Full Paper

Synthesis and Evaluation on Anticonvulsant and Antidepressant Activities of 5-Alkoxy-tetrazolo[1,5-*a*]quinazolines

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Several 5-alkoxy-tetrazolo[1,5-*a*]quinazoline derivatives have been synthesized by reacting 2,4-dichloroquinazoline with various phenols or aliphatic alcohol and then with sodium azide. The structures of these compounds have been confirmed by IR, MS, ^{1}H-NMR, and elementary analysis. Anticonvulsant activities were evaluated using the maximal electroshock (MES) test. Most of the synthesized compounds displayed weak anticonvulsant activity at a dose of 300 mg/kg. Antidepressant activities were investigated by forced swimming test. Two compounds, namely 5-(hexyloxy)tetrazolo[1,5-*a*]quinazoline and 5-(4-methoxyphenoxy)tetrazolo[1,5-*a*]quinazoline, showed significant antidepressant activity, which decreased the immobility time by 62.2 and 51.7% at 100 mg/kg dose level.

Keywords: Anticonvulsant / Antidepressant / Forced swimming test / Quinazoline / Tetrazole

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Introduction

In our earlier studies, we reported that 6-alkyloxyl-3,4-dihydro-2(1*H*)-quinolinones **I** showed good anticonvulsant activities in the maximal electroshock (MES) test [1]. In the following study, we introduced some heterocyclic rings to the first and second position of compounds **I** such as triazoles **II**, triazolones **III**, and triazones **IV** (Fig. 1) to investigate their contribution to the anticonvulsant activity [2–9]. Then, we researched the synthesis and anticonvulsant activities of the compounds **V** (Fig. 1), namely the bio-isoterism of compound **II** [10]. Research results indicate that the introduction of a heterocyclic ring to the first and second position of quinoline or phthalazine cause a remarkable increase in anticonvulsant activity.

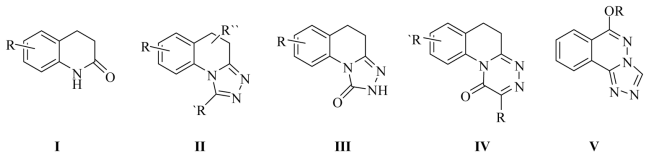
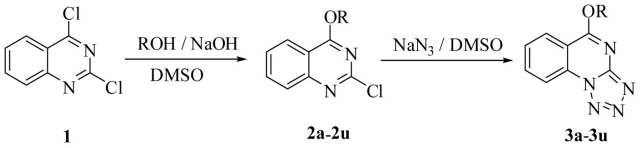


Figure 1. Structure of compound **I**, **II**, **III**, **IV**, and **V**.



Scheme 1. The synthesis route of the compounds.

Consequently, as part of our continuous effort to find better anticonvulsant agents among these compounds, a series of new 5-alkoxy-tetrazolo[1,5-*a*]quinazolines were synthesized as outlined in Scheme 1 and evaluated for their anticonvulsant activity using the MES test. Some interactions appear between anticonvulsant and antidepressant drugs [11]. For example, many anticonvulsants possess an antidepressive-like effect such as oxcarbaze-

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Abbreviations: forced swimming test (FST); maximal electroshock (MES); monoamine oxidase (MAO)

pine [12], piperine [13], lamotrigine [14], and some antidepressants also exhibit anticonvulsant activity such as doxepin [15]. Taking this into account, the antidepressant activities of the synthesized compounds were also determined by forced swimming test (FST).

Results and discussion

Synthesis

Compounds were prepared as outlined in Scheme 1. Compounds **2a–2u** were prepared by the reaction of compound **1** with various phenols or aliphatic alcohol in dimethyl sulfoxide in the presence of sodium hydroxide, which reacted further with sodium azide to afford compounds **3a–3u** [16]. Structures of these compounds have been confirmed by IR, MS, ^{1}H-NMR, and elementary analysis.

Pharmacological evaluations

Anticonvulsant activities of the synthesized compounds were determined by maximal MES test according to the phase-I tests of the anti-epileptic drug development (ADD) program [17, 18]. These compounds were also screened for their antidepressant activities in mice using the FST. The forced swimming test is a behavioral test used to predict the efficacy of antidepressant treatments [19]. It is used effectively in predicting the activity of a wide variety of antidepressants such as MAO inhibitors [20] and typical antidepressants [21]. It is also has a good predictive value for the antidepressant potency in humans [22].

The results of the preliminary anticonvulsant activities of **3a–3u** are summarized in Table 1. As shown in Table 1, compounds **3c**, **3e**, **3i**, **3k**, **3l**, **3p**, and **3q** exhibited completely protection at a dose of 300 mg/kg in the MES test. Compounds **3f**, **3g**, **3h**, **3j**, **3n**, **3o**, and **3s** displayed weak anticonvulsant activities. However, no compound exhibited activities at a dose of 30 mg/kg. Among all the compounds, **3b** protected completely against MES-induced seizure at a dose of 100 mg/kg, and is the best active compound in this series.

Taking into account that interactions appear between anticonvulsant and antidepressant drugs [11], antidepressant activities of the compounds were also investigated with the forced swimming test (FST) and the results revealed that the compounds prepared displayed antidepressant activitiy. The obtained data on antidepressant activities of the compounds and reference drug (Fluoxetine) are given in Table 2. In this study, all of the compounds except **3a**, **3b**, **3d**, **3k**, **3p**, and **3r** significantly reduced the duration of immobility times at 100 mg/kg compared to control ($p < 0.05$). Compounds **3c**, **3e–3i**, **3l**, and **3s** significantly reduced the duration of immobility times at 100 mg/kg dose level compared to control with $p < 0.01$. Among all synthesized compounds, 5-(hexyloxy)-tetrazolo[1,5-*a*]quinazoline **3f** was the most promising compound and reduced the immobility times by 66.9% at 100 mg/kg compared with Fluoxetine reducing immobility time by 52.3% at 30 mg/kg.

Table 1. Anticonvulsant activities of the compounds in MES.

Compound	R	MES[a]		
		30	100	300
3a	-CH_3	0/3	1/3	–[b]
3b	-C_2H_5	0/3	3/3	–[b]
3c	*i*-C_3H_7	0/3	2/3	3/3
3d	*n*-C_4H_9	0/3	0/3	0/3
3e	*n*-C_5H_{11}	0/3	1/3	3/3
3f	*n*-C_6H_{13}	0/3	0/3	2/3
3g	*n*-C_7H_{15}	0/3	0/3	2/3
3h	*n*-C_8H_{17}	0/3	0/3	1/3
3i	*n*-C_9H_{19}	0/3	2/3	3/3
3j	*n*-$C_{10}H_{21}$	0/3	0/3	1/3
3k	-C_6H_5	0/3	2/3	3/3
3l	-C_6H_4(*p*-OCH_3)	0/3	2/3	3/3
3m	-C_6H_4(*o*-OCH_3)	0/3	0/3	0/3
3n	-C_6H_4(*p*-CH_3)	0/3	0/3	2/3
3o	-C_6H_4(*o*-CH_3)	0/3	0/3	2/3
3p	-C_6H_4(*m*-CH_3)	0/3	2/3	3/3
3q	-C_6H_4(*p*-Cl)	0/3	1/3	3/3
3r	-C_6H_4(*o*-Cl)	0/3	0/3	0/3
3s	-C_6H_4(*m*-Cl)	0/3	0/3	1/3
3t	C_6H_3(2,4-Cl_2)	0/3	0/3	0/3
3u	-C_6H_4(*p*-F)	0/3	2/3	0/3

[a] Maximal electroshock test (number of animals protected/number of animals tested);
[b] dead.

Analyzing the antidepressant activities of the synthesized compounds **3a–3u**, the following SAR was gained. The length of the alkyl chain appears to have a direct impact on the antidepressant activity of the 5-alkoxyl derivatives. From compound **3a** to **3j**, as the alkyl-chain length increased, immobility times gradually decreased with compound **3f** (with the *n*-hexyloxy substituted group) being the most active. The trend reversed, however, when the alkyl chain had more than six carbons. In compounds **3k–3u** a substitution with phenoxyl groups was undertaken. Among of these compounds, compound **3l** (with *p*-OCH_3 phenoxyl-substituted group) was the most active compound, reducing the immobility time by 51.7%. Compound **3m** (with *o*-OCH_3 phenoxyl-substituted group) is less active compared with **3l**. Compared to the derivatives with different CH_3-substituted positions on the phenyl group (**3n**, **3o**, and **3p**), their rank of activity order was *p*-CH_3 > *o*-CH_3 > *m*-CH_3.

Table 2. Antidepressant activities of the compounds in FST.

Compound	R	Duration of immobility (s)	Change from control (%)
3a	-CH_3	–	–
3b	-C_2H_5	–	–
3c	*i*-C_3H_7	116.3 ± 17.63 **	−29.3
3d	*n*-C_4H_9	–	–
3e	*n*-C_5H_{11}	112.3 ± 14.91 **	−31.8
3f	*n*-C_6H_{13}	62.2 ± 12.58 **	−62.2
3g	*n*-C_7H_{15}	109.0 ± 18.72 **	−33.8
3h	*n*-C_8H_{17}	106.8 ± 28.86 **	−35.1
3i	*n*-C_9H_{19}	130.17 ± 15.03 **	−21.0
3j	*n*-$C_{10}H_{21}$	133.3 ± 18.57 *	−19.0
3k	-C_6H_5	–	–
3l	-C_6H_4(*p*-OCH_3)	85.2 ± 13.42 **	−51.7
3m	-C_6H_4(*o*-OCH_3)	125.8 ± 18.86 *	−23.7
3n	-C_6H_4(*p*-CH_3)	118.8 ± 27.13 *	−27.8
3o	-C_6H_4(*o*-CH_3)	125.8 ± 23.45 *	−23.6
3p	-C_6H_4(*m*-CH_3)	131.3 ± 24.97	−20.2
3q	-C_6H_4(*p*-Cl)	131.0 ± 22.44 *	−20.5
3r	-C_6H_4(*o*-Cl)	129.7 ± 27.93	−21.3
3s	-C_6H_4(*m*-Cl)	113.0 ± 18.79 **	−31.4
3t	C_6H_3(2,4-Cl_2)	136.5 ± 12.96 *	−17.1
3u	-C_6H_4(*p*-F)	124.3 ± 23.17 *	−24.5
Fluoxetine		61.3 ± 23.71 **	−62.8
Control		164.7 ± 15.04	–

Values represent the mean ± S.E.M. (n = 6).
Compounds prepared were administered at 100 mg/kg, Fluoxetine was administered at 30 mg/kg;
* significantly compared to control (Student's t-test; $0.01 < p < 0.05$);
** very significantly compared to control (Student's t-test; $p < 0.01$); – toxicity in mice.

Comparisons of the halogen-substituted derivatives indicated that different halogen atoms contributed to the antidepressant activity differently. Compared to the derivatives with different Cl-substituted positions on the phenyl ring (**3q**, **3r**, **3s**, and **3t**), their rank-of-activity order was *m*-Cl > *o*-Cl ≈ *p*-Cl > 2,4-Cl_2. Compound **3u** (with *p*-F-phenoxyl-substituted group) possess activity reducing the immobility times by 24.5%.

In conclusion, a series of 5-alkoxy-tetrazolo[1,5-*a*]quinazolines were synthesized and their anticonvulsant and antidepressant activities were investigated. Most of them showed weak anticonvulsant activity at a dose of 300 mg/kg. However, most of them exhibited significant antidepressant activities and 5-(hexyloxy)tetrazolo[1,5-a]quinazoline **3f** was the most promising compound decreasing immobility time by 62.2% at 100 mg/kg dose level. Further experiments are needed to explore the possible antidepressant mechanism and the work will be reported in detail in a series of forthcoming papers.

Experimental

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 an AV-300 (Bruker, Switzerland), and all chemical shifts were given in ppm relative to tetramethysilane. Mass spectra were measured on an HP1100*LC* (Agilent Technologies, USA). Elemental analyses were performed on a 204Q CHN (Perkin Elmer). Microanalyses of C, N, and H were performed using a Heraeus CHN Rapid Analyzer (Heraeus, Hanau, Germany). The major chemicals were purchased from Aldrich Chemical Corporation.

*General procedure for the synthesis of 5-alkoxy-tetrazolo[1,5-a]quinazoline **3a–3u***

The starting compound 2,4-dichloroquinazoline (compound **1**) (0.5 g, 2.5 mmol) and an appropriate alkanol or substituted phenol (3.0 mmol) were dissolved in dimethyl sulphoxide (30 mL), after dissolving, sodium hydroxide (0.1 g, 2.5 mmol) was added into the mixture and reacted at 50°C for about 15 h. Then NaN_3 (0.25 g, 3.75 mmol) was added and the reaction mixture was stirred at 65°C for another 32 h. The mixture was cooled and poured into ice water. The solid precipitate was filtered, washed with excessive cold water, dried, and was crystallized from ethanol. The yield, the melting point, and the spectral data of the compounds **3a**–**3u** are given below.

*5-Methoxytetrazolo[1,5-a]quinazoline **3a***

M.p.: 196–198°C; yield: 32%; IR (KBr) cm^{-1}: 1618 (C = N), 1307, 1192 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.53 (d, J = 8.3 Hz, 1H, H-9), 8.34 (d, J = 8.2 Hz, 1H, H-6), 8.03 (t, J = 8.0 Hz, 1H, H-8), 7.77 (t, J = 7.6 Hz, 1H, H-7), 4.35 (s, 3H, -OCH_3); MS m/z: 202 [M + 1]. Anal. calcd. for $C_9H_7N_5O$: C, 53.73; H, 3.51; N, 34.81. Found: C, 54.24; H, 3.59; N, 33.78.

*5-Ethoxytetrazolo[1,5-a]quinazoline **3b***

M.p.; 156–158°C; yield: 46%; IR (KBr) cm^{-1}: 1618 (C = N), 1305, 1191 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.52 (d, J = 8.4 Hz, 1H, H-9), 8.34 (d, J = 8.0 Hz, 1H, H-6), 8.05 (t, J = 7.9 Hz, 1H, H-8), 7.76 (t, J = 7.8 Hz, 1H, H-7), 4.82 (q, J = 7.1 Hz, 2H, -OCH_2-), 1.59 (t, J = 7.1 Hz, 3H, -CH_3); MS m/z: 216 [M + 1]. Anal. calcd. for $C_{10}H_9N_5O$: C, 55.81; H, 4.22; N, 32.54. Found: C, 55.93; H, 4.32; N, 32.21.

*5-Isopropoxytetrazolo[1,5-a]quinazoline **3c***

M.p.: 172–174°C; yield: 36%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.51 (d, J = 8.4 Hz, 1H, H-9), 8.33 (d, J = 8.1 Hz, 1H, H-6), 8.04 (t, J = 7.9 Hz, 1H, H-8), 7.75 (t, J = 7.8 Hz, 1H, H-7), 5.82 (m, J = 6.2 Hz, 1H, -OCH-), 1.55 (d, J = 6.2 Hz, 6H, -$(CH_3)_2$); IR (KBr) cm^{-1}: 1607 (C = N), 1302, 1186 (C-O-C); MS m/z: 230 [M + 1]. Anal. calcd. for $C_{11}H_{11}N_5O$: C, 57.63; H, 4.84; N, 30.55. Found: C, 57.82; H, 4.88; N, 30.45.

*5-Butoxytetrazolo[1,5-a]quinazoline **3d***

M.p.: 100–102°C; yield: 37%; IR (KBr) cm^{-1}: 1615 (C = N), 1302, 1190. (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.52 (d, J = 8.3 Hz, 1H, H-9), 8.28 (d, J = 8.2 Hz, 1H, H-6), 8.05 (t, J = 7.9 Hz, 1H, H-8), 7.76 (t, J = 7.7 Hz, 1H, H-7), 4.76 (t, J = 6.6 Hz, 2H, -OCH_2-), 1.95 (m, J = 7.1 Hz, 2H, -CH_2-), 1.59 (m, J = 7.4 Hz, 2H, -CH_2-), 1.04 (t, J = 7.4 Hz, 3H, -CH_3); MS m/z: 244 [M + 1]. Anal. calcd. for $C_{12}H_{13}N_5O$: C, 59.25; H, 5.39; N, 28.79. Found: C, 59.27; H, 5.36; N, 28.34.

5-(Pentyloxy)tetrazolo[1,5-a]quinazoline ***3e***

M.p. 112–114°C; yield: 51%; IR (KBr) cm^{-1}: 1609 (C = N), 1307, 1194 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.51 (d, *J* = 8.3 Hz, 1H, H-9), 8.33 (d, *J* = 8.0 Hz, 1H, H-6), 8.04 (t, *J* = 7.8 Hz, 1H, H-8), 7.76 (t, *J* = 7.7 Hz, 1H, H-7), 4.74 (t, *J* = 6.7 Hz, 2H, -OCH_2-), 1.97 (m, 2H, -CH_2-), 1.43–1.54 (m, 4H, -CH_2CH_2-), 0.97 (t, *J* = 7.0 Hz, 3H, -CH_3); MS *m*/*z*: 258 [M + 1]. Anal. calcd. for $C_{13}H_{15}N_5O$: C, 60.69; H, 5.88; N, 27.22. Found: C, 60.73; H, 5.90; N, 27.16.

5-(Hexyloxy)tetrazolo[1,5-a]quinazoline ***3f***

M.p.: 106–108°C; yield: 54%; IR (KBr) cm^{-1}: 1604 (C = N), 1300, 1192 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.52 (d, *J* = 8.2 Hz, 1H, H-9), 8.34 (d, *J* = 8.2 Hz, 1H, H-6), 8.05 (t, *J* = 7.8 Hz, 1H, H-8), 7.76 (t, *J* = 7.8 Hz, 1H, H-7), 4.75 (t, *J* = 6.7 Hz, 2H, -OCH_2-), 1.96 (m, 2H, -CH_2-), 1.38–1.58 (m, 6H, -$(CH_2)_3$-), 0.93 (t, *J* = 7.0 Hz, 3H, -CH_3); MS *m*/*z*: 272 [M + 1]. Anal. calcd. for $C_{14}H_{17}N_5O$: C, 61.98; H, 6.32; N, 25.81. Found: C, 62.21; H, 6.36; N, 25.57.

5-(Heptyloxy)tetrazolo[1,5-a]quinazoline ***3g***

M.p.: 110–112°C; yield: 30%; IR (KBr) cm^{-1}: 1602 (C = N), 1305, 1194 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.52 (d, *J* = 8.3 Hz, 1H, H-9), 8.33 (d, *J* = 8.2 Hz, 1H, H-6), 8.05 (t, *J* = 7.8 Hz, 1H, H-8), 7.76 (t, *J* = 7.8 Hz, 1H, H-7), 4.75 (t, *J* = 6.7 Hz, 2H, -OCH_2-), 1.96 (m, 2H, -CH_2-), 1.33–1.59 (m, 8H, -$(CH_2)_4$-), 0.91 (t, *J* = 6.5 Hz, 3H, -CH_3); MS *m*/*z*: 286 [M + 1]. Anal. calcd. for $C_{15}H_{19}N_5O$: C, 63.14; H, 6.71; N, 24.54. Found: C, 63.17; H, 6.72; N, 24.50.

5-(Octyloxy)tetrazolo[1,5-a]quinazoline ***3h***

M.p.: 96–98°C; yield: 59%; IR (KBr) cm^{-1}: 1605 (C = N), 1307, 1192 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.52 (d, *J* = 8.3 Hz, 1H, H-9), 8.34 (d, *J* = 8.2 Hz, 1H, H-6), 8.05 (t, *J* = 7.9 Hz, 1H, H-8), 7.76 (t, *J* = 7.7 Hz, 1H, H-7), 4.74 (t, *J* = 6.6 Hz, 2H, -OCH_2-), 1.96 (m, 2H, -CH_2-), 1.31–1.59 (m, 10H, -$(CH_2)_5$-), 0.88 (t, *J* = 6.6 Hz, 3H, -CH_3); MS *m*/*z*: 300 [M + 1]. Anal. calcd. for $C_{16}H_{21}N_5O$: C, 64.19; H, 7.07; N, 23.39. Found: C, 64.11; H, 7.06; N, 23.43.

5-(Nonyloxy)tetrazolo[1,5-a]quinazoline ***3i***

M.p.: 80–82°C; yield: 57%; IR (KBr) cm^{-1}: 1606 (C = N), 1306, 1194 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.45 (d, *J* = 8.3 Hz, 1H, H-9), 8.24 (d, *J* = 7.9 Hz, 1H, H-6), 7.98 (t, *J* = 7.8 Hz, 1H, H-8), 7.69 (t, *J* = 7.7 Hz, 1H, H-7), 4.68 (t, *J* = 5.9 Hz, 2H, -OCH_2-), 0.74–1.89 (m, 17H, -$(CH_2)_7CH_3$); MS *m*/*z*: 314 [M + 1]. Anal. calcd. for $C_{17}H_{23}N_5O$: C, 65.15; H, 7.40; N, 22.35. Found: C, 65.18; H, 7.43; N, 22.27.

5-(Decyloxy)tetrazolo[1,5-a]quinazoline ***3j***

M.p.: 102–104°C; yield: 47%; IR (KBr) cm^{-1}: 1605 (C = N), 1303, 1192 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.52 (d, *J* = 8.4 Hz, 1H, H-9), 8.33 (d, *J* = 8.3 Hz, 1H, H-6), 8.05 (t, *J* = 7.4 Hz, 1H, H-8), 7.76 (t, *J* = 8.0 Hz, 1H, H-7), 4.75 (t, *J* = 6.6 Hz, 2H, -OCH_2-), 1.96 (m, 2H, -CH_2-), 1.28–1.58 (m, 14H, -$(CH_2)_7$-), 0.87 (t, *J* = 6.4 Hz, 3H, -CH_3); MS *m*/*z*: 328 [M + 1]. Anal. calcd. for $C_{18}H_{25}N_5O$: C, 66.03; H, 7.70; N, 21.39. Found: C, 66.17; H, 7.72; N, 21.45.

5-Phenoxytetrazolo[1,5-a]quinazoline ***3k***

M.p.: 153–155°C; yield: 44%; IR (KBr) cm^{-1}: 1606 (C = N), 1307, 1198 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.60 (d, *J* = 8.4 Hz, 1H, H-9), 8.58 (d, *J* = 8.6 Hz, 1H, H-6), 8.14 (t, *J* = 7.9 Hz, 1H, H-8), 7.87 (t, *J* = 7.8 Hz, 1H, H-7), 7.32–7.55 (m, 5H, Ar-H); MS *m*/*z*: 264 [M + 1]. Anal. calcd. for $C_{14}H_9N_5O$: C, 63.87; H, 3.45; N, 26.60. Found: C, 63.90; H, 3.44; N, 26.59.

5-(4-Methoxyphenoxy)tetrazolo[1,5-a]quinazoline ***3l***

M.p.: 198–200°C; yield: 65%; IR (KBr) cm^{-1}: 1618 (C = N), 1307, 1194 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.52 (d, *J* = 8.7 Hz, 1H, H-9), 8.49 (d, *J* = 9.8 Hz, 1H, H-6), 8.06 (t, *J* = 7.9 Hz, 1H, H-8), 7.87 (t, *J* = 7.8 Hz, 1H, H-7), 7.17 (d, *J* = 9.2 Hz, 2H, Ar-H), 6.94 (d, *J* = 9.2 Hz, 2H, Ar-H), 3.80 (s, 3H, -OCH_3); MS *m*/*z*: 294 [M + 1]. Anal. calcd. for $C_{15}H_{11}N_5O_2$: C, 61.43; H, 3.78; N, 23.88. Found: C, 61.46; H, 3.74; N, 23.82.

5-(2-Methoxyphenoxy)tetrazolo[1,5-a]quinazoline ***3m***

M.p.: 220–222°C; yield: 60%; IR (KBr) cm^{-1}: 1604 (C = N), 1307, 1195 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.59 (d, *J* = 8.4 Hz, 2H, H-6, H-9), 8.13 (t, *J* = 7.9 Hz, 1H, H-8), 7.85 (t, *J* = 7.8 Hz, 1H, H-7), 7.04–7.36 (m, 4H, Ar-H), 3.75 (s, 3H, -OCH_3); MS *m*/*z*: 294 [M + 1]. Anal. calcd. for $C_{15}H_{11}N_5O_2$: C, 61.43; H, 3.78; N, 23.88. Found: C, 61.45; H, 3.74; N, 23.83.

5-(p-Tolyloxy)tetrazolo[1,5-a]quinazoline ***3n***

M.p.: 202–204°C; yield: 63%; IR (KBr) cm^{-1}: 1602 (C = N), 1307, 1203 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.59 (d, *J* = 8.4 Hz, 1H, H-9), 8.58 (d, *J* = 8.3 Hz, 1H, H-6), 8.14 (t, *J* = 7.9 Hz, 1H, H-8), 7.86 (t, *J* = 7.7 Hz, 1H, H-7), 7.19–7.32 (m, 4H, Ar-H), 2.44 (s, 3H, -CH_3); MS *m*/*z*: 278 [M + 1]. Anal. calcd. for $C_{15}H_{11}N_5O$: C, 64.97; H, 4.00; N, 25.26. Found: C, 64.99; H, 4.01; N, 25.23.

5-(o-Tolyloxy)tetrazolo[1,5-a]quinazoline ***3o***

M.p.: 177–179°C; yield: 54%; IR (KBr) cm^{-1}: 1605 (C = N), 1307, 1201 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.54 (d, *J* = 7.4 Hz, 1H, H-9), 8.52 (d, *J* = 7.0 Hz, 1H, H-6), 8.08 (t, *J* = 7.9 Hz, 1H, H-8), 7.80 (t, *J* = 7.7 Hz, 1H, H-7), 7.16–7.27 (m, 4H, Ar-H), 2.16 (s, 3H, -CH_3); MS *m*/*z*: 278 [M + 1]. Anal. calcd. for $C_{15}H_{11}N_5O$: C, 64.97; H, 4.00; N, 25.26. Found: C, 64.98; H, 4.02; N, 25.25.

5-(m-Tolyloxy)tetrazolo[1,5-a]quinazoline ***3p***

M.p.: 171–173°C; yield: 44%; IR (KBr) cm^{-1}: 1604 (C = N), 1307, 1197 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.59 (d, *J* = 8.4 Hz, 1H, H-9), 8.58 (d, *J* = 8.5 Hz, 1H, H-6), 8.14 (t, *J* = 7.9 Hz, 1H, H-8), 7.86 (t, *J* = 7.7 Hz, 1H, H-7), 7.11–7.41 (m, 4H, Ar-H), 2.44 (s, 3H, -CH_3); MS *m*/*z*: 278 [M + 1]. Anal. calcd. for $C_{15}H_{11}N_5O$: C, 64.97; H, 4.00; N, 25.26. Found: C, 64.98; H, 4.01; N, 25.24.

5-(4-Chlorophenoxy)tetrazolo[1,5-a]quinazoline ***3q***

M.p.: 190–192°C; yield: 51%; IR (KBr) cm^{-1}: 1606 (C = N), 1307, 1209 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.56 (d, *J* = 8.3 Hz, 1H, H-9), 8.55 (d, *J* = 8.1 Hz, 1H, H-6), 8.16 (t, *J* = 7.9 Hz, 1H, H-8), 7.87 (t, *J* = 7.8 Hz, 1H, H-7), 7.49 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.30 (d, *J* = 8.9 Hz, 2H, Ar-H); MS *m*/*z*: 298.5 [M + 1], 300.5 [M + 1]. Anal. calcd. for $C_{14}H_8ClN_5O$: C, 56.48; H, 2.71; N, 23.52. Found: C, 56.51; H, 2.72; N, 23.51.

5-(2-Chlorophenoxy)tetrazolo[1,5-a]quinazoline ***3r***

M.p.: 212–214°C; yield: 48%; IR (KBr) cm^{-1}: 1604 (C = N), 1307, 1201 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.62 (d, *J* = 8.3 Hz, 2H, H-6, H-9), 8.16 (t, *J* = 7.7 Hz, 1H, H-8), 7.89 (t, *J* = 7.7 Hz, 1H, H-7), 7.32–7.57 (m, 4H, Ar-H); MS *m*/*z*: 298.5 [M + 1], 300.5 [M + 1]. Anal. calcd. for $C_{14}H_8ClN_5O$: C, 56.48; H, 2.71; N, 23.52. Found: C, 56.50; H, 2.72; N, 23.49.

5-(3-Chlorophenoxy)tetrazolo[1,5-a]quinazoline ***3s***
M.p.: 222–224°C; yield: 46%; IR (KBr) cm^{-1}: 1606 (C = N), 1307, 1206 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.61 (d, *J* = 8.4 Hz, 1H, H-9), 8.54 (d, *J* = 8.1 Hz, 1H, H-6), 8.16 (t, *J* = 7.8 Hz, 1H, H-8), 7.88 (t, *J* = 7.6 Hz, 1H, H-7), 7.24–7.48 (m, 4H, Ar-H); MS *m/z*: 298.5 [M + 1], 300.5 [M + 1]. Anal. calcd. for $C_{14}H_8ClN_5O$: C, 56.48; H, 2.71; N, 23.52. Found: C, 56.51; H, 2.73; N, 23.48.

5-(2,4-Dichlorophenoxy)tetrazolo[1,5-a]quinazoline ***3t***
M.p.: 226–227°C; yield: 42%; IR (KBr) cm^{-1}: 1604 (C = N), 1307, 1196 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.63 (d, *J* = 8.6 Hz, 1H, H-9), 8.58 (d, *J* = 8.7 Hz, 1H, H-6), 8.18 (t, *J* = 7.8 Hz, 1H, H-8), 7.91 (t, *J* = 7.7 Hz, 1H, H-7), 7.58 (d, *J* = 2.1 Hz, 1H, Ar-H), 7.36 (q, *J* = 2.1 Hz, *J* = 8.8 Hz, 2H, Ar-H); MS *m/z*: 332 [M + 1]. Anal. calcd. for $C_{14}H_7Cl_2N_5O$: C, 50.63; H, 2.12; N, 21.09. Found: C, 50.66; H, 2.12; N, 21.05.

5-(4-Fluorophenoxy)tetrazolo[1,5-a]quinazoline ***3u***
M.p.: 208–210°C; yield: 59%; IR (KBr) cm^{-1}: 1604 (C = N), 1307, 1194 (C-O-C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.61 (d, *J* = 8.2 Hz, 1H, H-9), 8.56 (d, *J* = 8.5 Hz, 1H, H-6), 8.15 (t, *J* = 7.8 Hz, 1H, H-8), 7.87 (t, *J* = 7.7 Hz, 1H, H-7), 7.22 (d, *J* = 8.3 Hz, 2H, Ar-H) 7.31 (d, *J* = 8.3 Hz, 2H, Ar-H); MS *m/z*: 282 [M + 1]. Anal. calcd. for $C_{14}H_8FN_5O$: C, 59.79; H, 2.87; N, 24.90. Found: C, 59.82; H, 2.89; N, 24.86.

Pharmacology

The MES tests were carried out according to the phase-I tests of the anti-epileptic drug development (ADD) program [17, 18]. All compounds were tested for anticonvulsant activities with KunMing mice in the 18–22 g weight range purchased from the Laboratory of Animal Research, College of Pharmacy, Yanbian University. The tested compounds were dissolved in polyethylene glycol-400. In the test, each compound was administered at three dose levels (30, 100, and 300 mg/kg i.p., to a total of nine mice, using three for each dose) with anticonvulsant activity assessed at intervals of 30 min. 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.

Antidepressant activities were evaluated using the forced swimming test (FST) [19] with male KunMing mice in the 20–24 g weight range. 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 i.p. injection to the mice. Control animals received 3% aqueous solution of Tween 80. Thirty minutes later, the mice were dropped into a Plexiglas cylinder (25 cm height, diameter 10 cm containing water to a height of 10 cm at 23–25°C) and stayed for six minutes. After the first two minutes 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 four minutes of the 6-min test.

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