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Synthesis and Anticonvulsant Activity of 1-Formamide-triazolo[4,3-*a*]quinoline Derivatives

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Using 6-hydroxy-3,4-dihydro-2(1*H*)-quinolone as the starting material, a series of 1-formamide-triazolo[4, 3-*a*]quinoline derivatives (**6a-6n**) was synthesized, the anticonvulsant effect and neurotoxicity of the compounds was calculated with maximal electroshock test and rotarod tests with intraperitoneally injected in KunMing mice. The results demonstrated that compound 7-(hexyloxy)-4,5-dihydro-[1,2,4] triazolo[4,3-*a*]quinoline-1-carboxamide (**6d**) was the most active one and also had the lowest toxicity. In the anti-maximal electroshock potency test, it showed median effective dose (ED_{50}) of 30.1 mg/kg, median toxicity dose (TD_{50}) of 286 mg/kg, and the protective index of 9.5 which is greater than the reference drug carbamazepine with the protective index value of 6.0.

Key words: Synthesis, Triazole, Quinoline, Formamide, Anticonvulsant, Toxicity

INTRODUCTION

Epilepsy is a syndrome of different cerebral disorders of central nervous system (CNS), and it is characterized by paroxysmal, excessive and hypersynchronous discharges of large numbers of neurons (Gasior et al., 1997). Anticonvulsant drugs currently on the market are of unsatisfactory effectiveness in seizure control and cause adverse reactions such as drowsiness, ataxia, gastrointestinal disturbance, hepatotoxicity and megaloblastic anemia (Leppik, 1994; Perucca, 1996; Lin and Kadaba, 1997), and even life threatening conditions (Al-Soud et al., 2003). In recent years, the field of antiepileptic drug development is quite dynamic, affording many promising research opportunities. However, current therapy is directed towards reducing seizure frequency. Unfortunately, as many as 30% of medicated patients have inadequate seizure control, many antiepileptic drugs have serious side effects and lifelong medication may be required.

In our ongoing search for new compounds with anticonvulsant activity, firstly, we found 7-Alkoxy-3,4-dihydro-6-methoxyquinolin-2(1*H*)-one showed anticonvulsant activity (Quan et al, 2005), and the compounds incorporated triazole at the first and second position have shown marked anticonvulsant activity in the maximal electroshock (MES) test (Cui et al., 2005; Xie et al., 2005; Sun et al., 2006; Wei et al., 2007).

In pursuing our research in the area of anticonvulsant activity, compared with the anticonvulsant drugs, we found that most of them have a carboxamide group, for example (Fig. 1), the traditional anticonvulsant drug Cabamazepine and the new anticonvulsant drug Rufinamide, and so on. It inferred that carboxamide group was the key group, it may relate to the acceptor of anticonvulsant function. But there was no report about anticonvulsant activity of the carboxamide group linked to the triazolo[4,3-*a*]quinoline derivatives, so in this paper, we report the chemical and anticonvulsant properties of 1-formamide-triazolo[4,3-*a*]quinoline derivatives (**6a-6n**).

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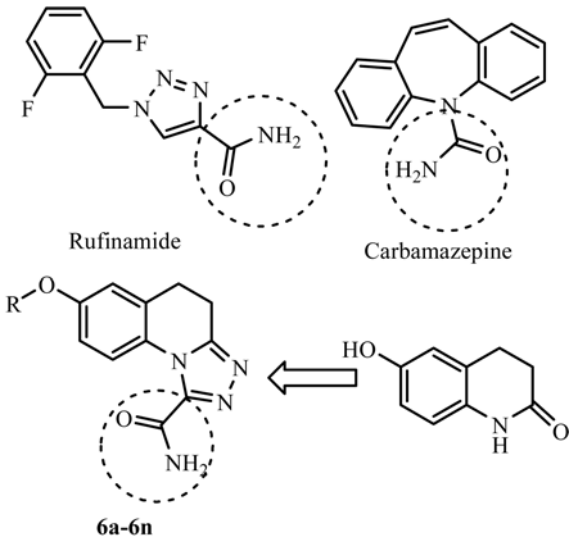


Fig. 1. The structure of Rufinamide Cabamazepine and **6a-6n**

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and were uncorrected. ^{1}H-NMR spectra were measured on a AV-300 (Bruker), and all chemical shifts were given in ppm relative to tetramethysilane. Mass spectra were measured on an HP1100LC (Agilent Technologies). Elemental analyses were performed on a 204Q CHN (Perkin Elmer). Microanalyses of C, N and H were performed using a Heraeus CHN Rapid Analyzer. The major chemicals were purchased from Alderich Chemical Corporation. All other chemicals were of analytical grade.

6-Alkoxy-3,4-dihydro-2(1*H*)-quinolones (2)

The starting compound **1** (10 mmol) and appropriate alkyl halide (10 mmol) 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 products **2a-2n** with a moderate yield (65-90%) and sufficient purity for the next stage.

6-Alkoxy-3,4-dihydro-1*H*-quinoline-2-thiones (3a-3n)

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), divided into multiple portions, was added one portion at a time after the previous portion had completely dissolved. Then, 6-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 (3*30 mL) 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 **3a-3n**. Yield 70-90%.

6-Alkoxy-3,4-dihydro-2-hydrazine-1*H*-quinolines (4a-4n)

A solution of compounds **3a-3n** (5 mmol) in 30 mL THF was added dropwise to a solution of hydrazine hydrate (25 mmol) in 20 mL THF at room temperature, then the mixture was stirred and heated at 60°C for 1 h. After the reaction, half of the solvent was evaporated under reduced pressure, the products were recrystallized from petroleum ether with a moderate yield, and then kept at 0°C for the next step. Yield 35-55%.

Ethyl 7-substituted-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxylate (5a-5n)

The 6-alkoxy-3,4-dihydro-2-hydrazine-1*H*-quinoline (4 mmol) was added to diethyl oxalate (30 mL), then the mixture was stirred and refluxed for 1h. After the reaction, the solvent was evaporated under reduced pressure, the products were recrystallized from petroleum ether with a moderate yield. And then kept for the next step.

Ethyl 7-propoxy-4,5-dihydro-[1,2,4]triazolo[4,3-*a*] quinoline-1-carboxylate (5a)

Yield 87.6%, mp 103-105°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.64 (d, 1H, J = 8.6 Hz, 9-Ar-H), 6.83-6.86 (m, 2H, 6- and 8-Ar-H), 4.51 (q, 2H, J = 7.1 Hz, $COOCH_2$), 3.94 (t, 2H, J = 6.5 Hz, OCH_2), 3.15 (t, 2H, J = 6.8 Hz, CH_2), 2.96 (t, 2H, J = 6.8 Hz, CH_2), 1.69-1.73 (m, 2H, CH_2), 1.47 (t, 3H, J = 7.1 Hz, CH_3), 1.04 (t, 3H, J = 7.4 Hz, CH_3). IR (KBr) 1725 cm^{-1}. MS m/z 302 (M+1). Anal. Calcd. for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63.71; H, 6.56; N, 13.91.

Ethyl 7-butoxy-4,5-dihydro-[1,2,4]triazolo[4,3-*a*] quinoline-1-carboxylate (5b)

Yield 89.5%, mp 97-101°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.65 (d, 1H, J = 9.2 Hz, 9-Ar-H), 6.82-6.87 (m, 2H, 6- and 8-Ar-H), 4.52 (q, 2H, J = 7.1 Hz, $COOCH_2$), 3.99 (t, 2H, J = 6.4 Hz, OCH_2), 3.16 (t, 2H, J = 7.0 Hz, CH_2), 2.97 (t, 2H, J = 7.0 Hz, CH_2), 1.59-1.80 (m, 4H, $(CH_2)_2$), 1.42 (t, 3H, J = 7.1 Hz, CH_3), 0.99 (t, 3H, J = 7.3 Hz, CH_3). IR (KBr) 1726 cm^{-1}. MS m/z 316 (M+1). Anal. Calcd. for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.61; H, 6.68; N, 13.50.

Ethyl 7-(pentyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxylate (5c)
Yield 90.8%, mp 98-100°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.63 (d, 1H, *J* = 8.7 Hz, 9-Ar-H), 6.81-6.85 (m, 2H, 6- and 8-Ar-H), 4.51 (q, 2H, *J* = 7.1 Hz, $COOCH_2$), 3.97 (t, 2H, *J* = 6.5 Hz, OCH_2), 3.15 (t, 2H, *J* = 6.8 Hz, CH_2), 2.96 (t, 2H, *J* = 6.8 Hz, CH_2), 1.56-1.79 (m, 6H, $(CH_2)_3$), 1.38 (t, 3H, *J* = 7.1 Hz, CH_3), 0.93 (t, 3H, *J* = 6.8 Hz, CH_3). IR (KBr) 1728 cm^{-1}. MS *m/z* 330 (M+1). Anal. Calcd. for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.49; H, 7.14; N, 12.81.

Ethyl 7-(hexyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxylate (5d)
Yield 92.3%, mp 58-70°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.64 (d, 1H, *J* = 9.1 Hz, 9-Ar-H), 6.81-6.85 (m, 2H, 6- and 8-Ar-H), 4.52 (q, 2H, *J* = 7.1 Hz, $COOCH_2$), 3.98 (t, 2H, *J* = 6.5 Hz, OCH_2), 3.16 (t, 2H, *J* = 6.9 Hz, CH_2), 2.97 (t, 2H, *J* = 6.9 Hz, CH_2), 1.38-1.78 (m, 8H, $(CH_2)_4$), 1.35 (t, 3H, *J* = 7.1 Hz, CH_3), 0.92 (t, 3H, *J* = 6.7 Hz, CH_3). IR (KBr) 1730 cm^{-1}. MS *m/z* 344 (M+1). Anal. Calcd. for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.54; H, 7.46; N, 12.33.

Ethyl 7-(heptyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxylate (5e)
Yield 91%, mp 77-79°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.64 (d, 1H, *J* = 9.1 Hz, 9-Ar-H), 6.82-6.87 (m, 2H, 6- and 8-Ar-H), 4.52 (q, 2H, *J* = 7.1 Hz, $COOCH_2$), 3.98 (t, 2H, *J* = 6.5 Hz, OCH_2), 3.16 (t, 2H, *J* = 6.9 Hz, CH_2), 2.97 (t, 2H, *J*= 6.9 Hz, CH_2), 1.39-1.88 (m, 10H, $(CH_2)_5$), 1.32 (t, 3H, *J* = 7.1 Hz, CH_3), 0.92 (t, 3H, *J*= 6.8 Hz, CH_3). IR (KBr) 1729 cm^{-1}. MS *m/z* 344 (M+1). Anal. Calcd. for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.54; H, 7.46; N, 12.33.

Ethyl 7-(octyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxylate (5f)
Yield 91%, mp 73-75°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.64 (d, 1H, *J* = 9.1 Hz, 9-Ar-H), 6.82-6.85 (m, 2H, Ar-H), 4.52 (q, 2H, *J* = 7.1 Hz, $COOCH_2$), 3.98 (t, 2H, *J* = 6.5 Hz, OCH_2), 3.16 (t, 2H, *J* = 6.9 Hz, CH_2), 2.97 (t, 2H, *J* = 6.9 Hz, CH_2), 1.43-1.78 (m, 12H, $(CH_2)_6$), 1.33 (t, 3H, *J* = 7.1 Hz, CH_3), 0.92 (d, 3H, *J*= 6.7 Hz, CH_3). IR (KBr) 1724 cm^{-1}. MS *m/z* 344 (M+1). Anal. Calcd. for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.54; H, 7.46; N, 12.33.

Ethyl 7-(benzyloxy)-4,5-dihydro-[1,2,4]triazolo [4,3-*a*]quinoline-1-carboxylate (5g)
Yield 87.6%, mp 114-118°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.66 (d, 1H, *J* = 8.7 Hz, 9-Ar-H), 7.33-7.45 (m, 5H, Ar-H), 6.85-6.94 (m, 2H, Ar-H), 5.09 (s, 2H, CH_2O), 4.51 (q, 2H, *J* = 7.1 Hz, $COOCH_2$), 3.15 (t, 2H, *J* = 6.9 Hz, CH_2), 2.96 (t, 2H, *J* = 6.9 Hz, CH_2), 1.47 (t, 3H, *J* = 7.1 Hz, CH_3). IR (KBr) 1725 cm^{-1}. MS *m/z* 350 (M+1). Anal. Calcd. for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.61; H, 5.51; N, 12.24.

Ethyl 7-(2-fluorobenzyloxy)-4,5-dihydro-[1,2,4] triazolo[4,3-*a*]quinoline-1-carboxylate (5h)
Yield 88.7%, mp 122-125°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.05 (d, 1H, *J* = 8.7 Hz, 9-Ar-H), 6.97-7.48 (m, 6H, Ar-H), 5.16 (s, 2H, CH_2O), 4.51 (q, 2H, *J* = 7.1 Hz, $COOCH_2$), 3.15 (t, 2H, *J* = 6.8 Hz, CH_2), 2.97 (t, 2H, *J* = 6.8Hz, CH_2). 1.46 (t, 3H, *J* = 7.1 Hz, CH_3). IR (KBr) 1727 cm^{-1}. MS *m/z* 368 (M+1). Anal. Calcd. for $C_{20}H_{18}FN_3O_3$: C, 65.39; H, 4.94; N, 11.44. Found: C, 65.61; H, 5.12; N, 11.41.

Ethyl 7-(3-fluorobenzyloxy)-4,5-dihydro-[1,2,4] triazolo[4,3-*a*]quinoline-1-carboxylate (5i)
Yield 87.8%, mp 126-128°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.68 (d, 1H, *J* = 9.0 Hz, 9-Ar-H), 7.03-7.42 (m, 6H, Ar-H), 5.10 (s, 2H, CH_2O-), 4.52 (q, 2H, *J* = 7.0 Hz, $COOCH_2$), 3.17 (t, 2H, *J* = 6.9 Hz, CH_2), 2.97 (t, 2H, *J* = 6.9 Hz, CH_2), 1.48 (t, 3H, *J* = 7.0 Hz, CH_3). IR (KBr) 1725 cm^{-1}. MS *m/z* 368 (M+1). Anal. Calcd. for $C_{20}H_{18}FN_3O_3$: C, 65.39; H, 4.94; N, 11.44. Found: C, 65.59; H, 5.08; N, 11.36.

Ethyl 7-(4-fluorobenzyloxy)-4,5-dihydro-[1,2,4] triazolo[4,3-*a*]quinoline-1-carboxylate (5j)
Yield 87.8%, mp 160-163°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.68 (d, 1H, *J* = 9.0 Hz, 9-Ar-H), 6.92-7.36 (m, 6H, Ar-H), 5.10 (s, 2H, CH_2O), 4.52 (q, 2H, *J* = 7.0 Hz, $COOCH_2$), 3.17 (t, 2H, *J* = 6.9 Hz, CH_2), 2.97 (t, 2H, *J* = 6.9 Hz, CH_2), 1.48 (t, 3H, *J* = 7.0 Hz, CH_3). IR (KBr) 1728 cm^{-1}. MS *m/z* 368 (M+1). Anal. Calcd. for $C_{20}H_{18}FN_3O_3$: C, 65.39; H, 4.94; N, 11.44. Found: C, 65.59; H, 5.08; N, 11.36.

Ethyl 7-(2-chlorobenzyloxy)-4,5-dihydro-[1,2,4] triazolo[4,3-*a*]quinoline-1-carboxylate (5k)
Yield 88%, mp 117-119°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.05 (d, 1H, *J* = 8.7 Hz, 9-Ar-H), 6.97-7.49 (m, 6H, Ar-H), 5.16 (s, 2H, CH_2O), 4.52 (q, 2H, *J* = 7.0 Hz, $COOCH_2$), 3.15 (t, 2H, *J* = 6.9 Hz, CH_2), 2.97 (t, 2H, *J* = 6.9 Hz, CH_2). 1.48 (t, 3H, *J* = 7.0 Hz, CH_3). IR (KBr) 1725 cm^{-1}. MS *m/z* 384 (M+1). Anal. Calcd. for $C_{20}H_{18}ClN_3O_3$: C, 62.58; H, 4.73; N, 10.95. Found: C, 62.47; H, 4.89; N, 10.99.

Ethyl 7-(3-chlorobenzyloxy)-4,5-dihydro-[1,2,4] triazolo[4,3-*a*]quinoline-1-carboxylate (5l)
Yield 91%, mp 115-117°C; ^{1}H-NMR ($CDCl_3$, 300 MHz):

7.68 (d, 1H, J = 9.0 Hz, 9-Ar-H), 6.92-7.36 (m, 6H, Ar-H), 5.10 (s, 2H, CH_2O), 4.52 (q, 2H, J = 7.0 Hz, $COOCH_2$), 3.17 (t, 2H, J = 6.9 Hz, CH_2), 2.97 (t, 2H, J = 6.9 Hz, CH_2), 1.48 (t, 3H, J = 7.1 Hz, CH_3). IR (KBr) 1729 cm^{-1}. MS m/z 384 (M+1). Anal. Calcd. for $C_{20}H_{18}ClN_3O_3$: C, 62.58; H, 4.73; N, 10.95. Found: C, 62.49; H, 4.79; N, 11.00.

Ethyl 7-(4-chlorobenzyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxylate (5m)

Yield 89.7%, mp 152-154°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.67 (d, 1H, J = 8.4 Hz, 9-Ar-H), 7.36 (d, 2H, J = 9.0 Hz, 2', 6'-Ar-H), 7.15 (s, 1H, 6-Ar-H), 7.08 (d, 2H, J = 9.0 Hz, 3', 5'-Ar-H), 6.99 (d, 1H, J = 8.4 Hz, 8-Ar-H), 5.06 (s, 2H, CH_2O), 4.52 (q, 2H, J = 7.1 Hz, $COOCH_2$),3.16 (t, 2H, J = 6.8 Hz, CH_2), 2.97 (t, 2H, J = 6.8 Hz, CH_2), 1.47 (t, 3H, J = 7.1 Hz, CH_3). IR (KBr) 1727 cm^{-1}. MS m/z 384 (M+1). Anal. Calcd. for $C_{20}H_{18}ClN_3O_3$: C, 62.58; H, 4.73; N, 10.95. Found: C, 62.50; H, 4.87; N, 10.91.

Ethyl 7-(4-methylbenzyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxylate (5n)

Yield 89.8%, mp 144-146°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.65 (d, 1H, J = 8.6 Hz, 9-Ar-H), 7.31 (d, 2H, J = 7.9 Hz, 2', 6'-Ar-H), 7.26 (s, 1H, 6-Ar-H), 7.20 (d, 2H, J = 7.9 Hz, 3', 5'-Ar-H), 6.92 (d, 1H, J = 8.6 Hz, 8-Ar-H), 5.05 (s, 2H, CH_2O), 4.52 (q, 2H, J = 7.2 Hz, $COOCH_2$), 3.16 (t, 2H, J = 6.8 Hz, CH_2), 2.96 (t, 2H, J = 6.8 Hz, CH_2), 2.37 (s, 3H, Ph-CH_3), 1.47 (t, 3H, J = 7.2 Hz, CH_3). IR (KBr) 1728 cm^{-1}. MS m/z 364 (M+1). Anal. Calcd. for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.35; H, 5.94; N, 11.49.

7-Substituted-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxamide (6a-6n)

Compounds **5a-5n** (3 mmol) were added into ammonia (30 mL) respectively, then the mixture was stirred for 1h at room temperature. After the reaction, the white precipitate was collected through filtration and dried in a vacuum.

7-Propoxy-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxamide (6a)

Yield 90.5%, mp 207-210°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.96 (d, 1H, J = 9.3 Hz, 9-Ar-H), 7.75 (s, 1H, NH), 6.93 (s, 1H, NH), 6.81-6.87 (m, 2H, 6- and 8-Ar-H), 3.95 (t, 2H, J = 6.2 Hz, CH_2), 3.12 (t, 2H, J = 6.6 Hz, CH_2), 2.98 (t, 2H, J = 6.6 Hz, CH_2), 1.76-1.82 (m, 2H, CH_2), 1.05 (t, 3H, J = 7.2 Hz, CH_3). IR (KBr) 1691 cm^{-1}. MS m/z 273 (M+1). Anal. Calcd. for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.52; H, 5.98; N, 20.48.

7-Butoxy-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxamide (6b)

Yield 88.9%, mp 207-211°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.95 (d, 1H, J = 9.7 Hz, 9-Ar-H), 7.73 (s, 1H, NH), 6.81-6.85 (m, 2H, 6- and 8-Ar-H), 6.14 (s, 1H, NH), 3.98 (t, 2H, J = 6.4 Hz, CH_2), 3.13 (t, 2H, J = 6.7 Hz, CH_2), 2.96 (t, 2H, J = 6.7 Hz, CH_2), 1.73-1.82 (m, 2H, CH_2), 1.43-1.56 (m, 2H, CH_2), 0.98 (t, 3H, J = 7.3 Hz, CH_3). IR (KBr) 1688 cm^{-1}. MS m/z 287 (M+1). Anal. Calcd. for $C_{15}H_{18}N_4O_2$: C, 62.92; H, 6.34; N, 19.57. Found: C, 62.73; H, 6.51; N, 19.70.

7-(Pentyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxamide (6c)

Yield 91.4%, mp 160-162°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.99 (d, 1H, J = 8.6 Hz, 9-Ar-H), 7.64 (s, 1H, NH), 6.84-6.89 (m, 2H, 6- and 8-Ar-H), 6.11 (s, 1H, NH), 3.96 (t, 2H, J = 6.4 Hz, CH_2), 3.13 (t, 2H, J = 6.7 Hz, CH_2), 2.96 (t, 2H, J = 6.7 Hz, CH_2), 1.29-1.88 (m, 6H, $(CH_2)_3$), 0.93 (t, 3H, J = 6.6 Hz, CH_3). IR (KBr) 1692 cm^{-1}. MS m/z 301 (M+1). Anal. Calcd. for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.75; H, 6.76; N, 18.49.

7-(Hexyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxamide (6d)

Yield 87.2%, mp 169-173°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.99 (d, 1H, J = 8.6 Hz, 9-Ar-H), 7.65 (s, 1H, NH), 6.82-6.86 (m, 2H, 6- and 8-Ar-H), 6.14 (s, 1H, NH), 3.96 (t, 2H, J = 6.5 Hz, CH_2), 3.12 (t, 2H, J = 6.8 Hz, CH_2), 2.95 (t, 2H, J = 6.8 Hz, CH_2), 1.25-1.80 (m, 8H, $(CH_2)_4$), 0.92 (t, 3H, J = 7.8 Hz, CH_3). IR (KBr) 1675 cm^{-1}. MS m/z 315 (M+1). Anal. Calcd. for $C_{17}H_{22}N_4O_2$: C, 64.95; H, 7.05; N, 17.82. Found: C, 64.76; H, 7.15; N, 17.91.

7-(Heptyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxamide (6e)

Yield 91.4%, mp 169-172°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.99 (d, 1H, J = 8.6 Hz, 9-Ar-H), 7.64 (s, 1H, NH), 6.82-6.85 (m, 2H, 6- and 8-Ar- H), 6.11 (s, 1H, NH), 3.96 (t, 2H, J = 6.4 Hz, CH_2), 3.13 (t, 2H, J = 6.7 Hz, CH_2), 2.96 (t, 2H, J = 6.7 Hz, CH_2), 1.31-1.91 (m, 10H, $(CH_2)_5$), 0.93 (t, 3H, J = 6.6 Hz, CH_3). IR (KBr) 1685 cm^{-1}. MS m/z 329 (M+1). Anal. Calcd. for $C_{18}H_{24}N_4O_2$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.81; H, 7.35; N, 17.26.

7-(Octyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxamide (6f)

Yield 86.9%, mp 161-163°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.19 (d, 1H, J = 8.6 Hz, 9-Ar-H), 7.80 (s, 1H, NH), 7.01-7.04 (m, 2H, 6- and 8-Ar-H), 6.15 (s, 1H,

NH), 4.14 (t, 2H, *J* = 6.5 Hz, CH_2), 3.31 (t, 2H, *J* = 6.9 Hz, CH_2), 3.13 (t, 2H, *J* = 6.9 Hz, CH_2), 1.47-1.98 (m, 12H, $(CH_2)_6$), 1.05 (d, 3H, *J* = 7.8 Hz, CH_3). IR (KBr) 1683 cm^{-1}. MS *m/z* 343 (M+1). Anal. Calcd. for $C_{19}H_{26}N_4O_2$: C, 66.64; H, 7.65; N, 16.36. Found: C, 66.54; H, 7.75; N, 16.31.

7-Benzyloxy-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxamide (6g)
Yield 90.9%, mp 217-219°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.05 (d, 1H, *J* = 8.7 Hz, 9-Ar-H), 7.42 (s, 1H, NH), 7.31-7.38 (m, 5H, Ar-H), 6.94 (m, 2H, 6- and 8-Ar-H), 5.79 (s, 1H, NH), 5.09 (s, 2H, CH_2O), 3.14 (t, 2H, *J* = 6.9 Hz, CH_2), 2.96 (t, 2H, *J* = 6.9 Hz, CH_2). IR (KBr) 1666 cm^{-1}. MS *m/z* 321 (M+1). Anal. Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.51; H, 5.23; N, 17.61.

7-(2-Fluorobenzyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxamide (6h)
Yield 92.4%, mp 190-193°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.67 (d, 1H, *J* = 8.9 Hz, 9-Ar-H), 7.52 (s, 1H, NH), 7.35-7.47 (m, 4H, Ar-H), 6.93 (m, 2H, 6- and 8-Ar-H), 5.81 (s, 1H, NH), 5.16 (s, 2H, CH_2O), 3.16 (t, 2H, *J* = 6.9 Hz, CH_2), 2.97 (t, 2H, *J* = 6.9 Hz, CH_2). IR (KBr) 1675 cm^{-1}. MS *m/z* 339 (M+1). Anal. Calcd. for $C_{18}H_{15}FN_4O_2$: C, 63.90; H, 4.47; N, 16.56. Found: C, 63.79; H, 4.56; N, 16.48.

7-(3-Fluorobenzyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxamide (6i)
Yield 93.8%, mp 206°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.06 (d, 1H, *J* = 9.6 Hz, 9-Ar-H), 7.46 (s, 1H, NH_2), 6.92-7.36 (m, 6H, Ar-H), 5.77 (s, 1H, NH_2), 5.09 (s, 2H, CH_2O), 3.15 (t, 2H, *J* = 6.9 Hz, CH_2), 2.97 (t, 2H, *J* = 6.9 Hz, CH_2). IR (KBr) 1676 cm^{-1}. MS *m/z* 339 (M+1). Anal. Calcd. for $C_{18}H_{15}FN_4O_2$: C, 63.90; H, 4.47; N, 16.56. Found: C, 63.79; H, 4.55; N, 16.63.

7-(4-Fluorobenzyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxamide (6j)
Yield 92.4%, mp 222-224°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.67 (d, 1H, *J* = 8.9 Hz, 9-Ar-H), 7.52 (s, 1H, NH_2), 6.85-7.44 (m, 6H, Ar-H), 5.77 (s, 1H, NH_2), 5.16 (s, 2H, CH_2O), 3.16 (t, 2H, *J* = 6.9 Hz, CH_2), 2.97 (t, 2H, *J* = 6.9 Hz, CH_2). IR (KBr) 1675 cm^{-1}. MS *m/z* 339 (M+1). Anal. Calcd. for $C_{18}H_{15}FN_4O_2$: C, 63.90; H, 4.47; N, 16.56. Found: C, 63.78; H, 4.56; N, 16.61.

7-(2-Chlorobenzyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxamide (6k)
Yield 92.4%, mp 196-198°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.67 (d, 1H, *J* = 8.9 Hz, 9-Ar-H), 7.49 (s, 1H, NH_2), 6.85-7.49 (m, 6H, Ar-H), 5.69 (s, 1H, NH_2), 5.16 (s, 2H, CH_2O), 3.16 (t, 2H, *J* = 6.9 Hz, CH_2), 2.97 (t, 2H, *J* = 6.9 Hz, CH_2). IR (KBr) 1685 cm^{-1}. MS *m/z* 355 (M+1). Anal. Calcd. for $C_{18}H_{15}ClN_4O_2$: C, 60.94; H, 4.26; N, 15.79. Found: C, 60.69; H, 4.38; N, 15.88.

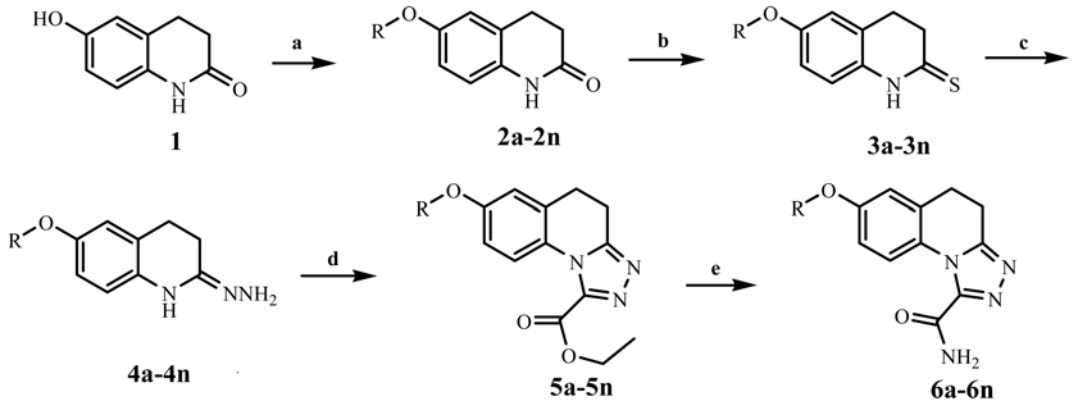
7-(3-Chlorobenzyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxamide (6l)
Yield 93.8%, mp 172-174°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.06 (d, 1H, *J* = 9.6 Hz, 9-Ar-H), 7.46 (s, 1H, NH_2), 6.92-7.38 (m, 6H, Ar-H), 5.77 (s, 1H, NH_2), 5.09 (s, 2H, CH_2O), 3.15 (t, 2H, *J* = 6.9 Hz, CH_2), 2.97 (t, 2H, *J* = 6.9 Hz, CH_2). IR (KBr) 1695 cm^{-1}. MS *m/z* 355 (M+1). Anal. Calcd. for $C_{18}H_{15}ClN_4O_2$: C, 60.94; H, 4.26; N, 15.79. Found: C, 60.78; H, 4.49; N, 15.89.

7-(4-Chlorobenzyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxamide (6m)
Yield 92.4%, mp 212-214°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.05 (d, 1H, *J* = 8.7 Hz, 9-Ar-H), 7.47 (s, 1H, NH_2), 7.28 (d, 2H, *J* = 7.2 Hz, 2', 6'-Ar-H), 7.36 (d, 2H, *J* = 7.2 Hz, 3', 5'-Ar-H), 6.90-6.94 (m, 2H, 6- and 8- Ar-H), 5.80 (s, 1H, NH_2), 5.05 (s, 2H, CH_2O), 3.14 (t, 2H, *J* = 6.9 Hz, CH_2), 2.96 (t, 2H, *J* = 6.9Hz, CH_2). IR (KBr) 1687 cm^{-1}. MS *m/z* 355 (M+1). Anal. Calcd. for $C_{18}H_{15}ClN_4O_2$: C, 60.94; H, 4.26; N, 15.79. Found: C, 60.88; H, 4.51; N, 15.87.

7-(4-Methylbenzyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxamide (6n)
Yield 92.3%, mp 184-186°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.02 (d, 1H, *J* = 8.4 Hz, 9-Ar-H), 7.63 (s, 1H, NH), 7.31 (d, 2H, *J* = 7.8 Hz, 2', 6'-Ar-H), 7.19 (d, 2H, *J* = 7.8 Hz, 3', 5'-Ar-H), 6.90-6.93 (m, 2H, 6- and 8- Ar-H), 6.10 (s, 1H, NH), 5.04 (s, 2H, CH_2O), 3.13 (t, 2H, *J* = 6.9 Hz, CH_2), 2.95 (t, 2H, *J* = 6.9 Hz, CH_2), 2.57 (s, 3H, Ph-CH_3). MS *m/z* 335 (M+1). Anal. Calcd. for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 16.76. Found: C, 68.01; H, 5.55; N, 16.61.

Pharmacology

The evaluation of the anticonvulsant activity followed the Anticonvulsant Drug Development Program (ADD) of the National Institute of Health following previously described testing procedures (USA). Adult male and female KunMing mice (18-25g) were used as experimental animals. Animals of the same age and weight were selected, in order to minimize biological variability. The animals were maintained on a 12 h light/dark cycle and allowed free access to food and water, except during the time they were removed from their cages for testing. The test substance was administered in 30% polyethylene glycol 400 (PEG) and 10%



a: RX/NaOH, CH_3CH_2OH, ref; b: P_2S_5, CH_3CN/TEA; c: $NH_2NH_2{\cdot}H_2O$/THF;
d: diethyl oxalate, ref; e: $NH_3{\cdot}H_2O/CH_3OH$, rt.

Scheme 1. The synthesis route

water. The drugs were administered intraperitoneally (i.p.) in mice in a volume of 0.05 mL/20 g body weight.

MES screening

Seizures were elicited with a 60-Hz alternating current of 50 mA intensity in mice. The current was applied via corneal electrodes for 0.2 sec. Protection against the spread of MES-induced seizures was defined as the abolition of the hind leg and tonic maximal extension component of the seizure. At 30 min after the administration of the compounds, the activities were evaluated in MES test.

Rotarod test

At 30 min after the administration of the compounds, the animals were placed and tested on a 1-in. diameter; knurled plastic rod rotating at 6 rpm for 1 min. The abilities of animals to maintain balance were tested. Neurotoxicity was indicated by the inability of the animal to maintain the equilibrium in each of three trials. The results are tabulated in Table I and Table II.

RESULTS

A series of Triazolo[4,3-a]quinoline derivatives (**5a-5n** and **6a-6n**) were synthesized and tested as anticonvulsant agents in KunMing mice against the maximal electroshock (MES) test, the results showed that the series of derivatives exhibit different anticonvulsant activities. No compound exhibited better anticonvulsant activity than reference drugs carbamazepine. The results demonstrated that compound 7-(hexyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-1-carboxamide (**6d**) was the most active one and also had the lowest toxicity. In the anti-MES potency test, it showed median effective dose (ED_{50}) of 30.1 mg/kg, median toxicity dose (TD_{50}) of 286 mg/kg, and the

Table I. Phase I: Quantitative anticonvulsant data in mice (i.p.)

Compound	R	MES (50mg/kg)	MES (100mg/kg)	Toxicity (300mg/kg)
5a	n-C_3H_7	1/3	2/3	1/3
5b	n-C_4H_9	3/3	3/3	2/3
5c	n-C_5H_{11}	3/3	3/3	2/3
5d	n-C_6H_{13}	1/3	3/3	3/3
5e	n-C_7H_{15}	1/3	2/3	2/3
5f	n-C_8H_{17}	0/3	1/3	3/3
5g	-CH_2Ph	0/3	0/3	2/3
5h	-CH_2Ph (*2*-F)	0/3	0/3	1/3
5i	-CH_2Ph (3-F)	0/3	2/3	2/3
5j	-CH_2Ph (*4*-F)	0/3	1/3	2/3
5k	-CH_2Ph (*2*-Cl)	0/3	1/3	2/3
5l	-CH_2Ph (3-Cl)	0/3	0/3	2/3
5m	-CH_2Ph (4-Cl)	0/3	0/3	1/3
5n	-CH_2Ph (4-CH3)	0/3	1/3	3/3
6a	n-C_3H_7	1/3	3/3	2/3
6b	n-C_4H_9	2/3	3/3	2/3
6c	n-C_5H_{11}	3/3	3/3	1/3
6d	n-C_6H_{13}	3/3	3/3	1/3
6e	n-C_7H_{15}	3/3	3/3	2/3
6f	n-C_8H_{17}	2/3	3/3	3/3
6g	-CH_2Ph	1/3	2/3	2/3
6h	-CH_2Ph (*2*-F)	1/3	3/3	2/3
6i	-CH_2Ph (3-F)	2/3	3/3	2/3
6j	-CH_2Ph (*4*-F)	0/3	2/3	3/3
6k	-CH_2Ph (*2*-Cl)	0/3	2/3	2/3
6l	-CH_2Ph (3-Cl)	0/3	1/3	2/3
6m	-CH_2Ph (4-Cl)	0/3	0/3	2/3
6n	-CH_2Ph (4-CH3)	0/3	1/3	3/3

Table 2. Phase II: Quantitative anticonvulsant data in mice (test drug administered i.p.)[a]

Compound	ED_{50} [b]	TD_{50} [c]	PI (TD_{50}/ED_{50})
5b	33.9 (21.3-49.8)[d]	213 (108.2-486.6)	6.3
5c	36.8 (11.9-56.9)	224 (132.6-368.0)	6.1
6b	43.0 (22.5-79.6)	216 (116.8-356.8)	5.0
6c	35.5 (18.6-57.3)	256 (153.2-452.3)	7.2
6d	30.1 (19.0-48.2)	286 (188.6-406.2)	9.5
6e	29.8 (18.2-41.0)	224 (142.6-422.2)	7.5
6f	43.2 (26.4-67.5)	182 (101.2-296.7)	4.2
6i	39.6 (25.6-51.6)	191 (106.1-360.0)	4.8
Carbamazepine	10.1 (6.01-22.1)	69.1 (39.2-110.0)	6.0

[a]All the tested compounds were dissolved in polyethylene glycol-400.
[b]The dose measured in mg/kg.
[c]Minimal neurotoxicity was determined by the rotarod test 30 min after the tested compounds were administrated.
[d]95% confidence limits given in parentheses.

protective index (PI) of 9.5 which is greater than the reference drug carbamazepine with PI value of 6.0.

DISCUSSION

Chemistry

Target compounds **6a-6n** were synthesized according to Scheme 1. Compounds **4a-4n** were prepared according to the reference method (Sun et al., 2009). Compound **5a-5n** were prepared according to the reference method (Zimmer et al., 1975). **4a-4n** were added to superfluous diethyl oxalate respectively, then the mixture was stirred and refluxed. Compounds **6a-6n** were obtained by compounds **5a-5n** reacting with concentrated ammonia spirit spreaded around CH_3OH at room temperature.

Pharmacology

Initial anticonvulsant evaluation of the 1-formamide-triazolo[4,3-*a*]quinolines were undertaken by following the anticonvulsant drug development (ADD) program protocol (Krall et al., 1978; Poter et al., 1984). The profile of anticonvulsant activity was established after i.p. injections by electrical and chemical tests. The electrical test employed was the Maximal Electroshock Seizure (MES) patern test. The acute neurological toxicity was determined in the rotarod test (Sun et al., 2006). The activity and toxicity profile for the tested compounds is summarized in Phase I, Table I along with the literature data for standard drug. All the compounds were active in the MES test, indicative of their ability to prevent seizure spread.

The results of preliminary (Phase I) screening of **5a-5n** and **6a-6n** are summarized in Table I. In the anti-MES test, after drug administration at 100 mg/kg dose, compounds **5b-5d**, **6a-6f, 6h** and **6i** showed 100% protection. Compounds **5b**, **5c** and **6c-6e** exhibited 100% protection after drug administration at 50 mg/kg dose. All the compounds showed different neurotoxicity at the maximum dose administered (300 mg/kg).

And compounds **6b**, **6f** and **6i** were showed more than half anti-MES activity. All the compounds showed different neurotoxicity at the maximum dose administered (300 mg/kg).

As a result of preliminary screening, compounds **5b**, **5c**, **6b-6f** and **6i** were then subjected to Phase II trials for quantification of their anticonvulsant activity and neurotoxicity in mice. This phase provides an evaluation of the ED_{50} and TD_{50} values. The 95%-confidence interval, slope of the regression line, and SE of the slope were then calculated. These data are shown in Table II which also includes comparisons with marketed antiepileptic drugs carbamazepine. No compound exhibited better anticonvulsant activity than reference drugs carbamazepine. Among the synthesized compounds, compound **6d** was the most active one and also had the lowest toxicity. In the anti-MES potency test, it showed median effective dose (ED_{50}) of 30.1 mg/kg, median toxicity dose (TD_{50}) of 286 mg/kg, and the protective index (PI) of 9.5 which is greater than the reference drug carbamazepine with PI value of 6.0.

The structure-activity relationship of the compounds **5a-5n** was analyzed using their activity in the MES test. For the 6 alkyl chain-substituted derivatives **5a-5f**, the length of the alkyl chain appeared to have a direct impact on the anticonvulsant activity of the 7-alkyloxyl derivatives. As the alkyl chain length increased from 3 to 8, the value of anticonvulsant activity gradually increased and the compound **5b** (with the 7-butoxy substituted group) had the

smallest ED_{50}. However, the trend reversed when the alkyl chain increased from 4 to 8. For the 8 phenyl-substituted derivatives **5g-5n**, no compound had MES activity under 50 mg/kg^{-1}. And the structure-activity relationship of the compounds **6a-6n** was analyzed using their activity in the MES test too. For the 6 alkyl chain-substituted derivatives **6a-6f**, the length of the alkyl chain appeared to have a direct impact on the anticonvulsant activity of the 6-alkyloxyl derivatives. As the alkyl chain length increased from 3 to 6, the value of ED_{50} gradually decreased and the compound **6e** (with the *n*-heptyl substituted group) had the smallest ED_{50}. However, the trend reversed when the alkyl chain increased from 7 to 8. For the 8 phenyl-substituted derivatives **6g-6n**, 3 compounds had MES activity under 50 mg/kg^{-1}. And among the substituted benzyloxyl, the position of the substituted group on the phenyl ring appeared to greatly influence the anticonvulsant activity; among the three fluorobenzyloxy substituted compounds **6h, 6i** and **6j**, the potency order was *m*-F > *o*-F > *p*-F. Among the four p-sub- stituted phenyl derivatives, the potency order was H > F > CH_3 > Cl. And generally speaking, the F substitut- ed compounds showed much more activity than the Cl substituted compounds. This structure-activity relationship might be explained by the lipid-water partition coefficients of the compounds, which affect the crossing of the blood-brain barrier by the compounds. The compound **6d** (with the *n*-hexyl substituted group) had an ED_{50} value of 30.1 mg/kg^{-1}, the ED_{50} was little biger than **6e**, but the TD_{50} of compound **6d** was much biger than **6e**, it possessed weaker neurotoxicity and had a PI value of 9.5. Therefore, compound **6d** could be considered a potentially useful and safe antiepileptic therapeutic.

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