the most potent anticonvulsants, with **4e** having ED_{50} values of 17.17 mg/kg and 24.55 mg/kg and protective index (PI = TD_{50}/ED_{50}) values of 41.9 and 29.3 in the MES and sc-PTZ tests, respectively, and **4f** having ED_{50} values of 19.7 mg/kg and 21.2 mg/kg and PI values of 36.5 and 33.9 in the MES and sc-PTZ tests, respectively. The PI values of **4e** and **4f** were many fold better than that of the marketed drugs phenytoin, carbamazepine, phenobarbital and valproate, which have PI values in the range of 1.6-8.1 in the MES test and <0.22-5.2 in the sc-PTZ test. Structure-activity relationships were also discussed.

Key words: Triazole[4,3-*a*]quinoline, Anticonvulsant, Maximal electroshock, Pentylenetetrazole, Neurotoxicity

INTRODUCTION

The derivatives of triazole exhibit a variety of biological activities, including anti-inflammatory (Labanauskas *et al.*, 2004), antimicrobial (Gulerman *et al.*, 2001), antithrombotic (Colin *et al.*, 2003), antiviral (Cunha *et al.*, 2003) and anticonvulsant activities (Lazrek *et al.*, 2001; Kane *et al.*, 1990). In our previous studies (Quan *et al.*, 2005; Cui *et al.*, 2005; Xie *et al.*, 2005), series of 6-alkoxy-2(1*H*) quinolones, 1-substituted-7-benzyloxy-4,5-dihydro-[1,2,4] triazole[4,3-*a*]quinolines and 7-alkoxy-4,5-dihydro-[1,2,4] triazole[4,3-*a*]quinolines (**I**) were synthesized and tested for anticonvulsant activity (Fig. 1). Of all of the synthesized derivatives, 7-(4-fluorobenzyloxy)-4,5-dihydro-[1,2,4]triazole [4,3-*a*]quinoline (**II**) displayed the best activity, having ED_{50} values of 11.8 mg/kg and 6.7 mg/kg in the maximal electroshock test (MES) and subcutaneous pentylenetetrazole-induced seizure (sc-PTZ) tests, respectively.

Intent on exploring effective compounds with lower neurotoxicity, compound **III** was designed and synthesized through the substitution of triazolone for triazole in compound **I**. The hypothesis was that a triazolone compound may have higher affinity for the receptor due to its carbonyl group, and thus may have increased anticonvulsant activity. There were some similar design reports (Gitto *et al.*, 2003; Zappala *et al.*, 2000; Chimirri *et al.*, 1999) to support this hypothesis. For instance, when triazolone was substituted for triazole in the precursor compound **IV** (8,9-dimethoxy-6-phenyl-11*H*-[1,2,4]triazole [4,5-*c*][2,3]benzodiazepine), a remarkable increase in anticonvulsant activity was observed. Therefore, based on this hypothesis, a series of 8-alkoxy-4,5-dihydro-[1,2,4] triazole[4,3-*a*]quinoline-1-one derivatives were prepared. Their structures were characterized using IR, ^{1}H-NMR, MS and elemental analysis techniques. Their anticonvulsant activity was evaluated using experimental epilepsy models in mice, including MES and sc-PTZ, and their neurotoxicity was evaluated in mice with the rotarod test.

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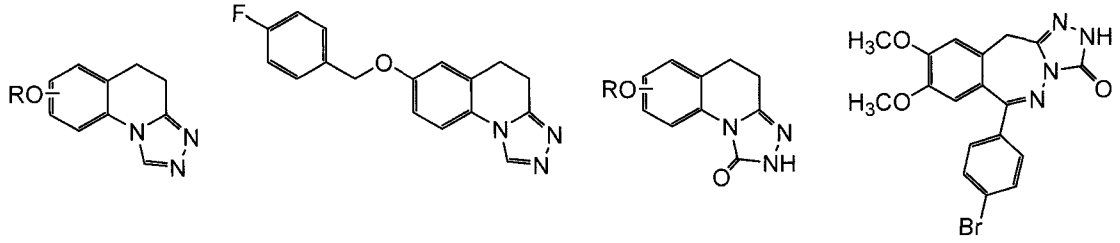


I II III IV

Fig. 1. Structure of compound I, II, III, and IV

MATERIALS AND METHODS

Melting points were determined on a microscope melting point apparatus and were uncorrected. IR spectra were recorded (in KBr) on a FT-IR 1730; ^{1}H-NMR spectra were measured on a BRUKER-300 instrument, and chemical shifts were expressed in ppm relative to tetramethylsilane as an internal standard. Mass spectra were measured on an AP12000 (EIS, 70eV). Elemental analyses of C, N and H were performed using a Heraeus CHN Rapid Analyzer.

Synthesis of 7-alkoxy-3,4-dihydro-2(1*H*)-quinolones (2a-2l)

The starting compound **1** and appropriate alkyl halide were added to a solution of sodium hydroxide in absolute methanol with stirring and refluxing for 3 h. The reaction mixture was cooled, and then poured into ice-water. The white precipitate was collected through filtration and dried in a vacuum to produce the crude product with a moderate yield and sufficient purity for the next stage.

Synthesis of 7-alkoxy-3,4-dihydro-1*H*-quinoline-2-thiones (3a-3l)

To a stirring mixture of acetonitrile and triethylamine in a three-necked round-bottomed flask in an ice bath, P_2S_5 (1.2 eq) was divided into multiple portions and added one portion at a time after the previous portion had completely dissolved. Then, 7-alkoxy-3,4-dihydro-2(1*H*)-quinolone was added, and the solution was refluxed for 3 h under nitrogen. After removing the solvent under reduced pressure, the residue was dissolved in dichloromethane (30 mL), washed with water (30 mL×3) and dried over anhydrous $MgSO_4$. Evaporation of the solvents gave a crude product, which was purified by silica gel column chromatography with dichloromethane to a light yellow solid.

General procedure for the synthesis of 8-alkoxy-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one derivatives (4a-4l)

A solution of **3a-3l** and methyl hydrazinecarboxylate (1.1eq) in cyclohexanol was refluxed for 48 h. The solution was evaporated to dryness under reduced pressure, and the oil residue was purified by silica gel column chromatography with dichloromethane:methanol (20:1).

8-Methyloxy-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one (4a)

m.p. 192-194°C; yield 32%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.75 (s, 1H, -CH_3), 2.88-2.92 (m, 4H, -CH_2-CH_2-), 6.72 (dd, 1H, J = 8.3, 2.5 Hz, H-7), 7.10 (d, 1H, J = 8.3 Hz, H-6), 7.99 (d, 1H, J = 2.5 Hz, H-9), 9.02 (s, 1H, -NH-). IR (KBr) cm^{-1}: 3417 (NH), 1716 (C=O); MS m/z 218 (M+1); *Anal.* Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.35. Found: C, 60.21; H, 5.28; N, 19.09.

8-Propyloxy-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one (4b)

m.p. 171-173°C; yield 29%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.06 (t, 3H, J = 7.0 Hz, -CH_3), 1.81-1.83 (m, 2H, -CH_2-), 3.97 (t, 2H, J = 6.5 Hz, OCH_2), 2.89-2.93 (m, 4H, -CH_2-CH_2-), 6.74 (dd, 1H, J = 8.3, 2.5 Hz, H-7), 7.15(d, 1H, J = 8.3 Hz, H-6), 7.96 (d, 1H, J = 2.5 Hz, H-9), 9.02 (s, 1H, -NH-). IR (KBr) cm^{-1}: 3415 (NH), 1708 (C=O); MS m/z 246 (M+1); *Anal.* Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.41; H, 6.32; N, 17.04.

8-Butyloxy-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one (4c)

m.p. 146-148°C; yield 34%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, 3H, J = 7.3 Hz, -CH_3), 1.48-1.53 (m, 2H, -CH_2-), 1.76-1.81 (m, 2H, -CH_2-), 4.02 (t, 2H, J = 6.4 Hz, -OCH_2-), 2.89-2.92 (m, 4H, -CH_2-CH_2-), 6.72 (dd, 1H, J = 8.3, 2.5 Hz, H-7), 7.15 (d, 1H, J = 8.3 Hz, H-6), 7.99 (d, 1H, J = 2.5 Hz, H-9) , 9.12 (s, 1H, -NH-). IR (KBr) cm^{-1}: 3420 (NH), 1706 (C=O); MS m/z 260 (M+1); *Anal.* Calcd. for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 64.56; H, 6.93; N, 16.03.

8-Amyloxy-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one (4d)

m.p. 124-126°C, yield 30%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3H, J = 7.0 Hz, -CH_3), 1.39-1.48 (m, 4H, -CH_2-CH_2-), 1.78-1.83 (m, 2H, -CH_2-), 4.01 (t, 2H, J = 6.5 Hz,

-OCH_2-), 2.90-2.92 (m, 4H, -CH_2-CH_2-), 6.72 (dd, 1H, *J* = 8.3, 2.5 Hz, H-7), 7.14 (d, 1H, *J* = 8.3 Hz, H-6), 7.99 (d, 1H, *J* = 2.5 Hz, H-9), 9.79 (s, 1H, -NH-). IR (KBr) cm^{-1}: 3417 (NH), 1702 (C=O); MS m/z 274 (M+1); *Anal.* Calcd. for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.79; H, 7.32; N, 15.03.

8-Hexyloxy-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one (4e)

m.p. 142-144°C; yield 31%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, *J* = 7.0 Hz, -CH_3), 1.35-1.46 (m, 4H, -CH_2-CH_2-), 1.48 (m, 2H, -CH_2-), 1.75-1.82 (m, 2H, -CH_2-), 4.01 (t, 2H, *J* = 6.4 Hz, -OCH_2-), 2.90 (m, 4H, -CH_2-CH_2-), 6.72 (dd, 1H, *J* = 8.3, 2.5 Hz, H-7), 7.15 (d, 1H, *J* = 8.3 Hz, H-6), 8.00 (d, 1H, *J* = 2.5 Hz, H-9), 9.68 (s, 1H, -NH-). IR (KBr) cm^{-1}: 3411 (NH), 1720 (C=O); MS m/z 288 (M+1); *Anal.* Calcd. for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 66.63; H, 7.03; N, 14.46.

8-Heptyloxy-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one (4f)

m.p. 107-109°C; yield 28%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H, *J* = 7.0 Hz, -CH_3), 1.31-1.38 (m, 6H, -CH_2-CH_2-CH_2), 1.74-1.76 (m, 2H, -CH_2-), 1.79-1.89 (m, 2H, -CH_2-), 4.01 (t, 2H, *J* = 6.5 Hz, -OCH_2-), 2.89-2.91 (m, 4H, -CH_2-CH_2-), 6.73 (dd, 1H, *J* = 8.3, 2.5 Hz, H-7), 7.14 (d, 1H, *J* = 8.3 Hz, H-6), 7.97 (d, 1H, *J* = 2.5 Hz, H-9), 9.88 (s, 1H, -NH-). IR (KBr) cm^{-1}: 3420 (NH), 1704 (C=O); MS m/z 302 (M+1); *Anal.* Calcd. for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 19.94. Found: C, 67.93; H, 7.59; N, 19.72.

8-Octyloxy-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one (4g)

m.p. 98-100°C; yield 34%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H, *J* = 7.0 Hz, -CH_3), 1.30-1.33 (m, 8H, -CH_2-CH_2-CH_2-CH_2-), 1.47 (m, 2H, -CH_2-), 1.75-1.82 (m, 2H, -CH_2-), 4.01 (t, 2H, *J* = 6.4 Hz, -OCH_2-), 2.91-2.92 (m, 4H, -CH_2-CH_2-), 6.73 (dd, 1H, *J* = 8.3, 2.5 Hz, H-7), 7.12 (d, 1H, *J* = 8.3 Hz, H-6), 7.97 (d, 1H, *J* = 2.5 Hz, H-9), 9.60 (s, 1H, -NH-). IR (KBr) cm^{-1}: 3426 (NH), 1710 (C=O); MS m/z 316 (M+1); *Anal.* Calcd. for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.68; H, 7.73; N, 13.58.

8-Benzyloxy-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one (4h)

m.p. 191-193°C; yield 35%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.88-2.93 (m, 4H, -CH_2-CH_2-), 5.13 (s, 2H, -OCH_2-), 7.34-7.49 (m, 5H, C_6H_5-), 6.81 (dd, 1H, *J* = 8.3, 2.5 Hz, H-7), 7.13 (d, 1H, *J* = 8.3 Hz,H-6), 8.11 (d, 1H, *J* = 2.5 Hz, H-9), 9.60 (s, 1H, -NH-). IR (KBr) cm^{-1}: 3450 (NH), 1714 (C=O); MS m/z 294 (M+1); *Anal.* Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.32; H, 5.38; N, 14.46.

8-(4-Fluoro-benzyloxy)-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one (4i)

m.p. 186-188°C; yield 32%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.93 (m, 4H, -CH_2-CH_2-), 5.09 (s, 2H, -OCH_2-), 7.09 (m, 3H, H-6, H-3', H-5'),7.46 (m, 3H, H-7, H-2', H-6'), 8.11 (d, 1H, *J* = 2.5 Hz, H-9), 9.28 (s, 1H, -NH-). IR (KBr) cm^{-1}: 3410 (NH), 1714 (C=O); MS m/z (M+1) 312; *Anal.* Calcd. for $C_{17}H_{14}FN_3O_2$: C, 65.59; H, 4.53; N, 13.50. Found: C, 65.72; H, 4.43; N, 13.36.

8-(4-Chloro-benzyloxy)-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one (4j)

m.p. 190-192°C; yield 30%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.93 (m, 4H, -CH_2-CH_2-), 5.01 (s, 2H, -OCH_2-), 7.35-7.43 (m, 4H, (*p*-Cl) C_6H_4-), 6.81 (dd, 1H, *J* = 8.3, 2.5 Hz, H-7), 7.16 (d, 1H, *J* = 8.3 Hz, H-6), 8.10 (d, 1H, *J* = 2.5 Hz, H-9), 9.54 (s, 1H, -NH-). IR (KBr) cm^{-1}: 3420 (NH), 1722 (C=O); MS m/z 328 (M+1); *Anal.* Calcd. for $C_{17}H_{14}ClN_3O_2$: C, 62.30; H, 4.31; N, 12.82. Found: C, 62.49; H, 4.20; N, 12.68.

8-(4-Methyl-benzyloxy)-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one (4k)

m.p. 168-170°C; yield 34%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H, CH_3), 2.92 (m, 4H, -CH_2-CH_2-), 5.19 (s, 2H, -OCH_2-), 7.20-7.38 (m, 5H, (*p*-CH_3)C_6H_4-), 6.81 (dd, 1H, *J* = 8.3, 2.5 Hz, H-7), 7.12 (d, 1H, *J* = 8.3 Hz, H-6), 8.12 (d, 1H, *J* = 2.5 Hz, H-9), 10.05 (s, 1H, -NH-). IR (KBr) cm^{-1}: 3422 (NH), 1704 (C=O); MS m/z 308 (M+1); *Anal.* Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.03; H, 5.32; N, 13.83.

8-(2-Fluoro-benzyloxy)-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one (4l)

m.p. 224-226°C; yield 32%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.94 (m, 4H, -CH_2-CH_2-), 5.19 (s, 2H, -OCH_2-), 6.83 (m, 1H, H-7), 7.08-7.21 (m, 3H, H-6, H-3', H-5'), 7.53-7.58 (m, 2H, H-4', H-6'), 8.13 (s, 1H, H-9), 9.28 (s, 1H, -NH-). IR (KBr) cm^{-1}: 3423 (NH), 1712 (C=O); MS m/z 312 (M+1); *Anal.*Calcd. for $C_{17}H_{14}FN_3O_2$: C, 65.59; H, 4.53; N, 13.50. Found: C, 65.38; H, 4.38; N, 13.83.

Pharmacology

Maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (sc-PTZ) and rotarod tests were carried out by the Antiepileptic Drug Development (ADD) Program, Epilepsy Branch, Neurological Disorders Program following previously described testing procedures (Krall *et al.*, 1978; Poter *et al.*, 1984). The compounds **4a-4l** were dissolved in polyethylene glycol-400 and evaluated for anticonvulsant activity in both sexes of C57B/6 mice, ranging from 18-22 g in weight and purchased from the Laboratory of Animal Research, College of Pharmacy, Yanbian University.

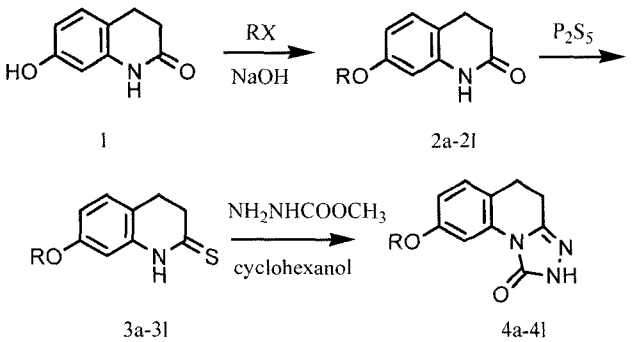
The preliminary pharmacology test (Phase I) was carried out as previously reported. Each compound was administered intraperitoneally at three dose levels (30, 100, and 300 mg/kg), and anticonvulsant activity and neurotoxicity were assessed 30 min and 4 h after administration. The most potent compounds in phase I screening were further tested in phase II where their anticonvulsant activity and neurotoxicity were quantified and expressed in terms of median effective dose (ED_{50}) and median toxic dose (TD_{50}), respectively. Groups of 10 mice were given a range of intraperitoneal 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 plots of these data, the respective ED_{50} and TD_{50} values, 95% confidence intervals, slopes of the regression line and the standard error of the slopes were calculated by means of a computer program written by the National Institute of Neurological Disorders and Stroke.

Neurologic deficits were detected in mice by the rotarod test. Neurotoxicity was indicated by the inability of an animal to maintain equilibrium on a 1-in. diameter, knurled plastic rod rotating at 6 rpm in each of three trials.

RESULT AND DISCUSSION

Chemistry

Based on previous studies in our laboratory, we designed and prepared 8-alkoxy-4,5-dihydro-[1,2,4]triazole[4,3-a] quinoline-1-one derivatives (**4a-4l**). Target compounds **4a-4l** were prepared following the reaction sequence shown in Fig. 2. Compounds **2a-2l** were synthesized as previously described (Quan *et al.*, 2005) briefly, compound **1** and the appropriate alkyl halide reacted in a solution of sodium hydroxide in methanol to produce compounds **2a-2l**. Reaction of compounds **2a-2l** with phosphorous pentasulfide in acetonitrile in the presence of triethylamine under nitrogen resulted in compounds **3a-3l**, which reacted further with methyl hydrazinocarboxylate in cyclohexanol to afford target compounds **4a-4l** according to the reference method (Maria *et al.*, 2000).



R:

a = CH_3	g = n-C_8H_{17}
b = n-C_3H_7	h = $CH_2C_6H_5$
c = n-C_4H_9	i = $CH_2C_6H_4$(p-F)
d= n-C_5H_{11}	j = $CH_2C_6H_4$(p-Cl)
e = n-C_6H_{13}	k = $CH_2C_6H_4$(p-CH_3)
f = n-C_7H_{15}	l = $CH_2C_6H_4$(o-F)

Fig. 2. Synthesis of compounds **4a-4l**

Pharmacology

The initial evaluation (phase I) of the anticonvulsant activity of synthesized compounds **4a-4l** (Table I) indicated that compounds **4e**, **4f**, **4g**, and **4h** displayed anticonvulsant activity at 30 mg/kg, while others displayed anticonvulsant activity at a dose of 100 mg/kg. All of these compounds exhibited no neurotoxicity at a dose of 300 mg/kg according to the initial rotarod test.

Compounds **4e**, **4f**, **4g**, and **4h** were then subjected to phase II trials for quantification of their anticonvulsant activity and neurotoxicity in mice. The data were also compared with the marketed anticonvulsant drugs, phenytoin sodium, carbamazepine, phenobarbital and valproate sodium (Table II). The most active compounds were found to be 8-hexyloxy-4,5-dihydro-[1,2,4]triazole [4,3-*a*]quinoline-1-one (**4e**) and 8-heptyloxy-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one (**4f**), having ED_{50} values of 17.7 mg/kg and 19.7 mg/kg in the MES test, and ED_{50} values of 24.5 mg/kg and 21.2 mg/kg in the sc-PTZ test, respectively. Although their anticonvulsant activity was weaker than

Table I. Phase I anticonvulsant and toxicity data in mice (i.p.)[a]

Compd	MES[b]		Sc-PTZ[c]		Rotarod toxicity	
	0.5h	4h	0.5h	4h	0.5h	4h
4a	100[d]	–[e]	300	–	–	–
4b	100	–	100	–	–	–
4c	100	–	100	–	–	–
4d	100	–	100	–	–	–
4e	30	–	30	–	–	–
4f	30	–	30	–	–	–
4g	30	–	100	–	–	–
4h	30	–	30	–	–	–
4i	100	–	100	–	–	–
4j	100	–	100	–	–	–
4k	100	–	100	–	–	–
4l	100	–	300	–	–	–

a) All of the tested compounds were dissolved in polyethylene glycol-400

b) The maximal electroshock test was conducted 30 min after administration of the test compounds

c) Subcutaneous pentylenetetrazol (85 mg/kg) was given 30 min after administration of the test compounds

d) Doses are in mg/kg

e) – = no activity at 300 mg/kg.

Table II. Phase II quantitative anticonvulsant data in mice (test drug administered i.p.)

Compd	ED_{50}[a]		Rotarod Toxicity	PI[b]	
	MES	sc-PTZ	TD_{50}[c]	MES	sc-PTZ
II[d]	11.8 (12.9-10.9)[f]	6.7 (5.7-7.9)	54.5 (46.1-64.5)	4.6	8.1
4e	17.2 (9.18-18.30)	24.5 (14.43-41.76)	>720	41.9	29.3
4f	19.7 (11.42-34.06)	21.2 (23.2-27.9)	>720	36.5	33.9
4g	23.7 (13.58-41.26)	>100	>746	31.5	7.4
4h	38.0 (24.13-59.93)	30.5 (16.99-54.97)	>864	22.7	28.3
Phenytoin[e]	9.5 (8.1-10.4)	>300	65.5 (52.5-72.9)	6.9	<0.22
Carbamazepin[e]	8.8 (5.5-14.1)	>100	71.6 (45.9-135)	8.1	<0.22
Phenobarbital[e]	21.8 (21.8-25.5)	13.2 (5.8-15.9)	69.0 (62.8-72.9)	3.2	5.2
Valproate[e]	272 (247-338)	149 (123-177)	426 (369-450)	1.6	2.9

a) Doses are in mg/kg
b) PI = TD_{50} / ED_{50}
c) Minimal neurotoxicity was determined by the rotarod test 30 min after administration of the test compounds
d) Data from Xie, ZF *et al.*, 2005
e) Data from Ucar, H *et al.*, 1998
f) The 95% confidence limits.

that of the marketed anticonvulsant agents phenytoin and carbamazepin, they exhibited much lower neurotoxicity. With TD_{50} value of 720 mg/kg and PI values of 41.9 or 36.5 in the MES test, they were obviously much safer than the marketed anticonvulsant agents, which had PI values ranging from 1.6-8.1 in the MES test.

These results indicated that a sudden and marked increase of anticonvulsant activity occurred when the alkyl chain at the C-8 position was lengthened to six carbons or more. Among the five aryl-substituted derivatives **4h-4l**, the non-substituted derivative **4h**, with MES ED_{50} of 38.0 mg/kg and sc-PTZ ED_{50} of 30.5 mg/kg, exhibited the highest activity, and its neurotoxicity (TD_{50} = 864 mg/kg; PI value = 22.9) was less than that of the marketed drugs. However, the other four compounds containing substituted benzyl groups exhibited weak activity in the experimental seizure models.

This series of compounds was found to have low neurotoxicity compared to compound **I**. None of the compounds showed an ataxic response in mice at a dose of 500 mg/kg. PI values of compounds **4e** and **4f** were 41.9 and 36.5 in the MES test, and were 29.3 and 33.9 in the sc-PTZ test, respectively, which were many fold higher than that of most of the marketed drugs. Compared with compound **II**, which had a MES PI value of 4.6 (Xie *et al.*, 2005), these results indicated that the lactam group in the fused five-member ring plays an important role in decreasing the neurotoxicity of this series of derivatives.

In conclusion, in the present study, two novel compounds, 8-hexyloxyl-4,5-dihydro-[1,2,4]triazole[4,3-*a*]quinoline-1-one (**4e**) and 8-heptyloxy-4,5-dihydro-[1,2,4]triazole[4,3-*a*] quinoline-1-one (**4f**), were found to possess anticonvulsant activity comparable to, but neurotoxicity much lower than, a number of marketed drugs. Further investigation on this novel class of compounds is in progress.

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