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Synthesis and Studies on Anticonvulsant and Antidepressant Activities of 5-Alkoxy-tetrazolo[1,5-a]quinolines

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A series of 5-alkoxy-tetrazolo[1,5-a]quinolines were synthesized to evaluate their anticonvulsant and antidepressant effects. Anticonvulsant effects and neurotoxicity of the compounds when injected intraperitoneally to mice were determined by a maximal electroshock (MES) test and a rotarod test, respectively. Only three of the synthesized compounds (**4a**, **4b**, **4c**) displayed anticonvulsant activity at a dose of 300 mg/kg. Most of the compounds significantly reduced immobility times during the forced swimming test (FST) at a dose of 100 mg/kg, indicative of antidepressant activity. Among the compounds, 5-(2-fluorobenzyloxy)tetrazolo[1,5-a]quinoline (**4k**) reduced immobility time by 66.85% at 30 mg/kg compared with the same dose of Fluoxetine, which reduced immobility time by 52.30%. According to the results of the 5-Hydroxytryptophan induced head-twitch test and yohimbine toxicity potentiation test, the noradrenergic system seems not to be involved in the antidepressant-like effect of compound 4k while the serotonergic system seems a little to be involved.

Key Words: Synthesis, Tetrazolo[1,5-a]quinoline, Anticonvulsant, Antidepressant, Forced swimming test

Introduction

Increasing evidence suggests that quinolinone derivatives possess a broad spectrum of biological activities such as antitumor,[1] antimalarial,[2] antiplatelet,[3] antidepressant,[4] antiulcer,[5] neuroleptic,[6] and cardiac stimulant[7] activities. In our earlier studies, we reported that 6-alkyloxyl-3,4-dihydro-2(1*H*)-quinolinones show good anticonvulsant activities in the MES and PZT-induced seizure test.[8]

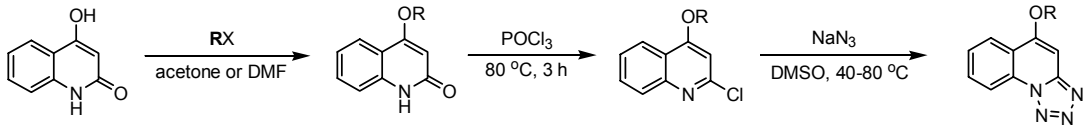
In the followed studies, we synthesized several [1,2,4]triazolo[4,3-a]quinoline derivatives and tested their anticonvulsant activities. We found that 1-substituted-7-benzyloxy-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinolines,[9] 7-alkoxyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinolines[10] and 5-alkoxy-[1,2,4] triazolo[4,3-a]quinolines [In press] had significant anticonvulsant activities.

As part of our continuous effort to find better anticonvulsant agents in this area, a series of new 5-alkoxy-tetrazolo[1,5-a] quinolines were synthesized as outlined in Scheme 1. Anticonvulsant activities and neurotoxicity of the synthesized compounds were determined by the maximal electroshock (MES) test and rotarod test according to the protocols for phase I tests of the antiepileptic drug development (ADD) program, which were developed by the National Institute of Neurological Disorders and Stroke.[11-12]

We also evaluated the antidepressant activities of the synthesized compounds using Porsolt's behavioral despair test/ forced swimming test (FST).[13] As the monoaminergic system is one of the most important targets in the therapies for depression,[14,15] we used two behavioral models to investigate the possible mechanism involving monoaminergic participation in the antidepressant-like effect of the single compound, **4k**, in this study.

Experimental

Chemistry. Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded (in KBr) on a FT-IR1730. ^{1}H-NMR spectra were measured on an AV-300 (Bruker, Switzerland, and all chemical shifts were given in ppm



R:

4a: -CH_3	4e: *n*-C_5H_{11}	4i: *n*-$C_{12}H_{25}$	4m: -$CH_2C_6H_4$ (*p*-F)	4q: -$CH_2C_6H_4$(*o*-Br)
4b: -C_2H_5	4f: *n*-C_6H_{13}	4j: -$CH_2C_6H_5$	4n: -$CH_2C_6H_4$ (*o*-Cl)	4r: -$CH_2C_6H_4$(*p*-Br)
4c: *n*-C_3H_7	4g: *n*-C_7H_{15}	4k: -$CH_2C_6H_4$ (*o*-F)	4o: -$CH_2C_6H_4$ (*m*-Cl)	4s: -$CH_2C_6H_4$(*p*-CH_3)
4d: *n*-C_4H_9	4h: *n*-C_8H_{17}	4l: -$CH_2C_6H_4$ (*m*-F)	4p: -$CH_2C_6H_3$ (*p*-Cl)	

Scheme 1. The synthesis route of the compounds

relative to tetramethysilane. Mass spectra were measured on an HP1100LC (Agilent Technologies, USA). Elemental analyses were performed on a 204Q CHN (Perkin Elmer, USA). Microanalyses of C, N, and H were performed using a Heraeus CHN Rapid Analyzer. The major chemicals were purchased from Sigma-Aldrich Corporation.

Based on previous studies in our laboratory, we designed and prepared a series of 5-alkoxy-tetrazolo[1,5-a]quinolines (**4a-4s**). Target compounds **4a-4s** were synthesized according to Scheme 1. The starting material 4-hydroxyquinolin-2(1*H*)-one reacted with the appropriate alkyl halide or benzyl chloride to obtain 4-alkoxyquinolinones (**2a-2s**) in DMF with stirring and refluxing.[16] Compounds **2a-2s** reacted further with $POCl_3$ at 80 °C to yield 2-chloro-4-alkoxyquinolines (**3a-3s**). Compounds **3a-3s** reacted with sodium azide in DMSO to obtain the target compounds, **4a-4s**.[17]

General procedures for the synthesis of the compounds 2a-2s: A mixture of 4-hydroxyquinolin-2(1*H*)-one (1.00 g, 6.2 mmol) and K_2CO_3 (1.71 g, 12.4 mmol) in DMF (50 mL) was heated at 90 °C for 2 h. The mixture was cooled to room temperature, then appropriate alkyl halides/benzyl chlorides (6.2 mmol) was added, and the mixture was heated at 50 ~ 90 °C for 4 ~ 12 h (TLC monitoring). The mixture was poured into ice water (200 mL); the precipitate that separated was collected by filtration, washed with water and ethyl acetate and then dried to give **2a-2s** with enough purity.

General procedures for the synthesis of the compounds 3a-3s: A solution of **2a-2s** (5 mmol) in appropriate $POCl_3$ and triethylamine (5 mmol) was heated for 3h at 80 °C. After removing the solvent under reduced pressure, the residue was dissolved in dichloromethane (40 mL), washed two times with saturated aqueous $NaHCO_3$ and once with saturated aqueous NaCl. The dichloromethane layer was dried over anhydrous $MgSO_4$. Evaporation of the solvents gave **2a-2u** that was pure enough.

General procedures for the synthesis of the compounds 4a-4s: To a solution of **3a-3s** (5 mmol) in DMSO (50 mL), sodium azide (0.49 g, 7.5 mmol) was added portionwise. The reaction mixture was stirred at 40 ~ 80 °C for 24 h. The white precipitate formed was filtered, washed with water and crystallized from ethyl acetate and dichloromethane. The yield, melting point and spectral data of each compound were given below.

5-Methoxytetrazolo[1,5-a]quinoline (4a): mp 222 ~ 224 °C; yield 81.2%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.14 (s, 3H, OCH_3), 7.01 (s, 1H, CH=), 7.68 (t, 1H, *J* = 7.7 Hz, H-7), 7.86 (t, 1H, *J* = 7.7 Hz, H-8), 8.26 (d, 1H, *J* = 8.3 Hz, H-9), 8.60 (d, 1H, *J* = 8.2 Hz, H-6). IR (KBr) cm^{-1}: 1127, 1224 (C-O-C), 1617 (C=N). MS (*m*/*z*): 201 (M+1). Anal. Calcd. for C10H8N4O: C, 59.99; H, 4.03; N, 27.99. Found: C, 60.11; H, 4.15; N, 27.85.

5-Ethoxytetrazolo[1,5-a]quinoline (4b): mp 216 ~ 218 °C; yield 74.5%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.65 (t, 3H, *J* = 6.98 Hz, CH_3), 4.36 (q, 2H, *J* = 6.97 Hz, OCH_2), 7.02 (s, 1H, CH=), 7.69 (t, 1H, *J* = 7.7 Hz, H-7), 7.87 (t, 1H, *J* = 7.5 Hz, H-8), 8.32 (d, 1H, *J* = 8.1 Hz, H-9), 8.63 (d, 1H, *J* = 8.2 Hz, H-6). IR (KBr) cm^{-1}: 1124, 1226 (C-O-C), 1617 (C=N). MS (*m*/*z*): 215 (M+1). Anal. Calcd. for C11H10N4O: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.85; H, 4.74; N, 26.02.

5-Propoxytetrazolo[1,5-a]quinoline (4c): mp 204 ~ 207 °C; yield 56.5%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.16 (t, 3H, *J* = 7.41 Hz, CH_3), 2.01 (m, 2H, *J* = 6.98Hz, CH_2), 4.21 (t, 2H, *J* = 6.38 Hz, OCH_2), 6.96 (s, 1H, CH=), 7.65 (t, 1H, *J* = 7.7 Hz, H-7), 7.83 (t, 1H, *J* = 7.8 Hz, H-8), 8.26 (d, 1H, *J* = 8.2 Hz, H-9), 8.57 (d, 1H, *J* = 8.3 Hz, H-6). IR (KBr) cm^{-1}: 1125, 1228 (C-O-C), 1618 (C=N). MS (*m*/*z*): 229 (M+1). Anal. Calcd. for C12H12 N4O: C, 63.15; H, 5.30; N, 24.55. Found: C, 63.25; H,5.43; N, 24.38.

5-Butoxytetrazolo[1,5-a]quinoline (4d): mp 178 ~ 181 °C; yield 64.6%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.05 (t, 3H, *J* = 7.38 Hz, CH_3), 1.59 (m, 2H, *J* = 7.46 Hz, CH_2), 1.97 (m, 2H, *J* = 6.94 Hz, CH_2), 4.26 (t, 2H, *J* = 6.33 Hz, OCH_2), 6.98 (s, 1H, CH=), 7.67 (t, 1H, *J* = 7.7 Hz, H-7), 7.85 (t, 1H, *J* = 7.8 Hz, H-8), 8.27 (d, 1H, *J* = 8.1 Hz, H-9), 8.59 (d, 1H, *J* = 8.3 Hz, H-6). IR (KBr) cm^{-1}: 1122, 1229 (C-O-C), 1616 (C=N). MS (*m*/*z*): 243 (M+1). Anal. Calcd. for C13H14N4O: C, 64.45; H, 5.82; N, 23.13. Found: C, 64.65; H,5.88; N, 23.31.

5-(Pentyloxy)tetrazolo[1,5-a]quinoline (4e): mp 158 ~ 160 °C; yield 78.2%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.99 (t, 3H, *J* = 7.13 Hz, CH_3), 1.43-1.61 (m, 4H, CH_2), 2.01 (m, 2H, *J* = 6.92 Hz, CH_2), 4.28 (t, 2H, *J* = 6.38 Hz, OCH_2), 7.00 (s, 1H, CH=), 7.70 (t, 1H, *J* = 7.7 Hz, H-7), 7.88 (t, 1H, *J* = 7.6 Hz, H-8), 8.30 (d, 1H, *J* = 8.2 Hz, H-9), 8.63 (d, 1H, *J* = 8.3 Hz, H-6). IR (KBr) cm^{-1}: 1124, 1226 (C-O-C), 1616 (C=N). MS (*m*/*z*): 257 (M+1). Anal. Calcd. for C14H16N4O: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.65; H,6.36; N, 21.59.

5-(Hexyloxy)tetrazolo[1,5-a]quinoline (4f): mp 148 ~ 150 °C; yield 67.8%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.92 (t, 3H, *J* = 6.87 Hz, CH_3), 1.37-1.59 (m, 6H, CH_2), 1.98 (m, 2H, *J* = 6.97 Hz, CH_2), 4.25 (t, 2H, *J* = 6.38 Hz, OCH_2), 6.97 (s, 1H, CH=), 7.66 (t, 1H, *J* = 7.6 Hz, H-7), 7.84 (t, 1H, *J* = 7.4 Hz, H-8), 8.26 (d, 1H, *J* = 8.1 Hz, H-9), 8.58 (d, 1H, *J* = 8.3 Hz, H-6). IR (KBr) cm^{-1}: 1129, 1225 (C-O-C), 1617 (C=N). MS (*m*/*z*): 271 (M+1). Anal. Calcd. for C15H18N4O: C, 66.64; H, 6.71; N, 20.73. Found: C, 66.78; H,6.85; N, 20.51.

5-(Heptyloxy)tetrazolo[1,5-a]quinoline (4g): mp 145 ~ 147 °C; yield 78.0%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.90 (t, 3H, *J* = 6.78 Hz, CH_3), 1.35-1.57 (m, 8H, CH_2), 1.98 (m, 2H, *J* = 7.06 Hz, CH_2), 4.25 (t, 2H, *J* = 6.24 Hz, OCH_2), 6.97 (s, 1H, CH=), 7.67 (t, 1H, *J* = 7.6 Hz, H-7), 7.85 (t, 1H, *J* = 7.5 Hz, H-8), 8.27 (d, 1H, *J* = 8.0 Hz, H-9), 8.59 (d, 1H, *J* = 8.2 Hz, H-6). IR (KBr) cm^{-1}: 1130, 1221 (C-O-C), 1618 (C=N). MS (*m*/*z*): 285 (M+1). Anal. Calcd. for C16H20N4O: C, 67.58; H, 7.09; N, 19.70. Found: C, 67.67; H,7.23; N, 19.59.

5-(Octyloxy)tetrazolo[1,5-a]quinoline (4h): mp 149 ~ 152 °C; yield 83.7%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, 3H, *J* = 6.61 Hz, CH_3), 1.32-1.58 (m, 10H, CH_2), 1.99 (m, 2H, *J* = 7.32 Hz, CH_2), 4.27 (t, 2H, *J* = 6.41 Hz, OCH_2), 6.70 (s, 1H, CH=), 7.69 (t, 1H, *J* = 7.7 Hz, H-7), 7.87 (t, 1H, *J* = 7.7 Hz, H-8), 8.30 (d, 1H, *J* = 8.2 Hz, H-9), 8.63 (d, 1H, *J* = 8.4 Hz, H-6). IR (KBr) cm^{-1}: 1128, 1225 (C-O-C), 1616 (C=N). MS (*m*/*z*): 299 (M+1). Anal. Calcd. for C17H22N4O: C, 68.43; H, 7.43; N, 18.78. Found: C, 68.67; H,7.61; N, 18.63.

5-(Dodecyloxy)tetrazolo[1,5-a]quinoline (4i): mp 108 ~ 110 °C; yield 88.6%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, 3H, *J* = 6.77 Hz, CH_3), 1.27-1.57 (m, 18H, CH_2), 1.99 (m, 2H, *J* = 6.95 Hz, CH_2), 4.27 (t, 2H, *J* = 6.36 Hz, OCH_2), 7.00 (s, 1H, CH=), 7.69 (t, 1H, *J* = 7.8 Hz, H-7), 7.87 (t, 1H, *J* = 7.3 Hz, H-8),

8.30 (d, 1H, J = 8.2 Hz, H-9), 8.63 (d, 1H, J = 8.2 Hz, H-6). IR (KBr) cm^{-1}: 1131, 1222 (C-O-C), 1615 (C=N). MS (*m/z*): 355 (M+1). Anal. Calcd. for C21H30N4O: C, 71.15; H, 8.53; N, 15.80. Found: C, 71.32; H, 8.64; N, 15.59.

5-(Benzyloxy)tetrazolo[1,5-a]quinoline (4j): mp 232 ~ 233 °C; yield 73.8%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.37 (s, 2H, OCH_2), 7.11 (s, 1H, CH=), 7.41-7.54 (m, 5H, Ar-H), 7.69 (t, 1H, J = 7.8 Hz, H-7), 7.86 (t, 1H, J = 7.7 Hz, H-8), 8.35 (d, 1H, J = 8.3 Hz, H-9), 8.64 (d, 1H, J = 8.3 Hz, H-6). IR (KBr) cm^{-1}: 1128, 1226 (C-O-C), 1621 (C=N). MS (*m/z*): 277 (M+1). Anal. Calcd. for C16H12N4O: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.63; H, 4.45; N, 20.21.

5-(2-Fluorobenzyloxy)tetrazolo[1,5-a]quinoline (4k): mp 243 ~ 245 °C; yield 64.3%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ5.44 (s, 2H, OCH_2), 7.15 (s, 1H, CH=), 7.21 (t, 1H, J = 7.9 Hz, Ar-H), 7.25 (d, 1H, J = 8.2 Hz, Ar-H), 7.42 (dd, 1H, J_1 = 6.1 Hz, J_2 = 13.3 Hz, Ar-H), 7.56 (t, 1H, J = 7.4 Hz, Ar-H), 7.69 (t, 1H, J = 7.7 Hz, H-7), 7.88 (t, 1H, J = 7.8 Hz, H-8), 8.31 (d, 1H, J = 8.3 Hz, H-9), 8.64 (d, 1H, J = 8.2 Hz, H-6). IR (KBr) cm^{-1}: 1128, 1227 (C-O-C), 1622 (C=N). MS (*m/z*): 295 (M+1). Anal. Calcd. for C16H11FN4O: C, 65.30; H, 3.77; N, 19.04. Found: C, 65.43; H, 3.86; N, 18.92.

5-(3-Fluorobenzyloxy)tetrazolo[1,5-a]quinoline (4l): mp 267 ~ 269 °C; yield 78.4%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.36 (s, 2H, OCH_2), 7.16 (s, 1H, CH=), 7.05 (t, 1H, J = 8.6 Hz, Ar-H), 7.21 (d, 1H, J = 9.7 Hz, Ar-H), 7.27 (d, 1H, J = 7.1 Hz, Ar-H), 7.36 (dd, 1H, J_1 = 7.8 Hz, J_2 = 13.7 Hz, Ar-H), 7.67 (t, 1H, J = 7.7 Hz, H-7), 7.85 (t, 1H, J = 7.4 Hz, H-8), 8.27 (d, 1H, J = 8.2 Hz, H-9), 8.52 (d, 1H, J = 8.3 Hz, H-6). IR (KBr) cm^{-1}: 1128, 1228 (C-O-C), 1622 (C=N). MS (*m/z*): 295 (M+1). Anal. Calcd. for C16H11FN4O: C, 65.30; H, 3.77; N, 19.04. Found: C, 65.45; H, 3.89; N, 18.91.

5-(4-Fluorobenzyloxy)tetrazolo[1,5-a]quinoline (4m): mp 262 ~ 264 °C; yield 69.8%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.33 (s, 2H, OCH_2), 7.15 (s, 1H, CH=), 7.14 (dd, 2H, J_1 = 8.4 Hz, J_2 = 15.2 Hz, Ar-H), 7.51 (dd, 1H, J_1 = 8.4 Hz, J_2 = 5.4 Hz, Ar-H), 7.69 (t, 1H, J = 7.7 Hz, H-7), 7.89 (t, 1H, J = 7.6 Hz, H-8), 8.31 (d, 1H, J = 8.3 Hz, H-9), 8.65 (d, 1H, J = 8.3 Hz, H-6). IR (KBr) cm^{-1}: 1128, 1227 (C-O-C), 1623 (C=N). MS (*m/z*): 295 (M+1). Anal. Calcd. for C16H11FN4O: C, 65.30; H, 3.77; N, 19.04. Found: C, 65.47; H, 3.84; N, 18.96.

5-(2-Chlorobenzyloxy)tetrazolo[1,5-a]quinoline (4n): mp 204 ~ 206 °C; yield 71.7%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.47 (s, 2H, OCH_2), 7.13 (s, 1H, CH=), 7.26-7.37 (m, 2H, Ar- H), 7.46-7.61 (m, 2H, Ar-H), 7.71 (t, 1H, J = 7.6 Hz, H-7), 7.89 (t, 1H, J = 7.6 Hz, H-8), 8.35 (d, 1H, J = 8.3 Hz, H-9), 8.65 (d, 1H, J = 8.2 Hz, H-6). IR (KBr) cm^{-1}: 1131, 1230 (C-O-C), 1624 (C=N). MS (*m/z*): 312 (M+1). Anal. Calcd. for C16H11ClN4O: C, 61.84; H, 3.57; N, 18.03. Found: C, 61.97; H, 3.69; N, 17.91.

5-(3-Chlorobenzyloxy)tetrazolo[1,5-a]quinoline (4o): mp 265 ~ 267 °C; yield 79.4%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.35 (s, 2H, OCH_2), 7.09 (s, 1H, CH=), 7.39-7.41 (m, 3H, Ar-H), 7.53 (s, 1H, Ar-H), 7.72 (t, 1H, J = 8.0 Hz, H-7), 7.90 (t, 1H, J = 7.8 Hz, H-8), 8.34 (d, 1H, J = 8.0 Hz, H-9), 8.65 (d, 1H, J = 8.4 Hz, H-6), 7.72-8.67 (m, 4H, Ar-H). IR (KBr) cm^{-1}: 1130, 1228 (C-O-C), 1625 (C=N). MS (*m/z*): 312 (M+1). Anal. Calcd. for C16H11ClN4O: C, 61.84; H, 3.57; N, 18.03. Found: C, 61.94; H, 3.66; N, 17.89.

5-(4-Chlorobenzyloxy)tetrazolo[1,5-a]quinoline (4p): mp 285 ~ 287 °C; yield 69.8%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.34 (s, 2H, OCH_2), 7.09 (s, 1H, CH=), 7.44 (d, 2H, J = 8.9 Hz, Ar-H), 7.48 (d, 2H, J = 8.9 Hz, Ar-H), 7.70 (t, 1H, J = 7.7 Hz, H-7), 7.90 (t, 1H, J = 7.5 Hz, H-8), 8.31 (d, 1H, J = 8.2 Hz, H-9), 8.65 (d, 1H, J = 8.3 Hz, H-6). IR (KBr) cm^{-1}: 1131, 1230 (C-O-C), 1624 (C=N). MS (*m/z*): 312 (M+1). Anal. Calcd. for C16H11ClN4O: C, 61.84; H, 3.57; N, 18.03. Found: C, 61.99; H, 3.72; N, 17.91.

5-(2-Bromobenzyloxy)tetrazolo[1,5-a]quinoline (4q): mp 220 ~ 222 °C; yield 74.2%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.45 (s, 2H, OCH_2), 7.12 (s, 1H, CH=), 7.29 (t, 1H, J = 8.5 Hz, Ar-H), 7.40 (t, 1H, J = 7.2 Hz, Ar-H), 7.58 (d, 1H, J = 7.5 Hz, Ar-H), 7.68 (d, 1H, J = 7.5 Hz, Ar-H), 7.71 (t, 1H, J = 7.0 Hz, H-7), 7.90 (t, 1H, J = 7.8 Hz, H-8), 8.37 (d, 1H, J = 8.1 Hz, H-9), 8.65 (d, 1H, J = 8.3 Hz, H-6). IR (KBr) cm^{-1}: 1130, 1229 (C-O-C), 1622 (C=N). MS (*m/z*): 356 (M+1). Anal. Calcd. for C16H11 BrN4O: C, 54.10; H, 3.12; N, 15.77. Found: C, 54.27; H, 3.32; N, 15.53.

5-(4-Bromobenzyloxy)tetrazolo[1,5-a]quinoline (4r): mp 286 ~ 287 °C; yield 80.2%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.32 (s, 2H, OCH_2), 7.09 (s, 1H, CH=), 7.41 (d, 2H, J = 8.2 Hz, Ar-H), 7.60 (d, 2H, J = 8.2 Hz, Ar-H), 7.70 (t, 1H, J = 7.8 Hz, H-7), 7.90 (t, 1H, J = 7.8 Hz, H-8), 8.31 (d, 1H, J = 8.3 Hz, H-9), 8.65 (d, 1H, J = 8.4 Hz, H-6). IR (KBr) cm^{-1}: 1130, 1227 (C-O-C), 1623 (C=N). MS (*m/z*): 356 (M+1). Anal. Calcd. for C16H11 BrN4O: C, 54.10; H, 3.12; N, 15.77. Found: C,54.23; H, 3.28; N, 15.56.

5-(4-Methylbenzyloxy)tetrazolo[1,5-a]quinoline (4s): mp 240 ~ 242 °C; yield 76.9%. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.33 (s, 2H, OCH_2), 7.10 (s, 1H, CH=), 7.26 (d, 2H, J = 7.9 Hz, Ar-H), 7.41 (d, 2H, J = 7.9 Hz, Ar-H), 7.68 (t, 1H, J = 7.7 Hz, H-7), 7.87 (t, 1H, J = 7.8 Hz, H-8), 8.33 (d, 1H, J = 8.1 Hz, H-9), 8.63 (d, 1H, J = 8.3 Hz, H-6). IR (KBr) cm^{-1}: 1126, 1225 (C-O-C), 1620 (C=N). MS (*m/z*): 291 (M+1). Anal. Calcd. for C17H14 N4O: C, 70.33; H, 4.86; N, 19.30. Found: C, 7.48; H, 3.94; N, 19.11.

Pharmacology. The anticonvulsant evaluation was undertaken following the protocols of the phase I tests of the ADD (Antiepileptic Drug Development) program.[11,12] Antidepressant activity of the derivatives was measured by FST.[13] The tested compounds were suspended in aqueous Tween 80 (3% v/v, 0.9% NaCl). KunMing mice (22 ± 2 g) were used for all pharmacology experiments. Mice were housed collectively in groups of ten in polycarbonate cages. They were maintained on a 12 h light/dark cycle in a temperature controlled (23 ± 2 °C) laboratory. Food and water were available ad libitum.

Anticonvulsant activity: All compounds were administered intraperitoneally (i.p.) at a volume of 0.005 mL/g body weight for mice at doses of 30, 100, or 300 mg/kg to three animals. Activity was evaluated using the MES test. The rotarod test was used to investigate the neurotoxicity of the compounds.

Maximal electroshock seizure (MES) test – 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 the hind-leg tonic extension component of the seizure.

Neurotoxicity – The rotarod test was used to evaluate neurotoxicity. The animal was placed on a 1 inch diameter wooden rod rotating at 6 rpm. Normal mice remain on the rod at this speed. Failure of the animal to remain on the rod for 1 min was taken to be a sign of neurologic toxicity.

Antidepressant activity: All compounds were administered intraperitoneally at a volume of 0.005 mL/g body weight for male mice at doses of 100 mg/kg to six animals. Antidepressant activity was evaluated using the FST test.

Forced swimming test (FST) – Male KunMing mice (20 - 24 g) were used in the forced swimming test.[13] On testing day, mice were assigned to different groups (n = 6 for each group). The synthesized compounds and the standard drug Fluoxetine were given as an intraperitoneal injection to mice. Control animals received 3% aqueous solution of Tween 80. Thirty minutes later, the mice were dropped one at a time into a Plexiglas cylinder (25 cm height, diameter 10 cm containing water to a height of 10 cm at 23 ~ 25 ^{o}C) and observed for 6 min. After the first 2 min of the initial vigorous struggling, the animals were immobile. A mouse was judged immobile if it floated in the water in an upright position and made only slight movements to prevent sinking. The total duration of immobility was recorded during the last 4 min of the 6 min test.

5-Hydroxytryptophan (5-HTP) induced mouse head-twitch test – To investigate whether the serotonergic system was involved in the antidepressant-like effect of compound **4k**, we performed a 5-HTP induced head-twitch test.[18,19] Mice were administered intraperitoneally with compound **4k** (100 mg/kg), Fluoxetine (FLU) (30 mg/kg) or 3% aqueous solution of Tween 80 30 min before DL-5-HTP (300 mg/kg, i.p.). Immediately after the second injection, mice were placed into plastic cages. Ten minutes later, the cumulative number of head twitches (rapid movements of the head with little or no involvement of the trunk) was recorded for 6 min.

Yohimbine toxicity potentiation test – To reveal whether the noradrenergic system is involved in the antidepressant-like effect of the compound **4k**, the yohimbine toxicity potentiation test was performed.[18,19] Mice were treated with compound **4k** (30, 50 and 100 mg/kg), clomipramine (30 mg/kg) or 3% aqueous solution of Tween 80 intraperitoneal injection 0.5 h prior to yohimbine administration (25 mg/kg, subcutaneous injection). The number of dead mice was calculated during a 20 h period after the injection of yohimbine.

Results and Discussion

As shown in Scheme 1, a series of 5-alkoxy-tetrazolo[1,5-a] quinolines were synthesized. The structures of new compounds were characterized by spectral methods and elementary analysis. All spectral data corroborated the assumed structures.

Anticonvulsant activities of the synthesized compounds were assessed by maximal electroshock (MES) as shown in Table 1. According to the results of the experiments, it is clear that anticonvulsant activities of all compounds were weak. Only 5-methoxytetrazolo[1,5-a]quinoline (**4a**), 5-ethoxytetrazolo[1, 5-a]quinoline (**4b**) and 5-propoxytetrazolo[1,5-a]quinoline (**4c**) exhibited activity against MES induced seizures at 300 mg/kg dose level. Neurotoxicity was not observed in any of the synthesized compounds at a dose of 300 mg/kg (Table 1).

Antidepressant activities of the compounds were investigated with the forced swimming test (FST). FST, a behavioral test, is commonly used to predict the activity of antidepressants.[13]

Table 1. Phase I anticonvulsant screening of the compounds

Compounds	MES[a]						Toxicity[b]					
	1/2 h			4 h			1/2 h			4 h		
	30	100	300	30	100	300	30	100	300	30	100	300
4a	0/3	0/3	***2/3***	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4b	0/3	0/3	***3/3***	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4c	0/3	0/3	***2/3***	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4d	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4e	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4f	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4g	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4h	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4i	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4j	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4k	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4l	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4m	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4n	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4o	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4p	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4q	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4r	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
4s	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3

[a]Maximal electroshock test (number of animals protected/number of animals tested). [b]Rotarod toxicity (number of animals exhibiting toxicity/number of animals tested).

Table 2. Antidepressant activities of the compounds evaluated by FST

Compounds	Dose (mg/kg)	Duration of immobility (s)	Change from control (%)
4a	100	138.5 ± 13.2[a]	−13.87
4b	100	105.8 ± 14.6[a]	−34.20
4c	100	141.7 ± 20.2	−11.88
4d	100	145.8 ± 23.3	−9.33
4e	100	115.3 ± 16.4[a]	−28.30
4f	100	155.8 ± 15.0	−3.11
4g	100	41.7 ± 11.7[a]	−74.07
4h	100	91.7 ± 19.7[a]	−42.97
4i	100	34.2 ± 4.9[a]	−78.73
4j	100	57.5 ± 14.1[a]	−64.24
4k	100	24.2 ± 7.4[a]	−84.95
	30	52.3 ± 16.6[a]	−66.85
4l	100	85.5 ± 12.5[a]	−46.83
4m	100	120.2 ± 14.2[a]	−25.25
4n	100	99.7 ± 12.8[a]	−38.00
4o	100	95.2 ± 28.3[a]	−40.80
4p	100	149.7 ± 17.9	−6.90
4q	100	158.3 ± 16.4	−1.55
4r	100	155.8 ± 13.4	−3.11
4s	100	153.8 ± 19.2	−4.35
Fluoxetine	30	76.7 ± 13.9[a]	−52.30
Control	5 mL/kg	160.8 ± 4.6	−

Values represent the mean ± S.E.M. (n = 6). [a]Significantly compared to control (student-t test; $p < 0.01$).

Table 3. Effect of 4 k (30, 50 and 100 mg/kg, i.p.) and Clomipramine (30 mg/kg, i.p.) on yohimbine-induced lethality in mice

Group	Dose (mg/kg)	Yohimbine (mg/kg)	Lethality	
			Total	Died
Control		25	8	1
Clomipramine	30	25	8	6[a]
4k	30	25	8	0
4k	50	25	8	1
4k	100	25	8	1

n = 8. [a]$p < 0.05$ compared with control (Fisher's exact test).

This method may also predict the antidepressant potency in humans.[20] The obtained data on the antidepressant activities of the compounds and fluoxetine are given in Table 2. In this study, all of the compounds except **4c**, **4d**, **4f**, **4p**, **4q**, **4r** and **4s** significantly reduced the duration of immobility times at 100 mg/kg compared to control ($p < 0.01$). Among all synthesized compounds, 5-(2-fluorobenzyloxy)tetrazolo[1,5-a]quinoline (**4k**) was the most promising compound and significantly reduced the duration of immobility time by 66.85% at a dose of 30 mg/kg compared with the control ($p < 0.01$).

Analyzing the antidepressant activities of synthesized compounds **4a**-**4s**, the following structure activity relationship was gained. From compounds **4a**-**4i**, as the length of the alkyl chain increased from one to 12, alternating variations of activity were observed. Compounds **4j**-**4s** were substituted by benzyl groups. Compared with compound **4j**, each compound with an F group

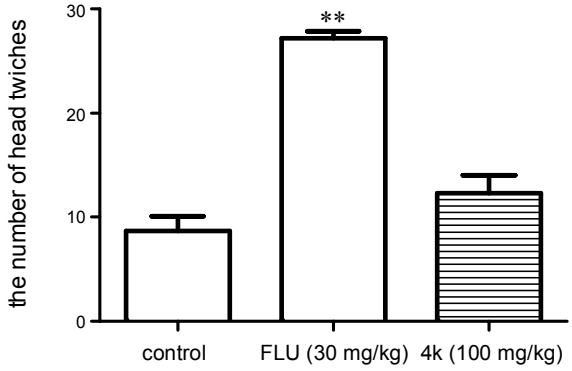


Figure 1. Effect of 4k (100 mg/kg, i.p.) or fluoxetine (FLU, 30 mg/kg, i.p.) on number of 5-HTP-induced head twitches in mice. Each column represents the mean ± S.E.M., n = 10. **$p < 0.01$, compared with control (Student t-test).

on the benzyl ring, except *p*-F, exhibited enhanced antidepressant activity. In contrast, compounds carrying *p*-Cl or *p*-Br on the benzyl ring showed lower activity. Comparisons of the halogen substituted derivatives indicated that different halides contributed to the anticonvulsant activity with a rank order of F > Cl > Br. Compared to the derivatives with different F-substituted positions on the benzyl ring, their rank of activity order was *o*-F > *m*-F > *p*-F. Rank of activity order of the Cl substituted derivatives was *o*-Cl = *m*-Cl >> *p*-Cl.

To investigate possible serotonergic involvement in the antidepressant-like effect of the compound **4k**, the 5-HTP induced head-twitch test was performed as shown in Figure 1. Pretreatment with FLU (30 mg/kg) significantly increased the cumulative number of head twitches, whereas pretreatment with **4k** (100 mg/kg) had little such effect. The results may indicate that there was little involvement of the serotonergic system in the antidepressant-like effects of compound **4k**.

Yohimbine can produce excessive noradrenaline release because it acts as an antagonist on presynaptic α-adrenoceptors and may be used to evaluate the noradrenergic effects of antidepressants.[21] To reveal whether the antidepressant-like effect of the compound **4k** is related to the noradrenergic system, the yohimbine toxicity potentiation test was performed and as shown in Table 3. Compound **4k** does not increase mouse mortality induced by yohimbine at doses of 30, 50, or 100 mg/kg, indicating that the noradrenergic system may not be involved in the antidepressant-like effect of compound **4k**.

Conclusion

A series of 5-alkoxy-tetrazolo[1,5-a]quinolines were synthesized, and their spectral data corresponded with the assumed structures. Only three of the synthesized compounds (**4a**, **4b**, **4c**) have shown anticonvulsant activity, however, the synthesized compounds have possessed remarkable antidepressant activity in general. Therefore, they may be really promising compounds for the treatment of depression. In fact, 5-(2-fluorobenzyloxy)tetrazolo[1,5-a]quinoline (**4k**) was the most promising compound and reduced immobility time by 66.85% at 30 mg/kg. Efforts to explore the possible antidepressant mecha-

nism of the compound **4k** indicated that the noradrenergic system seems not to be involved in the antidepressant-like effect of compound **4k** and the serotonergic system seems a little to be involved. Further studies should be initiated to reveal the mechanism of the antidepressant-like effect of the compound **4k**.

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