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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and anticonvulsant activity of 8-alkoxy-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine derivatives

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Abstract A novel series of 8-alkoxy-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine derivatives were synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy, and elemental analysis. The newly synthesized compounds were screened for their anticonvulsant activities by the maximal electroshock (MES) test and subcutaneous pentylenetetrazol (scPTZ) test, and their neurotoxic effects were determined by the rotarod neurotoxicity test. Compound 8-pentyloxy-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine (**3d**) besides being one of the most active compounds had the lowest toxicity. In the anti-MES potency test, it showed median effective dose (ED_{50}) of 17.5 mg/kg, and had protective index (PI) value of 6.5, which is slightly less than that of the prototype drug carbamazepine (PI = 8.1). Its value of ED_{50} and PI in the anti-scPTZ test were 21.2 and 5.4, respectively, the latter value (PI) of which is much greater than that of the prototype drug carbamazepine (ED_{50} >100, PI <0.72). Possible structure–activity relationship has been discussed.

Keywords Benzotriazoloazepine · Synthesis · Anticonvulsant activity

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Introduction

It is reported that about 1% of the world's population is afflicted with Epilepsy. Nearly 2.4 million new cases every year are being added to the reported figures (Secretariats of WHO/IBE/ILAE 2009; Paswerk and Hoofddorp, 2003). Although the current drugs provide adequate seizure control in many patients, it is roughly estimated that up to 28–30% of patients are poorly treated with the available antiepileptic drugs (AEDs) (Yogeeswari *et al.*, 2005; Taylor *et al.*, 2003). Therefore, continued search for safer and more effective AEDs is urgently necessary. In recent years, much efforts have been devoted to developing novel compounds as potential anticonvulsant agents (Bialer and White, 2010; Perucca *et al.*, 2007; Bialer *et al.*, 2007; Löschera and Schmidtb, 2006; Guan *et al.*, 2009; Amnerkar and Bhusari, 2010; Stefan and Feuerstein, 2007; Pollard and French, 2006; Donner and Snead, 2006).

Benzazepine derivatives exhibit broad pharmacological activity (Wei *et al.*, 2009; Rivas *et al.*, 2009; Bariwal *et al.*, 2008; Im *et al.*, 2004). Triazole compounds have wide variety of biological activities, the introduction of triazole ring to some activated molecules may significantly improve the biological activity of the parent molecule because of the superposition of biological activity (Sun *et al.*, 2008 and 2009; Cui *et al.*, 2005; Jin *et al.*, 2006; Hoelzemann *et al.*, 2010). Previously, we have reported some 1,3,4,5-tetrahydro-7-alkoxy-2*H*-1-benzazepin-2-one derivatives as moderately active anticonvulsant agents. In view of these and as a part of our enduring studies in the area of anticonvulsant agents, it was thought to be of beneficial interest to combine both pharmacophoric groups (benzazepine nucleus and triazole ring).

We have synthesized a series of 8-alkoxy-2,4,5,6-tetrahydro-1H-benzo[f][1,2,4]triazolo[4,3-a]azepin-1-one derivatives and evaluated their anticonvulsant activity (Piao *et al.*, 2011). In order to obtain compounds with better anticonvulsant activity, the following chemical structures were designed, and their anticonvulsant activity prediction using PASS software was performed. On the basis of computer-based prediction of anticonvulsant activity by PASS, the target compounds were synthesized through an appropriate synthetic sequence, and their anticonvulsant activity was evaluated by the maximal electroshock (MES)t and subcutaneous pentylenetetrazol (scPTZ) tests, while their neurotoxic effects were determined by the rotarod neurotoxicity test.

Results and discussion

Target compounds were prepared according to Scheme 1. The starting material 7-hydroxy-4,5-dihydro-1H-benzo [b]azepin-2(3H)-one previously synthesized using the method described previously by the present authors' group (Wei *et al.*, 2009) was reacted with appropriate alkyl halide to produce the compounds **1a–1o** (Ju and Rajender, 2004). The said compounds then were reacted with phosphorus pentasulfide in acetonitrile in the presence of triethylamine under nitrogen**,** and the resulting compounds **2a–2o** were reacted further with methyl hydrazine carboxylate in *n*-butanol to produce the target compounds **3a–3o**.

Pharmacological tests of the 8-alkoxy-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine (**3a–3o**) were conducted at the Epilepsy Branch of the National Institute of Neurological Disorders and Stroke (NINDS) following the protocol adopted by the Antiepileptic Drug Development (ADD) program (Krall *et al.*, 1978; Porter *et al.*, 1984).

The results of preliminary (phase I) screening of compounds **3a–3o** are summarized in Table 1. All the synthesized compounds exhibited anticonvulsant activities, among which seven compounds **3c–3h** and **3k** possessed anticonvulsant activities against MES-induced seizure at the dose of 30 mg/kg, and then seven compounds **3b**, **3l–3o,** and **3i–3j** were active at the dose of 100 mg/kg. The remaining one compound **3a** exhibited anti-MES effect only under the high dose of 300 mg/kg. In the anti-scPTZ test, nine compounds (**3c**, **3f–3g,** and **3i–3n**) exhibited anticonvulsant effects at the dose of 100 mg/kg, while compounds **3d** and **3e** showed such effect at the dose of 30 mg/kg. As a result of preliminary screening, compounds **3c–3g** and **3i–3n** were subjected to phase II trials for quantification of their anticonvulsant activities [indicated by MES, median effective dose (ED_{50}) and scPTZ, ED_{50}] and neurotoxicities [indicated by median toxic dose (TD_{50})] in mice (Table 2). On analyzing the activities of the synthesized compounds, the following structure–activity relationships (SAR) were obtained.

Table 1 Phase I anticonvulsant data in mice of compounds **3a–3o** (i.p.)

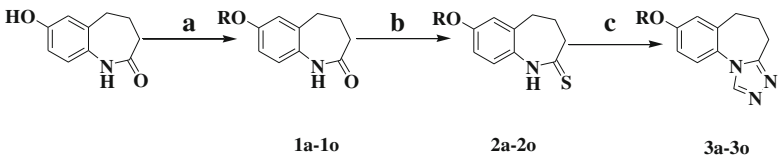
Compounds	R	MES[a]			**scPTZ**[a]	
		30[b]	100	300	30[b]	100
3a	$-CH_3$	0/3	1/5	5/5	0/5	0/5
3b	$-C_3H_7$	1/5	5/5	–	0/5	0/5
3c	$-C_4H_9$	5/5	–	–	2/5	5/5
3d	$-C_5H_{11}$	5/5	–	–	5/5	–
3e	$-C_6H_{13}$	5/5	–	–	4/5	–
3f	$-C_7H_{15}$	5/5	–	–	3/5	5/5
3g	$-PhCH_2$	5/5	–	–	0/5	5/5
3h	$-CH_2C_6H_4(o-Cl)$	5/5	–	–	0/5	0/5
3i	$-CH_2C_6H_4(m-Cl)$	3/5	5/5	–	0/5	5/5
3j	$-CH_2C_6H_4(p-Cl)$	3/5	5/5	–	0/5	5/5
3k	$-CH_2C_6H_4(o-F)$	5/5	–	–	2/5	5/5
3l	$-CH_2C_6H_4(m-F)$	3/5	5/5	–	0/5	5/5
3m	$-CH_2C_6H_4(p-F)$	3/5	5/5	–	1/5	5/5
3n	$-CH_2C_6H_4(p-Br)$	3/5	5/5	–	0/5	5/5
3o	$-CH_2C_6H_4(p-CH_3)$	3/5	5/5	–	0/5	0/5

All of the tested compounds were dissolved in DMSO

–, Not tested

[a] The maximal electroshock test was induced after 30 min past administration of the tested compounds

[b] Doses are denoted in mg/kg



1a-1o 2a-2o 3a-3o

R:

3a = -CH_3 3e= n-C_6H_{13} 3i = $CH_2C_6H_4$(*m*-Cl) 3m = $CH_2C_6H_4$(*p*-F)

3b = n-C_3H_7 3f = n-C_7H_{15} 3j = $CH_2C_6H_4$(*p*-Cl) 3n = $CH_2C_6H_4$(*p*-Br)

3c = n-C_4H_9 3g = $CH_2C_6H_5$ 3k = $CH_2C_6H_4$(*o*-F) 3o = $CH_2C_6H_4$(*p*-CH_3)

3d = n-C_5H_{11} 3h = $CH_2C_6H_4$(*o*-Cl) 3l = $CH_2C_6H_4$(*m*-F)

Scheme 1 The synthesis route of compounds **3a–3o**. Reagents: **a** RX, NaOH/C_2H_5OH, 80–92°C; **b** P_2S_5, $(C_2H_5)_3N$/CH_3CN, 86–92°C, 5–7 h; **c** $H_2NNHCOH$/$(CH_3)(CH_2)_3OH$, 140–150°C, 40–48 h

Table 2 Phase II quantitative anticonvulsant data in mice (test drug administered i.p.)

Compounds	ED_{50}^{a}		TD_{50}^{b}	PI^{c}	
	MES	scPTZ	Rotarod toxicity	MES	scPTZ
3b	73.3 (86.4–62.1)[d]	>100	–	–	–
3c	21.2 (24.4–18.4)[d]	36.7 (44.1–30.5)[d]	73.3 (86.5–62.2)[d]	3.5	2.0
3d	17.5 (18.5–16.5)[d]	21.2 (25.5–17.5)[d]	114.1 (137.2–94.9)[d]	6.5	5.4
3e	17.7 (21.2–14.8)[d]	24.6 (29.0–20.1)[d]	84.2 (100.9–70.3)[d]	4.8	3.4
3f	19.7 (22.5–17.2)[d]	26.4 (31.7–22.0)[d]	68.4 (78.0–60.0)[d]	3.5	2.6
3g	23.7 (27.1–20.1)[d]	78.9 (94.5–65.9)[d]	78.9 (89.9–69.3)[d]	3.3	1.0
3h	20.5 (24.1–17.5)[d]	>100	70.9 (81.8–61.5)[d]	3.4	<0.7
3i	29.5 (35.5–24.5)[d]	80.7 (96.7–67.4)[d]	119.8 (141.0–101.8)[d]	4.1	1.5
3j	27.4 (32.9–22.9)[d]	68.2 (81.3–57.3)[d]	98.6 (112.0–86.8)[d]	3.7	1.4
3k	19.0 (22.8–15.8)[d]	35.4 (41.8–30.0)[d]	84.9 (93.9–76.7)[d]	4.5	2.4
3l	27.4 (32.9–22.9)[d]	>100	>100	–	–
3m	27.4 (32.9–22.9)[d]	47.3 (56.4–39.7)[d]	97.4 (110.7–85.7)[d]	3.6	2.1
3n	27.0 (37.1–19.6)[d]	>100	96.2 (112.0–82.6)[d]	3.0	0.9
3o	27.4 (32.9–22.9)[d]	90.1 (108.1–75.1)[d]	82.9 (99.6–70.5)[d]	3.6	1.1
Phenobarbital[e]	21.8 (21.8–25.5)[d]	13.2 (8.8–15.9)[d]	69.0 (62.8–72.9)[d]	3.2	5.2
Phenytoin[e]	9.5 (8.1–10.4)[d]	>300	65.5 (52.5–72.9)[d]	6.9	<0.2
Valproate[e]	272 (247–338)[d]	149 (123–177)	426 (369–450)[d]	1.6	2.9
Carbam[e]	8.8 (5.5–14.1)[d]	>100	71.6 (45.9–135)[d]	8.1	<0.72

–, No activity at the corresponding dose

[a] ED_{50} median effective dose required to assure anticonvulsant protection in 50% animals

[b] TD_{50} median toxic dose eliciting minimal neurological toxicity in 50% animals

[c] PI (TD_{50}/ED_{50})

[d] 95% confidence limits given in parentheses

[e] Date from Ucar *et al.*, (1998)

In general, owing to the enhancement of molecular hydrophobicity and electronic polarization, the anticonvulsant activity of an organic compound might be increased remarkably after the introduction of a halogen atom. Particularly, the introduction of fluorine atoms may significantly change the molecular electronic distribution, increase the binding affinity of drug with receptor, and improve the biological activity of drug. The *ortho*-halogenated benzyloxy substituted compounds may be more suitable for binding with receptor in space. Among the 8-benzyloxy derivatives, the anticonvulsant activity of compounds containing substituted benzyloxy (*o*–F, *o*–Cl) was stronger than that of the compound with non-substituted benzyloxy (**3g**) in the anti-MES test, and the ED_{50} of **3i–3o** (*m*–Cl *p*–Cl, *m*–F, and *p*–F) was less than that of **3g** in the anti-MES test.

Both experimental models of epilepsy showed that the length of the alkyl chain appeared to have a direct impact on anticonvulsant activity of the 8-alkyloxyl derivatives. From compound **3a** to **3f**, as alkyl chain length increased, ED_{50} gradually increased with the compound **3d** being the most active. The trend reversed, however, when the alkyl chain had more than five carbon atoms. Among these derivatives, the most active compound was **3d,** and its ED_{50} in the MES and scMet tests were 17.5 and 21.2 mg/kg, respectively, resulting in PIs of 6.5 and 5.4, respectively, which are slightly less than that of the prototype drug carbamazepine (PI = 8.1) in the anti-MES test, and much greater than the PI in the anti-scPTZ test of carbamazepine (PI <0.72).

This may be because the hydrophilic-lipophilic property of the compound **3d** is relatively modest, which makes it easy to vehicle and pass through the blood–brain barrier.

The scPTZ has been reported to produce seizures by inhibiting γ-aminobutyric acid (GABA) neurotransmission (Hamilton and Russo, 1977; Bernasconi *et al.*, 1988), GABA is the main inhibitory neurotransmitter substance in the brain, and is widely implicated in epilepsy. Inhibition of GABA-ergic neurotransmission or activity has been shown to promote and facilitate seizures (Arnoldi *et al.*, 1990), while enhancement of GABA-ergic neurotransmission is known to inhibit or attenuate seizures. The standard anticonvulsant drugs used have also been shown to exert their anticonvulsant action by enhancing GABA-ergic neurotransmission and activity. The findings of the present study tend to suggest that the derivatives in this study

might have inhibited or attenuated PTZ-induced seizures in mice by enhancing GABA-ergic neurotransmission.

It has been reported that the voltage-gated Na^+ ion channel inhibit seizures by controlling neuronal excitability. Conventional anti-epileptics generally inhibit sodium currents (carbamazepine, phenobarbital, phenytoin, and valproate) or enhance GABA-ergic inhibition (benzodiazepines, phenobarbital, and valproate). The newly synthesized compounds may evoke sodium channel blocker activity (Piotr *et al.*, 2005; Ha *et al.*, 2002). Compounds (**3d–3f**) showed strong anticonvulsant activities in both experimental models of epilepsy, which may have a wide range of anticonvulsant effects.

Conclusions

In summary, we synthesized a series of 8-alkoxy-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine derivatives and tested their anticonvulsant activities and neurotoxicities using the MES test, scPTZ, and the rotarod tests after i.p. injection. The target compounds synthesized by incorporating a triazole ring into the parent compounds at the first and second positions of this compound, had significantly increased anticonvulsant activity compared to the parent compounds, and had improved anti-scPTZ activity compared to the benzazepine triazolone derivatives (Piao *et al.*, 2011). Among them, 8-pentyloxy-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine (**3d**) was the most active and had the lowest toxicity, with a MES ED_{50} of 17.5 mg/kg, and a PI of 6.5, which PI is slightly less than that of carbamazepine (PI = 8.1). Its scPTZ ED_{50} and PI were 21.2 mg/kg and 5.4, respectively, with these PIs being much greater than the PI of carbamazepine (ED_{50} >100, PI <0.72).

Materials and methods

Chemistry

Melting points were determined on X-5 microscope melting point apparatus, which were uncorrected. The IR spectra were recorded (in KBr) on a FT-IR (IRPRESTIGE-21). ^{1}H-NMR spectra were measured on an AV-300 (Bruker, Switzerland), and all the chemical shifts were given in parts per million relative to tetramethylsilane. Mass spectra were measured on a HP1100LC (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 Alderich Chemical Corporation. All other chemicals were of analytic grade (Scheme 1).

General procedure for preparation of compounds **2a–2o**

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, the compounds **1a–1o** (1.7 mmol) were added while stirring. The mixture was refluxed for 4–6 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 × 3), and dried over anhydrous $MgSO_4$. Evaporation of the solvents gave a crude product.

General procedure for preparation of compounds **3a–3o**

Crude products **2a–2o** (2 mmol) were reacted with methyl hydrazine carboxylate (4 mmol) in n-butanol 10 mL under nitrogen atmosphere for 40–48 h, the solvent was removed under reduced pressure, and the residue dissolved with ethy1 acetate, and washed with water 3 times. The ethy1 acetate layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was concentrated, and then the residue was purified by silica gel column chromatography (dichloromethane:Methanol = 35:1) to afford target compounds **3a–3o**.

*8-Methoxy-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine (**3a**)*

Yield: 79%, mp 123.2–124.5°C; IR (KBr)/cm: 1619, 1506 (C=N, C=C), 1233 (C–O); ^{1}H-NMR (300 MHz, MeOD) δ: 2.25–2.36 (m, 2H, C_5–H), 2.63 (t, J = 7.2 Hz, 2H, C_6–H), 2.87 (t, J = 7.2 Hz, 2H, C_4–H), 3.87 (s, 3H, O–CH_3), 6.98–7.05 (m, 2H, Ar–H), 7.44 (d, J = 8.4 Hz, 1H, Ar–H), 8.74 (s, 1H, triazole CH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.11–2.19 (m, 2H, C_5–H), 2.42–2.60 (m, C_6–H and DMSO), 2.73 (t, J = 6.9 Hz, 2H, C_4–H), 3.81 (s, 3H, –OCH_3), 6.96–7.09 (m, 2H, Ar–H), 7.44 (d, J = 8.7 Hz, 1H, Ar–H), 8.77 (s, 1H, triazole CH); ^{13}C-NMR (75 MHz, MeOD) δ: 20.8 (C_4), 28.6 (C_5), 29.6 (C_6), 54.7 ($C_{1'}$), 112.81 (C_9), 115.52 (C_7), 123.72 (C_{10}), 126.34 (C_{10a}), 135.92 (C_{6a}), 142.54 (C_1), 154.05 (C_{3a}), 160.12 (C_8). MS-APCI (positive ionization) *m/z*: 216 $(M + 1)^+$. Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52; found: C, 66.76; H, 6.08; N, 19.81.

*8-Propyloxy-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine (**3b**)*

Yield: 55%, mp 96.0–97.3°C; IR (KBr)/cm: 1618, 1506 (C=N, C=C), 1263 (C–O); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.99 (t, 3H, J = 7.2 Hz, –CH_3), 1.70–1.80 (m, 2H, alkyl $C_{2'}$–H), 2.12–2.18 (m, 2H, C_5–H), 2.47–2.56 (m, C_6–H and

DMSO), 2.73(t, 2H, $J = 6.3$ Hz, C_4–H), 3.98 (t, 2H, $J = 6.3$ Hz, alkyl $C_{1'}$–H), 6.95–7.06 (m, 2H, Ar–H), 7.42(d, 1H, $J = 8.4$ Hz, Ar–H), 8.76 (s, 1H, triazole CH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 10.8 ($C_{3'}$), 21.4 (C_4), 22.46 ($C_{2'}$), 28.7 (C_5), 30.1 (C_6), 69.8 ($C_{1'}$), 113.7 (C_9), 116.7 (C_7), 124.4 (C_{10}), 127.1 (C_{10a}), 136.0 (C_{6a}), 143.1 (C_1), 153.0 (C_{3a}), 158.8 (C_8); MS-APCI (positive ionization) *m/z*: 244 $(M + 1)^+$. Anal. Calcd. for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 68.90; H, 7.03; N, 17.49.

*8-Butyloxy-5,6-dihydro-4H-benzo[f][1,2,4]triazolo [4,3-a]azepine (**3c**)*

Yield: 51%, mp 108.6–110.2°C; IR (KBr)/cm: 1616, 1504 (C=N, C=C),1261 (C–O); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.94 (t, 3H, $J = 7.5$ Hz, –CH_3), 1.38–1.51 (m, 2H, alkyl $C_{3'}$–H), 1.66–1.76 (m, 2H, alkyl $C_{2'}$–H), 2.10–2.20 (m, 2H, C_5–H), 2.47–2.56 (m, C_6–H and DMSO), 2.73 (t, 2H, $J = 7.5$ Hz, C_4–H), 4.02 (t, 2H, $J = 6.6$ Hz, alkyl $C_{1'}$–H), 6.95–7.06 (m, 2H, Ar–H), 7.42 (d, 1H, $J = 8.4$ Hz, Ar–H), 8.75 (s, 1H, triazole CH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 14.1 ($C_{4'}$), 19.2 ($C_{3'}$), 21.4 (C_4), 28.7 (C_5), 30.1 (C_6), 31.1 ($C_{2'}$), 68.0 ($C_{1'}$), 113.7 (C_9), 116.7 (C_7), 124.4 (C_{10}), 127.1 (C_{10a}), 136.0 (C_{6a}), 143.1 (C1), 153.0 (C_{3a}), 158.8 (C_8); MS-APCI (positive ionization) *m/z*: 258 $(M + 1)^+$. Anal. Calcd. for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 69.87; H, 7.43; N, 16.51.

*8-Pentyloxy-5,6-dihydro-4H-benzo[f][1,2,4]triazolo [4,3-a]azepine (**3d**)*

Yield: 43%, mp 114.5–116.6°C; IR (KBr)/cm: 1616, 1504 (C=N, C=C), 1261 (C–O); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.90 (t, 3H, $J = 7.2$ Hz, –CH_3), 1.31–1.44 (m, 4H, alkyl $C_{3'}$–H, and $C_{4'}$–H), 1.70–1.76 (m, 2H, alkyl $C_{2'}$–H), 2.12–2.18 (m, 2H, C_5–H), 2.47–2.54 (m, C_6–H, and DMSO), 2.73 (t, 2H, $J = 7.5$ Hz, C_4–H), 4.01 (t, 2H, $J = 6.6$ Hz, H-1′), 6.95–7.06 (m, 2H, Ar–H), 7.41 (d, 1H, $J = 8.7$ Hz, Ar–H), 8.75 (s, 1H, triazole CH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 14.4 ($C_{5'}$), 21.4 (C_4), 22.3 ($C_{4'}$), 28.1 ($C_{3'}$), 28.7 (C_5), 28.8 ($C_{2'}$), 30.1 (C_6), 68.2 ($C_{1'}$), 113.6 (C_9), 116.6 (C_7), 124.4 (C_{10}), 127.1 (C_{10a}), 136.0 (C_{6a}), 143.1 (C_1), 153.0 (C_{3a}), 158.8 (C_8); MS-APCI (positive ionization) *m/z*: 272 (M^+). Anal. Calcd. for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80; N, 15.49. Found: C, 70.68; H, 7.79; N, 15.69.

*8-Hexyloxy-5,6-dihydro-4H-benzo[f][1,2,4]triazolo [4,3-a]azepine (**3e**)*

Yield: 40%, mp 112.3–113.8°C; IR (KBr)/cm: 1618, 1504 (C=N, C=C), 1260 (C–O); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.84–0.94 (m, 3H, –CH_3), 1.23–1.43 (m, 6H, alkyl $C_{3'}$–H, $C_{4'}$–H, and $C_{5'}$–H), 1.70–1.75 (m, 2H, alkyl $C_{2'}$–H), 2.12–2.18 (m, 2H, C_5–H), 2.47–2.56 (m, C_6–H and DMSO), 2.73 (t, 2H, $J = 6.9$ Hz, C_4–H), 4.01 (t, 2H, $J = 6.0$ Hz, alkyl $C_{1'}$–H), 6.96–7.06 (m, 2H, Ar–H), 7.41 (d, 1H, $J = 8.4$ Hz, Ar–H), 8.76 (s, 1H, triazole CH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 14.4 ($C_{6'}$), 21.4 (C_4), 22.6 ($C_{5'}$), 25.6 ($C_{3'}$), 28.7 (C_5), 29.1 ($C_{2'}$), 30.1 (C_6), 31.4 ($C_{4'}$), 68.2 ($C_{1'}$), 113.6 (C_9), 116.6 (C_7), 124.4 (C_{10}), 127.1 (C_{10a}), 136.0 (C_{6a}), 143.1 (C_1), 153.0 (C_{3a}), 158.8 (C_8); MS-APCI (positive ionization) *m/z*: 286 $(M + 1)^+$. Anal. Calcd. for $C_{17}H_{23}N_3O$: C, 71.55; H, 8.12; N, 14.72. Found: C, 71.34; H, 8.11; N, 15.02.

*8-Heptyloxy-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine (**3f**)*

Yield: 35%, mp 104.5–105.9°C; IR (KBr)/cm: 1616, 1504 (C=N, C=C), 1259 (C–O); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.87 (t, 3H, $J = 6.9$ Hz, –CH_3), 1.22–1.42 (m, 8H, alkyl $C_{3'}$–H, $C_{4'}$–H, $C_{5'}$–H, and $C_{6'}$), 1.67–1.77 (m, 2H, alkyl $C_{2'}$–H), 2.12–2.20 (m, 2H, C_5–H), 2.47–2.56 (m, C_6–H, and DMSO), 2.73 (t, 2H, $J = 7.2$ Hz, C_4–H), 4.00 (t, 2H, $J = 6.6$ Hz, H-1′), 6.94–7.05 (m, 2H, Ar–H), 7.41 (d, 1H, $J = 8.7$ Hz, Ar–H), 8.76 (s, 1H, triazole CH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 14.4 ($C_{7'}$), 21.4 (C_4), 22.5 ($C_{6'}$), 25.9 ($C_{5'}$), 28.7, (C_5), 28.9 ($C_{4'}$), 29.1 ($C_{3'}$), 30.1 (C_6), 31.7 ($C_{2'}$), 68.2 ($C_{1'}$), 113.7 (C_9), 116.7 (C_7), 124.4 (C_{10}), 127.1 (C_{10a}), 136.0 (C_{6a}), 143.1 (C_1), 153.0 (C_{3a}), 158.8 (C_8); MS-APCI (positive ionization) *m/z*: 300 $(M + 1)^+$. Anal. Calcd. for $C_{18}H_{25}N_3O$: C, 72.21; H, 8.42; N, 14.03. Found: C, 72.11; H, 8.40; N, 14.24.

*8-Benzyloxy-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine (**3g**)*

Yield: 44%, mp 139.0–140.4°C; IR (KBr)/cm: 1601, 1506 (C=N, C=C), 1229 (C–O); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.13–2.19 (m, 2H, C_5–H), 2.47–2.56 (m, C_6–H, and DMSO), 2.74 (t, 2H, $J = 7.2$ Hz, C_4–H), 5.16 (s, 2H, benzyl CH_2), 7.04–7.09 (m, 1H, Ar–H), 7.15–7.17 (m, 1H, Ar–H), 7.31–7.49 (m, 6H, Ar–H), 8.76 (s, 1H, triazole CH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 21.5 (C_4), 28.8 (C_5), 30.2 (C_6), 70.1 (benzyl C), 114.0 (C_9), 117.2 (C_7), 124.5 (C_{10}), 127.5 (C_{10}), 128.2 (phenyl C_2 and C_6), 128.4 (phenyl C_4), 129.06 (phenyl C_3 and C_5), 136.1 (C_{6a}), 137.3 (phenyl C_1), 143.1 (C_1), 153.0 (C_{3a}), 158.4 (C_8); MS-APCI (positive ionization) *m/z*: 292 $(M + 1)^+$. Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.05; H, 5.86; N, 14.64.

*8-(2-Chlorobenzyloxy)-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a][1]azepin (**3h**)*

Yield: 43%, mp 153.8–155.6°C. IR (KBr)/cm: 1607, 1506 (C=N, C=C), 1265 (C–O); ^{1}H-NMR (300 MHz, DMSO-d_6)

δ: 2.14–2.20 (m, 2H, C_5–H), 2.42–2.62 (m, C_6–H, and DMSO), 2.60–2.75 (m, 2H, C_4–H), 5.21 (s, 2H, benzyl CH_2), 7.06–7.20 (m, 2H, Ar–H), 7.40–7.64 (m, 5H, Ar–H), 8.77 (s, 1H, triazole CH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 21.5 (C_4), 28.7 (C_5), 30.1 (C_6), 67.7 (benzyl C), 114.0 (C_9), 117.1 (C_7), 124.6 (C_{10}), 127.7 (C_{10a}), 127.9 (phenyl C_5), 129.9 (phenyl C_6), 130.5 (phenyl C_3), 130.8 (phenyl C_4), 133.2 (phenyl C_2), 134.5 (phenyl C_1), 136.2 (C_{6a}), 143.1 (C_1), 153.0 (C_{3a}), 158.2 (C-8); MS-APCI (positive ionization) *m/z*: 326 $(M + 1)^+$. Anal. Calcd. for $C_{18}H_{16}ClN_3O$: C, 66.36; H, 4.95; N, 12.90. Found: C, 66.29; H, 4.94; N, 13.04.

*8-(3-Chlorobenzyloxy)-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine (**3i**)*

Yield: 44%, mp 113.2–117.7°C. IR (KBr)/cm: 1618, 1503 (C=N, C=C), 1261 (C–O); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.10–2.25 (m, 2H, C_5–H), 2.47–2.56 (m, C_6–H and DMSO), 2.74 (t, 2H, $J = 7.2$ Hz, C_4–H), 5.18 (s, 2H, benzyl CH_2), 7.06–7.10 (m, 2H, Ar–H), 7.43–7.62 (m, 5H, Ar–H), 8.77 (s, 1H, triazole CH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 21.4 (C_4), 28.7 (C_5), 30.1 (C_6), 69.0 (benzyl C), 114.0 (C_9), 117.2 (C_7), 124.5 (C_{10}), 126.7 (phenyl C-6), 127.6 (C_{10a}), 127.8 (phenyl C_2), 128.3 (phenyl C_4), 130.9 (phenyl C_5), 133.6 (phenyl C_3), 136.1 (C_{6a}), 139.8 (phenyl C_1), 143.1 (C_1), 153.0 (C_{3a}), 158.1 (C_8); MS-APCI (positive ionization) *m/z*: 326 $(M + 1)^+$. Anal. Calcd. for $C_{18}H_{16}ClN_3O$: C, 66.36; H, 4.95; N, 12.90. Found: C, 66.29; H, 4.94; N, 13.04.

*8-(4-Chlorobenzyloxy)-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine (**3j**)*

Yield: 39%, mp 166.6–168.2°C; IR (KBr)/cm: 1614, 1499 (C=N, C=C), 1261 (C–O); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.10–2.22 (m, 2H, C_5–H), 2.47–2.56 (m, C_6–H, and DMSO), 2.73–2.80 (m, 2H, C_4–H), 5.16 (s, 2H, benzyl CH_2), 7.04–7.16 (m, 2H, Ar–H), 7.41–7.50 (m, 5H, Ar–H), 8.76 (s, 1H, triazole CH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 21.5 (C_4), 28.7 (C_5), 30.1 (C_6), 69.2 (benzyl C), 114.1 (C9), 117.2 (C_7), 124.5 (C_{10}), 127.6 (C_{10a}), 129.0 (phenyl C_3 and C_5), 130.0 (phenyl C_2 and C_6), 133.0 (phenyl C_4), 136.1 (C_{6a}), 136.3 (phenyl C_1), 143.1 (C_1), 153.0 (C_{3a}), 158.2 (C_8); MS-APCI (positive ionization) *m/z*: 326 $(M + 1)^+$. Anal. Calcd. for $C_{18}H_{16}ClN_3O$: C, 66.36; H, 4.95; N, 12.90. Found: C, 66.23; H, 4.93; N, 12.92.

*8-(2-Fluorobenzyloxy)-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine (**3k**)*

Yield: 40%, mp 140.0–141.8°C; IR (KBr)/cm: 1618, 1492 (C=N, C=C), 1263 (C–O); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.11–2.21 (m, 2H, C_5–H), 2.47–2.56 (m, C_6–H, and DMSO), 2.74 (t, 2H, $J = 7.2$ Hz, C_4–H), 5.20 (s, 2H. benzyl CH_2), 7.06–7.12 (m, 1H, Ar–H), 7.17–7.20 (m, 1H, Ar–H), 7.23–7.31 (m, 2H, Ar–H), 7.40–7.48 (m, 2H, Ar–H), 7.56–7.62 (m, 1H, Ar–H), 8.77 (s, 1H,triazole CH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 21.4 (C_4), 28.7 (C_5), 30.1 (C_6), 64.4 (benzyl C), 113.9 (C_9), 115.9 (d, $J_{C-F} = 20.8$ Hz, phenyl C_3), 117.0(C_7), 124.0 (d, $J_{C-F} = 14.4$ Hz, phenyl C_1), 124.5 (C_{10}), 125.1 (phenyl C_5), 127.6 (C_{10a}), 131.0 (d, $J_{C-F} = 8.3$ Hz, phenyl C_4), 131.3 (phenyl C_6), 136.2 (C_{6a}), 143.1 (C_1), 153.0 (C_{3a}), 158.2 (C_8), 160.9 (d, $J_{C-F} = 244.8$ Hz, phenyl C_2); MS-APCI (positive ionization) *m/z*: 310 $(M + 1)^+$. Anal. Calcd. for $C_{18}H_{16}FN_3O$: C, 69.89; H, 5.21; N, 13.58. Found: C, 69.68; H, 5.20; N, 13.74.

*8-(3-Fluorobenzyloxy) -5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine (**3l**)*

Yield: 38%, mp 120.1–121.3°C; IR (KBr)/cm: 1597, 1508 (C=N, C=C), 1260 (C–O); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.13–2.19 (m, 2H, C_5–H), 2.47–2.56 (m, C_6–H and DMSO), 2.74 (t, 2H, $J = 7.2$ Hz, C_4–H), 5.19 (s, 2H, benzyl CH_2), 7.04–7.10 (m, 1H, Ar–H), 7.16–7.21 (m, 2H, Ar–H), 7.29–7.34 (m, 2H, Ar–H), 7.43–7.48 (m, 2H, Ar–H), 8.76 (s, 1H, triazole CH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 21.4 (C_4), 28.7 (C_5), 30.1 (C_6), 69.1 (benzyl C), 114.0 (C_9), 114.8 (d, $J_{C-F} = 21.7$ Hz, phenyl C_2), 115.2 (d, $J_{C-F} = 20.8$ Hz, phenyl C_4), 117.2 (C_7), 124.0 (d, $J_{C-F} = 2.2$ Hz, phenyl C_6), 124.5 (C_{10}), 127.6 (C_{10a}), 131.0 (d, $J_{C-F} = 8.3$ Hz, phenyl C_5), 136.1 (C_{6a}), 140.2 (d, $J_{C-F} = 7.4$ Hz, phenyl C_1), 143.1 (C_1), 153.0 (C_{3a}), 158.2 (C_8), 162.7 (d, $J_{C-F} = 242.2$ Hz, phenyl C_3); MS-APCI (positive ionization) *m/z*: 310 $(M + 1)^+$. Anal. Calcd. for $C_{18}H_{16}FN_3O$: C, 69.89; H, 5.21; N, 13.58. Found: C, 69.81; H, 5.19; N, 13.60.

*8-(4-Fluorobenzyloxy)-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine (**3m**)*

Yield: 40%, mp 145.0–146.2°C; IR (KBr)/cm: 1604, 1506 (C=N, C=C), 1229 (C–O); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.11–2.21 (m, 2H, C_5–H), 2.47–2.56 (m, C_6–H and DMSO), 2.74 (t, 2H, $J = 6.9$ Hz, C_6–H), 5.14 (s, 2H, benzyl CH_2), 7.04–7.16 (m, 1H, Ar–H), 7.14–7.16 (m, 1H, Ar–H), 7.20–7.27 (m, 2H, Ar–H), 7.44 (d, 1H, $J = 8.7$ Hz, Ar–H), 7.50–7.56 (m, 2H, Ar–H), 8.76 (s, 1H, triazole CH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 21.4 (C_4), 28.7 (C_5), 30.1 (C_6), 69.3 (benzyl C), 114.0 (C_9), 115.8 (d, $J_{C-F} = 21.2$ Hz, phenyl C_3 and C_5), 117.1 (C_7), 124.5 (C_{10}), 127.5 (C_{10a}), 130.5 (d, $J_{C-F} = 8.4$ Hz, phenyl C_2 and C_6), 133.4 (phenyl C_1), 136.1 (C_{6a}), 143.1 (C_1), 153.0 (C_{3a}), 158.3 (C_8), 162.3 (d, $J_{C-F} = 242.2$ Hz, phenyl C_4);

MS-APCI (positive ionization) *m/z*: 310 $(M + 1)^+$. Anal. Calcd. for $C_{18}H_{16}FN_3O$: C, 69.89; H, 5.21; N, 13.58. Found: C, 69.75; H, 5.17; N, 13.59.

*8-(4-Bromobenzyloxy)-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine (**3n**)*

Yield: 33%, mp 150.1–151.8°C; IR (KBr)/cm: 1614, 1497 (C=N, C=C), 1260 (C–O); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.13–2.18 (m, 2H, C_5–H), 2.47–2.56 (m, C_6–H and DMSO), 2.74 (t, 2H, $J = 7.2$ Hz, C_4–H), 5.15 (s, 2H, benzyl CH_2), 7.00–7.07 (m, 1H, Ar–H), 7.14–7.16 m, 1H, Ar–H), 7.42–7.46 (m, 2H, Ar–H), 7.61 (d, 2H, $J = 8.4$ Hz, Ar–H), 8.76 (s, 1H, trazolel CH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 21.4 (C_4), 28.7 (C_5), 30.1 (C_6), 69.2 (benzyl C), 114.0 (C_9), 117.2 (C_7), 121.5 (phenyl C_4), 124.5 (C_{10}), 127.5 (C_{10a}), 130.3 (phenyl C_2 and C_6), 131.9 (phenyl C_3 and C_5), 136.1 (C_{6a}), 136.7 (phenyl C_1), 143.1 (C_1), 153.0 (C_{3a}), 158.2 (C_8); MS-APCI (positive ionization) *m/z*: 370 $(M + 1)^+$. Anal. Calcd. for $C_{18}H_{16}BrN_3O$: C, 58.39; H, 4.36; N, 11.35. Found: C, 58.27; H, 4.35; N, 11.36.

*8-(4-Methylbenzyloxy)-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine (**3o**)*

Yield: 43%, mp 130.1–131.3°C; IR (KBr)/cm: 1608, 1504 (C=N, C=C), 1227 (C–O); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.10–2.22 (m, 2H, C_5–H), 2.32 (s, 3H, –CH_3), 2.47–2.56 (m, C_6-H, and DMSO), 2.70–2.80 (m, 2H, C_4–H), 5.11 (s, 2H, benzyl CH_2), 7.00–7.25 (m, 4H, Ar–H), 7.30–7.50 (m, 3H, Ar–H), 8.76 (s, 1H, triazole CH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 21.2 (CH_3), 21.4 (C_4), 28.7 (C_5), 30.1 (C_6), 69.9 (benzyl C), 114.0 (C_9), 117.2 (C_7), 124.4 (C_{10}), 127.4 (C_{10a}), 128.3 (phenyl C_2 and C_6), 129.5 (phenyl C_3 and C_5), 134.2 (phenyl C_4), 136.1 (C_{6a}), 137.7 (phenyl C_1), 143.1 (C_1), 153.0 (C_{3a}), 158.4 (C_8); MS-APCI (positive ionization) *m/z*: 306 $(M + 1)^+$. Anal. Calcd. for $C_{19}H_{19}N_3O$: C,74.73; H, 6.27; N, 13.76. Found: C, 74.51; H, 6.26; N, 13.91.

Pharmacology

The MES test, scPTZ test, and rotarod test were carried out by the ADD, Epilepsy Branch, National Institutes of Health, Bethesda, MD, USA (Krall *et al.*, 1978; Porter *et al.*, 1984). All the compounds were tested for their anticonvulsant activities with Swiss 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 DMSO.

In phase I screening (Table 1), each compound was administered at three dose levels (30, 100, and 300 mg/kg i.p.) with anticonvulsant activity and neurotoxicity being assessed at 30-min intervals after administration. Anticonvulsant efficacy was measured in the MES and the scPTZ tests. In the MES test, seizures were elicited with a 60 Hz, a.c. of 50 mA intensity in mice. The current was applied via corneal electrodes for 0.2 s. Abolition of the hind-limb tonic extensor component of the seizure indicated protection against the spread of MES-induced seizures. The scPTZ test involved subcutaneous injection of a convulsant dose of pentylenetetrazol (85 mg/kg in mice). Elevation of the pentylenetetrazol-induced seizure threshold was indicated by the absence of clonic spasms for at least 5-s duration over a 30-min period following administration of the test compound. Anticonvulsant drug-induced neurologic deficit was detected in mice by using the rotarod ataxia test.

Anticonvulsant activity was expressed in terms of the ED_{50}, and neurotoxicity was expressed as the TD_{50}. For determination of the ED_{50} and TD_{50} values, groups of 10 mice were given a range of i.p. doses of the tested compounds until at least three points were established in the range of 10–90% seizure protection or minimal observed neurotoxicity (Krall *et al.*, 1978; Porter *et al.*, 1984). 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 (Okada *et al.*, 1989).

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