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Synthesis and anticonvulsant activity of 8-alkoxy-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-one derivatives

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ABSTRACT

A series of novel 8-alkoxy-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-one derivatives were synthesized and screened for their anticonvulsant activities by the maximal electroshock (MES) test, subcutaneous pentylenetetrazol (scPTZ) test, and their neurotoxicity was evaluated by the rotarod neurotoxicity test (Tox). The results of these tests demonstrated that 8-heptyloxy-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-one (**3f**) and 8-hexyloxy -5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-one (**3e**) were the most promising compounds, with median effective dose (ED_{50}) of 17.6 and 17.9 mg/kg, and protective index (PI) of greater than 63.4 and 62.4 in the MES test, respectively. These PI values were higher than the PI value of the prototype antiepileptic drug carbamazepine. The scPTZ test showed that 8-pentyloxy-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-one (**3d**) was the most potent with ED_{50} value of 38.0 mg/kg and PI value of greater than 29.4, which is much safer than marketed drug carbamazepine. The possible structure–activity relationship was discussed.

1. Introduction

According to literature reports, currently available antiepileptic drugs (AEDs) provide adequate seizure control in many patients, still about 28–30% of patients are estimated to be poorly treated [1,2]. Therefore, continued search for safer and more effective AEDs is urgently necessary. Much efforts devoted in the recent years for the development of novel compounds as potential anticonvulsant agents [3–11].

Benzazepine derivatives exhibit a broad spectrum of pharmacological activity [12–15]. Triazole compounds have wide variety of biological activities, the introduction of triazole ring to some active molecules may significantly improve the biological activity of the parent molecule due to the superposition of biological activity [16–20]. In our search for new compounds with anticonvulsant activity, 1,3,4,5-tetrahydro-7- alkoxy-2*H*-1-benzazepin-2-one derivatives showed a moderate anticonvulsant activity, among which 1,3,4,5-tetrahydro-7-butyloxy-2*H*-1-benzazepin-2-one (**1b**), revealed as the best anticonvulsant activity with an effective dose of 52.8 mg/kg in the anti-MES test. In order to obtain compounds with better anticonvulsant activity, the target compounds were synthesized through a convenient synthetic sequence. The new compounds were evaluated as anticonvulsant agents in experimental epilepsy models, i.e., the maximal electroshock (MES) test, subcutaneous pentylenetetrazol (scPTZ) test, and neurotoxicity were evaluated by using the rotarod test.

2. Results and discussion

2.1. Chemistry

Target compounds were prepared according to Scheme 1. The starting material 1,3,4,5-tetrahydro-7-hydroxy -2*H*-1-benzazepin-2-one was synthesized using the method described in a former paper of our group [12], which reacted with appropriate alkyl halide to produce the compounds **1a**–**p** [12]. Compounds **1a**–**p** then reacted with phosphorus pentasulfide in acetonitrile in the presence of triethylamine under protection of nitrogen, and the resulting compounds **2a**–**p** reacted further with methyl hydrazine carboxylate in *n*-butanol to produce the target compounds **3a**–**p**. The structures of all the new compounds were confirmed by IR, ^{1}H NMR, MS and elemental analyses and their anticonvulsant activities have been initially screened.

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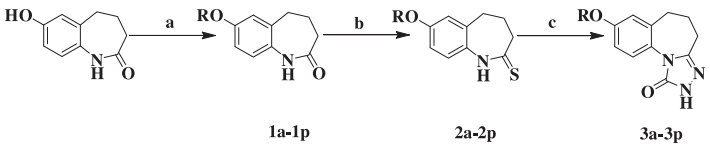

1a-1p 2a-2p 3a-3p

R:

3a = n- C_3H_7 3e = n-C_7H_{15} 3i = $CH_2C_6H_4$(*m*-Cl) 3m = $CH_2C_6H_4$(*p*-F)

3b = n-C_4H_9 3f =n-C_8H_{17} 3j = $CH_2C_6H_4$(*p*-Cl) 3o= $CH_2C_6H_4$(*p*-CH_3)

3c = n-C_5H_{11} 3g = $CH_2C_6H_5$ 3k = $CH_2C_6H_4$(*o*-F) 3p= $CH_2C_6H_4$(*p*-Br)

3d= n-C_6H_{13} 3h = $CH_2C_6H_4$(*o*-Cl) 3l = $CH_2C_6H_4$(*m*-F)

Reagents: (**a**) RX/C_2H_5OH, 80-92℃; (**b**) P_2S_5, $(C_2H_5)_3N$ /CH_3CN, 86-92℃, 5-7 h; (**d**) $H_2NNHCOOCH_3$/$(CH_3)(CH_2)_3OH$, 140-150℃, 40-48 h

Scheme 1. The synthesis route of compounds **3a**–**p**.

2.2. Pharmacology

Based on previous reports [21–23], we knew that trazoles have activity against both major and minor seizures. The MES test is regarded as the pharmacologic model of grand mal, and the scPTz test as the pharmacologic model of petit mal seizures. Therefore we carried out those two tests to evaluate the anticonvulsant activity of the synthesized compounds.

The results of preliminary (phase I) screening of compounds **3a**–**p** are summarized in Table 1. In the anti-MES test, all the synthesized compounds exhibited anticonvulsant activity, among which eight compounds (**3d**–**g**, **3j**, and **3l**–**n**) possessed anticonvulsant activity against MES-induced seizure at the dose of 30 mg/kg, and seven compounds (**3b**–**c**, **3h**–**i**, **3k** and **3o**–**p**) 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. As a result of preliminary screening, compounds **3b**–**p** were subjected to phase II trials for quantification of their anticonvulsant activity (indicated by ED_{50}) and neurotoxicity (indicated by TD_{50}) in mice (Table 2). Among these derivatives, the most potent compounds **3f** and **3m** exhibited similar activity with ED_{50} value of 17.6 mg/kg, furthermore, they had significantly lower neurotoxicity (TD_{50} > 1117.4 mg/kg, TD_{50} > 931.2 mg/kg, respectively) than the marked antiepileptic drug carbamazepine. And their PI value (PI > 63.4, PI > 52.6, respectively) was superior to that of carbamazepine (TD_{50} = 71.6 mg/kg, PI = 8.1) in the MES test.

Analyzing the activities of the synthesized compounds the following structure–activity relationships (SAR) were obtained. Generally, the anticonvulsant activity of an organic compound might be increased remarkably after the introduction of a halogen atom. So, some halogen substituted derivatives were designed and synthesized in this paper. Comparison of the halogen substituted derivatives indicated that different halogen atoms contributed to the anticonvulsant activity in the order of F > Cl > Br; the introduction of F atom on the benzyl ring led to stronger activity. Comparing the derivatives with different F-substitution positions on the benzyl ring, their activity order was *m*-F > *o*-F > *p*-F, and activity order of the Cl- and Br-atom substituted derivatives was *m*-Cl > *o*-Cl > *p*-Cl > *p*-Br. One electron donor derivative (**3o**) was also designed and prepared, and its activity was slightly low. The anticonvulsant activity of compounds containing substituted benzyloxy (*m*-F, *o*-F, *p*-F, *m*-Cl) was stronger than that of the compound with non-substituted benzyloxy (**3h**). The anticonvulsant activity of another four substituted-benzyloxy derivatives **3i**, **3k**, **3o** and **3p** was lower than that of the compound **3h**. The *m*-F-substituted derivative **3m** exhibited the strongest anticonvulsant activity.

Length of the alkyl chain appeared to have a direct impact on anticonvulsant activity of the 7-alkoxyl derivatives. From compound **3a** to **3g**, as alkyl chain length increased, ED_{50} gradually increased with the compound **3f** being the most active. However, the anticonvulsant activity decreased when alkyl chain number lengthened to 8.

In the anti-scPTz test, the synthesized compounds exhibited a less- to moderate-degree of anticonvulsant activity. As a result of preliminary screening, eight compounds (**3c**–**j**) were quantitatively evaluated for their anticonvulsant activity. They showed less effective against scPTZ-induced seizures but exhibited a high degree of protection against scPTz-induced seizures. 8-Pentyloxy-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-one (**3d**) was among the most active but also has the lowest toxicity. It showed the ED_{50} value of 38.0 mg/kg, and the PI of greater than 29.4, which is also much greater than the PI of the marked antiepileptic drug carbamazepine.

Pentylenetetrazole has been reported to produce seizures by inhibiting γ-aminobutyric acid (GABA) neurotransmission [24,25]. GABA is the main inhibitory neurotransmitter substance in the brain, and is widely implicated in epilepsy. Inhibition of GABAergic neurotransmission has been shown to promote and facilitate seizures [26], while enhancement of GABAergic neurotransmission is known to inhibit or attenuate seizures. The compound **3d** might enhance GABAergic neurotransmission.

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

Comp.	R	MES[b]			scPTZ[b]		
		30[c]	100	300	30[c]	100	300
3a	$-CH_3$	1/5	1/5	5/5	0/5	0/5	0/5
3b	$-C_3H_7$	1/5	4/5	–[d]	0/5	1/5	1/5
3c	$-C_4H_9$	2/5	5/5	–[d]	1/5	5/5	–[d]
3d	$-C_5H_{11}$	5/5	–[d]	–[d]	1/5	5/5	–[d]
3e	$-C_6H_{13}$	5/5	–[d]	–[d]	1/5	5/5	–[d]
3f	$-C_7H_{15}$	5/5	–[d]	–[d]	1/5	5/5	–[d]
3g	$-C_8H_{17}$	4/5	–[d]	–[d]	1/5	5/5	–[d]
3h	$-PhCH_2$	3/5	5/5	–[d]	1/5	1/5	1/5
3i	$-CH_2C_6H_4$(*o*-Cl)	3/5	5/5	–[d]	1/5	0/5	1/5
3j	$CH_2C_6H_4$(*m*-Cl)	4/5	–[d]	–[d]	1/5	1/5	1/5
3k	$-CH_2C_6H_4$(*p*-Cl)	2/5	5/5	–[d]	1/5	1/5	0/5
3l	$-CH_2C_6H_4$(*o*-F)	5/5	–[d]	–[d]	0/5	1/5	0/5
3m	$-CH_2C_6H_4$(*m*-F)	5/5	–[d]	–[d]	0/5	0/5	1/5
3n	$-CH_2C_6H_4$(*p*-F)	4/5	–[d]	–[d]	0/5	1/5	1/5
3o	$-CH_2C_6H_4$(*p*-CH_3)	3/5	4/5	–[d]	0/5	0/5	1/5
3p	$-CH_2C_6H_4$(*p*-Br)	1/5	5/5	–[d]	1/5	1/5	1/5

[a] All of tested compounds were dissolved in DMSO.
[b] The maximal electroshock test was induced after 30 min past administration of the tested compounds.
[c] Doses are denoted in milligrams per kilogram.
[d] Not tested.

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

Comp.	ED_{50}[a]		TD_{50}[b]	PI[c]	
	MES	scPTZ	Rotarod toxicity	MES	scPTZ
3b	75.5 (100–65.4)[d]	–[e]	> 931.2	> 12.3	–[e]
3c	37.3 (49.7–28.1)	65.8 (83.0–55.8)[d]	> 1117.4	> 29.9	> 17.0
3d	24.6 (28.4–21.3)	38.0 (50.3–28.2)	> 1117.4	> 45.4	> 29.4
3e	17.9 (18.6–17.2)	46.5 (54.5–41.2)	> 1117.4	> 62.4	> 24.0
3f	17.6 (18.3–16.9)	43.2 (54.3–38.3)	> 1117.4	> 63.4	> 25.9
3g	20.7 (25.6–15.8)	50.2 (60.6–44.5)	> 1117.4	> 54.0	> 22.2
3h	30.5 (37.3–24.9)	–	> 931.2	> 30.5	–
3i	32.9 (39.5–27.4)	–	> 931.2	> 28.3	–
3j	26.4 (31.0–22.5)	–	> 931.2	> 35.3	–
3k	40.1 (55.2–29.1)	–	> 931.2	> 23.2	–
3l	18.4 (21.6–15.7)	–	> 931.2	> 50.6	–
3m	17.6 (20.2–15.5)	–	> 931.2	> 52.9	–
3n	22.8 (27.4–19.0)	–	> 931.2	> 40.8	–
3o	50.0 (64.6–38.7)	–	> 931.2	> 18.6	–
3p	55.8 (75.7–41.2)	–	> 931.2	> 16.7	–
Carbam.	9.2 (6.9–11.7)	> 100	74.4 (59.1–87.5)	8.1	< 0.74

[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 protective index (TD_{50}/ED_{50}).
[d] 95% confidence limits given in parentheses.
[e] — = No activity at the corresponding dose.

3. Conclusions

A series of novel 8-alkoxy-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-one derivatives were synthesized. In the anti-MES test, all synthesized compounds displayed varying degrees of anticonvulsant activity, the compounds **3f** and **3e** possessed the most potential anticonvulsant activity with ED_{50} value of 17.6 mg/kg and 17.9 mg/kg, and had PI of greater than 63.4 and 62.4 respectively, which is much greater than the PI of the marked antiepileptic drug carbamazepine. Although **3m** with ED_{50} value of 17.6 mg/kg^{-1}, its PI (PI > 52.9 mg/kg) is less than that of **3e** (PI > 62.4). They can be used as a lead for further development of more potent anticonvulsant agents, and they might exhibit sodium channel blocker activity.

In the anti-scPTz test, the compound **3d** was among the most active but also has the lowest toxicity. It showed ED_{50} of 38.0 mg/kg, and PI of greater than 29.4, which is much safer than marketed drug carbamazepine. It might enhance GABAergic neurotransmission and exhibit sodium channel blocker activity.

4. Experimental section

4.1. Chemistry

Melting points were determined on X-5 microscope melting point apparatus, which were uncorrected. IR spectra were recorded (in KBr) on an FT-IR (IRPRESTIGE-21). ^{1}H NMR spectra were measured on an AV-300 (Bruker, Switzerland), and all 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 analytical grade.

4.2. General procedure for the preparation of ***2a–p***

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 **1a–p** (1.7 mmol) was 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.

4.3. General procedure for preparation of compounds ***3a–p***

Crude product **2a–p** (2 mmol) reacted with methyl hydrazine carboxylate (4mmol) 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 three times. The ethy1 acetate layer was dried over anhydrous $MgSO_4$, filtered, and concentrated the solvent, and the residue was purified by silica gel column chromatography (dichloromethane–methanol = 35:1) to afford target compounds **3a–p**.

4.3.1. 8-Methoxy-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (***3a***)

IR (KBr, ν, cm^{-1}): 3180 (N–H), 1714 (C=O), 1578, 1504, 1442 (C=N, C=C), 1264 (C–O); ^{1}H NMR (300 MHz, δ, ppm, DMSO-d_6): 2.05 (t, 2H, J = 7.1 Hz, C_5–H), 2.45–2.55 (m, C_6–H and DMSO), 2.58 (t, 2H, J = 6.8 Hz, C_4–H), 3.79 (s, O–CH_3), 6.90–7.00 (m, 2H, ar), 7.39 (d, 1H, J = 8.6 Hz, ar), 11.66 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 23.1 (C_5), 27.4 (C_4), 30.0 (C_6), 55.8 ($C_{1'}$), 112.8 (C_7), 115.6 (C_9), 125.5 (C_{10}), 126.0 (C_{10a}), 136.3 (C_{6a}), 147.0 (C_{3a}, C=N), 153.7 (C_1, C=O), 158.6 (C_8); MS (APCI) *m/z* (%): 260.1 (M^++1, 100); Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.27; H, 5.81; N, 18.12.

4.3.2. 8-Propyloxy-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (***3b***)

IR (KBr, ν, cm^{-1}): 3180 (N–H), 1714 (C=O), 1580, 1504, 1441 (C=N, C=C), 1262 (C–O); ^{1}H NMR (300 MHz, δ, ppm, DMSO-d_6): 0.98 (t, 3H, J = 7.4 Hz, CH_3), 1.67–1.80 (m, 2H, alkyl $C_{2'}$–H), 1.90–2.10 (m, 2H, C_5–H), 2.42–2.61 (m, C_4–H, C_6–H and DMSO), 3.95 (t, 2H, J = 6.5 Hz, O–CH_2), 6.91–6.98 (m, 2H, ar), 7.37 (d, 1H, J = 8.6 Hz, ar), 11.66 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 10.8 ($C_{3'}$), 22.5 ($C_{2'}$), 23.1 (C_5), 27.4 (C_4), 30.1 (C_6), 69.6 ($C_{1'}$), 113.2 (C_7), 116.2 (C_9), 125.5 (C_{10}), 125.9 (C_{10a}), 136.3 (C_{6a}), 147.0 (C_{3a}, C=N), 153.7 (C_1, C=O), 158.0 (C_8);

MS (APCI) *m/z* (%): 260.1 (M^++1, 100); Anal. Calcd. for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 64.65; H, 6.74; N, 16.15.

4.3.3. 8-Butyloxy-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (**3c**)

IR (KBr, ν, cm^{-1}): 3181 (N–H), 1714 (C=O), 1577, 1503, 1441 (C=N, C=C), 1263 (C–O); ^{1}H NMR (300 MHz, δ, ppm, DMSO-d_6): 0.94 (t, 3H, J = 7.0 Hz, CH_3), 1.40–1.48 (m, 2H, alkyl $C_{3'}$–H), 1.68–1.73 (m, 2H, alkyl $C_{2'}$–H), 1.90–2.20 (m, 2H, C_5–H), 2.45–2.58 (m, C_4–H, C_6–H and DMSO), 3.99 (t, 2H, J = 5.6 Hz, O–CH_2), 6.90–7.00 (m, 2H, ar), 7.37 (d, 1H, J = 8.4 Hz, ar), 11.66 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 14.2 ($C_{4'}$), 19.2 ($C_{3'}$), 23.1 (C_5), 27.4 (C_4), 30.1 (C_6), 31.2 ($C_{2'}$), 67.9 ($C_{1'}$), 113.2 (C_7), 116.2 (C_9), 125.5 (C_{10}), 125.9 (C_{10a}), 136.3 (C_{6a}), 147.0 (C_{3a}, C=N), 153.8 (C_1, C=O), 158.1 (C_8); MS (APCI) *m/z* (%): 274.1 (M^++1, 100); Anal. Calcd. for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 11.71. Found: C, 65.85; H, 7.08; N, 11.67.

4.3.4. 8-Pentyloxy-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (**3d**)

IR (KBr, ν, cm^{-1}): 3186 (N–H), 1713 (C=O), 1580, 1504, 1443 (C=N, C=C), 1267 (C–O); ^{1}H NMR (300 MHz, δ, ppm, DMSO-d_6): 0.73–0.10 (m, 3H, CH_3), 1.16–1.39 (m, 4H, alkyl $C_{3'}$–H, $C_{4'}$–H), 1.60–1.90 (m, 2H, alkyl $C_{2'}$–H), 1.90–2.18 (m, 2H, C_5–H), 2.45–2.58 (m, C_4–H, C_6–H and DMSO), 3.98 (t, 2H, J = 6.0 Hz, O–CH_2), 6.90–7.00 (m, 2H, ar), 7.36 (d, 1H, J = 8.6 Hz, ar), 11.66 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 14.4 ($C_{5'}$), 22.3 ($C_{4'}$), 23.1 (C_5), 27.4 (C_4), 28.2 ($C_{3'}$), 28.8 ($C_{2'}$), 30.0 (C_6), 68.1 ($C_{1'}$), 113.1 (C_7), 116.1 (C_9), 125.5 (C_{10}), 125.8 (C_{10a}), 136.3 (C_{6a}), 147.0 (C_{3a}, C=N), 153.7 (C_1, C=O), 158.0 (C_8); MS (APCI) *m/z* (%): 288.1 (M^++1, 100); Anal. Calcd. for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 66.68; H, 7.55; N, 14.59.

4.3.5. 8-Hexyloxy-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (**3e**)

IR (KBr, ν, cm^{-1}): 3186 (N–H), 1713 (C=O), 1578, 1503, 1443 (C=N, C=C), 1263 (C–O); ^{1}H NMR (300 MHz, δ, ppm, DMSO-d_6): 0.70–0.10 (m, 3H, CH_3), 1.27–1.50 (m, 6H, alkyl $C_{3'}$–H, $C_{4'}$–H, $C_{5'}$–H), 1.55–1.74 (m, 2H, alkyl $C_{2'}$–H), 1.90–2.18 (m, 2H, C_5–H), 2.45–2.58 (m, C_4–H, C_6–H and DMSO), 3.98 (t, 2H, J = 6.2 Hz, O–CH_2), 6.82–7.01 (m, 2H, ar), 7.36 (d, 1H, J = 8.6 Hz, ar), 11.66 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 14.4 ($C_{6'}$), 22.5 ($C_{5'}$), 23.1 (C_5), 25.6 ($C_{4'}$), 27.4 (C_4), 29.1 ($C_{3'}$), 30.0 (C_6), 31.4 ($C_{2'}$), 68.1 ($C_{1'}$), 113.1 (C_7), 116.1 (C_9), 125.5 (C_{10}), 125.8 (C_{10a}), 136.3 (C_{6a}), 147.0 (C_{3a}, C=N), 153.7 (C_1, C=O), 158.0 (C_8); MS (APCI) *m/z* (%): 302.1 (M^++1, 100); Anal. Calcd. for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.68; H, 7.84; N, 13.91.

4.3.6. 8-Heptyloxy-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (**3f**)

IR (KBr, ν, cm^{-1}): 3186 (N–H), 1713 (C=O), 1580, 1503, 1443 (C=N, C=C), 1265 (C–O); ^{1}H NMR (300 MHz, δ, ppm, DMSO-d_6): 0.72–0.91 (m, 3H, CH_3), 1.27–1.50 (m, 8H, alkyl $C_{3'}$–H, $C_{4'}$–H, $C_{5'}$–H, $C_{6'}$–H), 1.63–1.82 (m, 2H, alkyl $C_{2'}$–H), 1.90–2.20 (m, 2H, C_5–H), 2.43–2.58 (m, C_4–H, C_6–H and DMSO), 3.98 (t, 2H, J = 6.3 Hz, O–CH_2), 6.82–7.01 (m, 2H, ar), 7.36 (d, 1H, J = 8.6 Hz, ar), 11.65 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 14.4 ($C_{7'}$), 22.5 ($C_{6'}$), 23.1 (C_5), 25.9 ($C_{5'}$), 27.4 (C_4), 28.9 ($C_{4'}$), 29.1 ($C_{3'}$), 30.0 (C_6), 31.7 ($C_{2'}$), 68.1 ($C_{1'}$), 113.1 (C_7), 116.1 (C_9), 125.5 (C_{10}), 125.9 (C_{10a}), 136.2 (C_{6a}), 147.0 (C_{3a}, C=N), 153.7 (C_1, C=O), 158.0 (C_8); MS (APCI) *m/z* (%): 316.1 (M^++1, 100); Anal. Calcd. for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.53; H, 8.07; N, 13.29.

4.3.7. 8-Octyloxy-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (**3g**)

IR (KBr, ν, cm^{-1}): 3186 (N–H), 1710 (C=O), 1581, 1503, 1443 (C=N, C=C), 1264 (C–O); ^{1}H NMR (300 MHz, δ, ppm, DMSO-d_6): 0.70–0.90 (m, 3H, CH_3), 1.20–1.45 (m, 10H, alkyl $C_{3'}$–H, $C_{4'}$–H, $C_{5'}$–H, $C_{6'}$–H, $C_{7'}$–H), 1.66–1.90 (m, 2H, alkyl $C_{2'}$–H), 1.90–2.20 (m, 2H, C_5–H), 2.42–2.60 (m, C_4–H, C_6–H and DMSO), 3.98 (t, 2H, J = 6.3 Hz, O–CH_2), 6.90–7.00 (m, 2H, ar), 7.36 (d, 1H, J = 8.6 Hz, ar), 11.66 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 13.9 ($C_{8'}$), 22.1 ($C_{7'}$), 23.1 (C_5), 25.2 ($C_{3'}$), 27.4 (C_4), 28.6 ($C_{5'}$), 28.8 ($C_{4'}$), 29.1 ($C_{2'}$), 30.0 (C_6), 31.1 ($C_{6'}$), 68.1 ($C_{1'}$), 113.1 (C_7), 116.2 (C_9), 125.5 (C_{10}), 125.9 (C_{10a}), 136.2 (C_{6a}), 147.0 (C_{3a}, C=N), 153.7 (C_1, C=O), 158.0 (C_8); MS (APCI) *m/z* (%): 330.1 (M^++1, 100); Anal. Calcd. for $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.76. Found: C, 69.20; H, 8.42; N, 12.72.

4.3.8. 8-Benzyloxy-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (**3h**)

IR (KBr, ν, cm^{-1}): 3167 (N–H), 1703 (C=O), 1585, 1504, 1437 (C=N, C=C), 1244 (C–O); ^{1}H NMR (300 MHz, δ, ppm, DMSO-d_6): 2.00–2.08 (m, 2H, C_5–H), 2.44–2.60 (m, C_4–H, C_6–H and DMSO), 5.13 (s, 2H, CH_2), 7.00–7.10 (m, 2H, ar), 7.33–7.50 (m, 6H, ar), 11.67 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 23.1 (C_5), 27.4 (C_4), 30.0 (C_6), 69.9 (CH_2), 113.5 (C_7), 116.6 (C_9), 125.3 (C_{10}), 126.2 (C_{10a}), 128.2 ($C_{2,\ phenyl}$, $C_{6,\ phenyl}$), 128.4 ($C_{4,\ phenyl}$), 128.9 ($C_{3,\ phenyl}$, $C_{5,\ phenyl}$), 136.4 (C_{6a}), 137.3 ($C_{1,\ phenyl}$), 147.0 (C_{3a}, C=N), 153.7 (C_1, C=O), 157.5 (C_8); MS (APCI) *m/z* (%): 284.1 (M^++1, 100); Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.33; H, 5.70; N, 13.64.

4.3.9. 8-(4-Chlorobenzyloxy)-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (**3i**)

IR (KBr, ν, cm^{-1}): 3179 (N–H), 1715 (C=O), 1580, 1501, 1441 (C=N, C=C), 1261 (C–O); ^{1}H NMR (300 MHz, δ, ppm, DMSO-d_6): 2.00–2.10 (m, 2H, C_5–H), 2.43–2.60 (m, C_4–H, C_6–H and DMSO), 5.14 (s, 2H, CH_2), 6.90–7.10 (m, 2H, ar), 7.39 (d, 1H, J = 8.6 Hz, ar), 7.43–7.50 (m, 4H, ar), 11.67 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 23.1 (C_5), 27.3 (C_4), 30.0 (C_6), 69.0 (CH_2), 113.5 (C_7), 116.6 (C_9), 125.6 (C_{10}), 126.3 (C_{10a}), 128.9 ($C_{2,6,}$ phenyl), 130.0 ($C_{3,5,}$ phenyl), 132.9 (C_4, phenyl), 136.4 (C_{6a}, C_1, phenyl), 147.0 (C_{3a}, C=N), 153.7 (C_1, C=O), 157.5 (C_8); MS (APCI) *m/z* (%): 342.0 (M^++1, 100); Anal. Calcd. for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29. Found: C, 63.24; H, 4.84; N, 12.28.

4.3.10. 8-(2-Chlorobenzyloxy)-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (**3j**)

IR (KBr, ν, cm^{-1}): 3163 (N–H), 1694 (C=O), 1587, 1504, 1439 (C=N, C=C), 1244 (C–O); ^{1}H NMR (300 MHz, δ, ppm, DMSO-d_6): 2.00–2.10 (m, 2H, C_5–H), 2.43–2.63 (m, C_4–H, C_6–H and DMSO), 5.19 (s, 2H, CH_2), 7.00–7.13 (m, 2H, ar), 7.38–7.43 (m, 3H, ar), 7.51–7.60 (m, 1H, ar), 7.61–7.65 (m, 1H, ar), 11.68 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 23.1 (C_5), 27.3 (C_4), 30.0 (C_6), 67.6 (CH_2), 113.5 (C_7), 116.5 (C_9), 125.6 (C_{10}), 126.5 (C_{10a}), 127.9 (C_5, phenyl), 129.9 (C_6, phenyl), 130.4 (C3, phenyl), 130.7 (C_4, phenyl), 133.2 (C_2, phenyl), 134.6 (C_1, phenyl), 136.5 (C_{6a}), 147.0 (C_{3a}, C=N), 153.7 (C_1, C=O), 157.5 (C_8); MS (APCI) *m/z* (%): 342.0 (M^++1, 100); Anal. Calcd. for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29. Found: C, 63.19; H, 4.81; N, 12.25.

4.3.11. 8-(3-Chlorobenzyloxy)-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (**3j**)

IR (KBr, ν, cm^{-1}): 3175 (N–H), 1713 (C=O), 1578, 1503, 1443 (C=N, C=C), 1263 (C–O); ^{1}H NMR (300 MHz, δ, ppm, DMSO-d_6): 2.00–2.10 (m, 2H, C_5–H), 2.43–2.63 (m, C_4–H, C_6–H and DMSO), 5.16 (s, 2H, CH_2), 7.00–7.13 (m, 2H, ar), 7.37–7.50 (m, 4H, ar), 7.54 (s, 1H, ar), 11.68 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 23.1 (C_5), 27.3 (C_4), 30.0 (C_6), 68.9 (CH_2), 113.5 (C_7), 116.7 (C_9), 125.6 (C_{10}), 126.4 (C_{10a}), 126.7 (C_6, phenyl), 127.8 (C_2, phenyl), 128.3 (C_4, phenyl), 130.9 (C_5, phenyl), 133.6 (C_3, phenyl), 136.4 (C_{6a}), 139.9 (C_1, phenyl),

147.0 (C_{3a}, C=N), 153.7 (C_1, C=O), 157.5 (C_8); MS (APCI) *m/z* (%): 342.0 (M^++1, 100); Anal. Calcd. for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29. Found: C, 63.21; H, 4.77; N, 12.27.

4.3.12. 8-(4-Fluorobenzyloxy)-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (**3k**)

IR (KBr, ν, cm^{-1}): 3177 (N–H), 1715 (C=O), 1580, 1508, 1443 (C=N, C=C), 1263 (C–O); ^{1}H NMR (300 MHz, δ, ppm, DMSO-d_6): 2.00–2.10 (m, 2H, C_5–H), 2.43–2.60 (m, C_4–H, C_6–H and DMSO), 5.11 (s, 2H, CH_2), 7.00–7.10 (m, 2H, ar), 7.20–7.27 (m, 2H, ar), 7.39 (d, 1H, J = 8.6 Hz, ar), 7.50–7.55 (m, 2H, ar), 11.67 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 23.1 (C_5), 27.4 (C_4), 30.1 (C_6), 69.2 (CH_2), 113.5 (C_7), 115.7 (d, J_{C-F} = 21.2 Hz, $C_{3,5}$, phenyl), 116.6 (C_9), 125.5 (C_{10}), 126.3 (C_{10a}), 130.5 (d, J_{C-F} = 8.3 Hz, $C_{2,6}$, phenyl), 133.6 (d, J_{C-F} = 2.6 Hz, C_1, phenyl), 136.4 (C_{6a}), 147.0 (C_{3a}, C=N), 153.8 (C_1, C=O), 157.5 (C_8), 162.3 (d, J_{C-F} = 242.6 Hz, C_4, phenyl); MS (APCI) *m/z* (%): 326.0 (M^++1, 100); Anal. Calcd. for $C_{18}H_{16}FN_3O_2$: C, 66.45; H, 4.96; N, 12.92. Found: C, 66.32; H, 5.07; N, 12.89.

4.3.13. 8-(2-Fluorobenzyloxy)-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (**3l**)

IR (KBr, ν, cm^{-1}): 3167 (N–H), 1699 (C=O), 1587, 1506, 1439 (C=N, C=C), 1242 (C–O); ^{1}H NMR (300 MHz, δ, ppm, DMSO-d_6): 2.00–2.10 (m, 2H, C_5–H), 2.44–2.62 (m, C_4–H, C_6–H and DMSO), 5.17 (s, 2H, C**H$_2$**), 7.00–7.12 (m, 2H, ar), 7.20–7.31 (m, 2H, ar), 7.38–7.49 (m, 2H, ar), 7.55–7.62 (m, 1H, ar), 11.68 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 23.1 (C_5), 27.3 (C_4), 30.0 (C_6), 64.3 (d, J_{C-F} = 2.5 Hz, CH_2), 113.5 (C_7), 115.9 (d, J_{C-F} = 20.9 Hz, C_3, phenyl), 116.5 (C_9), 124.1 (d, J_{C-F} = 14.4 Hz, C_1, phenyl), 125.0 (d, J_{C-F} = 2.8 Hz, C_5, phenyl), 125.6 (C_{10}), 126.4 (C_{10a}), 131.0 (d, J_{C-F} = 8.1 Hz, C_4, phenyl), 131.2 (d, J_{C-F} = 3.5 Hz, C_6, phenyl), 136.4 (C_{6a}), 147.0 (C_{3a}, C=N), 153.7 (C_1, C=O), 157.5 (C_8), 160.9 (d, J_{C-F} = 244.5 Hz, C_2, phenyl); MS (APCI) *m/z* (%): 326.0 (M^++1, 100); Anal. Calcd. for $C_{18}H_{16}FN_3O_2$: C, 66.45; H, 4.96; N, 12.92. Found: C, 66.37; H, 4.98; N, 12.88.

4.3.14. 8-(3-Fluorobenzyloxy)-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (**3m**)

IR (KBr, ν, cm^{-1}): 3179 (N–H), 1713 (C=O), 1578, 1503, 1443 (C=N, C=C), 1263 (C–O); 1H NMR (300 MHz, δ, ppm, DMSO-d_6): 1.98–2.17 (m, 2H, C_5–H), 2.40–2.70 (m, C_4–H, C_6–H and DMSO), 5.18 (s, 2H, CH_2), 7.02–7.65 (m, 7H, ar), 11.69 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 23.1 (C_5), 27.4 (C_4), 30.1 (C_6), 69.1 (CH_2), 113.6 (C_7), 114.7 (d, J_{C-F} = 22.6 Hz, C_2, phenyl), 115.1 (d, J_{C-F} = 20.3 Hz, C_4, phenyl), 116.7 (C_9), 124.0 (C_6, phenyl), 125.6 (C_{10}), 126.4 (C_{10a}), 131.0 (d, J_{C-F} = 7.4 Hz, C_5, phenyl), 136.4 (C_{6a}), 140.3 (d, J_{C-F} = 5.0 Hz, C_1, phenyl), 147.0 (C_{3a}, C=N), 153.7 (C_1, C=O), 157.5 (C_8), 162.7 (d, J_{C-F} = 242.6 Hz, C_3, phenyl); MS (APCI) *m/z* (%): 326.0 (M^++1, 100); Anal. Calcd. for $C_{18}H_{16}FN_3O_2$: C, 66.45; H, 4.96; N, 12.92. Found: C, 66.34; H, 5.04; N, 12.85.

4.3.15. 8-(4-Methylbenzyloxy)-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (**3o**)

IR (KBr, ν, cm^{-1}): 3177 (N–H), 1711 (C=O), 1578, 1499, 1441 (C=N, C=C), 1260 (C–O); ^{1}H NMR (300 MHz, δ, ppm, DMSO-d_6): 1.98–2.10 (m, 2H, C_5–H), 2.31 (s, 3H, CH_3), 2.40–2.62 (m, C_4–H, C_6–H and DMSO), 5.08 (s, 2H, CH_2), 6.95–7.10 (m, 2H, ar), 7.18–7.25 (m, 2H, ar), 7.32–7.45 (m, 3H, ar), 11.67 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 21.2 (CH_3), 23.1 (C_5), 27.3 (C_4), 30.0 (C_6), 69.8 (CH_2), 113.5 (C_7), 116.6 (C_9), 125.6 (C_{10}), 126.1 (C_{10a}), 128.3 ($C_{2,6}$, phenyl), 129.5 ($C_{3,5}$, phenyl), 134.3 (C_4, phenyl), 136.3 (C_{6a}), 137.6 (C_1, phenyl), 147.0 (C_{3a}, C=N), 153.7 (C_1, C=O), 157.7 (C_8); MS (APCI) *m/z* (%): 322.1 (M^++1, 100); Anal. Calcd. for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08. Found: C, 70.87; H, 6.08; N, 13.04.

4.3.16. 8-(4-Bromobenzyloxy)-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one (**3p**)

IR (KBr, ν, cm^{-1}): 3163 (N–H), 1697 (C=O), 1584, 1503, 1441 (C=N, C=C), 1261 (C–O); ^{1}H NMR (300 MHz, δ, ppm, DMSO-d_6): 1.98–2.11 (m, 2H, C_5–H), 2.42–2.63 (m, C_4–H, C_6–H and DMSO), 5.12 (s, 2H, CH_2), 7.00–7.10 (m, 2H, ar), 7.37–7.48 (m, 3H, ar), 7.61 (d, 2H, J = 8.1 Hz, ar), 11.68 (s, 1H, NH); ^{13}C NMR (75 MHz, δ, ppm, DMSO-d_6): 23.1 (C_5), 27.4 (C_4), 30.0 (C_6), 69.1 (CH_2), 113.5 (C_7), 116.5 (C_9), 121.5 (C_4, phenyl), 125.6 (C_{10}), 126.3 (C_{10a}), 130.3 ($C_{2,6}$, phenyl), 131.8 ($C_{3,5}$, phenyl), 136.4 (C_{6a}), 136.8 (C_1, phenyl), 147.0 (C_{3a}, C=N), 153.7 (C_1, C=O), 157.5 (C_8); MS (APCI) *m/z* (%): 346.0 (M^++1, 100); Anal. Calcd. for $C_{18}H_{16}BrN_3O_2$: C, 55.97; H, 4.18; N, 10.88. Found: C, 55.81; H, 4.27; N, 10.84.

4.4. Pharmacology

The MES test, scPTZ test, and rotarod test were carried out by the Antiepileptic Drug Development Program (ADD), Epilepsy Branch, National Institutes of Health, Bethesda, MD, USA [27,28]. All compounds were tested for anticonvulsant activity 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 assessed at 30 min and 4 h intervals after administration. Anticonvulsant efficacy was measured in the MES test and the scPTZ 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. Abolition of the hind-leg 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 pentylenetrazol-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 median effective dose (ED_{50}), and neurotoxicity was expressed as the median toxic dose (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 compounds 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 [29].

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