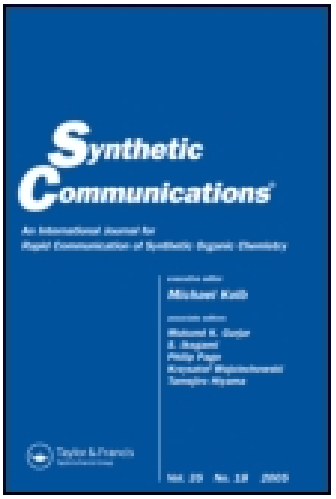

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis and Anticonvulsant Activity of 9-Alkoxy-6,7-dihydro-2H-benzo[c][1,2,4]triazolo[4,3-a]azepin-3[5H]-ones

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Accepted author version posted online: 06 Feb 2012.Published online: 14 May 2012.

To cite this article: Feng-Yu Piao, Cheng-Xi Wei, Rong-Bi Han, Wen-Bin Zhang, Wei Zhang & Ri-Shan Jiang (2012) Synthesis and Anticonvulsant Activity of 9-Alkoxy-6,7-dihydro-2H-benzo[c][1,2,4]triazolo[4,3-a]azepin-3[5H]-ones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:16, 2337-2345, DOI: 10.1080/00397911.2011.553762

To link to this article: http://dx.doi.org/10.1080/00397911.2011.553762

Synthetic Communications®, 42: 2337–2345, 2012

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.553762

SYNTHESIS AND ANTICONVULSANT ACTIVITY OF 9-ALKOXY-6,7-DIHYDRO-2*H*-BENZO[C][1,2,4]TRIAZOLO [4,3-a]AZEPIN-3(5*H*)-ONES

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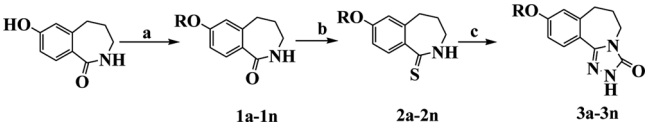
GRAPHICAL ABSTRACT



Abstract *A series of novel 9-alkoxy-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a] azepin-3(5*H*)-one derivatives was designed and synthesized starting from 2,3,4,5-tetrahydro-7-hydroxy-1H-2-benzazepin-1-one. The structures of these compounds were confirmed by mass, ^{1}H NMR infrared spectra, and elemental analysis. Their anticonvulsant activity was evaluated by maximal electroshock (MES) test, and their neurotoxic effects were determined by the rotarod neurotoxicity test. The results shown that **3k** was the most active compound with median effective dose (ED_{50}) of 27.3 mg/kg, median toxicity dose (TD_{50}) of 118.3 mg/kg, and protective index (PI) of 4.3. Possible structure–activity relationship is discussed.*

Keywords 9-Alkoxy-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a]azepin-3(5*H*)-one; anticonvulsant; synthesis

INTRODUCTION

Benazepine derivatives have always received much more attention because of their wide spread biological activities.[1–3] The present anti-hypertension drugs such as libezapril and benazeprilat contain the 2-oxo-benazepine basic skeleton, and growth hormones secretagogue L-692, 429, and L-739, 943 also contain the skeleton.[4] Synthesis and modification of their structures are the research focus in organic chemistry nowdays.[5–7]

Received September 15, 2010.

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Triazole compounds have a wide variety of biological activities, and the introduction of a triazole ring to some active molecules may significantly improve the biological activity of the parent molecule because of the superposition of biological activity.[8,9]

This study designed and synthesized a series of novel 9-alkoxy-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a]azepin-3(5*H*)-one derivatives, which have not been reported in the literature, and their structures were confirmed by mass spectrometry, infrared (IR), and NMR spectra. The anticonvulsant activity was evaluated by the maximal electroshock test (MES), and the neurotoxicity was measured by the rotarod test (Tox).[10,11]

RESULTS AND DISCUSSION

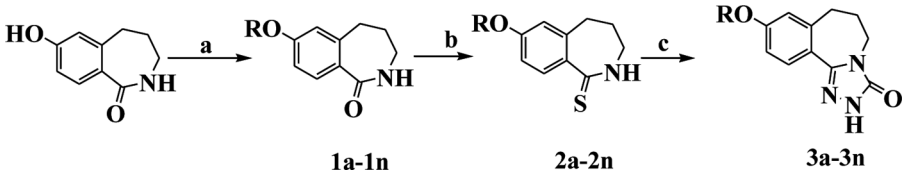
Chemistry

Target compounds **3a–3n** were prepared following the reaction sequence shown in Scheme 1.

The compounds **1a–1n** were synthesized using the method described in a previous paper by our group.[12] Compounds **1a–1n** then reacted with phosphorus pentasulfide in acetonitrile in the presence of triethylamine under a nitrogen atmosphere, and the resulting compounds (**2a–2n**) reacted further with methyl hydrazine carboxylate in *n*-butanol to produce the target compounds 9-alkoxy-6,7-dihydro-2-*H*-benzo[c][1,2,4]triazolo[4,3-a]azepin-3(5*H*)-one (**3a–3n**).[9,13,14]

Pharmacological Evaluations

The results of preliminary (phase I) screening of **3a**–**3n** are summarized in Table 1. Among all synthesized compounds at the dose of 100 mg/kg, all the five straight-chain alkoxy compounds could not exhibit anticonvulsant activity. Seven of nine substituted-benzyloxy compounds (except for **3h** and **3j**) exhibited different anticonvulsant activities, especially compound **3k**, (9-(2-chlorobenzyloxy)-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a]azepin-3(5*H*)-one, which exhibited the most potential activity. As a result of this preliminary screening, compounds **3g** and **3k** 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



Scheme 1. Synthetic route of compounds **3a–3n**. Reagents: (a) RX/C_2H_5OH, 80–92 °C; (b) P_2S_5, $(C_2H_5)_3N/CH_3CN$, 86–92 °C, 5–7 h; (c) $H_2NNHCOOCH_3/(CH_3)(CH_2)_3OH$, 140–150 °C, 5–8 d where R: **3a** = n-C_4H_9, **3b** = n-C_5H_{11}, **3c** = n-C_6H_{13}, **3d** = -CH_3, **3f** = $CH_2C_6H_4$(*m*-F), **3g** = $CH_2C_6H_4$(*p*-F), **3i** = $CH_2C_6H_4$(*m*-Cl), **3j** = $CH_2C_6H_4$(*p*-cl), **3k** = $CH_2C_6H_4$(*o*-Cl), **3m** = $CH_2C_6H_4$(*p*-Br), **3n** = $CH_2C_6H_5$.

Table 1. Primary evaluation of the synthesized compounds in anticonvulsant activity (ip)[a]

Compound	R	MES[b] (100[c])
3a	*n*-C_4H_9	0/3
3b	*n*-C_5H_{11}	0/3
3c	*n*-C_6H_{13}	0/3
3d	*n*-C_7H_{15}	0/3
3e	-CH_3	0/3
3f	-$CH_2C_6H_4$(*m*-F)	1/3
3g	-$CH_2C_6H_4$(*p*-F)	2/3
3h	-$CH_2C_6H_4$(*o*-F)	0/3
3i	-$CH_2C_6H_4$(*m*-Cl)	1/3
3j	-$CH_2C_6H_4$(*p*-Cl)	0/3
3k	-$CH_2C_6H_4$(*o*-Cl)	3/3
3l	-$CH_2C_6H_4$(*p*-CH_3)	1/3
3m	-$CH_2C_6H_4$(*p*-Br)	1/3
3n	-$CH_2C_6H_5$	1/3

[a]All of tested compounds were dissolved in DMSO.
[b]The maximal electroshock test was carried out 30 min after administration of the test compounds.
[c]Doses are denoted in milligrams per kilogram.

standard error (SE) of the slope were then calculated. These data are shown in Table 2, which also includes comparisons with marketed antiepileptic drug carbamazepine. As shown in Table 2, compound **3g** displayed anticonvulsant activity in the MES test, with ED_{50} values of 73.5 mg/kg, and compound **3k** displayed anticonvulsant activity in the MES test with ED_{50} values of 27.3 mg/kg and also displayed a TD_{50} of 118.3 mg/kg. No compounds exhibited more activity than reference drug Carbamazepine. In the sc-PTZ model, compound **3k** showed partial inhibition of the clonic and tonic seizures and death induced by PTZ (Table 3). PTZ has been reported to produce seizures by inhibiting γ-aminobutyric acid (GABA) neurotransmission.[15,16] Inhibition of GABAergic neurotransmission or activity has been shown to promote and facilitate seizures,[17] whereas enhancement of GABAergic neurotransmission is known to inhibit or attenuate seizures.

Analyzing the results of these pharmacology tests, the following simple structure-activity relationship was obtained. The straight–chain alkoxy compounds

Table 2. Quantitative anticonvulsant data in mice (ip)

Compound	R	ED_{50}[a]	TD_{50}[c]	PI[e]
3g	-$CH_2C_6H_4$ (*p*-F)	73.5 (68.5–78.8)[b]	—[d]	
3k	-$CH_2C_6H_4$ (*o*-Cl)	27.3 (20.9–36.6)	118.3 (102.6–136.5)	4.3
Carbamazepine		8.8 (5.5–14.1)	71.6 (45.9–135.0)	8.1

[a]Median effective dose required to assure anticonvulsant protection in 50% of animals.
[b]95% confidence limits given in parentheses.
[c]Median toxic dose eliciting minimal neurological toxicity in 50% of animals.
[d]Not tested.
[e]Protective index (TD_{50}/ED_{50}).

Table 3. Effect of compound **3k** on PTZ-induced convulsion in mice

Compound	Doses (mg/kg)	N	Test time (h)	Clonic (%)	Tonic (%)	Death (%)
DMSO	—	10	0.5	100	100	0
Carbam	50	10	0.5	100	0	10
3k	50	10	0.5	70	20	30

exhibit very low anticonvulsant activity, and the substituted groups on the benzyloxy and the position of the substituted group were greatly influenced the anticonvulsant activity. The activity order of the F position on the benzyloxy was *p*-F>*m*-F>*o*-F, and the activity order of the Cl position on the benzyloxy was *o*-Cl>*m*-Cl>*p*-Cl.

CONCLUSIONS

In conclusion, the results of this study demonstrated that 9-alkoxy-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a]azepin-3(5*H*)-one derivatives have potent anticonvulsant activity. Compound **3k** has the strongest anticonvulsant activity, and it much more active compared with the same substituted group without triazolone (2,3,4,5-tetrahydro-7-(2-chlorobenzyloxy)-1H-2-benzazepin-1-one). In addition, compound **3k** demonstrated antagonistic activity against seizures induced by PTZ. These experiments suggested that compound **3k** might activate glutamate decarboxylase (GAD) or inhibit (GABA)–aoxoglutarate aminotransferase (GABA-T).

EXPERIMENTAL

Chemistry

Melting points were determined on X-5 microscope melting-point apparatus, which were uncorrected. IR spectra were recorded (in KBr) on a FT-IR instrument (IRPRESTIGE-21). ^{1}HNMR spectra were measured on an AV-300 instrument (Bruker, Switzerland), and all chemical shifts were given in parts per million relative to tetramethylsilane. Mass spectra were measured on a HP1100LC instrument (Agilent Technologies, USA). Combustion analyses (C, H, and N) were performed on a PE-2400 (Shimadzu). Microanalyses of C, N, and H were performed using a Heraeus CHN rapid analyzer. The major chemicals were purchased from Aldrich Chemical Corporation. All other chemicals were of analytical grade.

Preparation of Compounds 3a–n

General procedure. Acetonitrile (1.0 mL) and triethylamine (0.6 mL) were placed in a three-necked, round-bottomed flask, to which P_2S_5 (0.4 g, 1.9 mmol) was added slowly in an ice bath and stirred until dissolved. Then **2a–2n** (1.7 mmol) were added with stirring. The mixture was refluxed for 7 h in a nitrogen atmosphere. After removing the solvent under reduced pressure, the residue was dissolved in 60 mL of dichloromethane, washed with water (60 mL × 3), and dried over anhydrous $MgSO_4$. Evaporation of the solvents gave a crude product. Crude product **2a–2n** reacted with methyl hydrazinocarboxylate (3.4 mmol) in *n*-butanol 10 mL under a nitrogen atmosphere for 4–8 days. The solvent was removed under reduced

pressure, and the residue was dissolved with ethy1 acetate and washed with water three times. The ethy1 acetate layer was dried with anhydrous $MgSO_4$, filtered, and concentrated, and the residue was purified by silica-gel column chromatography (dichloromethane – methanol = 35:1) to afford target compounds **3a–3n.**

(9-Butoxy-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a]azepin-3(5*H*)-one (3a). Yield: 30.8%, mp 212.2–213.6 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.93 (t, 3H, J = 7.3 Hz, CH_3), 1.39–1.49 (m, 2H, CH_2), 1.65–1.74 (m, 2H, CH_2), 2.04–2.08 (m, 2H, CH_2), 2.73 (t, 2H, J = 6.7 Hz, CH_2), 3.53 (t, 2H, J = 6.7 Hz, CH_2), 4.01 (t, 2H, J = 6.4 Hz, CH_2), 6.89–6.93 (m, 2H, Ar-H), 7.55 (d, 1H, J = 8.4 Hz, Ar-H), 11.75 (s, 1H, N-H). MS: m/z 273.2 (M^+); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.6, 155.1, 147.7, 141.2, 129.3, 119.9, 116.2, 113.3, 67.8, 38.9, 31.2, 27.9, 19.2, 14.1. IR (KBr), cm^{-1}: 3150, 1688. Anal. calcd. for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.74; H, 7.21; N, 15.29.

9-Pentyloxy-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a]azepin-3(5*H*)-one (3b). Yield: 52.9%, mp 200.0–201.1 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.90 (t, 3H, J = 6.8 Hz, CH_3), 1.37–1.38 [m, 4H, $(CH_2)_2$], 1.70–1.73 (m, 2H, CH_2), 2.05–2.09 (m, 2H, CH_2), 2.74 (t, 2H, J = 6.5 Hz, CH_2), 3.54 (t, 2H, J = 6.6 Hz, CH_2), 4.01 (t, 2H, J = 6.4 Hz, CH_2), 6.90–6.95 (m, 1H, Ar-H), 7.57 (d, 1H, J =8.4 Hz, Hz, Ar-H), 11.76 (s, 1H, N-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.6, 155.1, 147.7, 141.2, 129.3, 119.9, 116.2, 113.3, 68.0, 38.9, 31.2, 28.8, 28.1, 27.9, 22.3, 14.4. MS: m/z 287.2 (M^+). IR (KBr), cm^{-1}: 3150, 1690. Anal. calcd. for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 66.94; H, 7.54; N, 14.49.

9-Hexyloxy-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a]azepin-3(5*H*)-one (3c). Yield: 40.4%, mp 204.0–205.6 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.85–0.88 [m, 3H, CH_3], 1.31–1.41 (m, 6H, $(CH_2)_3$), 1.70–1.74 (m, 2H, CH_2), 2.01–2.09 (m, 2H, CH_2), 2.74 (t, 2H, J = 6.3 Hz, CH_2), 3.54 (t, 2H, J = 6.4 Hz, CH_2), 4.01 (t, 2H, J = 6.4 Hz, CH_2), 6.93–6.94 (m, 2H, Ar-H), 7.55 (d, 1H, J = 8.4 Hz, Ar-H), 11.76 (s, 1H, N-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.6, 155.1, 147.7, 141.2, 129.3, 119.9, 116.2, 113.3, 68.0, 38.9, 31.4, 31.2, 29.0, 27.9, 25.6, 22.5, 14.4. MS: m/z 301.2 (M^+). IR (KBr), cm^{-1}: 3150, 1688. Anal. calcd. for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.49; H, 7.76; N, 13.78.

9-Heptyloxy-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a]azepin-3(5*H*)-one (3d). Yield: 48.8%, mp 193.4–195.5 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.86–0.88 (m, 3H, CH_3), 1.28–1.40 (m, 8H, $(CH_2)_4$), 1.70–1.72 (m, 2H, CH_2), 2.04–2.09 (m, 2H, CH_2), 2.74 (t, 2H, J = 6.3 Hz, CH_2), 3.53 (t, 2H, J = 6.4 Hz, CH_2), 4.01 (t, 2H, J = 6.1 Hz, CH_2), 6.90–6.95 (m, 2H, Ar-H), 7.57 (d, 1H, J = 8.3 Hz, Ar-H), 11.77 (s, 1H, N-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.6, 155.1, 147.7, 141.2, 129.3, 119.9, 116.2, 113.3, 68.0, 38.9, 31.7, 31.2, 29.1, 28.9, 27.9, 25.9, 22.5, 14.4. MS: m/z 315.2 (M^+). IR (KBr), cm^{-1}: 3160, 1634. Anal. calcd. for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.47; H, 8.00; N, 13.29.

9-Methoxy-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a]azepin-3(5*H*)-one (3e). Yield: 45.0%, mp 213.1–214.5 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.08–2.10 (m, 2H, CH_2), 2.73–2.77 (m, 2H, CH_2), 3.52–3.56 (m, 2H, CH_2), 3.81 (s, 3H, CH_3), 6.92–6.96 (m, 2H, Ar-H), 7.59 (d, 1H, J = 8.1 Hz, Ar-H). 11.79 (s, 1H,

N-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.1, 155.0, 147.7, 141.2, 129.3, 120.0, 115.7, 112.9, 55.7, 38.9, 31.2, 27.9. MS: m/z 231.1 (M^+). IR (KBr), cm^{-1}: 3190, 1690. Anal. calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.51; H, 5.77; N, 18.01.

(9-(3-Fluorobenzyloxy)-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a] azepin-3(5*H*)-one (3f). Yield: 48.7%, mp 184.9–185.8 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.06–2.10 (m, 2H, CH_2), 2.75 (t, 2H, $J = 6.4$ Hz, CH_2), 3.54 (t, 2H, $J = 6.6$ Hz, CH_2), 5.18 (s, 2H, CH_2), 7.01–7.62 (m, 7H, Ar-H), 11.78 (s, 1H, N-H); ^{13}C NMR (75 MHz, MeOD): δ 163.0 (d, $J_{C\text{-}F} = 243.6$ Hz), 160.6, 155.4, 148.8, 141.0, 139.8 (d, $J = 7.6$ Hz), 130.0 (d, $J = 8.2$ Hz), 129.0, 122.7, 119.6, 116.0, 114.2 (d, $J = 21.2$ Hz), 113.7 (d, $J_{C\text{-}F} = 22.6$ Hz), 113.0, 68.7, 38.4, 30.4, 27.9. MS: m/z 325.1 (M^+). IR (KBr), cm^{-1}: 3160, 1688. Anal. calcd. for $C_{18}H_{16}FN_3O_2$: C, 66.45; H, 4.96; N, 12.92. Found: C, 66.32; H, 5.16; N, 12.85.

(9-(4-Fluorobenzyloxy)-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a] azepin-3(5*H*)-one (3g). Yield: 60.8%, mp 186.2–188.1 °C.^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.97–2.02 (m, 2H, CH_2), 2.62 (t, 2H, $J = 6.9$ Hz, CH_2), 3.00–3.06 (m, 2H, CH_2), 5.12 (s, 2H, CH_2), 6.89–7.69 (m, 7H, Ar-H), 10.44 (s, 1H, N-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0 (d, $J_{C\text{-}F} = 243.6$ Hz), 160.6, 155.4, 148.8, 141.0, 139.8 (d, $J = 7.6$ Hz), 130.0 (d, $J = 8.2$ Hz), 129.0, 122.7, 119.6, 116.0, 114.2 (d, $J = 21.2$ Hz), 113.7 (d, $J_{C\text{-}F} = 22.6$ Hz), 113.0, 68.7, 38.4, 30.4, 27.9. MS: m/z 325.1(M^+). IR (KBr), cm^{-1}: 3180, 1699. Anal. calcd. for $C_{18}H_{16}FN_3O_2$: C, 66.45; H, 4.96; N, 12.92. Found: C, 66.31; H, 5.19; N, 12.79.

(9-(2-Fluorobenzyloxy)-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a] azepin-3(5*H*)-one (3h). Yield: 52.1%, mp 229.6–230.7 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.05–2.10 (m, 2H, CH_2), 2.75 (t, 2H, $J = 6.5$ Hz, CH_2), 3.54 (t, 2H, $J = 6.6$ Hz, CH_2), 5.14 (s, 2H, CH_2), 6.99–7.62 (m, 7H, Ar-H), 11.78 (s, 1H, N-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.3 (d, $J_{C\text{-}F} = 241.9$ Hz), 160.2, 155.1, 147.6, 141.2, 133.4, 130.5, 129.3, 120.3, 116.6, 115.8 (d, $J_{C\text{-}F} = 21.1$ Hz), 113.6, 68.1, 39.0, 31.2, 27.8. MS: m/z 325.1 (M^+). IR (KBr), cm^{-1}: 3150, 1688. Anal. calcd. for $C_{18}H_{16}FN_3O_2$: C, 66.45; H, 4.96; N, 12.92. Found: C, 66.40; H, 5.06; N, 12.77.

(9-(3-Chlorobenzyloxy)-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a] azepin-3(5*H*)-one (3i). Yield: 48.7%, mp 194.0–197.4 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.06–2.10 (m, 2H, CH_2), 2.73–2.77 (m, 2H, CH_2), 3.53–3.57 (m, 2H, CH_2), 5.18 (s, 2H, CH_2), 7.03–7.62 (m, 7H, Ar-H), 11.78 (s, 1H, N-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.0, 155.1, 147.6, 141.3, 139.8, 133.6, 130.9, 129.4, 128.3, 127.9, 126.7, 120.5, 116.7, 113.6, 68.8, 38.9, 31.2, 27.8. MS: m/z 341.0 (M^+). IR (KBr), cm^{-1}: 3160, 1688. Anal. calcd. for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29. Found: C, 63.11; H, 4.92; N, 12.31.

(9-(4-Chlorobenzyloxy)-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a] azepin-3(5*H*)-one (3j). Yield: 50.8%, mp 246.6–249.1 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.05–2.21 (m, 2H, CH_2), 2.75 (t, 2H, $J = 6.4$ Hz, CH_2), 3.54 (t, 2H, $J = 6.5$ Hz, CH_2), 5.16 (s, 2H, CH_2), 6.99–7.80 (m, 7H, Ar-H), 11.79 (s, 1H, N-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.1, 155.0, 147.6, 141.3, 136.3, 133.0, 130.1, 129.4, 128.9, 120.4, 116.7, 113.6, 68.9, 38.9, 31.2, 27.8. MS: m/z 341.0 (M^+). IR

(KBr), cm^{-1}: 3148, 1692. Anal. calcd. for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29. Found: C, 63.09; H, 4.94; N, 12.35.

(9-(2-Chlorobenzyloxy)-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a] azepin-3(5*H*)-one (3k). Yield: 50.1%, mp 194.4–197.6 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.06–2.10 (m, 2H, CH_2), 2.74–2.78 (m, 2H, CH_2), 3.53–3.57 (m, 2H, CH_2), 5.21 (s, 2H, CH_2), 7.02–7.62 (m, 7H, Ar-H), 11.80 (s, 1H, N-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.0, 155.1, 147.6, 141.3, 134.4, 133.2, 130.8, 129.9, 129.4, 127.9, 120.6, 116.5, 113.5, 67.4, 38.9, 31.2, 27.8. MS: m/z 341.0 (M^+). IR (KBr), cm^{-1}: 3102, 1638. Anal. calcd. for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29. Found: C, 63.19; H, 4.94; N, 12.43.

(9-(4-Methylbenzyloxy)-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a] azepin-3(5*H*)-one (3l). Yield: 30.1%, mp 212.2–213.6 °C.^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.05–2.09 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.74 (t, 2H, $J = 6.4$ Hz, CH_2), 3.54 (t, 2H, $J = 6.6$ Hz, CH_2), 5.10 (s, 2H, CH_2), 6.97–7.60 (m, 7H, Ar-H), 11.77 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3, 156.1, 148.7, 142.3, 138.7, 135.2, 130.5, 130.4, 129.4, 121.3, 117.7, 114.7, 70.8, 40.0, 32.3, 28.9, 22.3. MS: m/z 321.2 (M^+). IR (KBr), cm^{-1}: 3150, 1692. Anal. calcd. for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08. Found: C, 71.11; H, 5.74; N, 13.13.

(9-(4-Brominebenzyloxy)-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a] azepin-3(5*H*)-one(3m). Yield: 31.7%, mp 246.4–246.8 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.05–2.10 (m, 2H, CH_2), 2.75 (t, 2H, $J = 6.5$ Hz, CH_2), 3.54 (t, 2H, $J = 6.6$ Hz, CH_2), 5.15 (s, 2H, CH_2), 6.99–7.62 (m, 7H, Ar-H), 11.78 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0, 155.1, 147.6, 141.2, 136.7, 131.9, 130.3, 129.3, 121.5, 120.4, 116.7, 113.6, 69.0, 38.9, 31.2, 27.8. MS: m/z 385.0 ($M + 1$). IR (KBr), cm^{-1}: 3125, 1692. Anal. calcd. for $C_{18}H_{16}BrN_3O_2$: C, 55.97; H, 4.18; N, 10.88. Found: C, 55.78; H, 4.01; N, 10.75.

9-Benzyloxy-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a]azepin-3(5*H*)-one (3n). Yield: 40.2%, mp 246.4–246.8 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.05–2.10 (m, 2H, CH_2), 2.73–2.77 (m, 2H, CH_2), 3.54 (t, 2H, $J = 6.4$ Hz, CH_2), 5.15 (s, 2H, CH_2), 6.99–7.61 (m, 8H, Ar-H), 11.78 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.2, 155.1, 147.6, 141.2, 137.2, 129.3, 128.9, 128.4, 128.3, 120.3, 116.6, 113.6, 69.8, 38.9, 31.2, 27.8. MS: m/z 307.1 (M^+). IR (KBr), cm^{-1}: 3160, 1690. Anal. calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.29; H, 5.67 N, 13.76.

Pharmacology

The MES test and the rotarod test were carried out by the standard described in the Antiepileptic Drug Development Program (ADD) of the National Institutes of Health (USA).[10,11] All compounds were tested for anticonvulsant activities with KunMing mice in the 18 to 22-g weight range purchased from the Laboratory of Animal Research, College of Pharmacy, Yanbian University. The tested compounds were dissolved in dimethylsulfoxide (DMSO). In phase I screening (Table 1), each compound was administered at the dose levels of 100 mg/kg for evaluating the anticonvulsant activity. Anticonvulsant efficacy was measured in the MES test. In the

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. The 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. Anticonvulsant drug–induced neurologic deficit was detected in mice by the rotarod ataxia test. Anticonvulsant activity was expressed in terms of ED_{50}, and neurotoxicity was expressed as TD_{50}. For determination of the ED_{50} and TD_{50} values, groups of 10 mice were given a range of intraperitoneal 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 plots of these data, the respective ED_{50}, TD_{50} values, and 95% confidence intervals were calculated by means of trimmed Spearman–Karber method.[18]

In chemically induced seizures, mice were given doses of convulsant drugs that could induce seizures at least 97% of animals. The dose of PTZ was 85 mg/kg. The test compounds and standard AED were administered ip in a volume of 50 mg/kg to groups of 10 mice 30 min before either ip and sc injection of PTZ. The mice were placed in individual cages and observed for 30 min, and the number of clonic seizures, tonic seizures, and the lethality were recorded.[10,11,19]

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (No. 30760290 and No.30860340) and Important Item Foundation of Ministry of Education P.R. China (No. 20070422029).

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