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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and evaluation of 7-substituted-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-ones as anticonvulsant and hypnotic agents

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Abstract A series of 7-substituted-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-ones was synthesized. The anticonvulsant effect and neurotoxicity of the compounds were evaluated with a maximal electroshock (MES) test and a rotated test in mice, respectively. Most of the compounds prepared exhibited anticonvulsant activities in the MES test, 7-(heptyloxy)-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (10) was the most active. In the anti-MES potency test, it showed a median effective dose (ED_{50}) of 19.0 mg/kg. The hypnotic effect of the compound **10** was initially investigated by using a pentobarbital-induced-sleep test. Middle (30 mg/kg) and high doses (60 mg/kg) of the compound **10** both significantly increased the pentobarbital-induced sleep from 20.9 ± 5.28 to 26.9 ± 6.14 and 45.67 ± 7.94 min, respectively.

Keywords 1,4-Benzoxazepin-5(2*H*)-one · Synthesis · Anticonvulsant · Maximal electroshock · Hypnosis

Introduction

Epilepsy, one of the most frequent neurological afflictions in man characterized by excessive temporary neuronal discharges resulting in uncontrolled convulsion, inflicts more than 2 million Americans and 60 million people worldwide (Strine *et al*., 2005). 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) (Kwan and Brodie, 2000; Spear, 2001). Moreover, many AEDs have serious side effects (Al-Soud *et al*., 2003; Meador, 2003), and lifelong medication may be required. Toxicity, intolerance, and lack of efficacy are the limitations of the current AEDs. Therefore, the continued search for safer and more effective new AEDs is necessary.

In our previous work, a series of derivatives of 6-alkoxy-3,4-dihydro-2(1*H*)-quinolinone were found to have anticonvulsant activities, among which 6-benzyloxy-3,4-dihydro-2(1*H*)-quinolinone (**I**) showed the strongest activity, with an ED_{50} value of 29.6 mg/kg in the maximal electroshock (MES) test and a TD_{50} value of greater than 300 mg/kg (Quan *et al*., 2005). 7-(4-Fluorobenzylamino)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**II**), the bioisoterism of compound **I**, has also been shown to inhibit seizure with an ED_{50} value of 31.7 mg/kg in MES (Piao *et al*., 2008). Desirable effects of these agents prompted us to investigate other heterocycles with similar pharmacological properties (Fig. 1).

As a part of our continuous efforts in this area, a series of 7-alkyloxyl-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-ones (**III**) were designed and synthesized in this study. Compounds **III**, the ring enlargement analogues of compounds **I** through inserting an oxygen atom, were anticipated to possess a better anticonvulsant activity. The anticonvulsant effect and neurotoxicity of the compounds were evaluated with a MES test and a rotarod test in mice, respectively. Seizure assays and neurotoxicity evaluations were according to the antiepileptic drug development (ADD) program which were developed by the National

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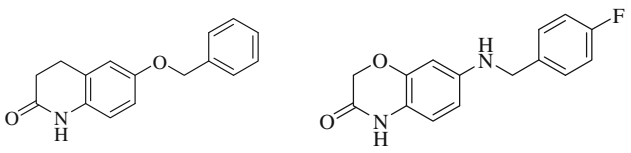


I II

Fig. 1 Structures of compounds **I** and **II**

Institute of Neurological and Communicative Disorders and Stroke (NINCDS) (Krall *et al*., 1978; Porter *et al*., 1984).

In addition, in the process of evaluating their anticonvulsant activity and neurotoxicity, strong hypnotic effects were discovered. Therefore, the hypnotic effect of the most active compound **10** was tested using a pentobarbital-induced-sleep test. The synthesized compounds were characterized using IR, ^{1}H-NMR, MS, and elemental analysis techniques (Scheme 1).

Experimental section

Chemistry

The melting points were determined in open capillary tubes. The IR spectra were recorded (In KBr) on a FT-IR1730. ^{1}H-NMR spectra were measured on an AV-300 (Bruker, Switzerland), and all chemical shifts were given in parts per million relative to tetramethysilane. Mass spectra were measured on an HP1100LC (Agilent Technologies, USA). Elemental analyses were performed on a 204Q CHN (Perkin–Elmer, USA). The major chemicals were purchased from Aldrich Chemical Corporation.

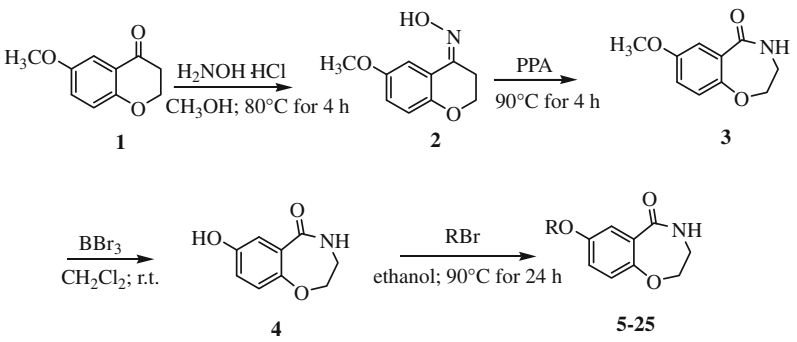
Synthesis of 6-methoxy-2,3-dihydrochromen-4-one oxime (**2**)

6-Methoxy-2,3-dihydrochromen-4-one (compound **1**) (7.8 g, 0.044 mol), pyridine (8 ml) and hydroxylamine hydrochloride (9.17 g, 0.132 mol) were placed into a round-bottomed flask containing 150 ml of methanol. The reaction mixture was stirred for 4 h at 70°C. After removing most of the solvent (1/4 was remained), the mixture was added to 100 ml of ice-water, filtered and then recrystallized from alcohol to get 7.95 g of a colorless solid. ^{1}H-NMR (DMSO-d_6, 300 MHz), δ 2.79 (t, 2H, $J = 6.1$ Hz, N–CH_2), 3.73 (s, 3H, O–CH_3), 4.11 (t, 2H, $J = 6.1$ Hz, O–CH_2), 6.82–7.26 (m, 3H, Ar–H), 11.26 (s, 1H, N–OH). IR (KBr) cm^{-1}: 3345 (O–H), 1616 (C=N). MS *m/z* 194 (M + 1).

Synthesis of 7-methoxy-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**3**)

Compound **2** (2.6 g, 0.013 mol) and polyphosphoric acid (PPA) (45 g) were placed into a three-necked round-bottomed flask. The mixture was heated and stirred with a blade stirrer at 90°C for 4 h. 100 ml water was added to the mixture after the temperature of the mixture was equal to room temperature, and then the aqueous layer was extracted with CH_2Cl_2 for three times. The combined organic layer was dried overnight with anhydrous magnesium sulphate. The evaporation of the solvent gave a crude product which was purified by silica gel column chromatography with CH_2Cl_2–CH_3OH (30:1) to give a white solid.

Scheme 1 Synthesis of Compounds **5–25**



R:

5: -C_2H_5	9: *n*-C_6H_{13}	13: -$CH_2C_6H_5$	17: -$CH_2C_6H_4$(*p*-Cl)	21: -$CH_2C_6H_4$(*p*-Br)
6: *n*-C_3H_7	10: *n*-C_7H_{15}	14: -$CH_2C_6H_4$ (*p*-F)	18: -$CH_2C_6H_4$(*m*-Cl)	22: -$CH_2C_6H_4$(*o*-Br)
7: *n*-C_4H_9	11: *n*-C_8H_{17}	15: -$CH_2C_6H_4$(*m*-F)	19: -$CH_2C_6H_4$ (*o*-Cl)	23: -CH_2 C_6H_4(*p*-CH_3)
8: *n*-C_5H_{11}	12: *n*-$C_{12}H_{25}$	16: -$CH_2C_6H_4$ (*o*-F)	20: -$CH_2C_6H_3$ (2,6-Cl_2)	24: -$CH_2C_6H_4$(*p*-OCH_3)
				25:-$CH_2C_6H_3$(3,4-$(OCH_3)_2$)

M.p. 90–92°C, yield = 62%. ^{1}H-NMR ($CDCl_3$, 300 MHz), δ 3.24 (q, 2H, $J = 5.2$ Hz, N–CH_2), 3.73 (s, 3H, O–CH_3), 4.17 (t, 2H, $J = 5.0$ Hz, O–CH_2), 6.96 (d, 1H, $J = 8.8$ Hz, Ar–H), 7.03 (dd, 1H, $J_1 = 2.9$ Hz, $J_2 = 8.8$ Hz, Ar–H), 7.16 (d, 1H, $J_1 = 2.9$ Hz, Ar–H). 8.34 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3204 (NH), 1674 (C=O). MS (*m/z*): 194 (M + 1).

Synthesis of 7-hydroxy-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (**4**)

To a stirred solution of boron tribromide (50 mmol) in anhydrous dichloromethane (20 ml), a dichloromethane solution of compound **3** (1.93 g, 10 mmol) was added dropwise and the reaction continued for 1 h at 0°C and an additional 2 h at 20°C. Following the addition of 30 ml ice cold water, the organic layer was separated and the aqueous layer extracted with ethyl acetate. The combined organic layer was dried overnight with anhydrous magnesium sulfate and evaporated under reduced pressure to get a brown solid which was recrystallized from alcohol to get a colorless solid. M.p. 118–120°C, yield = 90%, ^{1}H-NMR (DMSO-d6, 300 MHz) δ 3.20 (q, 2H, $J = 5.09$ Hz, –$NHCH_2$), 4.12 (t, 2H, $J = 5.09$ Hz, –OCH_2), 6.84–7.00 (m, 3H, Ar–H), 8.22 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3194 (NH), 1647 (C=O).

General procedure for the synthesis of 7-alkyloxyl-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-ones (**5**–**25**)

K_2CO_3 (1.24 g, 0.009 mol), absolute ethanol (50 ml), and 7-hydroxy-3,4-dihydrobenzo[*f*] [1,4]oxazepin-5(2*H*)-one (0.003 mol) were added to a 100 ml round-bottomed flask equipped with a reflux condenser. After the mixture was refluxed for 30 min, alkyl bromide, or benzyl chloride derivatives (0.004 mol) were added into the mixture. The reaction mixture was heated at reflux temperature for 24 h and poured into 100 ml of water. The aqueous layer was extracted with dichloromethane (30 ml × 3). The combined layer of dichloromethane was dried with anhydrous $MgSO_4$. The evaporation of the solvent gave a crude product which was purified by silica gel column chromatography with CH_2Cl_2–CH_3OH (30:1) to a white solid.

7-Ethoxy-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (**5**)

M.p. 126–128°C; yield 73%. ^{1}H-NMR (DMSO, 300 MHz): δ 1.30 (t, 3H, $J = 6.9$ Hz, –CH_2CH_3), 3.24 (q, 2H, $J = 5.1$ Hz, –$NHCH_2$–), 3.99 (q, 2H, $J = 6.9$ Hz, –OCH_2–), 4.17 (t, 2H, $J = 5.0$ Hz, –OCH_2–), 6.94 (d, 1H, $J = 8.8$ Hz, Ar–H), 7.02 (q, 1H, $J_1 = 2.9$ Hz, $J_2 = 8.8$ Hz, Ar–H), 7.14 (d, 1H, $J = 2.8$ Hz, Ar–H), 8.32 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3204 (NH), 1674 (C=O). MS (*m/z*): 208 (M + 1). Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.94; H, 6.54; N, 6.44.

7-Propoxy-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (**6**)

M.p. 65–67°C; yield 65%. ^{1}H-NMR (DMSO, 300 MHz): δ 0.96 (t, 3H, $J = 7.4$ Hz, –CH_2CH_3), 1.70 (m, 2H, $J = 7.0$ Hz, –CH_2–), 3.24 (q, 2H, $J = 5.2$ Hz, –$NHCH_2$–), 3.89 (t, 2H, $J = 6.5$ Hz, –OCH_2–), 4.17 (t, 2H, $J = 5.1$ Hz, –OCH_2–), 6.95 (d, 1H, $J = 8.8$ Hz, Ar–H), 7.02 (q, 1H, $J_1 = 3.0$ Hz, $J_2 = 8.8$ Hz, Ar–H), 7.15 (d, 1H, $J = 3.0$ Hz, Ar–H), 8.32 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3287 (NH), 1623 (C=O). MS (*m/z*): 222 (M + 1). Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.44; H, 6.57; N, 6.55.

7-Butoxy-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (**7**)

M.p. 80–82°C; yield 75%. ^{1}H-NMR (DMSO, 300 MHz): δ 0.92 (t, 3H, $J = 7.4$ Hz, –CH_2CH_3), 1.45 (m, 2H, $J = 7.3$ Hz, –CH_2–), 1.69 (m, 2H, $J = 6.6$ Hz, –CH_2–), 3.24 (q, 2H, $J = 5.1$ Hz, –$NHCH_2$–), 3.93 (t, 2H, $J = 6.4$ Hz, –OCH_2–), 4.17 (t, 2H, $J = 5.0$ Hz, –OCH_2–), 6.94 (d, 1H, $J = 8.8$ Hz, Ar–H), 7.02 (q, 1H, $J_1 = 2.8$ Hz, $J_2 = 8.8$ Hz, Ar–H), 7.14 (d, 1H, $J = 2.8$ Hz, Ar–H), 8.32 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3285 (NH), 1612 (C=O). MS (*m/z*): 236 (M + 1). Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.54; H, 7.43; N, 5.73.

7-(Pentyloxy)-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (**8**)

M.p. 57–59°C; yield 70%. ^{1}H-NMR (DMSO, 300 MHz): δ 0.88 (t, 3H, $J = 6.7$ Hz, –CH_2CH_3), 1.31–1.35 (m, 4H, –CH_2–), 1.68 (m, 2H, –CH_2–), 3.24 (q, 2H, $J = 5.0$ Hz, –$NHCH_2$–), 3.91 (t, 2H, $J = 6.4$ Hz, –OCH_2–), 4.17 (t, 2H, $J = 5.0$ Hz, –OCH_2–), 6.94 (d, 1H, $J = 8.8$ Hz, Ar–H), 7.02 (q, 1H, $J_1 = 2.8$ Hz, $J_2 = 8.8$ Hz, Ar–H), 7.14 (d, 1H, $J = 2.8$ Hz, Ar–H), 8.32 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3179 (NH), 1653 (C=O). MS (*m/z*): 250 (M + 1). Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.69; H, 7.83; N, 5.40.

7-(Hexyloxy)-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (**9**)

M.p. 58–60°C; yield 79%. ^{1}H-NMR (DMSO, 300 MHz): δ 0.96 (t, 3H, $J = 6.5$ Hz, –CH_2CH_3), 1.38–1.82 (m, 8H, –CH_2–), 3.34 (q, 2H, $J = 5.1$ Hz, –$NHCH_2$–), 4.01 (t, 2H, $J = 6.4$ Hz, –OCH_2–), 4.26 (t, 2H, $J = 5.0$ Hz, –OCH_2–),

7.03 (d, 1H, $J = 8.8$ Hz, Ar–H), 7.10 (q, 1H, $J_1 = 3.0$ Hz, $J_2 = 8.9$ Hz, Ar–H), 7.23 (d, 1H, $J = 3.0$ Hz, Ar–H), 8.32 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3224 (NH), 1636 (C=O). MS (*m/z*): 264 (M + 1). Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.66; H, 8.31; N, 5.10.

7-(Heptyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**10**)

M.p. 50–52°C; yield 71%. ^{1}H-NMR (DMSO, 300 MHz): δ 0.86 (t, 3H, $J = 6.8$ Hz, $–CH_2CH_3$), 1.35–1.38 (m, 8H, $–CH_2–$), 1.68 (m, 2H, $J = 6.5$ Hz, $–CH_2–$), 3.24 (q, 2H, $J = 5.2$ Hz, $–NHCH_2–$), 3.92 (t, 2H, $J = 6.4$ Hz, $–OCH_2–$), 4.17 (t, 2H, $J = 5.1$ Hz, $–OCH_2–$), 6.94 (d, 1H, $J = 8.8$ Hz, Ar–H), 7.02 (q, 1H, $J_1 = 3.1$ Hz, $J_2 = 8.8$ Hz, Ar–H), 7.14 (d, 1H, $J = 3.0$ Hz, Ar–H), 8.32 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3209 (NH), 1612 (C=O). MS (*m/z*): 278 (M + 1). Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.38; H, 8.31; N, 5.21.

7-(Octyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**11**)

M.p. 62–65°C; yield 84%. ^{1}H-NMR (DMSO, 300 MHz): δ 0.84 (t, 3H, $J = 6.6$ Hz, $–CH_2CH_3$), 1.26–1.39 (m, 10H, $–CH_2–$), 1.67 (m, 2H, $J = 6.6$ Hz, $–CH_2–$), 3.24 (q, 2H, $J = 5.1$ Hz, $–NHCH_2–$), 3.92 (t, 2H, $J = 6.4$ Hz, $–OCH_2–$), 4.17 (t, 2H, $J = 4.9$ Hz, $–OCH_2–$), 6.94 (d, 1H, $J = 8.8$ Hz, Ar–H), 7.02 (q, 1H, $J_1 = 3.0$ Hz, $J_2 = 8.8$ Hz, Ar–H), 7.14 (d, 1H, $J = 2.9$ Hz, Ar–H), 8.32 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3292 (NH), 1659 (C=O). MS (*m/z*): 292 (M + 1). Anal. Calcd. for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.30; H, 8.71; N, 4.67.

7-(Dodecyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**12**)

M.p. 82–84°C; yield 72%. ^{1}H-NMR (DMSO, 300 MHz): δ 1.84 (t, 3H, $J = 6.8$ Hz, $–CH_2CH_3$), 1.05–1.38 (m, 18H, $–CH_2–$), 1.68 (m, 2H, $J = 6.9$ Hz, $–CH_2–$), 3.25 (q, 2H, $J = 5.1$ Hz, $–NHCH_2–$), 3.92 (t, 2H, $J = 6.3$ Hz, $–OCH_2–$), 4.17 (t, 2H, $J = 5.0$ Hz, $–OCH_2–$), 6.94 (d, 1H, $J = 8.8$ Hz, Ar–H), 7.01 (q, 1H, $J_1 = 2.9$ Hz, $J_2 = 8.8$ Hz, Ar–H), 7.14 (d, 1H, $J = 2.8$ Hz, Ar–H), 8.32 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3199 (NH), 1677 (C=O). MS (*m/z*): 348 (M + 1). Anal. Calcd. for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.76; H, 9.63; N, 3.88.

7-(Benzyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**13**)

M.p. 132–134°C; yield 81%. ^{1}H-NMR (DMSO, 300 MHz): δ 3.25 (q, 2H, $J = 5.0$ Hz, –NHCH2–), 4.18 (t, 2H, $J = 4.9$ Hz, –OCH2–), 5.08 (s, 2H, $Ar–CH_2–$), 6.95–7.46 (m, 8H, Ar–H), 8.34 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3189 (NH), 1689 (C=O). MS (*m/z*): 270 (M + 1). Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.61; H, 5.67; N, 5.01.

7-(4-Fluorobenzyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**14**)

M.p. 142–144°C; yield 70%. ^{1}H-NMR (DMSO, 300 MHz): δ 3.24 (q, 2H, $J = 5.0$ Hz, $–NHCH_2–$), 4.18 (t, 2H, $J = 4.9$ Hz, $–OCH_2–$), 5.06 (s, 2H, $Ar–CH_2$), 6.95–7.52 (m, 7H, Ar–H), 8.53 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3210 (NH), 1656 (C=O). MS (*m/z*): 288 (M + 1). Anal. Calcd. for $C_{16}H_{14}FNO_3$: C, 66.89; H, 4.91; N, 4.88. Found: C, 67.08; H, 5.05; N, 4.69.

7-(3-Fluorobenzyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**15**)

M.p. 100–102°C; yield 75%. ^{1}H-NMR (DMSO, 300 MHz): δ 3.26 (q, 2H, $J = 5.2$ Hz, $–NHCH_2–$), 4.19 (t, 2H, $J = 4.9$ Hz, $–OCH_2–$), 5.12 (s, 2H, $Ar–CH_2–$), 6.96–7.48 (m, 7H, Ar–H), 8.34 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3210 (NH), 1650 (C=O). MS (*m/z*): 288 (M + 1). Anal. Calcd. for $C_{16}H_{14}FNO_3$: C, 66.89; H, 4.91; N, 4.88. Found: C, 66.99; H, 5.09; N, 4.62.

7-(2-Fluorobenzyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**16**)

M.p. 108–110°C; yield 65.0%. ^{1}H-NMR (DMSO, 300 MHz): δ 3.25 (q, 2H, $J = 5.0$ Hz, $–NHCH_2–$), 4.19 (t, 2H, $J = 4.9$ Hz, $–OCH_2–$), 5.12 (s, 2H, $Ar–CH_2–$), 6.96–7.57 (m, 7H, Ar–H), 8.36 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3291 (NH), 1662 (C=O). MS (*m/z*): 288 (M + 1). Anal. Calcd. for $C_{16}H_{14}FNO_3$: C, 66.89; H, 4.91; N, 4.88. Found: C, 67.03; H, 4.98; N, 4.64.

7-(4-Chlorobenzyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**17**)

M.p. 169–170°C; yield 94%. ^{1}H-NMR (DMSO, 300 MHz): δ 3.25 (q, 2H, $J = 5.0$ Hz, $–NHCH_2–$), 4.18 (t, 2H, $J = 4.7$ Hz, $–OCH_2–$), 5.09 (s, 2H, $Ar–CH_2–$), 6.96–7.46 (m, 7H, Ar–H), 8.34 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3190 (NH), 1657 (C=O). MS (*m/z*): 304 (M + 1). Anal. Calcd. for $C_{16}H_{14}ClNO_3$: C, 63.27; H, 4.65; N, 4.61. Found: C, 63.45; H, 4.79; N, 4.53.

7-(3-Chlorobenzyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**18**)

M.p. 88–90°C; yield 71%. ^{1}H-NMR (DMSO, 300 MHz): δ 3.25 (q, 2H, $J = 4.7$ Hz, –NHCH$_2$–), 4.19 (t, 2H, $J = 4.7$ Hz, –OCH$_2$–), 5.11 (s, 2H, Ar–CH$_2$–), 6.97–7.51 (m, 7H, Ar–H), 8.35 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3187 (NH), 1667 (C=O). MS (*m/z*): 304 (M + 1). Anal. Calcd. for $C_{16}H_{14}ClNO_3$: C, 63.27; H, 4.65; N, 4.61. Found: C, 63.39; H, 4.77; N, 4.48.

7-(2-Chlorobenzyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**19**)

M.p. 138–141°C; yield 49%. ^{1}H-NMR (DMSO, 300 MHz): δ 3.25 (q, 2H, $J = 5.0$ Hz, –NHCH$_2$–), 4.19 (t, 2H, $J = 5.0$ Hz, –OCH$_2$–), 5.14 (s, 2H, Ar–CH$_2$), 6.97–7.61 (m, 7H, Ar–H), 8.36 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3231 (NH), 1670 (C=O). MS (*m/z*): 304 (M + 1). Anal. Calcd. for $C_{16}H_{14}ClNO_3$: C, 63.27; H, 4.65; N, 4.61. Found: C, 63.42; H, 4.77; N, 4.48.

7-(2,6-Dichlorobenzyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**20**)

M.p. 126–128°C; yield 27%. ^{1}H-NMR (DMSO, 300 MHz): δ 3.28 (q, 2H, $J = 5.0$ Hz, –NHCH$_2$–), 4.20 (t, 2H, $J = 4.9$ Hz, –OCH$_2$–), 5.21 (s, 2H, Ar–CH$_2$–), 6.98–7.58 (m, 7H, Ar–H), 8.37 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3179 (NH), 1683 (C=O). MS (*m/z*): 338 (M + 1). Anal. Calcd. for $C_{16}H_{13}Cl_2NO_3$:C, 56.82; H, 3.87; N, 4.14. Found: C, 56.97; H, 3.96; N,4.01.

7-(4-Bromobenzyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**21**)

M.p. 169–171°C; yield 84%. ^{1}H-NMR (DMSO, 300 MHz): δ 3.24 (q, 2H, $J = 5.0$ Hz, –NHCH$_2$–), 4.18 (t, 2H, $J = 4.9$ Hz, –OCH$_2$–), 5.07 (s, 2H, Ar–CH$_2$–), 6.95–7.60 (m, 7H, Ar–H), 8.34 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3182 (NH), 1663(C=O). MS (*m/z*): 348 (M + 1). Anal. Calcd. for $C_{16}H_{14}BrNO_3$: C, 55.19; H, 4.05; N, 4.02. Found: C, 55.38; H, 3.84; N,4.26.

7-(2-Bromobenzyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**22**)

M.p. 159–161°C; yield 58%. ^{1}H-NMR (DMSO, 300 MHz): δ 3.27 (q, 2H, $J = 5.1$ Hz, –NHCH$_2$–), 4.20 (t, 2H, $J = 5.0$ Hz, –OCH$_2$–), 5.10 (s, 2H, Ar–CH$_2$–), 6.98–7.69 (m, 5H, Ar–H), 8.34 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3240 (NH), 1665 (C=O). MS (*m/z*): 348 (M + 1). Anal. Calcd. for $C_{16}H_{14}BrNO_3$: C, 55.19; H, 4.05; N, 4.02. Found: C, 55.37; H, 4.26; N, 3.79.

7-(4-Methylbenzyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**23**)

M.p. 168–169°C; yield 89%. ^{1}H-NMR (DMSO, 300 MHz): δ 2.3 (s, 3H, Ar–CH$_3$), 3.24 (q, 2H, $J = 5.1$ Hz, –NHCH$_2$–), 4.18 (t, 2H, $J = 5.0$ Hz, –OCH$_2$–), 5.03 (s, 2H, Ar–CH$_2$–), 6.94–7.33 (m, 7H, Ar–H), 8.33 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3200 (NH), 1658 (C=O). MS (*m/z*): 284 (M + 1). Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.36; H, 6.14; N, 4.75.

7-(4-Methoxybenzyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**24**)

M.p. 161–162°C; yield 47%. ^{1}H-NMR (DMSO, 300 MHz): δ 3.24 (q, 2H, $J = 5.1$ Hz, –NHCH$_2$–), 3.75 (s, 3H, –OCH$_3$), 4.18 (t, 2H, $J = 4.8$ Hz, –OCH$_2$–), 4.99 (s, 2H, Ar–CH$_2$–), 6.93–7.38 (m, 7H, Ar–H), 8.32 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3183 (NH), 1653 (C=O). MS (*m/z*): 230 (M + 1). Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.46; H, 5.89; N, 4.47.

7-(3,4-Dimethoxybenzyloxy)-3,4-dihydrobenzo[*f*][1,4] oxazepin-5(2*H*)-one (**25**)

M.p. 134–136°C; yield 36%. ^{1}H-NMR (DMSO, 300 MHz): δ 3.24 (q, 2H, $J = 5.0$ Hz, –NHCH$_2$–), 3.75 (m, 6H, –OCH$_3$), 4.18 (t, 2H, $J = 4.9$ Hz, –OCH$_2$–), 4.99 (s, 2H, Ar–CH$_2$–), 6.95–7.26 (m, 7H, Ar–H), 8.33 (s, 1H, –NH–). IR (KBr) cm^{-1}: 3172 (NH), 1676 (C=O). MS (*m/z*): 330 (M + 1). Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.74; H, 5.81; N, 4.25. Found: C, 65.89; H, 5.87; N, 4.18.

Pharmacology

The anticonvulsant activity of all the compounds was evaluated. The in vivo anticonvulsant activity was assessed by use of the standard described in the ADD program (Krall *et al*., 1978; Porter *et al*., 1984). The acute toxicity was evaluated by a rotarod test (Krall *et al*., 1978; Porter *et al*., 1984). In the rotarod test, hypnotic activity was found in some compounds, so the hypnotic effect of compound **10** was initially investigated by using the pentobarbital-induced-sleep test (Tsuji *et al*., 1996). All of the compounds, which were dissolved in 3% Tween-80, were evaluated for their anticonvulsant activity and compound **10** was evaluated for its hypnotic activity using KunMing mice, ranging in weight from 18 to 25 g and purchased

from the Laboratory of Animal Research, College of Pharmacy, Yanbian University.

Anticonvulsant activity and toxicity test in mice

The MES test was carried out by the methods described in the ADD of the National Institutes of Health (USA). Seizures were elicited with a 60 Hz alternating current of 50 mA intensity in mice (100% elicitation rate in normal mice). The current was applied via corneal electrodes for 0.2 s. Protection against the spread of MES-induced seizures was defined as the abolition of the hind leg and tonic maximal extension component of the seizure. At 30 min after the administration of the compounds, the activities were evaluated in MES test. In phase-I screening, each compound was administered at the dose levels of 30, 100, and 300 mg/kg for evaluating the preliminary anticonvulsant activity. For determination of the median effective dose (ED_{50}) the median toxic dose (TD_{50}), the phase-II screening was prepared. Groups of ten mice were given a range of intraperitoneal injection 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 plot of this data, the respective ED_{50} and TD_{50} values, 95% confidence intervals, slope of the regression line, and the standard error of the slope were calculated by means of a computer program written at National Institute of Neurological Disorders and Stroke.

The neurotoxicity of the compounds was measured in mice by the rotarod test. The mice were trained to stay on an accelerating rotarod of diameter 3.2 cm that rotates at 10 rpm. Trained animals were given i.p. injection of the test compounds. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the trials.

Pentobarbital-induced-sleep test in mice

Male and female mice (20–25 g) were averagely divided into seven groups of ten and housed in a breeding room with a 12 h light–dark cycle at 24 ± 1°C. Compound **10** and the zopiclone were dissolved in 3% Tween-80. Each group was i.p. injected with different doses of **10** and zopiclone (10, 30, and 60 mg/kg) 30 min before the intraperitoneal administration of pentobarbital sodium (45 mg/kg). Sleep time was considered as the difference between the time of loss and recovery of the righting reflex. A control group was i.p. treated with 3% Tween-80 alone to determine the duration of the hypnosis. The results were analyzed using one-way-ANOVA followed by Dunnet's test.

Results and discussion

Chemistry

6-Methoxy-2,3-dihydrochromen-4-one (**1**) was prepared by the method reported by Cai *et al.*, (2006). The Beckmann rearrangement reaction is a good method to obtain seven-membered heterocyclic amides, especially the 1,4-benzoxazepin-5(2*H*)-ones (Bhalerao and Thyagarajan, 1968). In this study, 6-methoxy-2,3-dihydrochromen-4-one (**1**) reacted with hydroxylamine chloride to form 6-methoxy-2,3-dihydrochromen-4-one oxime (**2**) with a high yield, which then, under the Lewis acid condition, using PPA in this case, became compound **3**. In this step, the product in the Beckmann rearrangement reaction was mostly the expected product, 7-methoxy-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (compound **3**), rather than the regioisomer. This might be ascribed to the greater difficulty for the aryl group to migrate. Demethylation of compound **3** by treatment with dichloromethane and boron tribromide, as described by Bauer, produced 7-hydroxy-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (compound **4**) (Bauer *et al.*, 1995). Then, compounds **5**–**25** were synthesized through the reaction of compound **4** with halogenated hydrocarbon and K_2CO_3 in ethanol.

Pharmacology

As with any other class of drugs, the preclinical discovery and development of a new chemical entity for the treatment of epilepsy rely heavily on the use of predictable animal models. At present, there are three in vivo models that are routinely used by most AED discovery programs. They include the MES, the subcutaneous pentylenetetrazol (sc-PTZ), and the kindling model. Of these, the MES and sc-PTZ seizure models represent the two animal seizure models most widely used in the search for new AEDs (White, 2003). In this study, the MES seizure model was used for preliminary (phase I) screening of target compounds **5**–**25** (Table 1). The results indicated that compounds **6**, **8**, **9**, **10**, **13**, **15**, and **16** displayed anticonvulsant activity at 100 mg/kg, while the others displayed anticonvulsant activity at a dose of 300 mg/kg. Almost all of these compounds exhibited neurotoxicity at a dose of 300 mg/kg, according to the initial rotarod test. Some compounds that displayed anticonvulsant activity 4 h after administration and no activity 12 h after administration were expected to have long-acting effects.

Compounds **6**, **8**, **9**, **10**, **13**, **15**, and **16** were then subjected to phase II trials for the quantification of their anticonvulsant activity and neurotoxicity in mice. The data were also compared with the marketed anticonvulsant drug phenobarbital (Table 2). The most active

Table 1 Phase I anticonvulsant and toxicity data in mice (i.p.)

Compds.	R	Dosage (mg/kg)	MES		Dosage (mg/kg)	Rotarod	
			0.5 h	4 h		0.5 h	4 h
5	$-C_2H_5$	100	1/3	0/3	100	0/3	0/3
6	*n*–C_3H_7	100	3/3	0/3	100	3/3	0/3
7	*n*–C_4H_9	100	2/3	2/3	100	3/3	0/3
8	*n*–C_5H_{11}	100	3/3	1/3	100	3/3	0/3
9	*n*–C_6H_{13}	100	3/3	2/3	100	3/3	0/3
10	*n*–C_7H_{15}	30	2/3	0/3	100	3/3	0/3
11	*n*–C_8H_{17}	100	2/3	1/3	100	2/3	0/3
12	*n*–$C_{12}H_{25}$	300	3/3	1/3	300	3/3	0/3
13	$-CH_2C_6H_5$	100	3/3	1/3	100	1/3	0/3
14	$-CH_2C_6H_4$ (*p*-F)	300	3/3	3/3	300	2/3	0/3
15	$-CH_2C_6H_4$ (*m*-F)	100	3/3	0/3	100	3/3	0/3
16	$-CH_2C_6H_4$ (*o*-F)	100	3/3	0/3	100	3/3	0/3
17	$-CH_2C_6H_4$ (*p*-Cl)	100	1/3	0/3	100	3/3	0/3
18	$-CH_2C_6H_4$ (*m*-Cl)	100	2/3	0/3	100	3/3	0/3
19	$-CH_2C_6H_4$ (*o*-Cl)	300	3/3	0/3	300	3/3	0/3
20	$-CH_2C_6H_3$ (*2,6*-Cl_2)	100	0/3	0/3	100	3/3	0/3
21	$-CH_2C_6H_4$(*p*-Br)	300	3/3	0/3	300	3/3	0/3
22	$-CH_2C_6H_4$(*o*-Br)	100	1/3	0/3	100	3/3	0/3
23	$-CH_2C_6H_4$(*p*-CH_3)	100	0/3	0/3	100	3/3	0/3
24	$-CH_2C_6H_4$(*p*-OCH_3)	100	0/3	0/3	100	0/3	0/3
25	$-CH_2C_6H_3$(3,4-$(OCH_3)_2$)	100	0/3	0/3	100	3/3	0/3

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

Compds.	R	ED_{50} (mg/kg) (MES)	TD_{50} (mg/kg) (Rotarod)	*PI*
6	*n*–C_3H_7	78.3 (66.8 ~ 91.9)	169.7 (144.6 ~ 199.1)	2.2
8	*n*–C_5H_{11}	56.8 (49.2 ~ 65.5)	105.7 (94.4 ~ 118.3)	1.9
9	*n*–C_6H_{13}	47.3 (41.0 ~ 54.6)	105.7 (93.8 ~ 118.3)	2.2
10	*n*–C_7H_{15}	19.0 (16.2 ~ 22.3)	47.3 (40.3 ~ 55.5)	2.5
13	$-CH_2C_6H_5$	73.1 (63.3 ~ 84.3)	76.2 (66.1 ~ 87.9)	1.0
15	$-CH_2C_6H_4$ (*m*-F)	73.1 (63.4 ~ 84.3)	73.1 (63.4 ~ 84.3)	1.0
16	$-CH_2C_6H_4$ (*o*-F)	45.6 (39.5 ~ 52.6)	52.8 (45.8 ~ 60.9)	1.2
Phenobarbital	–	21.8 (19.8 ~ 25.5)	69.0 (62.8 ~ 72.9)	3.2
Carbamazepine	–	11.8 (9.7–14.1)	76.1 (69.1–83.7)	6.4

compound was found to be 7-(heptyloxy)-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (**10**), which had an ED_{50} value of 19.02 mg/kg and a protective index ($PI = TD_{50}/ED_{50}$) value of 2.49. The compound **10** had better anticonvulsant activity than phenobarbital, but it exhibited higher neurotoxicity.

The length of the alkyl chain appeared to have a direct impact on the anticonvulsant activity of the 7-alkyloxyl derivatives. From compounds **5**–**10**, the increase in the length of the alkyl chain, from 2 to 7, paralleled the gradual increase in ED_{50}, and the compound **10**, with the *n*-heptyloxy substituted group, was the most active. The trend reversed, however, when the alkyl chain had more than seven carbon numbers. This suggested that the compound with the *n*-heptyloxy substituted group had the optimal lipid–water partition coefficient to cross the blood–brain barrier.

Some halogen-substituted derivatives were designed and synthesized in this study. Of those derivatives (**14**–**22**), only 7-(2-fluorobenzyloxy)-3,4-dihydrobenzo[*f*][1,4]oxazepin-

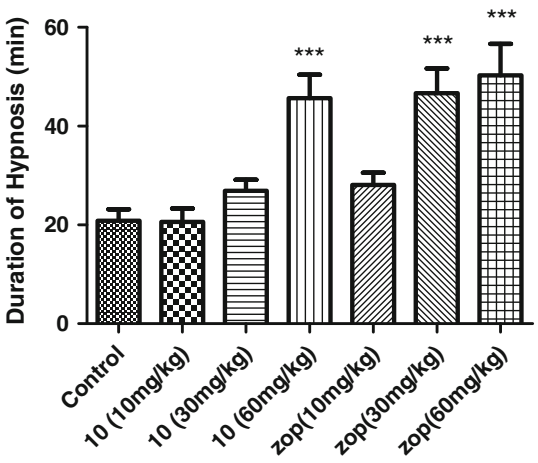


Fig. 2 Acute effects of compound **10** and zopiclone on the pentobarbital-induced-sleep test. Derivatives were injected i.p. 30 min before intraperitoneally injected (45 mg/kg) of pentobarbital sodium. Data represent means ± SEM of time between loss and recovery of the righting reflex. *** $P < 0.001$

5(2*H*)-one (**15**) and 7-(3-fluorobenzyloxy)-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (**16**) possessed relatively strong anticonvulsant activity with ED_{50} values of 73.1 and 45.6 mg/kg, respectively. All of the benzyloxy-substituted derivatives displayed lower anticonvulsant activity than that of the proper length alkoxyl-substituted derivatives. In those benzyloxy-substituted derivatives, different halogen atom substitutions contributed to the anticonvulsant activity in the order of F > Cl > Br; the introduction of an F atom on the benzyl ring increased the anticonvulsant activity in the *o* position but not in the *m* and *p* positions. Three electron-donor benzyloxy derivatives were also designed and prepared, containing *p*-CH_3, *p*-OCH_3, 3,4-$(OCH_3)_2$, respectively. The pharmacology test revealed that their activities were obviously lower than the halogen-substituted derivatives.

The hypnotic effect of compound **10** was initially investigated by using the pentobarbital-induced-sleep test which was most widely used in the evaluation of hypnotic effect. Zopiclone was used as the positive control. A low dose of **10** (10 mg/kg) did not increase the duration of hypnosis induced by pentobarbital (Fig. 2), the middle dose of **10** (30 mg/kg) slightly increased the pentobarbital-induced-sleep time without significant difference, while the high dose of **10** (60 mg/kg) can significantly increased the pentobarbital-induced-sleep time from 20.9 ± 2.31 to 45.7 ± 4.76 min. As shown in the Fig. 2, the activity of compound **10** was close to that of zopiclone at the high dose. It was clear that compound **10** could prolong the duration of the hypnosis induced by pentobarbital in a dose-dependent manner.

Conclusions

A series of 7-substituted-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-ones was synthesized. The anticonvulsant effect and neurotoxicity of the compounds were calculated with a MES test and a rotarod test with intraperitoneally injected mice. The results showed that all of the derivatives exhibited anticonvulsant activities. Among the synthesized compounds, 7-(heptyloxy)-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (**10**) was the most active. In the anti-MES potency test, it showed a stronger activity with median effective dose (ED_{50}) of 19.0 mg/kg compare with the reference drug phenobarbital (ED_{50} = 21.8 mg/kg). However, the value *PI* (2.49) of it is lower than phenobarbital (*PI* = 3.17). The hypnotic effect of compound **10** was also initially investigated in the pentobarbital-induced-sleep test, and the results revealed that it could prolong the duration of the hypnosis induced by pentobarbital in a dose-dependent manner.

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