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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of new benzotriazepin-5(*2H*)-one derivatives of expected antipsychotic activity

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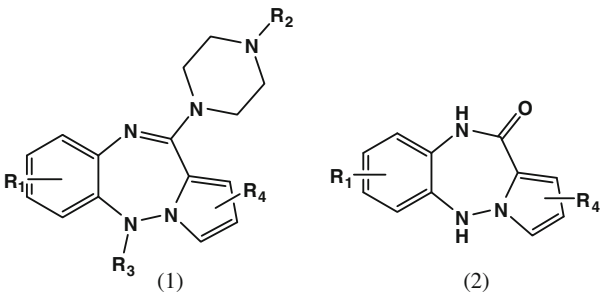
Abstract A new series of 3,4-dihydro-1*H*-benzo[e][1,2,4] triazepin-5(*2H*)-one derivatives were synthesized by cyclo-condensation of benzohydrazides (**II**, **IX**), derived from the reaction of *N*-methyl-isatoic anhydride with phenyl hydrazine and isonicotinic acid hydrazide, respectively, with formaldehyde, aromatic aldehydes in acidic medium or with carbon disulfide in alkaline medium, the last reaction was only carried out with benzohydrazide **II**. Benzotriazepinone derivatives **IV**,$\mathbf{V_{a–h}}$,**VI**, and **XI** were subjected to ptosis test using clozapine as a reference drug to evaluate their antipsychotic activity. It was found that 2-thioxobenzotriazepinone **VI** had the same antipsychotic activity as reference drug clozapine but with lesser side effects whereas it showed nonsignificant CNS depressant activity upon using forced swim pool test as well as no neurotoxicity when tested in mice using rotarod or horizontal screen tests.

Keywords Synthesis · Benzotriazepin-5(*2H*)-one · Antipsychotic activity · Clozapine

Introduction

Benzotriazepines are rarely mentioned in the literature and found to have various pharmacological activities among of which, central nervous system (Britton and Trepanier, 1980; Fischer *et al.*, 1984), anticancer (Kim and Taylor, 1992), CCK2 antagonist (Spencer *et al.*, 2008), and anti-inflammatory (Fernándeza *et al.*, 2004; Kaur and Talele, 2008) activities.

Benzotriazepine class is one of the most common classes which constitute our interest due to their CNS activity and their use as psychoactive agents (Britton and Trepanier, 1980). It was reported that compounds **1** and **2** are useful as neuroleptic agents in the treatment of psychotic disturbances such as schizophrenia (Fischer *et al.*, 1984).



(1) (2)

R_1,R_4=H, halogen,alkyl,alkoxy
R_2=H, alkyl
R_3=H, alkyl, alkenyl or benzyl

In view of these observations, we herein report the synthesis of some new benzotriazepin-5(*2H*)-ones derivatives hoping to be clozapine-like but with lower side effects.

Materials and methods

Chemistry

Melting points were determined with a Gallenkamp melting point apparatus (London, UK), and are uncorrected. IR spectra (KBr, cm^{-1}) were recorded on a Bruker Vector,

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22FT-IR Spectrometer (Bavaria, Germany). ^{1}HNMR spectra were recorded on Varian Gemini-200 (200 MHz) Spectrometer (CA, USA) using DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard (Chemical shift in δ, ppm). Electron impact mass spectra were determined at 70 eV using a GC/MS Shimadzu QP1000EX Spectrometer (Tokyo, Japan).Elemental analyses were determined using Heraeus or Vario EL-III (Elemntar) (Hanau, Germany) or Perkin Elmer Model 2400 (USA) CHN analyzers at the National Research Center and Microanalytical Center, Faculty of Science, Cairo University, Egypt.

All the results of the elemental analyses were in an acceptable error range. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck), and spots were visualized by iodine vapors or by irradiation with ultraviolet light (UV; 254 nm). All chemicals were purchased from Sigma Chemical (St. Louis, MO, USA).

*2-(Methylamino)-N′-phenylbenzohydrazide (**II**)*

To a mixture of *N*-methyl isatoic anhydride **I** (8.85 g, 0.05 mol) and phenyl hydrazine (6.48 g, 0.06 mol) in ethanol (50 ml), ten drops glacial acetic acid was added. The mixture was refluxed for 2 h, concentrated to half volume and then cooled. The separated solid was filtered and crystallized from aqueous ethanol to give the titled compound; yield: 85 %; m.p. = 132–134 °C as reported (Pestellini *et al.*, 1978; Schuler *et al.*, 2006).

*1-Methyl-3-(phenylamino)-2,3-dihydroquinazolin-4(1H)-one (**III**)*

To a solution of benzohydrazide **II** (2.41 g, 0.01 mol) in ethanol (50 ml), 1 ml 40 % formalin and ten drops of glacial acetic acid were added. The reaction mixture was heated under reflux for 18 h, concentrated to half volume and then poured into cold water (100 ml). The separated solid was filtered, dried, and crystallized from ethanol to give the titled compound in a yield of 87.5 %, m.p. = 163–165 °C as reported (Legrand and Lozac'h, 1984). IR: v = 3324 (NH), 3031 (CH, aromatic), 2994 (CH, aliphatic), 1671 (CO), 1496 (C=C) cm^{-1}; ^{1}HNMR: δ = 2.91(s, 3H, NCH_3), 4.67(s, 2H, CH_2N), 6.78–7.79 (m, 9H, ArH), 8.38 (s, 1H, NH, exch.) ppm; MS *m/z* (rel.int.) = 253 (M^+, 9.1), 161 (34.6), 92 (42.6), 77 (100). Analysis for $C_{15}H_{15}N_3O$ (253.30): Calcd: C, 71.13; H, 5.97; N, 16.59. Found: C, 70.95; H, 5.85; N; 16.67 %.

*1-Methyl-3-phenyl-3,4-dihydro-1H-benzo[e][1,2,4]triazepin-5(2H)-one (**IV**)*

To a solution of benzohydrazide **II** (2.41 g, 0.01 mol) in ethanol (50 ml), 1 ml 40 % formalin and ten drops of glacial acetic acid were added. The reaction mixture was stirred at room temperature for 2 h and then poured into water (100 ml). The separated solid was filtered, dried, and crystallized from ethanol to give the titled compound; yield: 43.5 %; m.p. = 198–199 °C. IR: v = 3163 (NH), 3040 (CH, aromatic), 2980 (CH, aliphatic), 1651 (CO), 1493 (C=C) cm^{-1}; ^{1}HNMR: δ = 3.08(s, 3H, N CH_3), 5.12 (s, 2H, CH_2N), 6.61–7.77 (m, 9H, ArH), 10.03 (s, 1H, NH, exch.) ppm MS *m/z* (rel.int.) = 255 (M^+ + 2, 2.1), 254 (M^++1, 2.7), 253 (M^+, 8.6), 134 (14.8), 77 (100). Analysis for $C_{15}H_{15}N_3O$ (253.30): Calcd: C, 71.13; H, 5.97; N, 16.59. Found: C, 70.88; H, 5.59; N, 16.27 %.

*General procedure for preparation of compounds (**V**$_{a–h}$)*

A mixture of benzohydrazide **II** (2.41 g, 0.01 mol) and the appropriate aromatic aldehyde (0.01 mol) in glacial acetic acid (20 ml) was heated under reflux for 6 h. The reaction mixture was concentrated to half volume and poured into cold water (100 ml). The separated solid was filtered, dried, and crystallized from suitable solvent to give the titled compounds.

*1-Methyl-2,3-diphenyl-3,4-dihydro-1H-benzo[e][1,2,4]triazepin-5(2H)-one (**V**$_a$)*

Yield: 90 %; m.p. = 190–192 °C; crystallized from ethanol; ^{1}HNMR: δ = 2.95 (s, 3H, NCH_3), 5.88 (s, 1H, benzylic H), 6.70–7.81 (m, 14H, ArH), 8.31 (br s, 1H, NH, exch.) ppm; MS *m/z* (rel.int.) = 330(M^+ + 1, 9.6), 329 (M^+, 23.1), 194 (21.8), 134 (44.2), 77 (100). Analysis for $C_{21}H_{19}N_3O$ (329.40): Calcd: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.41; H, 5.93; N, 12.63 %.

*2-(4-Chlorophenyl)1-methyl-3-phenyl-3,4-dihydro-1H-benzo[e][1,2,4] triazepin-5(2H)-one (**V**$_b$)*

Yield: 90 %; m.p. = 227–228 °C; crystallized from ethanol. IR: v = 3239 (NH), 3023 (CH, aromatic), 2954 (CH, aliphatic), 1655 (CO), 1494 (C=C) cm^{-1}; ^{1}HNMR: δ = 2.98 (s, 3H, NCH_3), 5.99 (s, 1H, benzylic H), 6.80–7.83 (m, 13H, ArH), 8.44 (br s, 1H, NH, exch.) ppm. Analysis for $C_{21}H_{18}ClN_3O$ (363.5): Calcd: C, 69.32; H, 4.99; N, 11.55. Found: C, 69.52; H, 4.65; N, 11.37 %.

*2-(4-Methoxyphenyl)1-methyl-3-phenyl-3,4-dihydro-1H-benzo[e][1,2,4] triazepin-5(2H)-one (**V**$_c$)*

Yield: 93 %; m.p. = 251–253 °C; crystallized from dioxane/DMSO (4:1). IR: v = 3241 (NH), 3016 (CH, aromatic), 2959 (CH, aliphatic), 1649 (CO), 1499 (C=C) cm^{-1}; ^{1}HNMR: δ = 2.93 (s, 3H, NCH_3), 3.74(s, 3H, OCH_3), 5.82 (s, 1H, benzylic H), 6.71–7.81 (m, 13H, ArH),

8.29(brs, 1H, NH, exch.) ppm. Analysis for $C_{22}H_{21}N_3O_2$ (359.42): Calcd: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.37; H, 6.15; N, 11.50 %.

*2-(4-Nitrophenyl)1-methyl-3-phenyl-3,4-dihydro-1H-benzo[e][1,2,4] triazepin-5(2H)-one (**V_d**)*

Yield: 78 %; m.p. = 227–229 °C; crystallized from dioxane; ^{1}HNMR: δ = 3.04 (s, 3H, NCH_3), 6.19 (s, 1H, benzylic H), 6.78–8.29 (m, 13H, ArH), 8.53 (brs, 1H, NH, exch.) ppm; MS *m/z* (rel.int.) = 376 (M^+ + 2, 1.6), 375 (M^+ + 1, 3), 374 (M^+, 9.8), 269 (16.6), 194 (10.2), 134 (13.4),77 (100). Analysis for $C_{21}H_{18}N_4O_3$ (374.39): Calcd: C, 67.37; H, 4.85; N, 14.96. Found: C, 67.08; H, 4.74; N, 14.71 %.

*2-(4-Hydroxyphenyl)1-methyl-3-phenyl-3,4-dihydro-1H-benzo[e][1,2,4] triazepin-5(2H)-one (**V_e**)*

Yield: 66 %; m.p. = 222–223 °C; crystallized from ethanol; ^{1}HNMR: δ = 2.95 (s, 3H, NCH_3), 5.81 (s, 1H, benzylic H), 6.77–7.88 (m, 14H, ArH), 8.29 (brs, 1H, NH, exch.), 9.586 (s, 1H, OH, exch.) ppm. Analysis for $C_{21}H_{19}N_3O_2$ (345.39): Calcd: C, 73.03; H, 5.54; N, 12.17 %. Found: C, 72.88; H, 5.4; N, 11.88 %.

*2-(2-Nitrophenyl)1-methyl-3-phenyl-3,4-dihydro-1H-benzo[e][1,2,4] triazepin-5(2H)-one (**V_f**)*

Yield: 79.4 %; m.p. = 216–217 °C; crystallized from ethanol:dioxane (1:1); ^{1}HNMR: δ = 3.04 (s, 3H, NCH_3), 6.56 (s, 1H, benzylic H), 6.86–7.94 (m, 14H, ArH), 8.35 (brs, 1H, NH, exch.) ppm. Analysis for $C_{21}H_{18}N_4O_3$-(374.39): Calcd: C, 67.37; H, 4.85; N, 14.96. Found: C, 67.15; H, 4.78; N, 14.71 %.

*2-(4-Bromophenyl)-1-methyl-3-phenyl-3,4-dihydro-1H-benzo[e][1,2,4] triazepin-5(2H)-one (**V_g**)*

Yield: 93 %; m.p. = 236–238 °C; crystallized from ethanol:dioxane (1:1); ^{1}H N MR: δ = 3.0 (s, 3H, NCH_3), 5.97 (s, 1H, benzylic H), 6.80–7.85 (m, 14H, ArH), 8.40 (brs, 1H, NH, exch.) ppm. Analysis for $C_{21}H_{18}BrN_3O$ (408.29): Calcd: C, 61.78; H, 4.44; N, 10.29. Found: C, 61.47; H, 4.35; N, 10.13 %.

*2-(3,4,5-Trimethoxyphenyl)1-methyl-3-phenyl-3,4-dihydro-1H-benzo[e] [1,2,4]triazepin-5(2H)-one (**V_h**)*

Yield: 86 %; m.p. = 188–190 °C; crystallized from ethanol:dioxane (3:1); ^{1}HNMR: δ = 2.97 (s, 3H, NCH_3), 3.59 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 5.81 (s, 1H, benzylic H), 6.57–7.81 (m, 11H, ArH) 8.41(brs, 1H, NH, exch.) ppm. Analysis for $C_{24}H_{25}N_3O_4$ (419.47):Calcd: C, 68.72; H, 6.01; N, 10.02. Found: C, 68.69; H, 5.88; N, 9.99 %.

*1-Methyl-3-phenyl-2-thioxo-3,4-dihydro-1H-benzo[e][1,2,4]triazepin-5(2H)-one (**VI**)*

To a solution of benzohydrazide **II** (2.41 g, 0.01 mol) and potassium hydroxide (0.056 g, 0.01 mol) in 95 % ethanol (20 ml), carbon disulfide (0.08 g, 0.01 mol) was added and the solution was heated under reflux for 18 h. The reaction mixture was concentrated to half volume and poured into cold water (100 ml). The separated solid was filtered, dried, and crystallized from ethanol to give the titled compound.

Yield: 85 %; m.p. = 198–200 °C; ^{1}HNMR: δ = 4.14 (s, 3H, NCH_3), 6.64–8.14 (m, 9H, ArH), 8.83 (s, 1H, NH, exch.) ppm; MS *m/z* (rel.int.) = 284 (M^+ + 1, 6.4), 283 (M^+, 25.5), 134 (51.1), 77 (100). Analysis for $C_{15}H_{13}N_3OS$ (283.35): Calcd: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.73; H, 4.63; N, 15.18 %.

*N′-[2-(Methylamino)benzoyl]nicotinohydrazide (**VIII**)*

A mixture of *N*-methyl-isatoic anhydride (**I,** 8.85 g, 0.05 mol) and nicotinic acid hydrazide (6.85 g, 0.05 mol) in ethanol (50 ml)-containing ten drops of glacial acetic acid was heated under reflux for 8 h. The solid precipitated out after cooling was filtered, dried, and crystallized from dioxane:DMSO(4:1)to give the titled compound; yield: 90.28 %, m.p.: 229–230 °C as reported (Reddy and Reddy, 1988).

*N′-[2-(Methylamino)benzoyl]isonicotinohydrazide (**IX**)*

A mixture of *N*-methyl-isatoic anhydride(**I**, 8.85 g, 0.05 mol) and isonicotinic acid hydrazide (6.85 g, 0.05 mol) in ethanol (50 ml)-containing ten drops of glacial acetic acid was heated under reflux for 18 h. The reaction mixture was cooled and diluted with small amount of water (5 ml). The separated solid was filtered, dried, and crystallized from aqueous ethanol to give the titled compound.

Yield: 73 %; m.p. = 158–159 °C; ^{1}HNMR: δ = 2.84 (s, 3H, NCH_3), 6.66–7.86 (m, 8H, ArH), 8.83 (brs, 1H, NH, exch.), 10.58 (brs, 1H, NHCO), 10.64 (brs, 1H, NHCO). Analysis for $C_{14}H_{14}$ N_4O_2 (270.29): Calcd: C, 62.21; H, 5.22; N, 20.73. Found: C, 61.93; H, 5.23; N, 20.72 %.

*N-(1-Methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)nicotinamide (**X**)*

To a solution of *N*'-(2-(methylamino)benzoyl)nicotinohydrazide (**VIII**, 1.77 g, 0.01 mol) in ethanol (50 ml), 40 % formalin (1 ml), and ten drops of glacial acetic acid were added. The reaction mixture was stirred at room temperature for 18 h and then neutralized with ammonia

solution. The formed solid was filtered, washed with petroleum ether (60/80) and crystallized from ethanol:petroleum ether (1:1) to give the titled compound.

Yield: 76 %; m.p. = 165–167 °C; ^{1}HNMR: $\delta = 2.91$ (s, 3H, NCH_3), 4.78 (s, 2H, CH_2N), 6.87–9.08 (m, 8H, ArH), 11.20 (s, 1H, NH, exch.) ppm; MS *m/z* (rel. int.) = 282 (M^+, 25), 161 (100), 118 (50), 105 (75), 64 (40). Analysis for C_{15} $H_{14}N_4O_2$ (282): Calcd: C, 63.82; H, 4.96; N, 19.85. Found: C,63.52; H, 5.23; N, 19.51 %.

*3-Isonicotinoyl-1-methyl-3,4-dihydro-1H-benzo[e][1,2,4]triazepin-5(2H)-one (**XI**)*

To a solution of *N*′-(2-(methylamino)benzoyl)isonicotinohydrazide (**IX**, 1.77 g, 0.01 mol) in ethanol (50 ml), 40 % formalin (1 ml), and ten drops of glacial acetic acid were added. The reaction mixture was stirred at room temperature for 18 h and then neutralized with ammonia solution. The formed solid was filtered and crystallized from ethanol to give the titled compound.

Yield: 77 %; m.p. = 187–188 °C. IR: $\nu = 3185$ (NH), 3045 (CH, aromatic), 2995 (CH, aliphatic), 1702 (CO), 1630 (CO), 1504 (C=C) cm^{-1}; ^{1}HNMR: $\delta = 2.91$ (s, 3H, NCH_3), 4.78 (s, 2H, CH_2N), 6.87–8.83 (m, 8H, ArH) 11.31 (s, 1H, NH, exch.) ppm; MS *m/z* (rel.int.) = 283($M^+ + 1$, 2.9), 282 (M^+, 5), 120 (15.1), 106 (20.9), 78 (100). Analysis for $C_{15}H_{14}$ N_4O_2 (282): Calcd: C; 63.82; H, 4.96; N, 19.85. Found: C, 63.69; H, 4.65; N, 19.52 %.

Pharmacological studies

Male albino mice weighing 20–25 g were obtained from the Laboratory Animal Services Center, Faculty of Veterinary Medicine, Zagazig University, Zagazig, Egypt. The animals were maintained on a 12-h light/dark cycle under regulated temperature (25 ± 2 °C) and humidity (50 ± 10 %) as well as fed with standard diet and water ad libitum. They were allowed to acclimate 7 days before use. This protocol was approved by the Animal Care and Use Committee of the Pharmacology department, Faculty of Veterinary Medicine, Zagazig University.

Ptosis test

It was carried out according to the method described by Chen and Bohner (1965). Mice were divided into 13 equal groups ($n = 6$). The first group was labelled as control and injected i.p. with the solvent (DMSO) while the second group was injected (i.p.) with clozapine at a dose of 3 mg/kg. The tested compounds (**IV**, $\mathbf{V_{a–h}}$, **VI**, **XI**) were injected (i.p.) to the other groups at a dose of 3 mg/kg. Every mouse was observed for the presence or absence of complete ptosis. The ptosis was rated as the fraction of the eyelid closure from normal. The ptosis ratio was made 4 for complete ptosis, 3 for 3/4, 2 for ½, and 1 for 1/4 ptosis.

Forced swim pool test

The forced swim pool method (FSP) described by Porsolt *et al.*, (1978) was followed. Mice were classified into 13 groups, each of six and then injected i.p. with solvent (control), reference drug clozapine, and test compounds (**IV**, $\mathbf{V_{a–h}}$, **VI**, **XI**) at a dose of 3 mg/kg body weight 30 min before the test session. Two swim sessions were conducted; an initial 15 min pre-test followed by a 5 min test 24 h later. The animals were placed in a chamber (diameter: 45 cm, height: 20 cm) containing water up to height of 15 cm at 25 ± 2 °C. The period of immobility (passive floating without struggling and making only those movements which are necessary to keep its head above the surface of water) during the 5 min test period was measured and recorded.

Neurotoxicity screening

Rotarod test

Minimal motor impairment was measured in mice by the rotarod test (Dunham and Miya, 1957). The mice were trained to stay on an accelerating rotarod that rotates at 4–10 rpm. The rod diameter was 3.2 cm. Trained mice were classified into 13 groups, each of six and then injected i.p. with DMSO (control), clozapine, and test compounds (**IV**, $\mathbf{V_{a–h}}$, **VI**, **XI**) at a dose of 3 mg/kg body weight. Neurotoxicity was determined 30 min post treatment as the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of three trials.

Horizontal screen test

Neural impairment was also determined by failure of mice to perform successfully the horizontal screen test (Coughenour *et al.*, 1977). The apparatus consisted of a 13 × 14 cm^2 wire screens which was mounted horizontally on a steel rod. The rod was supported at both ends and could be inverted through an arc of 180°. Trained mice were classified into 13 groups, each of six and then injected i.p. with DMSO (control), clozapine, and test compounds (**IV**, $\mathbf{V_{a–h}}$, **VI**, **XI**) at a dose of 3 mg/kg body weight. The animals were placed individually on the top of the screen and the rod was then rotated (mice unable to climb to an upright position within 1 min were rated as failures 30 min after drugs administration, two values were recorded: (A) The number of mice that fall from the screen and (B) The number of mice that fail to climb the top of the screen (i.e., the sum of those that remain clinging to the bottom of the screens and those that falls from the screen).

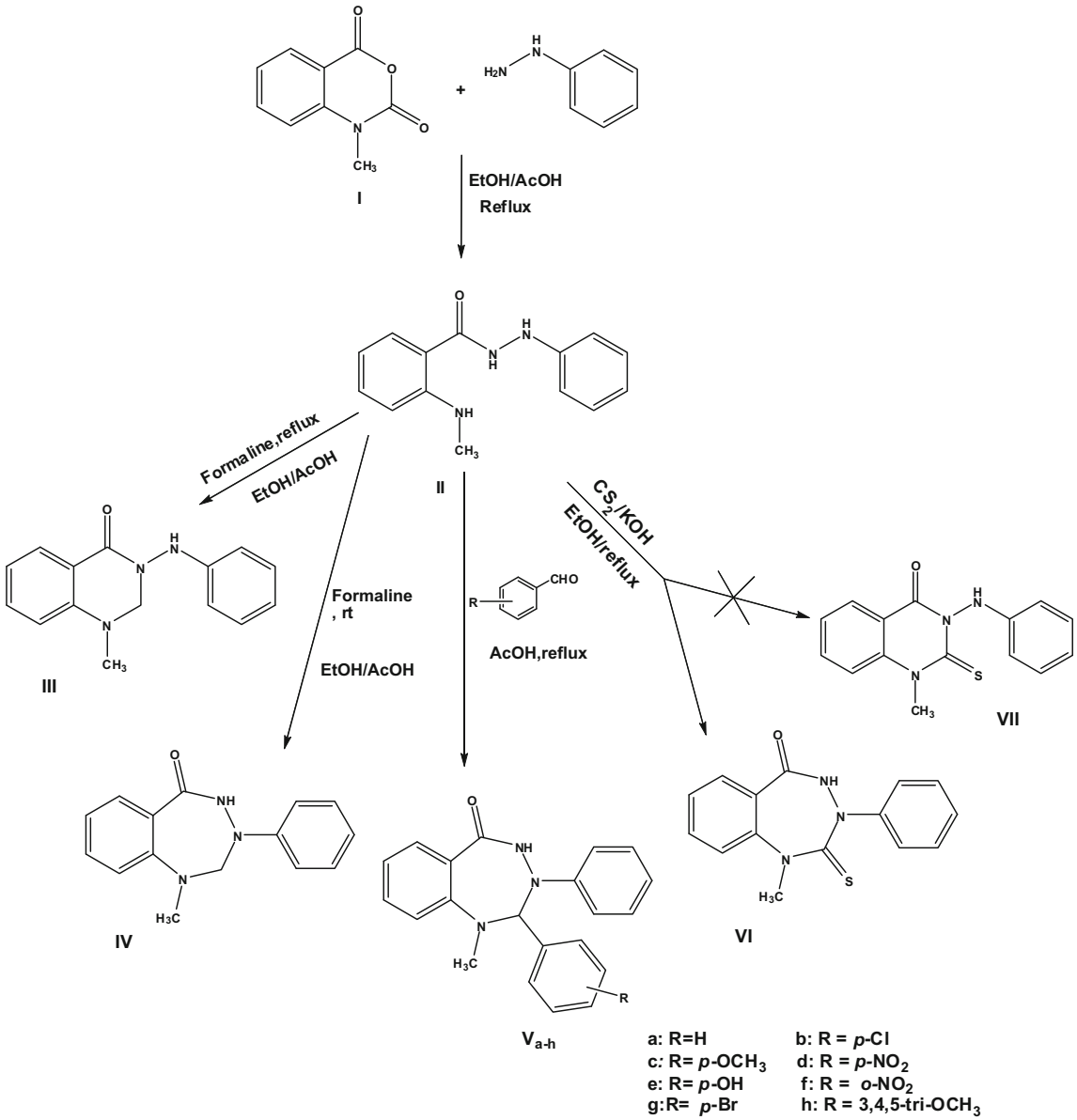
Pentylenetetrazole seizure pattern test (PTZ)

Mice were divided into 13 equal groups ($n = 6$). The first group was injected i.p. with DMSO (control) while clozapine and tested compounds were injected (i.p.) to the other groups at the same dose level. The anticonvulsant activities of the compounds were determined against pentylenetetrazole-induced seizures (Fisher, 1989). One hour later, mice were injected with pentylenetetrazole 70 mg/kg subcutaneously in scruff of neck. After 2–4 min of PTZ injection, the animals develop sequence of excitement, myoclonic jerks, clonic seizures, one or more maximal tonic seizures and finally death. Seizure latency was defined as the time elapsed from injection of PTZ to the first two the myoclonic jerks of the forelimbs. This has been considered to be the first sign of the beginning of seizure activity (Osonoe *et al.*, 1994). Animals devoid of generalized convulsions were considered to be protected and their results were represented as protection percentage.

Results and discussion

Chemistry

In this study, the novel benzotriazepin-5(2*H*)-one derivatives (**IV**, $\mathbf{V_{a–h}}$, **VI**) were prepared starting from the benzohydrazide key intermediate **II** which was obtained



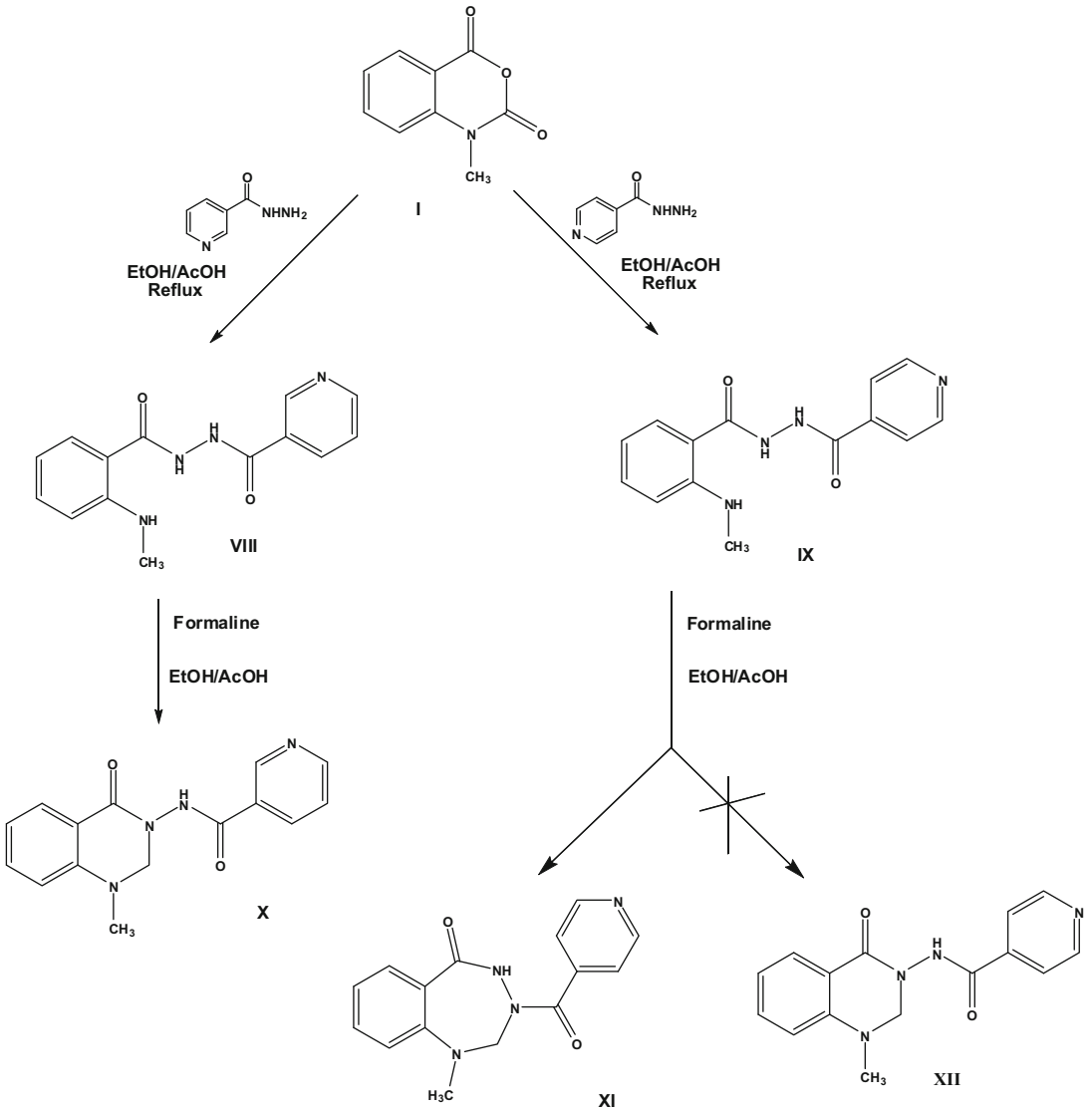
Scheme 1 Synthetic pathways for preparation of the novel benzotriazepinones (**IV**, $\mathbf{V_{a–h}}$, **VI**)

through condensation of *N*-methylisatoic anhydride (**I**) with phenylhydrazine as shown in Scheme 1.

The benzohydrazide intermediate **II** underwent internal *Mannich* reaction at two different reaction conditions. The first method depends on heating the intermediate **II** and formalin at reflux in ethanol-containing catalytic amount of glacial acetic acid to afford the six-membered quinazolinone derivative **III.** The second one depends on stirring the same reactants at room temperature to afford the seven-membered benzotriazepin-5(2*H*)-one derivative **IV.**

The difference in the appearance of methylene and NH signals in each of the obtained compounds **IV** and **III** in the ^{1}HNMR spectra indicates the difference in their cyclization, whereas in compound **IV**, benzotriazepin-5(2*H*)-one derivative, the singlet of methylene (N–CH_2–N) at $\delta = 5.12$ ppm and that of CONH at $\delta = 10.03$ ppm appeared more deshielded than those, (N–CH_2–N) at $\delta = 4.67$ ppm and (N–NH) at $\delta = 8.38$ ppm, of compound **III** which is a 2,3-dihydroquinazolinone derivative. This result is also documented by the fragmentation study of mass spectra for both compounds whereas the presence of fragment of $m/z = 161$ (1-methyl-2,3-dihydroquinazolin-4(1*H*)-one), in the mass spectrum of compound **III** and its absence in that of compound **IV** is a good evidence that the compound **III** is a 2,3-dihydroquinazolinone derivative while compound **IV** is a benzo[e][1,2,4]triazepin-5(2*H*)-one derivative.

Acid catalyzed condensation of benzohydrazide **II** with different aromatic aldehydes furnished a new series of benzo[e][1,2,4] triazepin-5(2*H*)-ones ($\mathbf{V_{a–h}}$),whereas the ^{1}HNMR of benzotriazepin-5(2*H*)-one compounds ($\mathbf{V_{a,c,h}}$) revealed the appearance of benzylic proton singlets at $\delta = 5.88$, 5.82, and 5.81 ppm, respectively, and the methyl



Scheme 2 Synthetic pathways for preparation of the novel compounds **X** and **XI**

singlet of NCH_3 at 2.95, 2.93, and 2.97 ppm, respectively, in addition to D_2O exchangeable NH-proton which appeared as broad singlets at $\delta = 8.31$, 8.29, and 8.41 ppm, respectively. Also the mass spectra for such compounds ($\mathbf{V_{a–h}}$) revealed the absence of the fragment of $m/z = 161$ which is characteristic for 2,3-dihydroquinazolinone.

Moreover, cyclocondensation of benzohydrazide **II** was conducted using carbon disulfide in hot ethanolic KOH solution to afford the novel benzo[e][1,2,4]triazepin-5(2*H*)-one (**VI**) rather than the expected 2,3-dihydroquinazolin-5(2*H*)-one (**VII**). This is attributed to the availability of the electron pair of the aniline nitrogen rather than that of the amidic nitrogen.

The appearance of NH-proton and N–CH_3 protons singlets in ^{1}HNMR spectrum for the formed compound **VI** at $\delta = 8.83$ and 4.14 ppm, respectively, which seems to be more deshielded than those for the 2,3-dihydroquinazolinone is an indication that the formed compound is benzo[e][1,2,4]triazepin-5(2*H*)-one derivative. Also, mass spectrum of compound **VI** confirmed its seven-membered structure.

Similarly, condensation of *N*-methyl-isatoic anhydride (**I**) with nicotinic acid hydrazide or isonicotinic acid hydrazide afforded the benzohydrazides **VIII** or **IX** as shown in Scheme 2. The intermediate **VIII** was cyclized through internal *Mannich* reaction using formalin at room temperature to afford the six-membered quinazolinone derivative **X**.

On the other side, cyclization of the intermediate **IX** using the same reaction condition afforded the seven-membered benzotriazepin-5(2*H*)-one derivative **XI** rather than the expected six-membered quinazolinone derivative **XII**. This may be attributed to the higher reactivity of isonicotinic nitrogen rather than the benzamide nitrogen.

The chemical structures of the compounds **X** and **XI** were verified using ^{1}HNMR and mass spectra whereas the mass spectra is the most differential tool between the chemical structures for compounds **X** and **XI**. Both compounds **X** and **XI** have the same molecular weight which appears at $m/z = 282$ with intensity of 25 and 5, respectively. The fragmentation study of mass spectra of these compounds indicates the great difference in fused ring structure of each whereas the existence of fragment of $m/z = 161$ (100 %),1-methyl-2,3-dihydroquinazolin-4(1*H*)-one, is associated with the mass spectrum of compound **X**, while its absence in the mass spectrum of compound **XI** is an indication that cyclization of *N*′-[2-(methylamino)benzoyl]isonicotinohydrazide (**IX**) afforded benzo[e] [1,2,4] triazepin-5(2*H*)-one structure.

Pharmacological studies

The newly synthesized benzotriazepin-5(2*H*)-one derivatives (**IV**, $\mathbf{V_{a–h}}$, **VI**, **XI**) were tested for their antipsychotic activities via ptosis test (Chen and Bohner, 1965) using clozapine as a reference drug. In addition, the CNS depressant activities for such compounds were also examined using forced swim pool test (Porsolt *et al.*, 1978). Also, their neurotoxicity was determined using both rotarod (Dunham and Miya, 1957) and horizontal screen (Coughenour *et al.*, 1977) tests. These compounds were also screened for their anticonvulsant activities against pentylenetetrazole (PTZ)-induced seizures (Fisher, 1989). This is to explore the highly active compound as antipsychotic with least side effects in comparison with reference drug clozapine. It was observed from Table 1 that compounds **IV**, **VI**, and **XI** showed the same antipsychotic activity as the reference drug clozapine whereas they caused complete ptosis in mice at a dose of 3 mg/kg body weight. Moreover, other benzotriazepin-5(2*H*)-one derivatives containing phenyl ring, with electron donating group at para position, at 2-position ($\mathbf{V_{c,e}}$) showed a high antipsychotic activity but their values still 25 % lesser than that of the reference drug clozapine.

The results presented in Table 2 revealed that, in general, benzotriazepinones (**IV**, $\mathbf{V_{b,c,e,f,g}}$, **XI**) and clozapine caused significant CNS depressant activity in mice upon using forced swim test as indicated from their higher immobility times. Other benzotriazepinones showed non significant change in the immobility time and so, these derivatives may be useful as antidepressants (Mao *et al.*, 2008).

In addition, the neurotoxicity for such novel compounds were determined using both rotarod and horizontal screen tests in comparison with the reference drug clozapine (Tables 3, 4). Through analysis of Table 3, it was observed that benzotriazepinones $\mathbf{V_{a,d,h}}$ and **VI** showed no neurotoxicity at all while clozapine exhibited the highest toxicity in mice at a dose level of 3 mg/kg upon using rotarod test. It was observed from the results presented in Table 4 that

Table 1 Effect of test compounds and clozapine (3 mg/kg, i.p.) on mice using ptosis test

Compounds	Ptotic scoring	% Effect
Control	0 (no ptosis)	0.0
IV	4 (complete ptosis)	100.0
$\mathbf{V_a}$	0 (no ptosis)	0.0
$\mathbf{V_b}$	2 (1/2 ptosis)	50.0
$\mathbf{V_c}$	3 (3/4 ptosis)	75.0
$\mathbf{V_d}$	2 (1/2 ptosis)	50.0
$\mathbf{V_e}$	3 (3/4 ptosis)	75.0
$\mathbf{V_f}$	0 (no ptosis)	0.0
$\mathbf{V_g}$	0 (no ptosis)	0.0
$\mathbf{V_h}$	2 (1/2 ptosis)	50.0
VI	4 (complete ptosis)	100.0
XI	4 (complete ptosis)	100.0
Clozapine	4 (complete ptosis)	100.0

Table 2 Effect of test compounds and clozapine (3 mg/kg, i.p.) on mice using the forced swim test

Compounds	Immobility time (s)	
	Before treatment	Post treatment[a]
Control	117 ± 4.2	120 ± 5.1
IV	129 ± 5.1	178 ± 7.2*
$\mathbf{V_a}$	120 ± 3.8	118 ± 6.2
$\mathbf{V_b}$	125 ± 4.3	156 ± 5.3*
$\mathbf{V_c}$	123 ± 3.4	141 ± 3.5*
$\mathbf{V_d}$	129 ± 7.2	125 ± 6.3
$\mathbf{V_e}$	128 ± 3.7	151 ± 5.4*
$\mathbf{V_f}$	120 ± 3.5	141 ± 6.5*
$\mathbf{V_g}$	115 ± 7.1	140 ± 5.2*
$\mathbf{V_h}$	119 ± 4.1	135 ± 6.1
VI	127 ± 4.3	129 ± 6.9
XI	120 ± 4.2	190 ± 8.2*
Clozapine	121 ± 6.6	194 ± 5.2*

Significantly different at $P < 0.05$ (unpaired student's t test)

Each value represents the mean ± SD of six animals

[a] After 30 min from injection reference drug or tested compounds

Table 3 Rotarod test in mice injected by the test compounds or clozapine (3 mg/kg i.p.)

Compound	Rotarod toxicity[a] 30 min
Control	0/6
IV	4/6
$\mathbf{V_a}$	0/6
$\mathbf{V_b}$	4/6
$\mathbf{V_c}$	2/6
$\mathbf{V_d}$	0/6
$\mathbf{V_e}$	2/6
$\mathbf{V_f}$	2/6
$\mathbf{V_g}$	2/6
$\mathbf{V_h}$	0/6
VI	0/6
XI	5/6
Clozapine	5/6

[a] Rotarod toxicity (number of animals exhibiting toxicity/number of animals tested). Each value represents the mean ± SD of six animals

compounds $\mathbf{V_{a,d,h}}$ and **VI** showed neither severe (A) nor minor (B) neurotoxicity at all while clozapine exhibited the highest severe toxicity (A) on using horizontal screen test. It was found that all benzotriazepinones (**IV**,$\mathbf{V_{a–h}}$,**VI**, **X**) and also clozapine can not protect animals against pentylenetetrazole (PTZ)-induced seizures and so, these compounds were considered to be devoid of any anticonvulsant activity.

It is apparent from Table 1 that compounds **IV**, **VI**, and **XI**, were the most active ones whereas their antipsychotic

Table 4 Horizontal screen test in mice injected by the test compounds or clozapine (3 mg/kg i.p.)

Compound	*A*	%Neurotoxicity	*B*	%Neurotoxicity
Control	0/6	0	0/6	0
IV	3/6	50	0/6	0
$\mathbf{V_a}$	0/6	0	0/6	0
$\mathbf{V_b}$	2/6	33.3	2/6	33.3
$\mathbf{V_c}$	1/6	16.7	0/6	0
$\mathbf{V_d}$	0/6	0	0/6	0
$\mathbf{V_e}$	1/6	16.7	0/6	0
$\mathbf{V_f}$	1/6	16.7	1/6	16.7
$\mathbf{V_g}$	1/6	16.7	1/6	16.7
$\mathbf{V_h}$	0/6	0	0/6	0
VI	0/6	0	0/6	0
XI	2/6	33.3	1/6	16.7
Clozapine	3/6	50	1/6	16.7

A number of mice fall from the screen. *B* number of mice that fail to climb the top of the screen

activity was equal to that of the reference drug clozapine (Table 1). Moreover, these compounds were characterized by being of lower side effects which often associated with clozapine treatment such as prolonged sedation (Table 2) and neurotoxicity (Tables 3, 4), among them compound **VI** had the least side effects. It was also noted that benzotriazepinone derivatives ($\mathbf{V_{a–h}}$)-containing phenyl ring at 2-position in general have lower antipsychotic activity than that of the unsubstituted analog **IV**.

Studying the effect of different substitution of the phenyl ring on the antipsychotic activity (Table 1) revealed that the presence of electron donating groups at para position (compounds $\mathbf{V_{c,e}}$) showed a higher activity than that containing electron withdrawing substitution (compounds $\mathbf{V_{b,d,g}}$) but additional substitution on the phenyl ring even by electron donating group led to decreasing the activity (compound $\mathbf{V_h}$) may be due to steric factor. Ortho substitution with electron withdrawing group as seen in compound $\mathbf{V_f}$ abolish the activity at all.

Conclusions

It could be concluded that a new series of 3,4-dihydro-1*H*-benzo[e][1,2,4]triazepin-5(2*H*)-one derivatives (**IV**, $\mathbf{V_{a–h}}$, **VI**, and **XI**) were synthesized with high purity and excellent yield starting from benzohydrazides **II** and **IX**, respectively. Benzotriazepinone **VI** had the same antipsychotic activity as clozapine but with lesser side effects whereas it showed nonsignificant CNS depressant activity on using forced swim test as well as no neurotoxicity upon using rotarod or horizontal screen tests. Also,

benzotriazepinones **IV** and **XI** showed the same antipsychotic activity as the reference drug clozapine whereas they caused complete ptosis in mice. All benzotriazepinones were devoid from any anticonvulsant activity and clozapine as well.

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Conflict of interest The authors have declared that there are no conflicts of interest.

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