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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design and synthesis of 6-alkyoxyl[1,2,4]triazolo[1,5-*a*]quinazoline derivatives with anticonvulsant activity

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Abstract A series of novel 6-alkyoxyl[1,2,4]triazolo[1,5-*a*]quinazoline derivatives were synthesized in this study. The anticonvulsant activity of all the target compounds **4a**–**4s**, characterized by IR, ^{1}H-NMR and MS, were evaluated using Maximal electroshock test. The pharmacological results showed that some of the compounds displayed positive anticonvulsant activity. Among them, 6-(benzyloxy)-[1,2,4]triazolo[1,5-*a*]quinazoline (**4a**) was the most active compound with an ED_{50} value of 78.9 mg/kg and a PI value of 9.0.

Keywords Synthesis · Triazole · Triazolo[1,5-*a*]quinazoline · Anticonvulsant · Maximal electroshock

Introduction

There is no doubt that epilepsy belongs to the most encountered neurological conditions since the disease affects approximately 1% of the population (Strine *et al.*, 2005). Around 75–80% of epileptic patients may be provided with adequate seizure control with the help of the available antiepileptic drugs. The therapeutic failure in 20–25% of patients and serious side effects in the available antiepileptic drugs has stimulated intensive research on novel antiepileptic drugs (Spear, 2001; Bootsma *et al.*, 2009; Kennedy and Lhatoo, 2008).

In the efforts to get those agents, we had reported (Xie *et al.*, 2005; Cui *et al.*, 2005; Guan *et al.*, 2008; Cui *et al.*, 2007) several [1,2,4]triazolo[4,3-*a*]quinoline derivatives (Fig. 1), which showed considerable anticonvulsant activities. As a part of our continuous research in this area, we designed and synthesized several new [1,2,4]triazolo[1,5-*a*]quinazoline derivatives, which are the bioisoterisms of [1,2,4]triazolo[4,3-*a*]quinolines. From the structure–activity relationships of [1,2,4]triazolo[4,3-*a*]quinoline derivatives, we found that introduction of alkyoxyl groups into the aryl moiety significantly enhanced the anticonvulsant efficacy. Hence, in this study, the [1,2,4]triazolo[1,5-*a*]quinazoline derivatives with alkyoxyl groups in the 6th position were synthesized expecting to have a promising effect in dealing with the epilepsy.

Their structures were characterized using IR, ^{1}H-NMR, MS, and elemental analysis techniques. Their anticonvulsant activities were evaluated with maximal electroshock (MES) test in intraperitoneally injected mice.

Experimental section

Chemistry

Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded (in KBr) on a FT-IR1730 (Perkin-Elmer, USA). ^{1}H-NMR spectra were measured on a BRUKER-300 (Bruker Bioscience, Billerica, MA, USA), and all chemical shifts were given in ppm relative to tetramethysilane. Mass spectra were measured on an HP1100LC (Hewlett-Packard, PaloAlto, CA, USA). Microanalyses of C, N, and H were performed using a Heraeus CHN Rapid Analyzer (Heraeus GmbH, Hanau, Germany). The major chemicals were purchased from Sigma-Aldrich Corporation.

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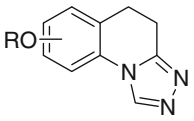
Fig. 1 [1,2,4]triazolo[4,3-*a*]quinolines



*Synthesis of 8,9-dihydro-[1,2,4]triazolo[1,5-a]quinazolin-6(7H)-one (**1**)*

Cyclohexane-1,3-dione (2 g, 17.9 mmol) and dimethoxy-N,N-dimethylmethanemine (DMF-DMA) (2.56 g, 21.4 mmol) were mixed and heated at 60°C. 2*H*-1,2,4-triazol-3-amine was added after the mixture was completely homogenized, and then the reaction temperature was raised to 105°C. The mixture was solidified for a few minutes, cooled, and diluted with propan-2-ol. The precipitate was filtered off and recrystallized from DMF. Yield: 91.3%; mp 209–211°C. ^{1}H-NMR (CDCl3, 300 MHz): δ 2.38–2.45 (m, 2H, H-8), 2.78 (t, 2H, $J = 6$ Hz, H-7), 3.53 (t, 2H, $J = 6.3$ Hz, H-9), 8.59 (s, 1H, H-5), 9.31 (s, 1H, H-2). MS m/z 189.1 (M + 1). Anal. Calcd. For C9H8N4O: C 57.44, H 4.28, N 29.77. Found: C 57.31, H 4.38, N 29.65.

*Synthesis of 7-bromo-8,9-dihydro-[1,2,4]triazolo [1,5-a]quinazolin-6(7H)-one (**2**)*

Compound **1** (3.00 g, 16.0 mmol), *N*-bromosuccinimide (NBS) (4.26 g, 23.9 mmol), and small amounts of benzoyl peroxide were placed into a 100-ml round-bottomed flask containing 50 ml of CCl_4 equipped with a reflux condenser connected with a drying tube. The mixture was stirred at 100°C for 6 h. After cooling, it was filtered and washed with dichloromethane. The evaporation of the dichloromethane gave a crude product, which was purified by silica gel column chromatography with CH_2Cl_2–CH_3OH (30:1). Yield: 90.6%; mp 322–324°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.78–3.25 (m, 4H, H-8, H-9), 5.98 (s, 1H, H-7), 8.70 (s, 1H, H-5), 9.38 (s, 1H, H-2). MS *m/z* 270 (M + 1). Anal. Calcd. for $C_9H_9BrN_4O$: C 40.17; H 3.37; N 20.82. Found: C 40.03; H 3.24; N 20.96.

*Synthesis of [1,2,4]triazolo[1,5-a]quinazolin-6-ol (**3**)*

Compound **2** (3.50 g, 13.1 mmol) and K_2CO_3 (2.17 g, 15.7 mmol) were placed into a 100-ml round-bottomed flask containing 50 ml of ethanol. The mixture was refluxed for 15 min, and then the solvent was removed under reduced pressure. The residue was dissolved with 50 ml ice–water, and the solution was neutralized with 10% HCl solution. The precipitate was filtered off and dried in vacuo to give a crude product, which was purified by silica gel column chromatography with CH_2Cl_2–CH_3OH (10:1). Yield: 88.4%; mp 348–349°C. ^{1}H-NMR (DMSO, 300 MHz): δ 7.12 (d, 1H, $J = 8.07$, H-9), 7.76 (d, 1H, $J = 8.22$ Hz, H-7), 7.93 (t, 1H, $J = 8.25$ Hz, H-8), 8.64 (s, 1H, H-5), 9.52 (s, 1H, H-2), 11.65 (s, 1H, –OH). MS *m/z* 187 (M + 1). Anal. Calcd. for $C_9H_6N_4O$: C 58.06, H 3.25, N 30.09. Found: C 58.27, H, 3.06, N 30.23.

The general procedure for the synthesis of 6-alkyoxyl[1,2,4]triazolo[1,5-*a*]quinazoline (**4a**–**4s**)

Compound **4** (0.45 g, 2.4 mmol) and K_2CO_3 (0.40 g, 2.9 mmol) were added to 20 mL DMF. The mixture was stirred and heated at 80°C for 0.5 h, then various kinds of substituted benzyl chloride (2.4 mmol) were added, and the reaction temperature was raised to 100°C. After stirring for about 3 h, the solvent was removed under reduced pressure. Residue was extracted with dichloromethane and dried over anhydrous $MgSO_4$. Evaporation of the solvents got a crude product, which was purified by silica gel column chromatography with CH_2Cl_2–CH_3OH (50:1) to obtain compounds, **4a**–**4s**. The yield, melting point, and spectral data of each compound were given below.

*6-(Benzyloxy)-[1,2,4]triazolo[1,5-a]quinazoline (**4a**)*

Yield: 72.1%; mp 163–165°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.35 (s, 2H, –OCH_2–), 7.09 (d, 1H, $J = 8.07$ Hz, H-9), 7.40–7.52 (m, 5H, Ar–H), 7.89 (t, 1H, $J = 8.18$ Hz, H-8), 7.99 (d, 1H, $J = 8.34$ Hz, H-7), 8.49 (s, 1H, H-5), 9.71 (s, 1H, H-2); IR (KBr) cm^{-1}: 1620, 1601, 1549 (C=N); MS *m/z* 277 (M + 1); Anal. Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.33; H, 4.25; N, 20.43.

*6-(2-Fluorobenzyloxy)-[1,2,4]triazolo[1,5-a]quinazoline (**4b**)*

Yield: 70.2%; mp 166–168°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.41 (s, 2H, –OCH_2–), 7.13–8.03 (m, 7H, H-7, H-8, H-9, Ar–H), 8.49 (s, 1H, H-5), 9.68 (s, 1H, H-2); IR (KBr) cm^{-1}: 1622, 1600, 1549 (C=N); MS *m/z* 295 (M + 1); Anal. Calcd. for $C_{16}H_{11}FN_4O$: C, 65.30; H, 3.77; N, 19.04. Found: C, 65.10; H, 3.92; N, 18.81.

*6-(3-Fluorobenzyloxy)-[1,2,4]triazolo[1,5-a]quinazoline (**4c**)*

Yield: 69.4%; mp 159–161°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.35 (s, 2H, –OCH_2–), 7.05-8.03 (m, 7H, H-7, H-8, H-9, Ar–H), 8.50 (s, 1H, H-5), 9.71 (s, 1H, H-2); IR (KBr) cm^{-1}: 1621, 1601, 1548 (C=N); MS *m/z* 295 (M + 1); Anal. Calcd. for $C_{16}H_{11}FN_4O$: C, 65.30; H, 3.77; N, 19.04. Found: C, 65.11; H, 3.89; N, 19.22.

*6-(4-Fluorobenzyloxy)-[1,2,4]triazolo[1,5-a]quinazoline (**4d**)*

Yield: 70.2%; mp 189–191°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.30 (s, 2H, –OCH_2–), 7.06–8.02 (m, 7H, H-7, H-8, H-9, Ar–H), 8.49 (s, 1H, H-5), 9.67(s, 1H, H-2); IR (KBr) cm^{-1}: 1620, 1601, 1549 (C=N); MS *m/z* 295 (M + 1); Anal. Calcd. for $C_{16}H_{11}FN_4O$: C, 65.30; H, 3.77; N, 19.04. Found: C, 65.11; H, 3.64; N, 18.83.

*6-(2-Chlorobenzyloxy)-[1,2,4]triazolo[1,5-a]quinazoline (**4e**)*

Yield: 71.4%; mp 202–203°C. ^{1}H-NMR ($CDCl_3$ 300 MHz): δ 5.45 (s, 2H, –OCH_2–), 7.10–8.04 (m, 7H, H-7, H-8, H-9, Ar–H), 8.50 (s, 1H, H-5), 9.73 (s, 1H, H-2); IR (KBr) cm^{-1}: 1622, 1600, 1551 (C=N); MS *m/z* 312 (M + 1) 314 (M + 3); Anal. Calcd. for $C_{16}H_{11}ClN_4O$: C, 61.84; H, 3.57; N, 18.03. Found: C, 61.62; H, 3.69; N, 18.21.

*6-(3-Chlorobenzyloxy)-[1,2,4]triazolo[1,5-a]quinazoline (**4f**)*

Yield: 68.3%; mp 196–198°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.32 (s, 2H, –OCH_2–), 7.04–8.03 (m, 7H, H-7, H-8, H-9, Ar–H), 8.50 (s, 1H, H-5), 9.70 (s, 1H, H-2); IR (KBr) cm^{-1}: 1622, 1601, 1550 (C=N); MS *m/z* 312 (M + 1) 314 (M + 3); Anal. Calcd. for $C_{16}H_{11}ClN_4O$: C, 61.84; H, 3.57; N, 18.03. Found: C, 61.71; H, 3.45; N, 18.25.

*6-(4-Chlorobenzyloxy)-[1,2,4]triazolo[1,5-a]quinazoline (**4g**)*

Yield: 70.6%; mp 190–192°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.31 (s, 2H, –OCH_2–), 7.04–8.01 (m, 7H, H-7, H-8, H-9, Ar–H), 8.49 (s, 1H, H-5), 9.66 (s, 1H, H-2); IR (KBr) cm^{-1}: 1620, 1601, 1549 (C=N); MS *m/z* 312 (M + 1), 314 (M + 3); Anal. Calcd. for $C_{16}H_{11}ClN_4O$: C, 61.84; H, 3.57; N, 18.03. Found: C, 61.62; H, 3.38; N, 18.27.

*6-(2,4-Dichlorobenzyloxy)-[1,2,4]triazolo[1,5-a]quinazoline (**4h**)*

Yield: 65.4%; mp 237–239°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.41(s, 2H, –OCH_2–), 7.08–8.06 (m, 6H, H-7, H-8, H-9, Ar–H), 8.50 (s, 1H, H-5), 9.70 (s, 1H, H-2); IR (KBr) cm^{-1}: 1624, 1601, 1551 (C=N); MS *m/z* 346 (M + 1), 348 (M + 3); Anal. Calcd. for $C_{16}H_{10}Cl_2N_4O$: C, 55.67; H, 2.92; N, 16.23. Found: C, 55.84; H, 2.78; N, 16.11.

*6-(2-Bromobenzyloxy)-[1,2,4]triazolo[1,5-a]quinazoline (**4i**)*

Yield: 71.3%; mp 199–201°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.41(s, 2H, –OCH_2–), 7.09–8.03 (m, 7H, H-7, H-8, H-9, Ar–H), 8.50 (s, 1H, H-5), 9.73 (s, 1H, H-2); IR (KBr) cm^{-1}: 1622, 1601, 1549 (C=N); MS *m/z* 356 (M + 1), 358 (M + 3); Anal. Calcd. for $C_{16}H_{11}BrN_4O$: C, 54.10; H, 3.12; N, 15.77. Found: C, 54.29; H, 2.94; N, 15.61.

*6-(4-Methbenzyloxy)-[1,2,4]triazolo [1,5-a]quinazoline (**4j**)*

Yield: 72.5%; mp 158–159°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.40 (s, 3H, –CH_3), 5.30 (s, 2H, –OCH_2–), 7.07–7.99 (m, 7H, H-7, H-8, H-9, Ar–H), 8.48 (s, 1H, H-5), 9.64 (s, 1H, H-2); IR (KBr) cm^{-1}: 1620, 1601, 1549 (C=N); MS *m/z* 291 (M + 1); Anal. Calcd. for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.49; H, 4.99; N, 19.48.

*6-(4-Methoxybenzyloxy)-[1,2,4]triazolo [1,5-a]quinazoline (**4k**)*

Yield: 69.8%; mp 179–181°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 3.83 (s, 3H, –OCH_3), 5.26 (s, 2H, –OCH_2–), 6.87-7.97 (m, 7H, H-7, H-8, H-9, Ar–H), 8.48 (s, 1H, H-5), 9.64 (s, 1H, H-2); IR (KBr) cm^{-1}: 1620, 1601, 1549 (C=N); MS *m/z* 307 (M + 1); Anal. Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.50; H, 4.76; N, 18.15.

*4-(([1,2,4]Triazolo[1,5-a]quinazolin-6-yloxy)methyl)benzonitrile (**4l**)*

Yield: 66.7%; mp 248–250°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.42 (s, 2H, –OCH_2–), 7.03–8.06 (m, 7H, H-7, H-8, H-9, Ar–H), 8.50 (s, 1H, H-5), 9.70 (s, 1H, H-2); IR (KBr) cm^{-1}: 1620, 1601, 1549 (C=N); MS *m/z* 302 (M + 1); Anal. Calcd. for $C_{17}H_{11}N_5O$: C, 67.77; H, 3.68; N, 23.24. Found: C, 67.96; H, 3.79; N, 23.08.

*2-(([1,2,4]Triazolo[1,5-a]quinazolin-6-yloxy)methyl)benzonitrile (**4m**)*

Yield: 61.8%; mp 230–232°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.54 (s, 2H, –OCH_2–), 7.14–8.05 (m, 7H, Ar–H), 8.50 (s, 1H, H-5), 9.70 (s, 1H, H-2); IR (KBr) cm^{-1}: 1620, 1601, 1549 (C=N); MS *m/z* 302 (M + 1); Anal. Calcd. for $C_{17}H_{11}N_5O$: C, 67.77; H, 3.68; N, 23.24. Found: C, 67.61; H, 3.50; N, 23.39.

*6-Butoxy-[1,2,4]triazolo[1,5-a]quinazoline (**4n**)*

Yield: 71.8%; mp 140–142°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.93 (t, 3H, $J = 7.29$ Hz, $–CH_3$), 1.55–1.70 (m, 2H, $–CH_2–$), 1.91–2.00 (m, 2H, $–CH_2–$), 4.24 (t, 2H, $J = 6.33$ Hz, $–OCH_2–$), 7.01 (d, 1H, $J = 7.74$ Hz, H-9), 7.86–7.97 (m, 2H, H-7, H-8), 8.49 (s, 1H, H-5), 9.65 (s, 1H, H-2); IR (KBr) cm^{-1}: 1618, 1599, 1549 (C=N); MS *m/z* 243(M + 1); Anal. Calcd. for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.13.Found: C, 64.64; H, 5.98; N, 23.29 .

*6-(Pentyloxy)-[1,2,4]triazolo[1,5-a]quinazoline (**4o**)*

Yield: 70.5%; mp 133–135°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.98 (t, 3H, $J = 7.16$ Hz, $–CH_3$), 1.42–1.61 (m, 4H, $–CH_2–CH_2–$), 1.93–2.02 (m, 2H, $–CH_2–$), 4.23 (t, 2H, $J = 6.37$ Hz, $–OCH_2–$), 6.98 (d, 1H, $J = 7.72$ Hz, H-9), 7.84–7.94 (m, 2H, H-7, H-8), 8.48 (s, 1H, H-5), 9.64 (s, 1H, H-2); IR (KBr) cm^{-1}: 1618, 1599, 1549 (C=N); MS *m/z* 257 (M + 1); Anal. Calcd. for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.84; H, 6.11; N, 22.04.

*6-(Hexyloxy)-[1,2,4]triazolo[1,5-a]quinazoline (**4p**)*

Yield: 68.7%; mp 128–129°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.96 (t, 3H, $J = 6.67$ Hz,$–CH_3$), 1.38–1.40 (m, 6H, $–CH_2–CH_2–$), 1.56–1.59 (m, 2H, $–CH_2–$), 4.22 (t, 2H, $J = 6.35$ Hz, $–OCH_2–$), 6.98 (d, 1H, $J = 7.67$ Hz, H-9), 7.84–7.94 (m, 2H, H-7, H-8), 8.48 (s, 1H, H-5), 9.63 (s, 1H, H-2); IR (KBr) cm^{-1}: 1619, 1600, 1549 (C=N); MS *m/z* 271 (M + 1); Anal. Calcd. for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73. Found: C, 66.83; H, 6.60; N, 20.88.

*6-(Heptyloxy)-[1,2,4]triazolo[1,5-a]quinazoline (**4q**)*

Yield: 69.3%; mp 130–132°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, 3H, $J = 6.14$ Hz, $–CH_3$), 1.25–1.45 (m, 6H, $–CH_2–CH_2–CH_2–$), 1.52–1.59 (m, 2H, $–CH_2–$), 1.94–1.99 (m, 2H, $–CH_2–$), 4.23 (t, 2H, $J = 6.41$ Hz, $–OCH_2–$), 7.00 (d, 1H, $J = 7.86$ Hz, H-9), 7.86–7.96 (m, 2H, H-7, H-8), 8.48 (s, 1H, H-5), 9.65 (s, 1H, H-2); IR (KBr) cm^{-1}: 1619, 1601,1549 (C=N); MS *m/z* 285 (M + 1); Anal. Calcd. for $C_{16}H_{20}N_4O$: C, 67.58; H, 7.09; N, 19.70. Found: C, 67.79; H, 6.92; N, 19.91.

*6-(Octyloxy)-[1,2,4]triazolo[1,5-a]quinazoline (**4r**)*

Yield: 70.6%; mp 118–119°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.90 (t, 3H, $J = 6.77$ Hz, $–CH_3$),1.31–1.38 (m, 8H, $–CH_2–CH_2–CH_2–CH_2–$), 1.52–1.64 (m, 2H, $–CH_2–$), 1.92–2.01 (m, 2H, $–CH_2–$), 4.24 (t, $J = 6.42$ Hz, 2H, $–OCH_2–$), 7.01 (d, 1H, H-9), 7.87–7.97 (m, 2H, H-7, H-8), 8.49 (s, 1H, H-5), 9.66 (s, 1H, H-2); IR (KBr) cm^{-1}: 1620, 1601, 1549 (C=N); MS *m/z* 299 (M + 1); Anal. Calcd. for $C_{17}H_{22}N_4O$: C, 68.43; H, 7.43; N, 18.78. Found: C, 68.68; H, 7.26; N, 18.94.

*6-(Decyloxy)-[1,2,4]triazolo[1,5-a]quinazoline (**4s**)*

Yield: 67.9%; mp 128–130°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, 3H, $J = 6.57$ Hz, $–CH_3$), 1.27–1.42 (m, 12H, $–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2–$), 1.52–1.55 (m, 2H, $–CH_2–$), 1.92–2.03 (m, 2H, $–CH_2–$), 4.21 (t, 2H, $J = 6.30$ Hz, $–OCH_2–$), 6.96 (d, 1H, $J = 7.68$ Hz, H-9), 7.82–7.92 (m, 2H, H-7, H-8), 8.46 (s, 1H, H-5), 9.62 (s, 1H, H-2); IR (KBr) cm^{-1}: 1620, 1601, 1549 (C=N); MS *m/z* 327 (M + 1); Anal. Calcd. for $C_{19}H_{26}N_4O$: C, 69.91; H, 8.03; N, 17.16. Found: C, 70.14; H, 7.92; N, 17.30.

Pharmacology

All the titled compounds (**4a**–**4s**) were screened for their anticonvulsant activities by means of the most-adopted seizure models—the Maximal electroshock seizure (MES) test. The MES test was carried out according to the standard described in the Antiepileptic Drug Development Program (ADD) of the National Institutes of Health (USA). All the compounds, dissolved in DMSO, were tested with KunMing mice in the 18–22 g weight range purchased from the Laboratory of Animal Research, College of Pharmacy, Yanbian University.

Maximal electroshock seizure (MES) test

The MES test was carried out by the methods described in the ADD of the National Institutes of Health (USA) (Krall *et al.*, 1978; Porter *et al.*, 1984). 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 s. Protection against the spread of MES-induced seizures was defined as the abolition of tonic maximal extension of the hind leg. At 30 min after the administration of the compounds, the activities were evaluated in MES test. In phase-I screening, each compound was administered at the dose levels of 100 mg/kg for evaluating the preliminary anticonvulsant activity. For determination of the median effective dose (ED_{50}) and the median toxic dose (TD_{50}), the phase-II screening was prepared. Groups of ten mice were given a range of intraperitoneal (i.p.) doses of the tested compound until at least three points were established in the range of 10–90% seizure protection or minimal observed neurotoxicity. From the plot of these data, the respective ED_{50} and 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 by the National Institute of Neurological Disorders and Stroke.

Neurotoxicity screening (NT)

The neurotoxicity of the compounds were measured in mice by the rotarod test (Krall *et al.*, 1978; Porter *et al.*, 1984). 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

Chemistry

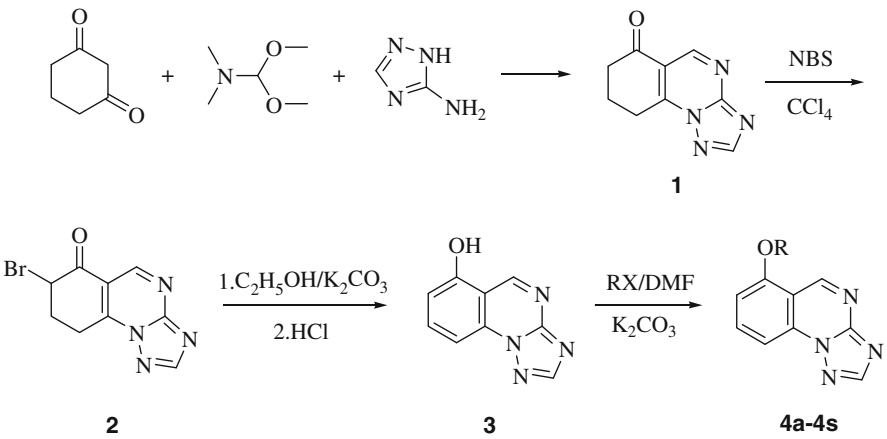
To obtain compounds with anticonvulsant activities, we designed and synthesized several new 6-alkyoxyl[1,2,4]-triazolo[1,5-*a*]quinazoline derivatives. The synthesis of 6-alkyoxyl[1,2,4]triazolo[1,5-*a*]quinazolines has not been reported before this study. As shown in Scheme 1, The starting material cyclohexane-1,3-dione reacted with dimethoxy-*N*, *N*-dimethylmethanemine (DMF–DMA) and aminotriazole to form 8,9-dihydro-[1,2,4]triazolo[1,5-*a*]quinazolin-6(7*H*)-one (**1**) in a good yield of 91.3% (Shikhaliev *et al.*, 2005). In the next step, several methods were tested to achieve the dehydrogenation product of the intermediate **1** (such as treating the intermediate with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), or sulphur powder coupled with nitrobenzene, or $SOCl_2$, and so on); however, no expected product was obtained. Finally, the dehydrogenation product (**3**) was

Table 1 Preliminary evaluation of compounds **4a**–**4s** in the MES in mice (i.p.)

Compounds	R	MES (100 mg/kg)
4a	$-CH_2C_6H_5$	4/5[a]
4b	$-CH_2C_6H_4$(*o*-F)	2/5
4c	$-CH_2C_6H_4$(*m*-F)	0/5
4d	$-CH_2C_6H_4$(*p*-F)	0/5
4e	$-CH_2C_6H_4$(*o*-Cl)	0/5
4f	$-CH_2C_6H_4$(*m*-Cl)	0/5
4g	$-CH_2C_6H_4$(*p*-Cl)	0/5
4h	$-CH_2C_6H_3$(2,4-Cl_2)	0/5
4i	$-CH_2C_6H_4$(*o*-Br)	2/5
4j	$-CH_2C_6H_4$(*p*-CH_3)	1/5
4k	$-CH_2C_6H_4$(*p*-OCH_3)	0/5
4l	$-CH_2C_6H_4$(*p*-CN)	1/5
4m	$-CH_2C_6H_4$(*o*-CN)	1/5
4n	*n*-C_4H_9	0/5
4o	*n*-C_5H_{11}	3/5
4p	*n*-C_6H_{13}	2/5
4q	*n*-C_7H_{15}	2/5
4r	*n*-C_8H_{17}	1/5
4s	*n*-$C_{10}H_{21}$	0/5

[a] Number of animals protected/number of animals tested

Scheme 1 Synthesis route of target compounds (**4a**–**4s**)



R:

4a: $-CH_2Ph$
4b: $-CH_2Ph$(*o*-F)
4c: $-CH_2Ph$(*m*-F)
4d: $-CH_2Ph$(*p*-F)
4e: $-CH_2Ph$(*o*-Cl)
4f: $-CH_2Ph$(*m*-Cl)
4g: $-CH_2Ph$(*p*-Cl)
4h: $-CH_2Ph$(2,4-Cl_2)
4i: $-CH_2Ph$(*o*-Br)
4j: $-CH_2Ph$(*p*-CH_3)
4k: $-CH_2Ph$(*p*-OCH_3)
4l: $-CH_2Ph$(*p*-CN)
4m: $-CH_2Ph$(*o*-CN)
4n: *n*-C_4H_9
4o: *n*-C_5H_{11}
4p: *n*-C_6H_{13}
4q: *n*-C_7H_{15}
4r: *n*-C_8H_{17}
4s: *n*-$C_{10}H_{21}$

Table 2 Quantitative anticonvulsant data of **4a** in mice (i.p.)

Compound	R	ED_{50} (mg/kg)	TD_{50} (mg/kg)	PI (TD_{50}/ED_{50})
4a	$-CH_2C_6H_5$	78.9 (66.9–91.0)	710.1 (615.5–819.1)	9.0
Carbamazepine	–	11.8 (9.7–14.1)	76.1 (69.1–83.7)	6.4
Valproate	–	272 (247–338)	426 (369–450)	1.6

obtained by bromination and dehydrobromination with the total yield of 80%. 7-bromo-8,9-dihydro-[1,2,4]triazolo[1,5-*a*]quinazolin-6(7H)-one (**2**) was obtained by bromination of compound **1** with *N*-bromosuccinimide (NBS) in the CCl_4, which then, under the condition of dehydrobromination, using K_2CO_3 in this case, became [1,2,4]-triazolo[1,5-*a*]quinazolin-6-ol (**3**). Compounds **4a**–**4s** were finally achieved by reacting compound **3** with halogenated hydrocarbon in *N*,*N*-dimethylformamide (DMF) in the presence of K_2CO_3. The structures of new compounds were characterized by spectral methods and elementary analysis. All spectral data corroborated the assumed structures.

Pharmacology

The MES seizure model was used for preliminary (phase **I**) screening of compounds **4a**–**4s**, and the results are presented in Table 1. As shown in Table 1, some of the compounds were active in the MES test at the dose of 100 mg/kg, indicative of their ability to prevent seizure spread. Among the benzyl group-substituted derivatives (**4a**–**4m**), six compounds **4a**, **4b**, **4i**, **4j**, **4l**, and **4m** showed protection against MES-induced seizure in varying degrees at the dose of 100 mg/kg. It seemed that introduction of electron-donor group (**4b**–**4i** and **4l**–**4m**) or electron-withdrawing group (**4j**–**4k**) on the benzyl ring both decreased the anticonvulsant activity (compared with **4a**, non-substituted in the ring of benzyl group). Six alkoxy-substituted derivatives (**4n**–**4s**) were also designed and prepared, all of them expressed anticonvulsant activity except **4n** and **4s**. The length of the alkoxyl chain appeared to have impact on anticonvulsant activity of the alkoxy-substituted derivatives (**4n-4s**). From **4o** to **4s**, as the alkoxyl chain length increased, anticonvulsant activity gradually decreased, with the compound **4o** (with the 6-pentyloxy group) being the most active compound.

Among all the compounds, 6-(benzyloxy)-[1,2,4]triazolo[1,5-*a*]quinazoline (**4a**) exhibited the most potential anticonvulsant activity against MES-induced seizure, which was subjected to phase **II** trials for quantification of its anticonvulsant activity (indicated by ED_{50}) and neurotoxicity (indicated by TD_{50}) in mice. Results of the quantitative test for the **4a**, along with the data on the standard drugs carbamazepine and valproate, are reported in Table 2. 6-(benzyloxy)-[1,2,4]triazolo[1,5-*a*]quinazoline (**4a**), which gave an ED_{50} value of 78.9 mg/kg, displayed a weaker anticonvulsant activity compared with carbamazepine (ED_{50} = 11.8 mg/kg), but a higher activity compared with valproate (ED_{50} = 272 mg/kg). Moreover, compound **4a** showed a better PI compared with carbamazepine and valproate (9.0 vs. 6.4 and 1.6) because of its low neurotoxicity (TD_{50} = 710 mg/kg).

Conclusion

Nineteen novel 6-alkyoxyl[1,2,4]triazolo[1,5-*a*]quinazoline derivatives were synthesized in this study. Their anticonvulsant activities were evaluated using maximal electroshock (MES) test. The results of pharmacology showed that some of the compounds displayed anticonvulsant activities in varying degrees at the dose of 100 mg/kg. Among them, 6-(benzyloxy)-[1,2,4]triazolo[1,5-*a*]quinazoline (**4a**) was the most active compound with the ED_{50} value of 78.9 mg/kg, and PI value of 9.0, which were higher than those of carbamazepine and valproate.

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