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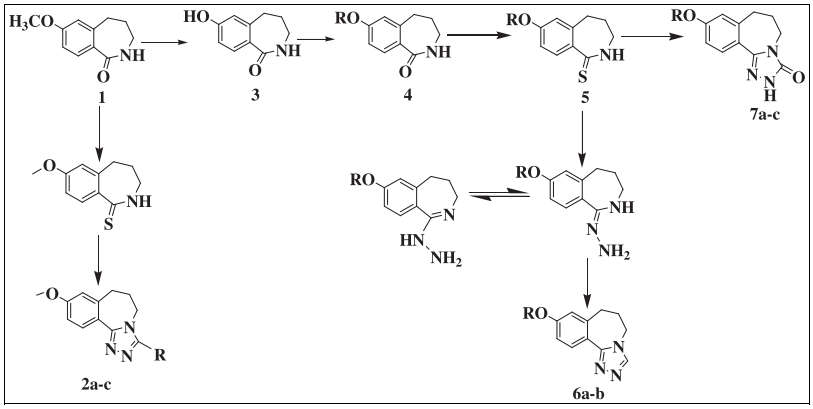

Eight new benzotriazoloazepine derivatives have been synthesized starting from 7-methoxy-2,3,4,5-tetrahydro-1*H*-2-benzo[c]azepin-1-one. The compounds **2a–c** have been synthesized by the reaction of 7-methoxy-2,3,4,5-tetrahydro-1*H*-2-benzo[c]azepin-1-thione with various hydrazides. Reaction of **5** with hydrazine hydrate, followed by treatment of the resultant hydrazone with formic acid, gave corresponding 9-alkoxy-6,7-dihydro-5H-benzo[c][1,2,4]triazolo[4,3-a]azepine(6**a**,**b**). Cyclization of **5** with methyl carbazate gave 9-alkoxy-6,7-dihydro-2H-benzo[c][1,2,4]triazolo[4,3-a]azepin-3(5H)-one (7**a–c**). The structures of the compounds were confirmed by their elemental analysis and spectral data. Their anticonvulsant activities have been initially screened.

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INTRODUCTION

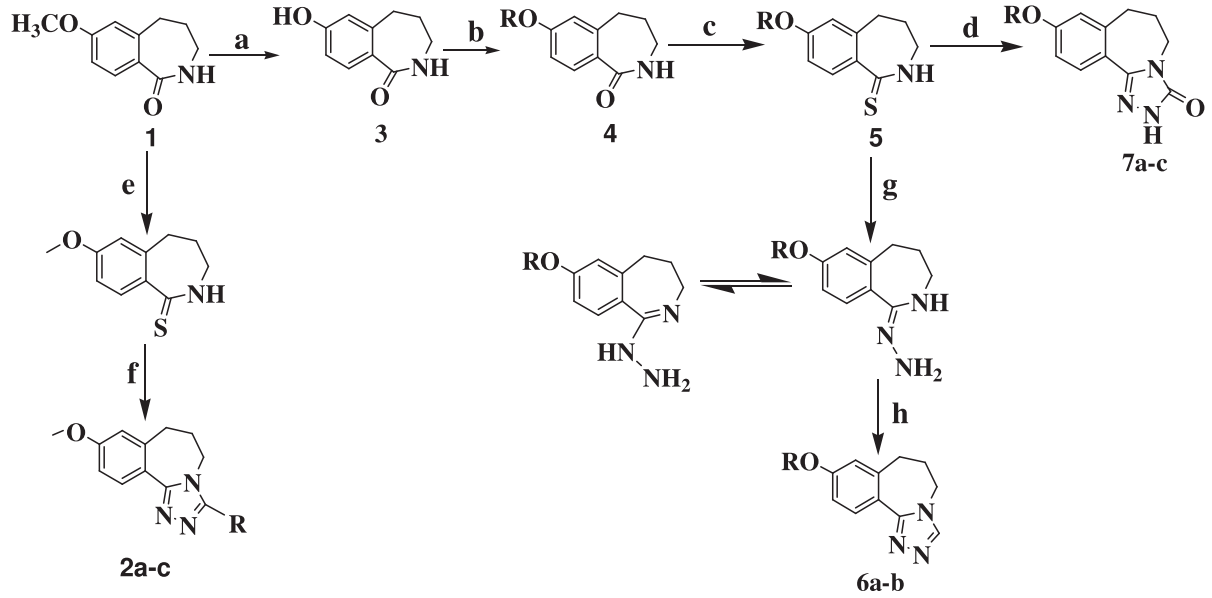
Benzazepine derivatives have exhibit broad pharmacological activity [1–4]. Synthesis and modification of their structure is one of the research focuses in organic chemistry nowadays [5, 6]. According to the literature reports, triazole compounds have wide variety of biological activities, the introduction of triazole ring to some active molecules may significantly improve the biological activity of the parent molecule due to the superposition of biological activity [7–10]. In the course of work on new pharmacologically active of benzazepine derivatives, extensive efforts have been made to find more compounds with potential biological activity. Despite wide applications, it has been observed that there is scant information on the synthesis and anticonvulsant activities of benzo[c][1,2,4]triazolo[4,3-a]azepine derivatives in the literature. As part of our ongoing research work on benzazepine derivatives, we became interested in the design and synthesis of new fused tricyclic heterocyclic compounds **2a–c, 6a**,**b**, and **7a–c**.

Upon continuation of our studies on the synthesis of benzazepine derivatives with potential anticonvulsant activity, new tricyclic heterocyclic framework is designed through a convenient synthetic sequence. Finding a correlation between a compound structure and its biological activity is very difficult, because of complexity of biological systems. Therefore, some novel benzotriazoloazepine derivatives have been synthesized, and their anticonvulsant activities have been initially screened. Each compound was administered at the dose levels of 100 mg/kg and 30 mg/kg for evaluating the anticonvulsant activity.

RESULTS AND DISCUSSION

The compound **1** was synthesized using the method described in a former paper of our group [1]. 7-Methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one **1** was reacted with phosphorus pentasulfide in the presence of triethylamine in refluxing acetonitrile to give the thioxo derivatives, which reacted with acetohydrazide and 2-chlorobenzohydrazide in *n*-butanol under nitrogen atmosphere, respectively, gave the corresponding compounds **2a–c**. The compound **5** was reacted with hydrazine hydrate in refluxing ethanol to yield monosubstituted hydrazine, which reacted with formic acid to provide corresponding the compounds **6a**,**b.** Cyclization of **5** with

Scheme 1. The synthesis route of compounds **2a–c, 6a**,**b**, and **7a–c**. Reagents: (a) BBr_3/CH_2Cl_2, 16–17 h (b) RX/C_2H_5OH, 80–92°C; (c and e) P_2S_5, $(C_2H_5)_3N$ /CH_3CN, 86–92°C, 5–7 h; (d) $H_2NNHCOOCH_3$/ $(CH_3)(CH_2)_3OH$, 140–150°C, 5–8 d; (f) $H_2NNHCOR$/ $(CH_3)(CH_2)_3OH$, 110–115°C, 28–48 h; (g) N_2H_4/ C_2H_5OH, 90–95°C, 36 h; (h) HCOOH, 90–95°C, 30–36 h.



methyl carbazate gave 9-alkoxy-6,7-dihydro-2H-benzo[c] [1,2,4] triazolo[4,3-a]azepin-3(5H)-one **7a–c** (Scheme 1)**.** The structures of all the new compounds were confirmed by ^1H NMR, MS, and elemental analyses, and their anticonvulsant activities have been initially screened.

Compounds **1** and **4** were prepared according to a former paper of our group [1].

General procedure for the preparation of compounds 2a–c. Acetonitrile (1.0 mL) and triethylamine (0.6 mL) were placed in a three-necked round-bottomed flask, to which P_2S_5 (1.9 mmol) was added slowly in an ice bath and was stirred until dissolved [9]. Then, compound **1** (1.7 mmol) was added while stirring. The mixture was refluxed for 5–7 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 × 3), and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude product, which reacted with various hydrazides (2 mmol) in *n*-butanol (15 mL) for 28–48 h at 110–115°C under nitrogen atmosphere. The solvent was removed under reduced pressure, and the residue dissolved with ethyl acetate and washed with water three times. The ethyl acetate layer was dried with anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 20:1) to afford target compounds **2a–c**.

The preparation of compound **5** was done under the same condition as mentioned earlier [9].

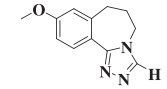
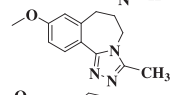
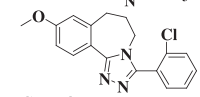
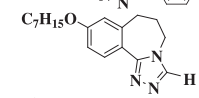
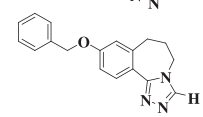
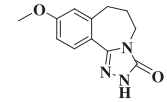
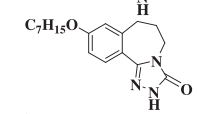
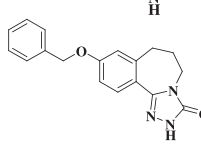
General procedure for the preparation of compounds 6a,b. A stirred suspension of **5** (3 mmol) in ethanol (20 mL) and hydrazine monohydrate (3 mL) was refluxed for 36 h [11–13]. After cooling, the solvent was removed under reduced pressure, the residue was dissolved in 60 mL of ethyl acetate or dichloromethane, washed with water (60 × 3), and dried over anhydrous $MgSO_4$. Drying and evaporation of the solvent gave a crude product, which was dissolved in formic acid (10 mL); the mixture was refluxed for 30–36 h, then the excess acid was evaporated under reduced pressure, and the residue was dissolved in 60 mL of ethyl acetate or dichloromethane, washed with water (60 × 3), and dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 20:1) to afford target compounds **6a**,**b**.

General procedure for the preparation of compounds 7a–c. Crude product **5** (2 mmol) reacted with methyl hydrazinocarboxylate (4 mmol) in *n*-butanol 10 mL under nitrogen atmosphere for 4–8 d, the solvent was removed under reduced pressure, and the residue dissolved with ethyl acetate and washed with water three times [9]. The ethyl acetate layer was dried with anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 35:1) to afford target compounds **7a–c.**

Anticonvulsant activity. The anticonvulsant activities of the compounds synthesized have been initially screened (Table 1). The maximum electroshock (MES) test carried out according to the standard described in the Antiepileptic Drug Development Program of the National Institutes of Health [14, 15]. 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

Table 1

Primary evaluation of compounds **2a–c**, **6a**,**b**, and **7a–c** in anticonvulsant activity.[a]

Comp.		MES[b,c] 100[d]	MES[b,c] 30[d]
2a		0/3	—[e]
2b		0/3	—[e]
2c		3/3	3/5
6a		3/3	5/5
6b		3/3	4/5
7a		1/3	—[e]
7b		3/3	1/5
7c		3/3	1/5
Carbam.[f]		3/3	5/5

[a]All of tested compounds were dissolved in DMSO; Test Drug Administered i.p.
[b]The maximal electroshock test was carried out 30 min after administration of the test compounds.
[c]Doses are denoted in mg/kg.
[d]The effective number in three or five tested mice is given.
[e]Not tested.
[f]The reference drug.

University. The tested compounds were dissolved in DMSO. Each compound was administered at the dose levels of 100 mg/kg and 30 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 test compounds were administered i.p.

EXPERIMENTAL

Melting points were determined on X-5 microscope melting point apparatus, which were uncorrected. ^{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). 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. All other chemicals were of analytical grade.

9-Methoxy-6,7-dihydro-5H-benzo[c][1,2,4]triazolo[4,3-a] azepine (2a). Yield: 80.8%, mp. 83.5–84.6°C. ^{1}H NMR (DMSO, 300 MHz) δ: 2.15–2.24 (m, 2H, CH_2), 2.69 (t, J = 6.8 Hz, 2H, CH_2), 3.82 (s, 3H, CH_3), 4.01 (t, J = 6.6 Hz, 2H, CH_2), 6.94–6.97 (m, 2H, Ar-H), 7.74 (d, 1H, J = 8.1 Hz, Ar-H), 8.57(s, 1H, CH═N). MS (APCI, positive mode) *m/z*: 216.1 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.86; H, 6.01; N, 19.38.

9-Methoxy-3-methyl-6,7-dihydro-5H-benzo[c][1,2,4]triazolo [4,3-a]azepine (2b). Yield: 47.4 %, mp. 138.5–140.1°C. ^{1}H NMR (DMSO, 300 MHz) δ: 2.24–2.28 (m, 2H, CH_2), 2. 45 (s, 3H, CH_3), 2.71 (t, J = 6.8 Hz, 2H, CH_2), 3.82–3.90 (m, 5H, OCH_3, CH_2), 6.90–6.92 (m, 2H, Ar-H), 7.72 (d, 1H, J = 9.2 Hz, Ar-H). MS (APCI, positive mode) *m/z*: 230.1 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.01; H, 6.51; N, 18.43.

3-(2-Chlorophenyl)-9-methoxy-6,7-dihydro-5H-benzo[c] [1,2,4]triazolo[4,3-a]azepine (2c). Yield: 50.0 %, mp. 112.3–113.5° C. ^{1}H NMR (DMSO, 300 MHz) δ: 2.20–2.27 (m, 2H, CH_2), 2.77 (t, J = 6.8 Hz, 2H, CH_2), 3.64 (t, J = 6.8 Hz, 2H, CH_2), 3.84 (s, 3H, CH_3), 7.00–7.03 (m, 2H, Ar-H), 7.38–7.80 (m, 5H, Ar-H). MS (APCI, positive mode) *m/z*: 326.0 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{16}ClN_3O$: C, 66.36; H, 4.95; N, 12.90. Found: C, 66.30; H, 4.88; N, 12.65.

9-Heptyloxy-6,7-dihydro-5H-benzo[c][1,2,4]triazolo[4,3-a] azepine (6a). Yield: 42.8 %, mp. 101.1–101.6°C. ^{1}H NMR (DMSO, 300 MHz) δ: 0.86–0.89 (m, 3H, CH_3), 1.25–1.35 (m, 8H, $(CH_2)_4$), 1.71–1.75 (m, 2H, CH_2), 2.21 (t, J = 6.3 Hz, 2H, CH_2), 2.70 (t, J = 6.8 Hz, 2H, CH_2), 4.00–4.04 (m, 4H, $(CH_2)_2$), 6.92–6.95 (m, 2H, Ar-H), 7.73 (d, 1H, J = 8.0 Hz, Ar-H), 8.53 (s, 1H, CH═N). MS (APCI, positive mode) *m/z*: 300.2 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{25}N_3O$: C, 72.21; H, 8.42; N, 14.03. Found: C, 72.18; H, 8.39; N, 13.98.

9-Benzyloxy-6,7-dihydro-5H-benzo[c][1,2,4]triazolo[4,3-a] azepine (6b). Yield: 48.0 %, mp. 125.6–127.2°C. ^{1}H NMR (DMSO, 300 MHz) δ: 2.14–2.26 (m, 2H, CH_2), 2.70 (t, J = 6.7 Hz, 2H, CH_2), 4.02 (t, 2H, J = 6.6 Hz, CH_2), 5.17 (s, 2H, CH_2), 7.02–7.10 (m, 2H, Ar-H), 7.31–7.51 (m, 5H, Ar-H), 7.76 (d, J = 8.4 Hz, 2H, Ar-H), 8.56 (s, 1H, CH═N). MS (APCI, positive mode) *m/z*: 292.0 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 72.18; H, 5.73; N, 13.98.

9- Methoxy -6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a] [2] azepin-3(5*H*)-one (7a). Yield: 45.0 %, mp. 213.1–214.5°C. ^{1}H NMR (DMSO, 300 MHz) δ: 2.08–2.10 (m, 2H, CH_2), 2.70–2.80 (m, 2H, CH_2), 3.54 (t, J = 6.3 Hz, 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). MS (APCI, positive mode) *m/z*: 232.1 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.41; H, 5.77; N, 18.01.

9-Heptyloxy-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a][2] azepin-3(5*H*)-one (7b). Yield: 48.8 %, mp. 193.4–195.5°C. ^{1}H NMR (DMSO, 300 MHz) δ: 0.80–0.88 (m, CH_3), 1.22–1.45 (m, 8H, $(CH_2)_4$), 1.68–1.80 (m, 2H, CH_2), 2.04–2.09 (m, 2H, CH_2), 2.74 (t, J = 6.3 Hz, 2H, CH_2), 353 (t, J = 6.4 Hz, 2H, CH_2), 4.01 (d, 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). MS (APCI, positive mode)

m/z: 316.1 $[M+H]^+$. 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, 13.23.

9-Benzyloxy-6,7-dihydro-2*H*-benzo[c][1,2,4]triazolo[4,3-a][2] azepin-3(5*H*)-one (7c). Yield: 50.2 %, mp. 246.4–246.8°C. ^{1}H NMR (DMSO, 300MHz) δ: 2.05–2.10 (m, 2H, CH_2), 2.75 (t, J = 5.9 Hz, 2H, CH_2), 3.54 (t, 2H, J = 6.4 Hz, CH_2), 5.15 (s, 2H, CH_2), 6.95–7.10 (m, 2H, Ar-H), 7.30–7.50 (m, 5H, Ar-H), 7.59 (d, 1H, J = 8.4 Hz, Ar-H), 11.78 (s, 1H, NH). MS (APCI, positive mode) *m/z*: 308.1 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.29; H, 5.50 N, 13.76.

CONCLUSIONS

During this work, we succeeded in synthesizing eight new benzotriazoloazepine derivatives from 7-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one. Anticonvulsant activities of these new compounds have been initially screened. Further investigations are under progress to enlarge the scope of these heterocycles and evaluate their anticonvulsant activities.

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