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Research Article

SYNTHESIS, ANTICONVULSANT, BENZOTRIAZOLOAZEPINES

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ABSTRACT

A series of novel 3-Substituted-1,3,4,5-Tetrahydro-2H-benzo [b] azepine-2-one Derivatives (4, 5, 7, 10, 12, 5a-j, 8a-e) were synthesized from 1,2,3,4-Tetrahydro-1-naphthalenone. The structures of these compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, MASS spectra and elemental analysis. Their anticonvulsant activity was evaluated the maximal electroshock (MES) test, subcutaneous pentylenetetrazol (scPTZ) test, and their neurotoxicity was evaluated by the rotarod neurotoxicity test. Compound 4 showed the maximum anticonvulsant activity against MES (ED_{50}=26.4, PI =3.2) and against scPTZ (ED_{50}=40.2, PI =2.1). Possible structure–activity relationship is discussed.

Keywords: Anticonvulsant activity, Toxicity, Benzotriazoloazepine, Synthesis.

INTRODUCTION

Benzazepine derivatives exhibit broad pharmacological activity (Wei, et al., 2009; Rives, et al., 2009; Bariwal, et al., 2008 and Im, et al., 2004). In our search for new compounds with anticonvulsant activity, 1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (compound 10) showed a moderate anticonvulsant activity (ED_{50}=65.7, thence, compound 10 was used as a lead compound, which structure was optimized and a series of benzazepine derivatives were synthesized (Figure 1). Firstly, the derivatives of the 5(6,7) -substituted with alkoxy groups of the compound 1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (aniline lactam) were synthesized and their anticonvulsant activity were evaluated. Among them, compound 6-octyloxy-1,3,4,5-tetrahydro-2H- benzo [b] azepin-2-one (compound Ⅰ) was the most active with median effective dose (ED_{50}) of 20.4 mg/kg, and protective index (PI) value of 20.1 in the MES test, and its values of ED_{50} and PI in the anti-scPTZ test were 70.6 and 5.4, respectively. Among

their cyclized derivatives, compound Ⅱ and compound Ⅲ were more potent than other compounds, the ED_{50} value of anti-MES activity of compound Ⅱ was 9.8 mg/kg (PI=4.2), but it did not show the anti-scPTZ activity at dose of 100 mg/kg. The ED_{50} values of anti-scPTZ activity and anti-MES activity of compound Ⅲ were 17.5 mg/kg (PI=6.5), 21.2 mg/kg (PI=5.4), respectively. Compound Ⅲ demenstrated a good anti-scPTZ activity and anti-MES activity.

In the benzamide lactam derivatives, the compound Ⅳ showed the highest level of activity, its ED_{50} values of anti-MES activity and anti-scPTZ activity were 13.2 mg/kg (PI=6.0), 32.9 mg/kg (PI=2.4), respectively.

Secondary amino group ($\left[-\overset{\overset{H}{|}}{\underset{\cdot\cdot}{N}}-\right]$) and O atom ($\left[-\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}-\right]$) could be regarded as generalized Bioisosterism. Bioisosterism, can be defined as the property by which the substituents, or groups with similar physical or chemical properties, impart similar biological properties to a chemical compound is a useful strategy for both medicinal chemistry and rational design of new drugs. Therefore, 8-alkylamino-5, 6-dihydro-4*H*-benzo[f] [1,2,4] triazolo [4,3-a]azepine derivatives were synthesized and their anticonvulsant activity were evaluated. Among them, 8-heptylamino-5, 6-dihydro-4H-benzo[f] [1,2,4] triazolo [4,3-a] azepine (compound Ⅴ) was the most promising, which besides being one of the most active compound had the lowest toxicity. Its ED_{50} value of anti-MES activity was 19.0 mg/kg (PI=14.8).

The amide bond is a key functional group in organic chemistry. It plays a major role in many antiepileptic drugs contain an amide bond. For example, Phenytoin, Diazepam, Oxazepam, Carbamazepine and Oxcarbazepine. Generally, primary and secondary amines can form hydrogen bonds as either donor or acceptor. Amide bonds can increase the affinity of the receptor and ligand. But unfortunately, compound VI did not exhibit anticonvulsant activity at a dose of 100 mg/kg in both animal modles. N-alkylation on the amide bond can increases the hydrophobicity of the compound, so its ability to pass through the blood-brain barrier can be improved. Among the N-alkylated products, compound Ⅶ has shown the best anticonvulsant activity, which ED50 values of anti-MES activity and anti-scPTZ activity were 36.5 mg/kg (PI=4.5), 68.2 mg/kg (PI=2.4), respectively.

Without knowing the three-dimensional structure of the receptor, the compound with the best activity and low toxicity was selected to cultivate single crystal and its structure was studied by the single crystal X-ray diffraction (SXRD), which single crystal diffraction data was used to as the template, the lowest energy conformation of the template molecule is chosen as the most possible Pharmacological conformation, the Three-Dimensional Quantitative Structure Activity Relationships can be studied by Comparative Molecular Field Analysis (CoMFA). The CoMFA is used to deduce some target properties, design new compounds and quantitatively predict the activity intensity of new compounds.

In order to do this, the target compounds were synthesized through a convenient synthetic sequence (Figures 2 and 3 and scheme 1). 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.

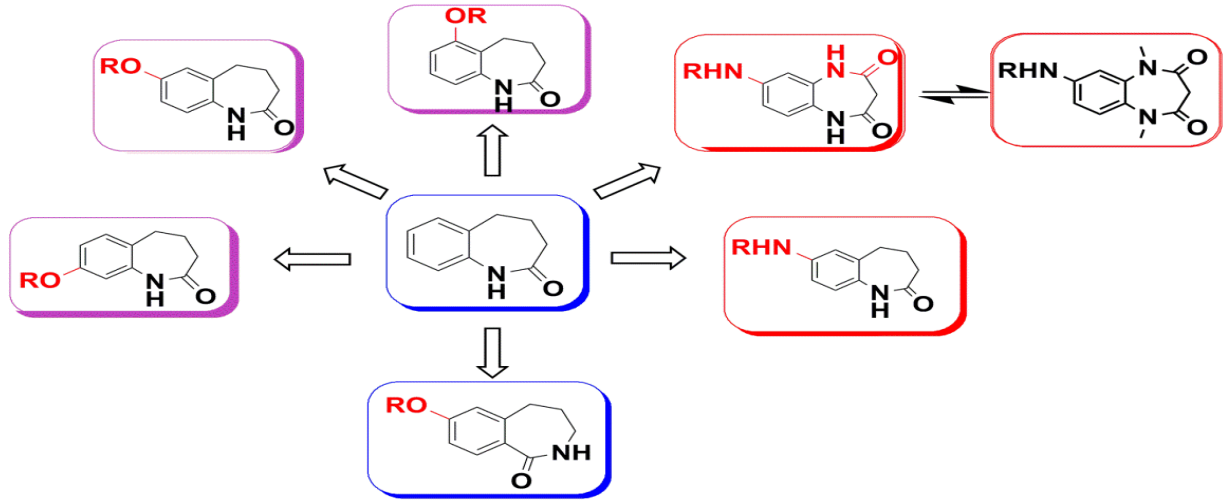


Figure 1: Structures of the previously synthesized benzazepine derivatives.

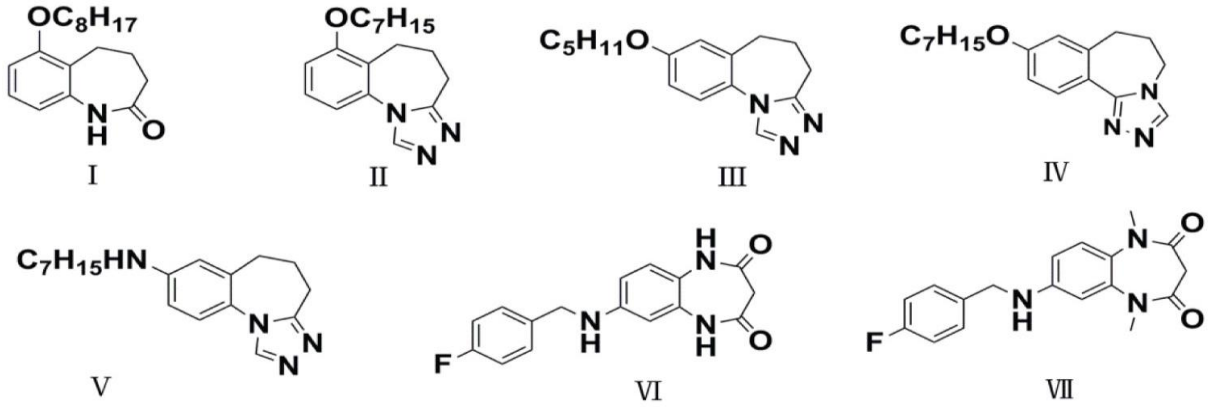


Figure 2: Structures of compounds with better anticonvulsant activities.

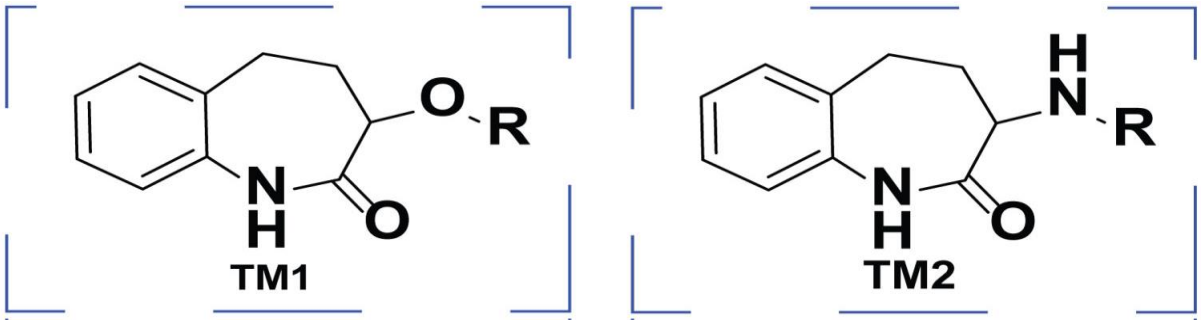


Figure 3: Structures of compounds 5a-j and 8a-e.

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). 1H-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.

The target compounds were prepared according to Scheme 1. The compounds 1 and 2 were synthesized using the method described in a former paper (Hoyt, *et al.*, 2007 and Pérez-Medina, *et al.*, 2012), compounds 2 reacted with potassium acetate to produce the compounds 3, which reacted with potassium carbonate to produce the compounds 4, the compounds 4 reacted with halogenated hydrocarbons and methyl iodide to give the compounds 5a-i and 5j respectively. The secondary amines were obtained from the corresponding azide and compounds 2. Compound 12 was synthesized from 1-tetralone as raw mateial by oximation, rearrangement, thiolation and cyclization. The structures of all the new compounds were confirmed by IR, 1H NMR, MS, and elemental analyses.

The synthesis of 2-Bromo-3,4-dihydro-1(2H)-naphthalenone oxime (1)

The compound was synthesized using a previously described method (Boyer, *et al.*, 1988).

Yield: 94%. white. mp. 129.2-131.3℃. IR (KBr), cm^{-1}: 3164(N-H), 1671(C=N) , 654(C-Br). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (1H, s, NH), 7.35-7.19 (4H, m, Ar-H), 5.78 (1H, t, J=3.0Hz, C_2-H), 3.39-3.28 (1H, m, C_4-H), 2.82-2.77 (1H, m, C_4-H), 2.39-2.31 (1H, m, C_3-H), 2.25-2.13 (2H, m, C_3-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.13 (C_1), 136.67(C_{4a}), 133.09 (C_6), 129.84 (C_5), 128.05 (C_7), 126.59 (C_8), 122.33 (C_{8a}), 47.01 (C_2), 40.23 (C_3), 30.31 (C_4). MS: m/z 241. 02 (M+1).

The synthesis of 3-Bromo-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (2)

The compound was synthesized using a previously described method (Hoyt, et al., 2007).

Yield: 90%. yellow. mp. 157.4-159.2℃. IR (KBr), cm^{-1}: 3191(N-H), 1681(C=O) , 702(C-Br). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (1H, s, NH), 7.31-7.03 (5H, m, Ar-H), 4.58-4.52 (1H, m, C_3-H), 3.03-2.96 (1H, m, C_5-H), 2.84-2.62 (3H, m, C_5-H and C_4-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 168.99 (C_2), 136.63 (C_{5a}), 133.11 (C_{9a}), 129.86 (C_7), 128.05 (C_8), 126.60 (C_6), 122.29 (C_9), 46.97 (C_3), 40.20 (C_5), 30.31(C_4). MS: m/z 239.10 (M).

The synthesis of 3-Acetoxy-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (3)

Compound 2 (2.4 g, 10 mmol), potassium acetate (5.9 g, 60 mmol) and anhydrous acetonitrile (100 mL) were placed into a reaction bottle, the mixture was stirred at 70 ℃ for 0.5 hour, then to this mixture was slowly added dropwise 18-crown-6 (50 mg, 0.2 mmol) dissolved in 10 mL of anhydrous acetonitrile, which was refluxed and tested with TLC plate after the drop wise addition.

After completion of the reaction, the solvent was removed under reduced pressure, extracted three times with ethyl acetate and washed with saturated brine, The organic phases was dried over anhydrous $MgSO_4$. Evaporation of the solvents gave a crude product, which was recrystallized from 95% ethanol to give 2.04 g of yellow crystals and 85% yield.

Yield: 85%. yellow. mp. 159.9-160.1℃. IR(KBr), cm^{-1}: 3204(N-H), 1743(O-C=O) , 1680(C=O). ^{1}H NMR (300 MHz, CDCl3): δ 8.22 (1H, s, NH), 7.27-7.08 (4H, m, Ar-H), 5.08 (1H, dd, J_1=9.0 Hz , J_2=12.0 Hz C_3-H), 3.06-2.94 (1H, m, C_4-H), 2.75-2.63 (1H, m, C_4-H), 2.54-2.48 (1H, m, C_5-H), 2.42-2.31 (1H, m, C_5-H), 2.12(3H, s, alkyl $C_{2`}$-H). $^{13}$C NMR(75MHz, CDCl3): δ 170.55 ($C_2$), 170.08 ($C_{1`}$), 136.08 (C_{5a}), 133.58 (C_{9a}), 129.61 (C_7), 127.95(C_8), 126.26 (C_6), 122.56 (C_9), 70.07 (C_3), 34.18 (C_5), 27.78 (C_4), 20.72 ($C_{2`}$).

The synthesis of 3-Hydroxy-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (4)

Compound 3 (2.4 g, 11 mmol) and methanol (150 mL) were placed into a reaction bottle, then the mixture was stirred at room temperature until the compound 3 was completely dissolved, then to this mixture was added potassium carbonate (181 mg, 1.32 mmol). The reaction mixture was stirred at room temperature for 4 hand tested with TLC. After completion of the reaction, the solvent was removed under reduced pressure, extracted three times with ethyl acetate and washed with saturated brine, The organic phases was dried over anhydrous MgSO4. Evaporation of the solvents gave a crude product, which was recrystallized from methanol: 95% ethanol（1:1）to give 1.65 g of white crystals and 85% yield.

Yield: 85%. white. mp. 143.8-144.0℃. IR (KBr), cm-1: 3345(O-H), 3204(N-H), 1684(C=O). 1H NMR (300 MHz, CDCl3): δ 8.50 (1H, s, NH), 7.26-7.01 (4H, m, Ar-H), 4.19-4.11 (1H, m, C3-H), 3.64-3.63 (1H, d, J=6.0 Hz, O-H), 3.03-2.91 (1H, m, C_5-H), 2.76-2.62 (2H, m, C_4-H), 2.13-2.03 (1H, m, C_5-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 175.88 (C_2), 135.69 (C_{5a}), 134.06 (C_{9a}), 129.78 (C_7), 127.71 (C_8), 125.37 (C_6), 122.10 (C_9), 67.88 (C_3), 38.51 (C_5), 28.06 (C_4). MS: m/z 177. (M+1).

General procedure for preparation of compounds 5a–j

Compound 4 (354 mg, 2 mmol), sodium hydroxide (120 mg, 1.5 mmol) and 25 mL 95% ethanol were placed in a round bottom flask and stirred for 2.5 h in an oil bath at 88℃, then to this mixture was slowly added drop wise halogenated hydrocarbons (1.5 mmol) dissolved in 5 mL of 95% ethanol, which was refluxed and tested with TLC plate after the drop wise addition. After completion of the reaction, the solvent was removed under reduced pressure, extracted

three times with ethyl acetate and washed with saturated brine. The organic phases was dried over anhydrous $MgSO_4$. Evaporation of the solvents gave a crude product, which was purified by column chromatography (PE: EA=7: 1). The yield was 35-40%.

3-Propoxy-1,3,4,5-tetrahydro-2H-benzo[b]azepan-2-one (5a)

Yield: 40%. yellow. mp. 70.4℃. IR (KBr), cm^{-1}: 3396(N-H), 2948(C-H), 1648(C=O), 1112(C-O-C). ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.17 (5H, m, Ar-H), 4.35-4.25 (1H, m, C_3-H), 4.03-3.95 (1H, m, alkyl $C_{1`}$-H),3.56-3.44 (2H, m, $C_5$-H), 2.90-2.79 (1H, m, $C_4$-H), 2.57-2.53 (2H, m, alkyl $C_{2`}$-H), 1.67-1.58 (1H, m, C_4-H), 0.92-0.87 (3H, t, J=15.0Hz, alkyl $C_{3`}$-H). $^{13}C$ NMR(75MHz, $CDCl_3$): δ 173.73 ($C_2$), 139.95 ($C_{5a}$), 135.86 ($C_{9a}$), 129.22 ($C_7$), 127.81($C_8$), 126.85 ($C_6$), 123.06 ($C_9$), 67.82 ($C_3$), 50.14 ($C_{1`}$), 38.63 (C_5), 27.90 (C_4), 21.44 ($C_{2`}$), 11.52 ($C_{3`}$).

3-Pentyloxy-1,3,4,5-tetrahydro-2H-benzo[b]azepan-2-one (5b)

Yield: 38%. yellow. mp. 66.1-67.6℃. IR (KBr), cm^{-1}: 3459(N-H), 2952(C-H), 1650(C=O),1021(C-O-C). ^1H NMR (300 MHz, $CDCl_3$): δ 7.26-7.10 (5H, m, Ar-H), 4.31-4.21 (1H, m, C_3-H), 3.92-3.90 (1H, m, C_5-H), 3.48-3.38 (2H, m, alkyl $C_{1`}$-H), 2.81-2.71 (1H, m, $C_5$-H), 2.52-2.47 (2H, m, $C_4$-H), 1.96-1.86 (1H, m, alkyl $C_{2`}$-H), 1.21-1.20 (5H, m, alkyl $C_{2`}$-H, $C_{3`}$-H, and $C_{4`}$-H), 0.80-0.76 (3H, t, J=6.0Hz, alkyl $C_{5`}$-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 173.71 (C_2), 139.87 (C_{5a}), 135.86 (C_{9a}), 129.24 (C_7), 127.84 (C_8), 126.90 (C_6), 123.08 (C_9), 67.84 (C_3), 48.53 ($C_{1`}$), 38.67 ($C_5$), 29.20 ($C_4$), 27.91 ($C_{2`}$), 27.81 ($C_{3`}$), 22.34 ($C_{4`}$), 14.00 ($C_{5`}$).

3-Hexyloxy-1,3,4,5-tetrahydro-2H-benzo[b]azepan-2-one (5c)

Yield: 40%. yellow. mp. 59.6-60.7℃. IR (KBr), cm^{-1}: 3437(N-H), 2946(C-H), 1657(C=O), 1101(C-O-C). ^1H NMR (300 MHz, $CDCl_3$): δ 7.33-7.17 (4H, m, Ar-H), 4.38-4.28 (1H, m, C_3-H), 4.00-3.95 (1H, m, C_5-H), 3.63-3.46 (2H, m, alkyl $C_{1`}$-H), 2.90 - 2.79 (m, 1H, $C_5$-H), 2.59-2.46 (2H, m, $C_4$-H), 2.03-1.93 (1H , m, alkyl $C_{2`}$-H), 1.27 (7H, m, alkyl $C_{2`}$-H, $C_{3`}$-H, $C_{4`}$-H, and $C_{5`}$-H), 0.85 (3H, t, J=6.00 Hz, alkyl $C_{6`}$-H). $^{13}C$ NMR (75MHz, $CDCl_3$): δ 173.66 ($C_2$), 139.90 ($C_{5a}$), 135.85 ($C_{9a}$), 129.22 ($C_7$), 127.82 ($C_8$), 126.85 ($C_6$), 123.05 ($C_9$), 67.81 ($C_3$), 48.48 ($C_{1`}$), 38.68 (C_5), 29.72 (C_4), 29.19 ($C_{2`}$), 27.90 ($C_{3`}$), 27.80 ($C_{4`}$), 22.32 ($C_{5`}$), 13.98 ($C_{6`}$).

3-Heptoxy-1,3,4,5-tetrahydro-2H-benzo[b]azepan-2-one (5d)

Yield: 40%. yellow. mp. 53.6-54.5℃. IR (KBr), cm^{-1}: 3336(N-H), 2926(C-H), 1648(C=O), 1168(C-O-C). ^1H NMR (300 MHz, $CDCl_3$): δ 7.26-7.10 (4H, m, Ar-H), 4.31-4.21 (1H, m, C_3-H), 3.95-3.87 (1H, m, C_5-H), 3.53-3.38 (2H, m, alkyl $C_{1`}$-H), 2.79-2.71 (m, 1H, $C_5$-H), 2.52-2.41 (2H, m, $C_4$-H), 1.95-1.85 (1H, m, alkyl $C_{2`}$-H), 1.18 (9H, m, alkyl $C_{2`}$-H, $C_{3`}$-H, $C_{4`}$-H, $C_{5`}$-H and $C_{6`}$-H), 0.78-0.75 (3H, t, J=6.0Hz, alkyl $C_{7`}$-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 173.64(C_2), 139.91 (C_{5a}), 135.84 (C_{9a}), 129.20 (C_7), 127.80 (C_8), 126.82 (C_6), 123.04 (C_9), 67.80 (C_3), 48.47 ($C_{1`}$), 38.67 ($C_4$), 31.67 ($C_{2`}$), 28.90 ($C_{3`}$), 28.1 3($C_{4`}$), 27.01($C_{5`}$), 22.53 ($C_{6`}$), 14.05 ($C_{7`}$). MS: m/z 275. (M).

3-Octyloxy-1,3,4,5-tetrahydro-2H-benzo[b]azepan-2-one (5e)

Yield: 40%. white. mp. 52.0-52.2℃. IR (KBr), cm^{-1}: 3452(N-H), 2947(C-H), 1651(C=O), 1147(C-O-C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.17 (4H, m, Ar-H), 4.38-4.31 (1H, m, C_3-H), 4.03-3.59 (1H, m, C_5-H), 3.59-3.46 (2H, m, alkyl $C_{1`}$-H,), 2.86–2.84 (1H, m,$C_5$-H), 2.60-2.53 (2H,m, $C_4$-H), 2.02-1.92 (1H ,m, alkyl $C_{2`}$-H), 1.24 (11H ,d, J=6.0 Hz, alkyl $C_{2`}$-H $C_{3`}$-H, $C_{4`}$-H, $C_{5`}$-H, $C_{6`}$-H and $C_{7`}$-H), 0.86 (3H ,t, J=4.0Hz, alkyl $C_{8`}$-H). $^{13}$C NMR (75MHz, $CDCl_3$): δ 173.65 ($C_2$), 139.91 ($C_{5a}$), 135. 86($C_{9a}$), 129.22($C_7$), 127.82($C_8$), 126.86 ($C_6$), 123.07 ($C_9$), 67.80 ($C_3$), 48.52 ($C_{1`}$), 38.69 (C_5), 31.74 (C_4), 29.20 ($C_{2`}$), 29.16 ($C_{3`}$), 28.14($C_{4`}$), 27.91 ($C_{5`}$), 27.06 ($C_{6`}$), 22.61 ($C_{7`}$), 14.10($C_{8`}$).

3-((4-Fluorobenzyl)oxy)-1,3,4,5-tetrahydro-2H-benzo[b]azepan-2-one (5f)

Yield: 38%. yellow. mp. 98.4-100.1℃. IR (KBr), cm^{-1}: 3437(N-H), 2947(C-H), 1657(C=O),1020(C-F). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-6.90 (9H, m, Ar-H), 5.34 (1H, d, J=15.0 Hz, benzyl CH_2), 4.78 (1H, d, J=15.0 Hz, benzyl CH_2), 4.21-4.05 (1H, m, C_3-H), 2.58-2.33 (3H, m, C_4-H and C_5-H), 2.01-1.92 (1H, m, C_4-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 174.3 (C_2), 162.22 (d, J_{C-F} =247.5Hz, phenyl C_4), 139.64(C_{5a}), 135.84 (C_{9a}), 132.88 (d, J_{C-F} =3.0Hz, phenyl C_1), 130.10 (d, J_{C-F}=8.3Hz, phenyl C_2 and C_6), 129.32 (C_7), 127.88 (C_8), 127.23 (C_6), 123.26 (C_9), 115.47 (d, J_{C-F}=19.5Hz, phenyl C_3 and C_5), 67.92 (C_3), 51.23 (benzyl C) , 38.77 (C_5) , 27.72 (C_4).

3-((4-Chlorobenzyl)oxy)-1,3,4,5-tetrahydro-2H-benzo[b]azepan-2-one (5g)

Yield: 38%. yellow. mp. 112.4-113.1℃. IR (KBr), cm^{-1}: 3266(N-H), 2932(C-H), 1653(C=O),770(C-Cl). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17-7.04 (9H, m, Ar-H), 5.19 (1H, d, J=15.0 Hz, benzyl CH_2), 4.69 (1H, d, J=15.0 Hz, benzyl CH_2), 4.00-3.98 (1H, m, C_3-H), 2.40-2.21 (3H, m, C_4-H and C_5-H), 1.87-1.85 (1H, m, C_4-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 174.31 (C_2), 139.61 (phenyl C_4), 135.75 (phenyl C_1), 135.51 (C_{5a}), 133.53 (C_{9a}), 129.67 (phenyl C_3 and C_5), 129.39(C_7), 128.79 (phenyl C_2 and C_6), 127.93 (C_8), 127.29 (C_6), 123.15 (C_9), 67.94 (C_3), 51.36 (benzyl C), 38.77 (C_5), 27.77 (C_4).

3-((4-Bromobenzyl)oxy)-1,3,4,5-tetrahydro-2H-benzo[b]azepan-2-one (5h)

Yield: 38%. yellow. mp. 127.2-127.7℃. IR (KBr), cm^{-1}: 3268(N-H), 2937(C-H), 1652(C=O),707(C-Br). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28(2H, d, J=6.0 Hz, Ar-H), 7.18-7.06 (4H, m, Ar-H), 7.02 (2H, d, J=6.0 Hz, Ar-H), 5.18 (1H, d, J=15.0 Hz, benzyl CH_2), 4.70 (1H, d, J=15.0 Hz, benzyl CH_2), 4.00-3.97 (1H, m, C_3-H), 2.43-2.31 (3H, m, C_4-H and C_5-H), 1.89-1.84 (1H, m, C_4-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 174.33 (C_2), 139.63 (phenyl C_4), 136.07 (phenyl C_1), 135.73(C_{5a}), 131.73 (phenyl C_3 and C_5), 130.02 (phenyl C_2 and C_6), 129.41 (C_{9a}), 127.93 (C_7), 127.28 (C_8), 123.12 (C_6), 121.67(C_9), 67.97 (C_3), 51.39 (benzyl C), 38.77 (C_5), 27.80 (C_4) . MS: m/z 346. (M^+).

3-((4-Methylbenzyl)oxy)-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (5i)

Yield: 38%. white. mp. 109.6℃. IR (KBr), cm^{-1}: 3418(N-H), 2947(C-H), 1639(C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-6.93 (8H, m, Ar-H), 5.18 (1H, d, J =15.0 Hz, benzyl CH_2), 4.72 (1H, d, J = 15.0 Hz, benzyl CH_2), 3.99 (1H, m, C_3-H), 2.47-2.36 (2H, m, C_5-H), 2.34-2.27 (1H, m, C_4-H), 2.17 (3H, s, benzyl CH_3), 1.91-1.84 (1H, m, C_4-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 174.21(C_2), 139.94 (phenyl C_1), 137.27 (phenyl C_4), 135.81(C_{5a}), 134.04 (C_{9a}), 129.28 (phenyl C_3 and C_5), 129.24 (C_7), 128.18 (phenyl C_2 and C_6), 127.79 (C_8), 127.07 (C_6) , 123.30 (C_9), 67.98 (C_3), 51.75 (benzyl $C_{1'}$), 38.83 (C_5), 27.79 (C_4), 21.19 (CH_3).

The synthesis of 3-Methoxy-1,3,4,5-tetrahydro-2H-benzo[b]azepan-2-one (5j)

Compound 4 (177.2 mg, 1.6 mmol) and 5 ml of tetrahydrofuran were placed in a round bottom flask and stirred for 10 min in an ice bath, to this mixture was added NaH (240 mg, 1 mmol) and stirred for 1 h, then methyl iodide (227 mg, 1.6 mmol) was added the reaction mixture, which was stirred for 24 h at room temperature and monitored with TLC plates. After completion of the reaction, the solvent was removed under reduced pressure, to this mixture was added water dropwise, extracted three times with ethyl acetate and washed with saturated brine. The organic phases were dried over anhydrous $MgSO_4$. Evaporation of the solvents gave a crude product, which was purified by column chromatography (PE: EA = 9: 1). The yield was 40%.

Yield: 40%. white. mp. 84.7℃. IR (KBr), cm^{-1}: 3336(N-H), 2951(C-H), 1654(C=O), 1112(C-O-C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.15 (4H, m, Ar-H), 4.05 (1H, bs, C_3-H), 3.46 (3H, s, alkyl $C_{1'}$-H), 2.89-2.79 (1H, m, C_5-H), 2.62-2.56 (2H, m, C_4-H), 2.04-1.98 (1H, m, C_5-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 174.15 (C_2), 141.23 (C_{5a}), 134.99 (C_{9a}), 129.24 (C_7), 127.82 (C_8), 126.77 (C_6), 122.51 (C_9), 67.97 (C_3), 38.59 ($C_{1'}$), 35.62 (C_5), 27.85 (C_4). MS: m/z 191. (M).

The synthesis of 3-Azido-1,3,4,5-tetrahydro-2H-benzo[b]azepan-2-one (6)

The compound was synthesized using a previously described method (Boyer, *et al.*, 1988 and Pérez-Medina, *et al.*, 2012).

Yield: 90%. black. mp. 146.9-147.2℃. IR (KBr), cm^{-1}: 3439(N-H), 3071(C-H), 2105(N_3), 1669(C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.16 (4H, m, Ar-H), 7.03 (1H, d, J=6.0Hz, Ar-H), 3.91-3.85 (1H, m, C_3-H), 3.06-2.94 (1H, m, C_5-H), 2.77-2.71 (1H, m, C_5-H), 2.60-2.46 (1H, m, C_4-H), 2.37-2.27 (1H, m, C_4-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 171.61 (C_2), 136.17 (C_{5a}), 133.39 (C_{9a}), 129.73 (C_7), 128.09 (C_8), 126.47 (C_6), 122.46 (C_9), 59.09 (C_3), 34.91 (C_5), 28.33(C_4).

Preparation of 3-amino-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (7)

The compound was synthesized using a previously described method (Boyer, *et al.*, 1988 and Pérez-Medina, *et al.*, 2012).

Yield: 78%. black. mp. 147.3-147.5℃. IR (KBr), cm^{-1}: 3490(N-H), 3052(C-H), 1670(C=O). ^{1}H NMR (300 MHz, DMSO): δ 9.72(1H, s, N-H),7.26-6.95 (4H, m, Ar-H), 3.16(1H, t, J=9.0 Hz, C_3-H), 2.73-2.60 (1H, m, C_5-H), 2.35-2.21 (2H, m, C_4-H), 1.93-1.73 (1H, m, C_5-H). ^{13}C NMR

(75MHz, DMSO): δ 169.20 (C_2), 137.25 (C_{5a}), 133.33 (C_{9a}), 130.26 (C_7), 128.21 (C_8), 126.12 (C_6), 122.70 (C_9), 50.18 (C_3), 33.68 (C_5) , 27.81(C_4). MS: m/z 177. (M).

General procedure for preparation of compounds 8a-8c

Compound **7** (352 mg, 2 mmol) was dissolved in 10 ml of methanol, to the reaction mixture was added dropwise the corresponding substituted benzaldehyde (2.2 mmol) under nitrogen. The reaction was carried out at room temperature for 2 h and monitored with TLC plates. After completion of the reaction, to the reaction mixture was added $NaBH_4$ and stirred for 2~4 h, monitored with TLC plates. After completion of the reaction, the organic phases was dried over anhydrous $MgSO_4$ and filtered. Evaporation of the solvents gave a crude product, which was recrystallized from isopropanol to give the corresponding substituted benzyl derivative in 80% yield.

3-Propylamino-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (8a)

Yield: 38%. yellow. mp. 109.0℃. IR (KBr), cm^{-1}: 3356 (N-H), 3055 (C-H), 1674 (C=O). ^{1}H NMR (300 MHz, DMSO): δ 9.75(1H, s, NH)7.26-7.20 (2H, m, Ar-H), 7.09 (1H, t, J=9.0 Hz, Ar-H), 6.98 (1H, d, J=9.0 Hz, Ar-H), 3.00-2.93 (1H, m, C_3-H), 2.63-2.59 (2H, m, alkyl $C_{1'}$-H), 2.48-2.42 (1H, m, C_5-H), 2.31-2.23 (1H, m, C_5-H), 2.16-2.08 (1H, m, C_4-H), 1.84-1.74 (1H, m, C_4-H), 1.34-1.23 (2H, m, alkyl $C_{2'}$-H), 0.79 (3H, m, J=9.0Hz, alkyl $C_{3'}$-H). ^{13}C NMR (75MHz, DMSO): δ 174.65 (C_2), 138.34 (C_{5a}), 134.50 (C_{9a}), 129.81 (C_7), 127.70 (C_8), 125.31 (C_6), 122.26 (C_9), 58.39 (C_3), 50.31 (C_5), 37.83 (alkyl $C_{1'}$), 28.95 (C_4), 23.44 (alkyl $C_{2'}$), 12.19 (alkyl $C_{3'}$).

3-Octylamino-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (8b)

Yield: 40%. yellow. mp.153.1℃. IR (KBr), cm^{-1}: 3205(N-H), 2922(C-H), 1681(C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55(1H, s, NH)7.27-7.21 (4H, m, Ar-H), 3.75 (1H, bs, C_3-H), 2.93 (4H, bs, C_5-H and alkyl $C_{1'}$-H), 1.25-1.22 (13H, m, alkyl $C_{2'}$-H, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H, $C_{6'}$-H, $C_{7'}$-H), 0.85-0.82 (2H, m, alkyl $C_{7'}$-H, $C_{8'}$-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 168.71 (C_2), 135.32 (C_{5a}), 132.55 (C_{9a}), 129.92 (C_7), 128.46 (C_8), 127.01 (C_6), 123.15 (C_9), 57.06 (C_3), 47.84 (alkyl $C_{1'}$), 33.45 (C_5), 31.70 (C_4), 29.16 (alkyl $C_{2'}$), 29.07 (alkyl $C_{3'}$), 27.89 (alkyl $C_{4'}$), 26.79 (alkyl $C_{5'}$), 26.19 (alkyl $C_{6'}$), 22.57 (alkyl $C_{7'}$), 14.05 (alkyl $C_{8'}$).

3-Benzylamino-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (8c)

Yield: 80%. yellow. mp. 160.4-160.9℃. IR (KBr), cm^{-1}: 3313(N-H), 2948(C-H), 1663(C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-6.99 (10H, m, Ar-H), 3.87-3.83 (1H, d, J=15.0 Hz benzyl CH_2), 3.50-3.45 (1H, d, J = 15.0 Hz, benzyl CH_2), 3.33-3.27 (1H, m, C_3-H), 2.96-2.85 (1H, m, C_5-H), 2.68-2.61 (1H, m, C_5-H), 2.56-2.43 (1H, m, C_4-H), 2.02-1.92 (1H, m, C_4-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 175.33 (C_2), 140.08 (C_{9a}), 136.50 (C_{5a}), 134.74 (phenyl C_1), 129.79(C_7), 128.35 (phenyl C_2 and C_6), 128.24 (phenyl C_3 and C_5), 127.65(C_8), 126.93 (C_6), 126.18 (C_9), 122.15 (pheyl C_4), 57.85 (C_3), 52.64 (benzyl $C_{1'}$), 37.82 (C_5), 29.07(C_4). MS: m/z 289. (M+23).

3-((4-Methylbenzyl)oxy)-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (8d)

Yield: 82%. yellow. mp. 156.4-156.6℃. IR (KBr), cm^{-1}: 3333(N-H), 2947(C-H), 1667(C=O). ^1H NMR (300 MHz, DMSO): δ 9.79 (1H, s, N-H), 7.23-7.18 (2H, m, Ar-H), 7.12-7.03 (5H, m, Ar-H), 6.98-6.95 (1H, m, Ar-H), 3.70-3.65 (1H, m, benzyl CH_2), 3.37-3.32 (1H, m, benzyl CH_2), 3.04-2.98 (1H, m, C_3-H), 2.67-2.60 (2H, m, C_5-H), 2.34-2.28 (2H, m, C_4-H), 2.23 (3H, s, benzyl CH_3). ^{13}C NMR (75MHz, DMSO): δ 174.45 (C_2), 138.29 (C_{5a}), 138.01 (C_{9a}), 125.93 (pheylC_1), 134.45(phenyl C_3), 129.82 n(C_7), 129.12 (phenyl C_2 and C_6), 128.09 (phenyl C_3 and C_5), 127.71(C_8), 125.31(C_6), 122.24 (C_9), 57.51 (C_3), 51.44 (benzyl C), 37.82 (C_5), 28.98 (C_4), 21.11 (CH_3).

3-4-nitrobenzylamino-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (8e)

Yield: 81%. yellow. mp. 189.4-190.0℃. IR (KBr), cm^{-1}: 3518(N-H), 3052(C-H), 1664(C=O), 1514(N-O_2) . ^1H NMR (300 MHz, DMSO): δ 9.83 (1H, s, N-H), 8.13 (2H, d, J=9.0 Hz, Ar-H), 7.54 (2H, d, J=9.0 Hz, Ar-H), 7.26-7.18 (2H, m, Ar-H), 7.10-7.05 (1H, m, Ar-H), 6.97 (1H, d, J=6.0 Hz, Ar-H), 3.92 (1H, d, J=15.0 Hz, benzyl CH_2), 3.55 (1H, d, J=15.0 Hz, benzyl CH_2), 3.05 (1H, t, J=9.0 Hz, C_3-H), 2.74-2.63 (2H, m, C_5-H), 2.41-2.30 (1H, m, C_4-H), 1.97-1.87 (1H, m, C_4-H). ^{13}C NMR (75MHz, DMSO): δ 174.24 (C_2), 149.76 (C_{5a}), 146.68(C_{9a}), 138.23 ((phenyl C_4), 134.40((phenyl C_1), 129.83(C_7), 128.97(phenyl C_3 and C_5), 127.73(C_8), 125.34(C_6), 123.70(pheyl C_2 and C_6), 122.28(C_9), 58.02 (C_3), 51.01 (benzyl C), 37.74 (C_5), 28.94(C_4).

The synthesis of 3,4-dihydro-1(2H)-naphthalenone oxime (9)

The compound was synthesized using a previously described method (Wei, *et al.*, 2009).

Yield: 86%. white. mp. 77.4-80.1℃. IR (KBr), cm^{-1}: 3285(O-H), 1483(C=N). ^1H NMR (300 MHz, $CDCl_3$): δ 8.90(1H, s, NH), 7.89(1H, d, J=6.0 Hz, OH), 7.30-7.14 (3H, m, Ar-H), 2.84 (2H, t, J= 6.0 Hz, C_2-H), 2.77 (2H, t, J= 4.0 Hz, C_4-H),1.89 (2H, m, C_3-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 155.44 (C_1), 139.81 (C_{10}), 130.51 (C_5), 129.21 (C_7), 128.69 (C_9), 126.48 (C_6), 124.06 (C_8), 29.82 (C_2), 23.80 (C_4), 21.32(C_3). MS: m/z 162.1 (M+1).

The synthesis of 1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one (10)

The compound was synthesized using a previously described method (Wei, *et al.*, 2009)

Yield: 95%. white. Mp. 138.2-139.1℃. IR (KBr), cm^{-1}: 3185(N-H), 2973(C-H), 1666(C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 8.19 (1H, s, NH), 7.24 (2H, t, J=9.0 Hz, Ar-H), 7.16-7.14 (1H, m, Ar-H), 7.00(1H, d, J=6.0 Hz, Ar-H), 2.81 (2H, t, J=7.5 Hz, C_3-H), 2.37 (2H, t, J=7.5 Hz, C_5-H), 2.29-2.19 (2H, m, C_4-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 175.52 (C_2), 137.92 (C_{5a}), 134.31 (C_7), 129.85 (C_{9a}), 127.49 (C_8), 125.67 (C_6), 121.87 (C_9), 32.79 (C_3), 30.34 (C_5), 28.55 (C_4). MS: m/z 184.1 (M+23).

The synthesis of 1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-thione (11)

The compound was synthesized using a previously described method (Zhang, *et al.*, 2012).

Yield: 74%. white. Mp. 135.5-135.8℃. IR (KBr), cm^{-1}: 3150(N-H), 2931(C-H), 1112(C=S). ^1H NMR (300 MHz, DMSO): δ 11.72 (1H, s, NH), 7.28-7.05 (4H, m, Ar-H), 2.64-2.61 (4H, m, CH_2), 2.22-2.18 (2H, m, CH_2). ^{13}C NMR (75MHz, DMSO): δ 205.88 (C_2), 139.48 (C_{5a}),

134.68 (C_7), 130.16 (C_{9a}), 127.77 (C_8), 126.87 (C_6), 122.35 (C_9), 42.42 (C_3), 31.85 (C_5), 29.68 (C_4).

The synthesis of 5, 6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine (12)

The compound was synthesized using a previously described method (Wui, *et al.*, 2012).

Yield: 45%. white. Mp. 139.7-141.7℃. IR (KBr), cm^{-1}: 3114(N-H), 2935(C-H), 1531(C=N). ^{1}H NMR (300 MHz, DMSO): δ 8.85 (1H, s, NH), 7.54-7.43 (4H, m, Ar-H), 2.76 (2H, t, J=9.0 Hz, CH_2), 2.58-2.51 (2H, m, CH_2), 2.23-2.13 (2H, m, CH_2), ^{13}C NMR (75MHz, DMSO): δ 152.94 (C_3), 143.17 (C_1), 134.50 (C_{6a}), 134.35 (C_{10}), 131.03 (C_7), 128.86 (C_8), 128.45 (C_9), 123.32 (C_{10a}), 29.96 (C_6), 28.90 (C_5), 21.50 (C_4).

Pharmacology

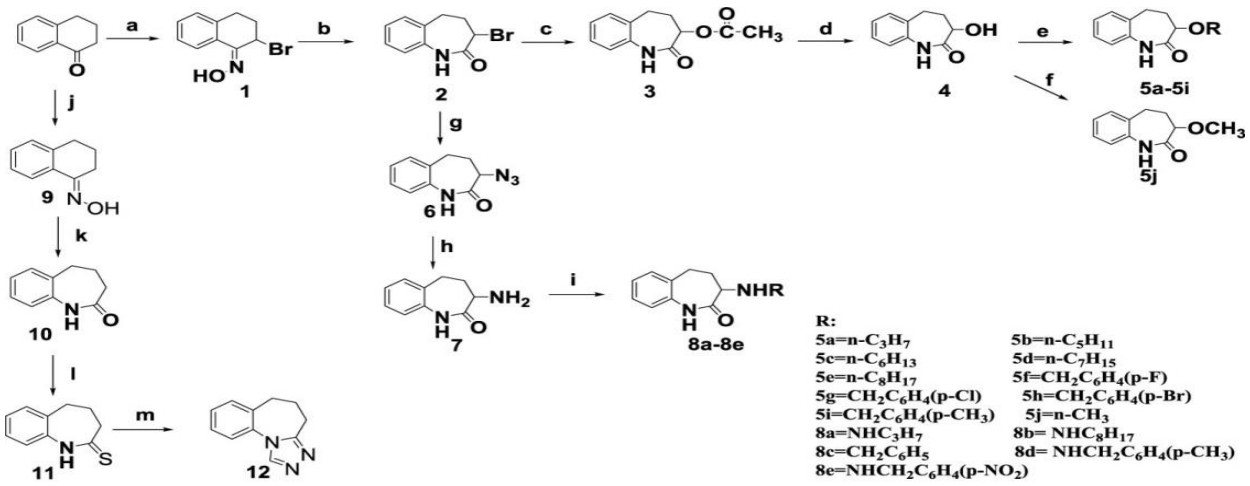
The MES test, scPTZ test, and rotarod test were carried out by the Antiepileptic Drug Development Program (ADD), Epilepsy Branch, National Institutes of Health, Bethesda, MD, USA (Krall, *et al.*, 1978 and Porter, *et al.*, 1984). All compounds were tested for anticonvulsant activity with Swiss mice 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 pentylenetrazolinduced seizure threshold was indicated by the absence of clonic spasms for at least 5s 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 (Okada, *et al.*, 1989).

RESULTS AND DISCUSSION

Chemistry

The target compounds were prepared according to Scheme 1. The compounds 1 and 2 were synthesized using the method described in a former paper (Pérez-Medina, *et al.*, 2012 and Boyer, *et al.*, 1988), compounds 2 reacted with potassium acetate to produce the compounds 3, which reacted with potassium carbonate to produce the compounds 4, the compounds 4 reacted with halogenated hydrocarbons and methyl iodide to give the compounds 5a-i and 5j respectively. The secondary amines were obtained from the corresponding azide and compounds 2. Compound 12 was synthesized from 1-tetralone as raw mateial by oximation, rearrangement, thiolation and cyclization.

The compound 5j, however, could not be obtained via the above etherification method. Therefore, the compound 5 were used to synthesize compound 5j in the presence of CH_3I and NaH via the O-methylation reaction.



Reagants: (a) Br,H_2NOH• HCl,NaAC/CH_3OH refulxing,7d ; (b) PPA 120-125°, 20-25min ; (c) KOAc,18-crown-6/CH_3CN70°, 5d; (d) K_2CO_3/MeOH refulxing4-6h ; (e) RBr,NaOH/C_2H_5OH(95%) ,88; (f) CH_3I, NaH/THF,24h.(g) NaN_3, NaI/DMF , 24h; (h) PhP_3,H_2O/THF, 60°, 2h; (i) RBr, KI, K_2CO_3/CH_3CN(8a-8b), 60°, 4h;RCHO/$NaBH_4$(8c-8e);(j) H_2NOH• HCl/NaAC refulxing; (k)PPA 110-120°, 20-25min. (l) P_2S_5 , $(C_2H_5)_3N$/CH_3CN, 88°, 3h; (m) N_2H_4· H_2O/HCOOH, 90°, 3-4h

Scheme 1: The synthesis route of the target compounds.

Pharmacology

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.

In phase I screening (Table 1), each compound was administered at two dose levels (30 and 100 mg/kg i.p.) with anticonvulsant activity and neurotoxicity assessed at 30 min intervals after administration. Anticonvulsant efficacy was measured in the MES test and the sc-PTZ test. In the MES test, seizures were elicited with a 60 Hz alternating current of 50 mA intensity in mice. Simultaneously clinical application of antiepileptic drugs phenytoin, carbamazepine, phenobarbital and valproate as a control was carried out. The results are shown in Table 2.

In the preliminary (phase I) screening, eleven compounds (3, 4, 5a, 5g-j, 7, 8a, 8c, 10) exhibited anticonvulsant activity at the dose of 100 mg/kg. Of these, only one compound 5 showed anticonvulsant activity against convulsions induced by sc-PTZ at the dose of 100 mg/kg. However, these compounds showed no antagonism against MES-induced seizure at 30 mg/kg.

Table 1: Phase I Anticonvulsant Data in Mice of Compounds 4,5a-j, 7,8a-8,10,12 (i.p.)[a.]

Comp.	R	MES test[b]		ScPTZ[b]
		30[c]	100	100
3	-OAc	2/3	3/3	1/3
4	-OH	2/3	3/3	3/3
5a	*n*-C_3H_7	0/3	3/3	1/3
5b	*n*-C_5H_{13}	0/3	2/3	1/3
5c	*n*-C_6H_{13}	—[d]	1/3	0/3
5d	*n*-C_7H_{15}l)	—[d]	0/3	0/3
5e	*n*-C_8H_{17}	—[d]	0/3	0/3
5f	-$CH_2C_6H_4$(*p*-F)	—[d]	0/3	0/3
5g	-$CH_2C_6H_4$(*p*-Cl)	0/3	3/3	0/3
5h	-$CH_2C_6H_4$(*p*-Br)	0/3	3/3	0/3
5i	-$CH_2C_6H_4$(*p*-CH_3)	0/3	3/3	0/3
5j	*n*-CH_3	1/3	3/3	0/3
7	0	1/3	3/3	1/3
8a	-NHC_3H_7	0/3	3/3	0/3
8b	-NHC_8H_{17}	—[d]	1/3	0/3
8c	-$NHCH_2C_6H_5$	0/3	3/3	2/3
8d	-$NHCH_2C_6H_4$(*p*-CH_3)	—[d]	1/3	0/3
8e	-$NHCH_2C_6H_4$(*p*-NO_2)	—[d]	0/3	0/3
10	no	0/3	3/3	2/3
2	-Br	—[d]	0/3	0/3
12	no	—[d]	0/3	0/3

[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

In the phase II pharmacology test, eleven compounds were quantitatively evaluated for their anticonvulsant activity (indicated by ED_{50}) and neurotoxicity (indicated by TD_{50}) by intraperitoneal (i.p.) administration, and the 95% confidence limits were calculated (Table 2). Among these, 9 compounds (3, 4, 5a, 5g-h, 5j, 7, 8a, 8c) were more active than compound 10

in the MES test. The introduction of alkoxy and alkylamino groups at the 3-position of 1,3,4,5-tetrahydro-2H-benzo [b] azepin-2-one enhanced the anticonvulsant effects of the synthesized compounds. Of these, only one compound 5 showed more active than compound 10 in the sc-PTZ test. Among the 3-substituted benzyloxy derivatives, the order of the activities of halogen substituents was Br>Cl>F.

This result is partly in contradictory to the previous studies in activity data. Among the 5, 6, 7-substituted benzyloxy derivatives of 1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (compound 10), the order of the activities of halogen substituent was F>Cl>Br.

However, since the current activity data is only the result of the modification of the C-3 position, it is not possible to determine whether this rule is a common feature until all the positions on the ring have been modified.

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

Comp.	ED[50a]		TD[50b]	PI[c]	
	MES	ScPTZ	Rotarod Toxicity	MES	ScPTZ
3	30.2 (25.1-35.4)	109.6 [129.7-92.6]	173.5	5.8	1.6
4	26.4 (22.7-30.7)	40.2 [56.3-28.7]	83.3	3.2	2.1
5a	58.8 (49.1 -70.6)		153.7	2.6	—[e]
5b	87.1 (74.3-102.1)	—[e]	83.3	1	—[e]
5g	54.8 (46.3-64.7)	—[e]	94.4	1.7	—[e]
5h	49.1 (40.9-58.8)	—[e]	120.4	2.5	—[e]
5i $_3$	68.2 (56.5-82.4)	—[e]	120.4	1.8	—[e]
5j	45.5 (34.9 -51.8)	—[e]	136	3	—[e]
7	47.4 (40.7-55.1)	109.6[129.7-92.6]	282.3	5.6	2.6
8a	52.6 (44.8-61.5)	—[e]	153.7	2.9	—[e]
8c	52.6 (44.8-61.5)	91.3[108-77.1]	120.4	2.3	1.3
10	65.7 (54.0-79.9)	91.3[108-77.1]	120.4	1.9	1.3
Phenytoin	9.5 (8.1-10.4)	＞300	65.5(52.5-72.9)	6.9	＜0.22
Carbamazepin	8.8 (5.5-14.1)	＞100	71.6 (45.9-135)	8.1	＜0.22
Phenobarbital	21.8 (21.8-25.5)	13.2	69 (62.9-72.9)	3.2	5.2
Valproate	272 (247-338)	149	426 (369-450)	1.6	2.9

[a]ED50-median effective dose required to assure anticonvulsant protection in 50% animals.
[b]TD50-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]Not tested.
[f]Date from Ucar, *et al.*, 1998

Compound 4 showed the maximum anticonvulsant activity against MES (ED_{50}=26.4, PI =3.2) and against scPTZ (ED_{50}=40.2, PI =2.1). The ED_{50} of compound 4 was less than the ED_{50} of phenytoin sodium, phenobarbital and carbamazepine in the MES test but much higher than the ED_{50} of sodium valproate. Furthermore, compound 4 showed the much better anticonvulsant activity against scPTZ than phenytoin sodium, phenobarbital and carbamazepine.

The anticonvulsant effects of our synthesized compounds that showed antagonism against MES in the MES test models might be achieved through inhibiting the voltage-gated Na^+ channel, i.e., activating the inhibitor for the Na^+ channel (Adam, *et al.*, 2005; Hongling, *et al.*, 2010 and Helen, *et al.*, 2006). The anti-epileptic effects of the drugs that showed antagonism against sc-PTZ in the anti-sc-PTZ test models were considered to be achieved through activating neurons that produced γ-aminobutyric acid as their output (GABAergic neurons) (Okada, *et al.*, 1989; Feiganspan, *et al.*, 1994 and Loscher, *et al.*, 1982).

CONCLUSION

The results of the present study demonstrated that 3-(alkylamino, alkoxy)-1,3,4,5-Tetrahydro-2H-benzo[b]azepine-2-one derivatives have potent anticonvulsant activity. In particular, compound 4 showed better anticonvulsant activity in both models.

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REFERENCES

1. Adam, CE; Thomas, S and George, L (2005) "Voltage Gated ion Channels: Targets for Anticonvulsant Drugs." ***Curr Top Med Chem*** 5: 15-30.
2. Bariwal, JB1; Upadhyay, KD; Manvar, AT; Trivedi, JC; Singh, JS; Jain, KS and Shah, AK (2008) "1,5-Benzothiazepine, a versatile pharmacophore: a review." ***Eur J Med Chem*** 43: 2279-2290.
3. Feigenspan; A and Bormann; J (1994) "Facilitation of GABAergic signaling in the retina by receptors stimulating adenylate cyclase." ***Proc Nat Acad Sci USA*** 91: 10893-10897.
4. Helen; CL and Lily; YJ (2006) "The distribution and targeting of neuronal voltage-gated ion channels." ***Nat Rev Neurosci*** 7: 548-562.
5. Hongling; Z; Christopher; K and Javier; C (2010) "Sigma receptor activation inhibits voltage-gated sodium channels in rat intracardiac ganglion neurons." ***Int J Physiol Pathophysiol Pharmacol*** 2: 1-11.
6. Hoyt, SB; London, C; Gorin, D; Wyvratt, MJ; Fisher, MH; Abbadie, C; Felix, JP; Garcia, ML; Li X; Lyons, KA; McGowan, E; MacIntyre, DE; Martin, WJ; Priest,

BT; Ritter, A; Smith, MM; Warren, VA; Williams, BS; Kaczorowski, GJ and Parsons, WH (2007) "Discovery of a novel class of benzazepinone Na(v)1.7 blockers: potential treatments for neuropathic pain." ***Bioorg Med Chem Lett*** 17: 4630-4634.

7. Im, I; Webb, TR; Gong, YD; Kim, JI and Kim, YC (2004) "Solid-phase synthesis of tetrahydro-1,4-benzodiazepine-2-one derivatives as a β-turn peptidomimic library." ***J Combinat Chem*** 6: 207-213
8. Krall, RL; Penry, JK; White, BG; Kupferberg, HJ and Swinyard, EA (1978) "Antiepileptic drug development: II. Anticonvulsant drug screening." ***Epilepsia*** 19: 409-428.
9. Loscher, W (1982) "Relationship Between GABA Concentrations in Cerebrospinal Fluid and Seizure Excitability." ***J Neurochemistr*** 38: 293-295.
10. Okada, R; Negishi, N and Nagaya, H (1989) "The Role of the Nigrotegmental GABAergic Pathway in the Propagation of Pentylenetetrazol-Induced Seizures" ***Brain Res*** 480: 383-387.
11. Pérez-Medina, C; Patel, N; Robson, M; Badar, A; Lythgoeb, MF and Årstad E (2012) "Evaluation of a 125I-labelled benzazepinone derived voltage-gated sodium channel blocker for imaging with SPECT." ***Organic & Biomolecular Chemistry*** 10: 9474-9480.
12. Porter, RJ; Cereghino, JJ; Gladding, GD; Hessie, BJ; Kupferberg, HJ and Scoville; B (1984) "Antiepileptic drug development program." ***Cleveland Clin*** 51: 293-305.
13. Rivas, FM; Stables, JP; Murphree, L; Edwankar, RV; Edwankar, CR; Huang, S; Jain, HD; Zhou, H; Majumder, S; Sankar, S; Roth, BL; Ramerstorfer, J; Furtmüller, R; Sieghart, W and Cook, JM (2009) "Antiseizure activity of novel gamma-aminobutyric acid (A) receptor subtype-selective benzodiazepine analogues in mice and rat models." ***J Med Chem*** 52: 1795-1798.
14. Boyer, SK; Pfund, RA; Portmann, RE; Sedelmeier, GH and Wetter, HF (1988) "Notiz zur Synthese Eines Optisch Aktiven Ace-Hemmers mit Amino-oxo-benzazepin-1-alkansä ure-Struktur mittels enantiokonvergierender kristallisationsinduzierter Racemat-Trennung." ***Helvetica Chimica Acta*** 71: 337-343
15. Wei, CX; Zhang, W; Quan, ZS; Han, RB; Jiang, RS and Piao, FY (2009) "Synthesis, Anticonvulsant Evaluation of 2,3,4,5-Tetrahydro-7-alkoxy-1H-2-benzazepin- 1-ones." ***Letters in Drug Design & Discovery*** 6: 548-553.
16. Wu, HF; Han, RB; Jin, CZ and Piao, FY (2016) "Synthesis of Novel 8-alkylamino-5;6-dihydro-4H-benzo[f][1;2;4]triazolo[4;3-a]azepines as Anticonvulsant Agents." ***CNS & Neurological Disorders - Drug Targets*** 15: 999.
17. Zhang, WB; Han, RB; Zhang, W; Jiang, RS and Piao FY (2012) "Synthesis and anticonvulsant activity of 8-alkoxy-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-one derivatives." ***Med Chem Res*** 21: 2587–2594.

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