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Full Length Research Paper

Synthesis and neuropharmacological activity of some quinoxalinone derivatives

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Eight quinoxalinone derivatives were synthesized and investigated for some neuropharmacological effects (analgesia, sedation, convulsion, anxiety, memory and psychosis) in mice and rats. In the CNS depressant activity, N,N-dibenzyl-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide is the most active, while the other compounds appear variously dose-dependent. Only three of the compounds showed anxiolytic effect, with N,N-dibenzyl-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide showing the highest activity at 2.5 mg/kg. At the dose of 30 mg/kg, 6-nitro-1,4-dihydroquinoxaline-2,3-dione showed a better anxiolytic effect in mice than diazepam (dose: 1 mg/kg), while 1,2,3,4-tetrahydroquinoxaline-2,3-dione (dose: 25 mg/kg) showed a comparative effect to diazepam. 6-Chloro-1,4-dihydro-quinoxaline-2,3-dione and N,N-dibenzyl-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide showed significant anticonvulsant action. None of the compounds showed any analgesic or antidopaminergic effect. The LD₅₀ (24 h) calculated for the compounds were between 74 and 160 mg/kg i.p.

Key words: Quinoxalin-2-ones, quinoxaline-2,3-diones, sedative effect, anticonvulsant activity, anxiolytic activity.

INTRODUCTION

Quinoxalines, including their fused-ring derivatives, display diverse pharmacological activities. For example, some display antibacterial (Badran et al., 2003; El-Hawash et al., 1999; El-Gendy et al., 1995; Nasr, 2002; Refaat et al., 2004), antifungal (Kurasawa et al., 1986; Sanna et al., 1999), anticancer (Monge et al., 1995; Sanna et al., 1999; Carta et al., 2001), antimalarial (Crowther et al., 1949; Rangisetty et al., 2001), anti-tubercular (Jaso et al., 2003), and antidepressant (Sarges et al., 1990) activities. Also, some quinoxalin-2-ones **1** and quinoxaline-2,3-diones **2** (Figure 1) have been reported to show antimicrobial (Ali et al., 2000; Obafemi and Akinpelu, 2005), novel, potent antithrombotic (Ries et al., 2003), anti-pain and anti-inflammatory (Wendt and Ledig, 1969; Warner and Lubner, 1979; Su and Bock, 2005) activities.

A class of receptors for excitatory amino acids (EAAs)

is the ionotropic receptors. In this class is the 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propanoic acid (AMPA), **3**, receptors (Figure 1). AMPA receptors have been found to be involved in both seizure initiation and seizure maintenance (Loscher, 1998; Rogawski and Donevan, 1999). Therefore, inhibitors of AMPA receptor activity may be useful as neuroprotective agents. Compounds acting as AMPA antagonists are now generally known to be potentially useful for the prevention and treatment of a broad range of acute and chronic neurological disorders (Chimirri et al., 1999).

In the literature are described different series of AMPA receptor antagonists, one of which is based on the quinoxaline-2,3-dione structure **2**, which have high affinity and selectivity. Typical examples are 7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (CNQX), **4**; 6-(1H-imidazol-1-yl)-7-nitro-1,4-dihydroquinoxaline-2,3-dione (YM90K), **5**; [7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-3,4-dihydroquinoxalin-1(2H)-yl]acetic acid (YM872), **6**; 1-[4-(carboxymethyl)-7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl]-1H-pyrrole-3-carboxylic acid (Lu112313), **7**; 6-nitro-2,3-dioxo-1,2,3,4-tetrahydro-

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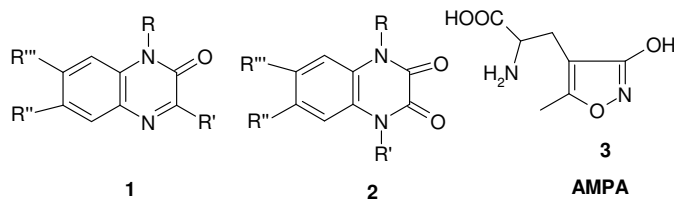


Figure 1. Quinoxalin-2-ones **1** and quinoxaline-2,3-diones **2**.

enzof]quinoxaline-7-sulfonamide (NBQX), **8** and an analog of the 2,3-quinoxalinediones, 9-(1H-imidazol-1-yl)-8-nitropyrazolo[1,5-c]quinazoline-2,5(3H,6H)-dione (Ro-48-8587), **9** (Figure 2). Many of these compounds have been reported to exhibit anticonvulsant activity in animal models of epilepsy: NBQX (Loscher and Honack, 1994; Nordholm et al., 1997), YM90K (Kodama et al., 1999), Lu112313 (Loscher et al., 1999).

In continuation of our studies on quinoxaline compounds (Obafemi and Akinpelu, 2005), some simple 2,3-quinoxalinediones, containing electron-donating and electron-withdrawing groups and two 2-quinoxalinones, with only one carbonyl functional group, were synthesized and screened for neuropharmacological activity in mice and rats (analgesia, sedation, convulsion, anxiety, memory and psychosis).

EXPERIMENTAL

General

Melting points were determined with open capillary tubes on a Gallenkamp (variable heater) melting point apparatus (uncorrected). Infrared spectra were recorded as KBr pellets on a Buck spectrometer. ^1H - and ^{13}C -NMR spectra were run on a Bruker-AC-250 and JEOL-JNM-GX 400-MHz spectrometer (δ in ppm relative to Me_4Si and H_3PO_4). Mass spectra were run on a Finnigan MAT 312 machine.

Synthesis of 1, 2, 3, 4-tetrahydroquinoxaline-2,3-dione (10)

A powdered mixture of oxalic acid dihydrate (5.0 g, 39.7 mmol) and 1, 2-diaminobenzene (4.3 g, 39.8 mmol) was put in an open beaker and 1 mL of water added and mixed thoroughly. The mixture was irradiated in a domestic microwave (MW) oven at an emitted power of 400 W for 3 min. 100 mL of water was added, followed by further irradiation for 1 min. to give a clear solution and then left to stand at room temperature to afford colorless needles of **10** (6.4 g, 99%). (m.p. > 340°C, Obafemi and Pfliederer, 1994) m.p. > 340°C). Other physical and spectroscopic data were identical to those of authentic sample.

Synthesis of 6-chloro-1, 4-dihydroquinoxaline-2,3-dione (11), 6-methyl-1,4-dihydroquinoxaline-2,3-dione (12) and 6-nitro-1,4-dihydroquinoxaline-2,3-dione (13).

Compounds **11**, **12** and **13** were prepared following the procedure described for compound **10**. Quinoxalinedione **11** was obtained as ash-gray colored crystals (m.p. > 320°C), lit.(Obafemi and Pfliederer, 1994) m.p. > 320°C in 98% yield. IR (KBr): ν_{max} 3145,

3046, 1695, 1390 cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6): δ 7.08 (s, 3H, C (5)-H, C (7)-H, C (8)-H), 11.95 (s, br, 2H, 2NH, exchangeable with D_2O). MS: in m/z (rel. %): 196 (90), 168 (69), 140 (18), 113 (20), 105 (100), 78 (28).

Compounds **12** was obtained as white crystals (m.p. > 300°C, lit.(Obafemi and Pfliederer, 2005) m.p. > 300°C) in 98% yield. IR (KBr): ν_{max} 3180, 2985, 1695 cm^{-1} . ^1H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H, CH_3), 6.89 (d, 1H, C (8)-H), 6.94 (s, 1H, C (5)-H), 7.03 (d, 1H, C (7)-H), 11.88 (s, 1H, NH, D_2O exchangeable), 11.92 (s, 1H, NH, D_2O exchangeable). MS: in m/z (rel. %): 176 (100), 148 (72), 120 (50), 105 (47), 93 (47), 77 (46).

Compound **13** was obtained as dark-brown crystals (m.p. > 320°C) in 97% yield. IR (KBr): ν_{max} 3442 (w), 3050, 1690, 1535, 1330 cm^{-1} . ^1H NMR (400 MHz, DMSO-d_6): δ 7.15 (d, 1H, C (8)-H), 7.82 – 7.89 (m, 2H, C (5)-H and C (7)-H), 12.15 (s, 1H, NH, D_2O exchangeable), 12.36 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (50 MHz, DMSO-d_6): δ 155.0 (C = O), 154.6 (C = O), 141.9, 131.4, 125.8, 118.4, 115.3, 110.2 MS: 207 (M^+). Anal. Calc. for $\text{C}_8\text{H}_5\text{N}_3\text{O}_4$ (207.1): C 46.39, H 2.43, N 20.29; found: C 46.21, H 2.50, N 20.13.

Synthesis of 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonyl chloride (14a)

Pure and dry **10** (5.0 g, 30.9 mmol) was added in small portions to chlorosulfonic acid (21 mL, 10 mmol equiv.) at room temperature, after which the resulting mixture was heated at 110°C for 8 h. The reaction mixture was cooled in ice and then poured into crushed ice to give white solid. The product was filtered and washed three times with cold water and dried. The solid was recrystallized from dry toluene-acetone mixture to give white crystals of 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonyl chloride **14a** (m.p. 330°C (dec.)) in 88% yield. IR (KBr): ν_{max} 3380, 1680, 1355, 1140 cm^{-1} . MS: in m/z (rel. %): 262 (5.3), 260 (14.0), 225 (48.1), 161 (100), 133 (45.4), 105 (70.5), 78 (45.2), 51 (82.3). Anal. Calc. for $\text{C}_8\text{H}_5\text{ClN}_2\text{O}_4\text{S}$ (260.55): C 36.86, H 1.93, N 10.75; found: C 36.59, H 2.01, N 10.90.

Synthesis of N,N-dibenzyl-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide (14)

2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonyl chloride (10.0 g, 38.4 mmol) was dissolved in dry dimethylformamide (DMF) (200 mL), followed by addition of dibenzylamine (15 mL, 78 mmol) and the resulting mixture was kept under stirring at room temperature for 10 h. The reaction mixture was then poured into water (500 mL) to give a foamy white precipitate. Recrystallization from aqueous ethanol gave white crystals of **14** (12.1 g, 75%) (m.p. > 300°C). IR (KBr): ν_{max} 3330 (NH), 1682 (C=O), 1601, 1350, 1175 (SO_2) cm^{-1} . Anal. Calc. for $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_4\text{S}$ (421.47): C 62.69, H 4.54, N 9.97; Found: C 62.52, H 4.55, N 9.78.

Synthesis of 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonyl azide (15)

2,3-Dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonyl chloride (**14**) (2.0 g, 7.8 mmol) was dissolved in acetone (50 mL) and sodium azide (1.0 g, 15.4 mmol) in minimum amount of water was added in drops with continuous stirring. The mixture was stirred at room temperature for 8 h. Acetone was removed under reduced pressure followed by addition of water to give crude crystals of **15**. Recrystallization from ethanol gave pure crystals of **15** (m.p. > 330 °C (dec.)) (Obafemi and Akinpelu. 1994) m.p. > 330 °C) in 92 % yield. IR (KBr): ν_{max} 3320, 2150, 1690, 1360, 1165 cm^{-1} . ^1H NMR (400 MHz, DMSO-d_6). δ 7.95 – 7.19 (m, 3H, Ar-H), 12.74 (s, 1H, NH, D_2O

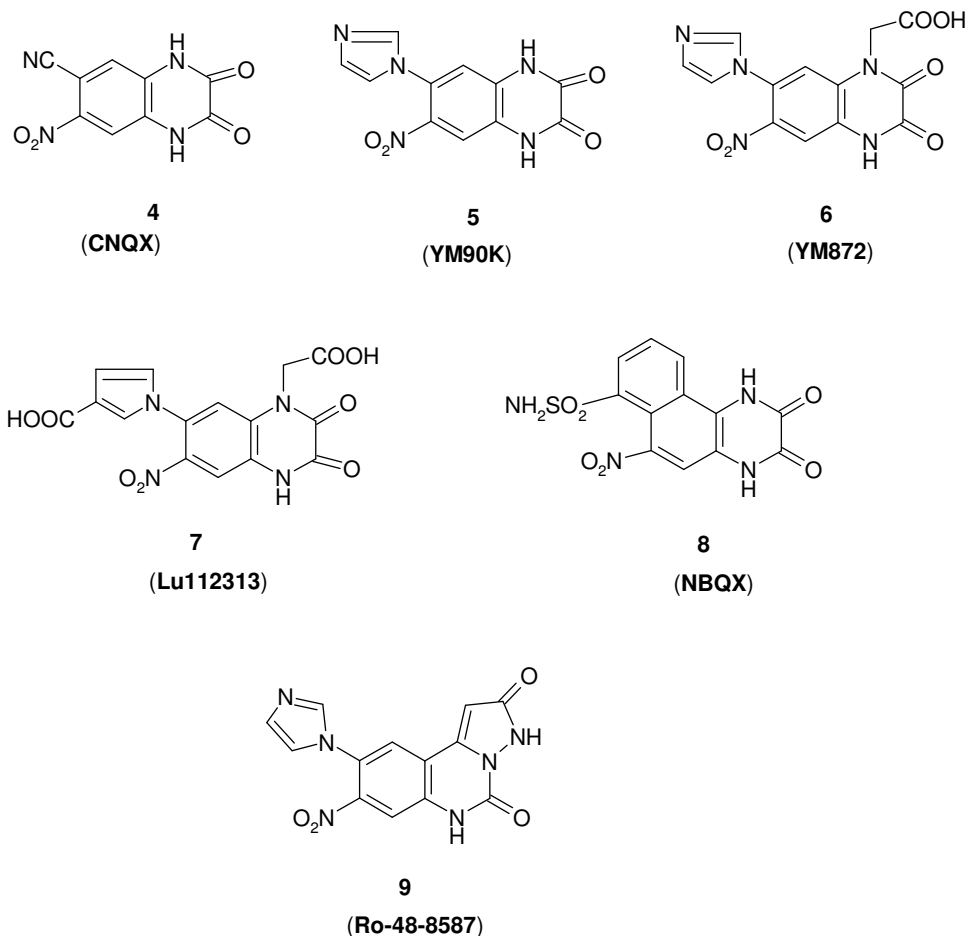


Figure 2. 2-Amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propanoic acid (AMPA) receptor antagonists.

exchangeable), 12.92 (s, 1H, NH, D₂O exchangeable). MS: in m/z (rel. %): 267 (100), 239 (17.0), 225 (18.3), 211 (6.0), 161 (10.0), 133 (5.0), 105 (22.1). Anal. Calc. for C₈H₅N₅O₄S (267.22): C 35.96, H 1.89, N 26.21 found: C 35.65, H 1.91, N 26.13.

Synthesis of 1-acetyl-1H-indole-2, 3-dione (16a)

Isatin (5.0 g, 34 mmol) was added to acetic anhydride (80 mL) and the mixture heated with continuous stirring at 90 – 100°C for 3 h. The reaction mixture was allowed to cool and then left in a fridge to give fine yellow crystals of 1-acetyl isatin. The product was filtered and the solvent was reduced to half to get more of the product (m.p. 143 – 144°C) in 82 % yield. IR (KBr): ν_{\max} 1770, 1750, 1715, 1605, 1466, 1387, 1338, 1280, 1265, 1168 cm⁻¹. ¹H NMR (200 MHz, DMSO-d₆): δ 8.37 (d, 1H, C(7)-H), 7.30-7.73 (m, 3H, Ar-H), 2.70 (s, 3H, CH₃). ¹³C NMR (50 MHz, DMSO-d₆): δ 180.1 (C=O), 169.5 (C=O), 157.8 (C=O), 148.5 (Q), 138.7 (CH), 126.1 (CH), 125.1 (CH), 119.1 (Q), 118.2 (CH), 26.2 (CH₃).

Conversion of 16a to N-[2-(3-Oxo-3, 4-dihydroquinoxalin-2-yl) phenyl] acetamide (16)

1-acetyl isatin (5.0 g, 26.4 mmol) was dissolved in ethanol (50 mL) in an open beaker. The solution was then irradiated (pulsed) in a microwave (MW) oven for 2 min. Ortho-phenylenediamine (2.9 g,

26.8 mmol) in ethanol (30 mL) was added and the resulting mixture again irradiation in a MW oven (400 W) for 2 min (at 30 sec intervals) and the solution allowed to cool at room temperature, to give white crystals of **16** (m.p. 291 – 292°C (Wiedermannova et al., 2000) m.p. 285 – 286°C) in 93 % yield. IR (KBr): ν_{\max} 3260, 1675, 1642, 1588, 1545, 1320 cm⁻¹. ¹H NMR (200 MHz, DMSO-d₆): δ 1.95 (s, 3H, CH₃), 7.10 – 7.83 (m, 8H, Ar-H), 9.78 (s, 1H, NH, D₂O exchangeable), 12.50 (s, 1H, NH, D₂O exchangeable). ¹³C NMR (DMSO-d₆): δ 168.7 (C = O), 157.6 (C = O), 155 (Q), 137.5 (Q), 133.0 (Q), 132.7 (Q), 131.4 (CH), 130.9 (CH) 130.2 (CH), 129.2 (CH), 128.4 (Q), 123.9 (CH), 123.7 (CH), 115.8 (CH), 24.4 (CH₃). Anal. Calc. for C₁₆H₁₃N₃O₂ (279.29): C 68.81, H 4.69, N 15.05; Found: C 68.72, H 4.66, N 15.00.

Synthesis of 3-(2-aminophenyl) quinoxalin-2(1H)-one (17)

Compound **16** (5.0 g, 17.9 mmol) was dissolved in 50% aqueous ethanol (50 mL) and KOH (5.0 g) was added and the reaction mixture was heated to reflux with stirring for 4 h. The resulting solution was concentrated, using a rotatory evaporator under vacuum, to half its volume and then acidified with acetic acid. The solution obtained was left to stand to give yellow crystals of **17** (m.p. 258 – 260°C, lit. (Wiedermannova et al., 2000) m.p. 261-262°C). IR (KBr): ν_{\max} 3420 (NH), 1680 (C=O), 1630, 1580 cm⁻¹. Anal. Calc. for C₁₄H₁₁N₃O (237.26): C 70.87, H 4.67, N 17.71; Found: C 70.68, H 4.60, N 17.56.

Animals

Wister rats (180–195 g) of both sex, and albino mice of both sex (18–27 g) (Vom strain; National Veterinary Research Institute, Vom, Nigeria) were used. All the animals were bred and housed in well lit and aerated room in the Animal House, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife according to standard animal care protocols. All animals had free access to drinking water and standard commercial diet (Guinea Feeds Brand, Bendel Feeds and Flour Mills Ltd, Ewu, Nigeria). The cages were cleaned regularly every 24 h.

Drugs

The drugs used for the experiments in this report are diazepam (Roche, Basel Switzerland), phenobarbitone sodium (Sigma Chemical Co, St Louis, USA), 1, 5-pentamethylenetetrazole (Aldrich, Milwaukee, USA), quinoxalinone derivatives strychnine HCL (BDH Chemical Ltd, England). All drugs were administered dissolved in normal saline and/or dimethyl sulphoxide (DMSO) on each day of the experiment.

LD₅₀ determination in mice

The method described by Locke (1983) was used in determining LD₅₀, which is the index of acute toxicity. In this method, animals (mice) were treated with each of the eight quinoxalinone derivatives after 5 days of adaptation to the laboratory. Each compound was administered at ten different doses- 20, 40, 60, 80, 100, 120, 140, 160, 180 and 200 mg/kg via the intraperitoneal rout (n=10 for each dose level). The mice were observed hourly for the first 8 h and thereafter six hourly for 24 h and continued once a day up to 14 days (Wafai and Mehta, 1986). Number of deaths was recorded. The LD₅₀ was calculated after 24 h using the arithmetic method of Spearman-Kärber (Hayes, 1989) and the results were validated by an internet hosted computer program of the United States Environmental Protection Agency (USEPA)-Probit Analysis Program for the Determination of LC/EC values, Version 1.5 (USEPA, 2004).

Novelty-induced behaviours in mice

Novelty-induced behaviours were assessed and evaluated by the method previously described by Ajayi and Ukponmwan (1994). The behaviours scored were rearing, line crossing, grooming, face wash, genital licking, stretching, urination and defecation; all were summed as total locomotor activity. The animals were placed directly from home cages into an opaque plexiglas observation cage (45 x 25 x 25 cm) with only one side transparent for observation. All animals were observed and assessed singly in the plexiglas cage, after the administration of the test drugs or normal saline. Each animal was used only once, with the plexiglas cleaned with 70% alcohol after each assessment to remove olfactory cue from one animal to the other (Brown et al., 1999). The time of the experiments was kept constant (9a.m – 4 p.m. daily) to avoid changes in biological rhythm (Siqueira et al., 1998). The laboratory was brightly lit, with an ambient temperature of 27± 2°C.

The frequency of each of the episodic behaviours was quantified by using a counter and a timer. The total frequency was summed up for each animal and totaled for the 30 minutes of observation time. Each of the test compounds (10-17) was injected intraperitoneally to mice and the effect on the total activity was compared to the normal saline (10ml/kg) control groups.

Anticonvulsant effect in mice

The method of Soaje-Echaque and Lim was used. Mice were divided into different treatment groups. The test compounds **10-17** (20-100 mg/kg) were administered i.p to the animals, while 20 mg/kg phenobarbitone was used as a standard anticonvulsant drug (Siqueira et al., 1998). Control animals received an equal volume of saline (10 ml/kg). After 30 min 1, 5-pentamethylenetetrazol (80 mg/kg i.p) was administered to all animals. The percentage of animals protected (not showing convulsion within 60 min after 1,5-pentamethylenetetrazol (80 mg/kg-i.p) injection) was recorded (Siqueira et al., 1998). Similarly, strychnine (2 mg/kg i.p) was administered to another set of animals to induce convulsion and the protection offered by the test compounds **10-17** was also recorded

Anxiolytic effect in mice

Anxiety state was examined in mice using the elevated plus-maze model (Pellow et al., 1985; Handley and Mithani, 1984). The use of the elevated plus-maze as a model for testing anxiolytic effect of candidate drugs was validated in mice by Lister in 1987 (Lister, 1987). The test is based on the natural aversion of rodents for open spaces and heights, and utilizes an elevated plus-maze with two open and two closed arms. The plus-maze was made of wood and consisted of two open arms 30 × 5 cm. and two enclosed arms 30 × 5 × 15 cm. The arms extended from a central platform 5 × 5 cm. The open arms, the central platform and the floor of the closed arms were painted black. The apparatus was mounted on a wooden base, raising it 38.5 cm. above the floor. The open arms contained a slight ledge 4 mm high, to prevent the mice from slipping and falling off the edge. To eliminate any lingering olfactory cues, the apparatus was cleaned between each examination using 70% ethyl alcohol. Each trial was recorded for 5 min with the following behaviours scored:

- open arm entries
- closed arm entries
- time spent in the open arm
- time spent in the closed arm

The index of open arm avoidance, interpreted as level of anxiety (Trullas and Skolnick, 1993) was calculated as:

$$[100 - (\% \text{ time on open arm} + \% \text{ entries into open arms} / 2)]$$

The effects of the test compounds 10-17 on anxiety in mice were compared with the effect of the anxiolytic dose (1 mg/kg, i.p.) of diazepam (Abdel-Barry and Al-Hakeim, 2000), a standard anti-anxiety drug (Haefely, 1984). Doses of the test compounds which did not affect motor coordination were used in the investigation of the anxiolytic potential of the test compounds (Reddy and Kulkarni, 1997). Mice of both sexes (20-27 g), naive to the apparatus and treatments were used for all the experiments and each mouse was used only once. Each mouse was placed in the center of the open arms after 25 min of intraperitoneal injection of the test compounds, reference drug or normal saline and the observation was made for 5 min (Lister, 1987, 1990; Trullas and Skolnick, 1993; Brown et al., 1999).

Amphetamine-induced stereotypy

The method of Siqueira et al., (1998) was used in determining the effect of the test compounds on amphetamine-induced stereotypy. Mice were allowed a minimum of 30 min to acclimatize to the observation cages prior to the experiments. Test compounds **10-17**

were given 30 min before (dl)-amphetamine (35 mg/kg, i.p). Each mouse was individually observed for 2 min in observation cages (45 x 25 x 25 cm) at 10, 20, 30 and 45 min after (d, l) – amphetamine. Stereotyped behavior was scored as follows: Complete absence of stereotyped behaviour (0); presence of stereotyped movements of the head and intermittent sniffing (1); sniffing and chewing (2), chewing and intense licking (3). The assessment was rated by a skilled independent observer who was blind to the treatment.

Apomorphine-induced stereotypy

The method of Siqueira et al. (1998) was used in determining the effect of the test extracts on the apomorphine induced stereotypy. Mice were allowed a minimum of 30 min to acclimatize to the observation cages prior to the experiments. Test drugs were given 30 min before apomorphine (35 mg/kg, i.p). Each mouse was individually observed for 2 min in observation cages (45 x 25 x 25 cm) at 10, 20, 30 and 45 min after apomorphine. Stereotyped behavior was scored as follows: Complete absence of stereotyped behaviour (0); presence of stereotyped movements of the head and intermittent sniffing (1); sniffing and chewing (2), chewing and intense licking (3). The assessment was rated by a skilled independent observer who was blind to the treatment.

Pain threshold (hot plate, 51°C) in mice

The hot plate test is a good model for assessing candidate drugs for analgesic activity (Le Bars et al., 2001; Vogel, 2002). It consists of introducing the animal into an open ended cylindrical space with a floor consisting of a metallic plate that is heated by a thermode (Bibby model, Hotplate SH3, Stuart Scientific, U.K.). The experimental protocol consists of dividing animals into treatment dose groups of at least five mice per group:

1. Group one mice were acutely treated with the test compounds 10-8-17 alone.
2. Group two mice were acutely treated with morphine (10 mg/kg, i.p.) alone.

Pain threshold (paw pressure) in rats

Pain sensitivity to noxious paw pressure was assessed in rats (120-130 g) by the method of Randall and Selitto (1957) as modified by Ukponmwan et al (1986) Nociception was measured using the analgesiometer (Analgy Meter, Number 15877, UgoBasile, Milan, Italy) at 0, 30, 60, and 120 min after the administration of doses of test compounds 10-17. Analgesia was expressed as analgesiomeric scores (AMS) g mm⁻² pressure (Ukponmwan et al, 1986). The cut off value was measured by a squeak or paw withdrawal. Animals scoring above 150 g mm⁻² during control testing were not used for further experimentation. The experimental protocol employed in this study is as follows. Rats were divided into groups of at least 5 rats each:

1. Animals in group one were treated acutely with physiological saline (SAL 10 ml/kg, i.p.)
2. A second group of rats received the test compounds 10-17 and the analgesiomeric score was taken at 0', 30', 60' and 120'.

Statistical analysis

Results of the experiments and observations are expressed as mean ± standard error of mean (s.e.m) in this report. The significance of differences between groups was determined using one-

way analysis of variance (ANOVA), followed by post hoc analysis using the Student-Newman-Keuls test. In the determination of median lethal dose (LD₅₀), the Spearman-Kärber arithmetic method was used. The results were validated by a computer programme developed by the United States Environmental Protection Agency (USEPA)-Probit Analysis Program for the Determination of LC/EC values, Version 1.5 (2004). In all the observations, statistical significance was accepted at p values less than or equal to 0.001. In all these statistical determinations, a computer programme-the Primer of Biostatistics (Version 3.01) was used (Glantz, 1992).

RESULTS

Synthesis of the compounds

The 2,3-quinoxalinediones 10-13 were synthesized by the reaction of appropriate benzene-1,2-diamines with oxalic acid dihydrate under microwave irradiation (Obafemi and Akinpelu, 2005). Compound 10 was chlorosulfonated by its reaction with excess chlorosulfonic acid at about 110 °C to give 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonyl chloride 14a. The reaction of the quinoxalinesulfonyl chloride with dibenzylamine gave N,N-dibenzyl-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide, 14. In a similar manner, compound 14a was allowed to react with sodium azide to give 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonyl azide 15 (Figure 3).

The quinoxalinone derivative 16 was synthesized starting from 1H-indole-2,3-dione (isatin). Isatin was allowed to react with acetic anhydride to give 1-acetyl-1H-indole-2,3-dione 16a, which was reacted with benzene-1,2-diamine in ethanol, under microwave irradiation, where a ring opening-ring closure steps had proceeded to give N-[2-(3-oxo-3,4-dihydroquinoxaline-2-yl) phenyl] acetamide 16. Compound 16 was subjected to hydrolysis, using KOH in aqueous ethanol, to yield 3-(2-aminophenyl) quinoxalin-2-one 17 (Figure 4).

Calculated LD₅₀ for the test compounds

The LD₅₀ calculated for each of the test compounds is as shown in Table 1. Compound 14 showed the lowest LD₅₀ of 74 mg/kg, i.p while compound 12 showed the highest LD₅₀ of 160 mg/kg, i.p, with other compounds having LD₅₀ values comparable to compound 12.

Total locomotor activity in mice

The entire test compounds (10-17) exhibited significant (p ≤ 0.001) inhibition of total locomotor activity in mice in a dose-dependent manner (Table 1). The maximum dose (100 mg/kg, i.p.) that induced maximal inhibition of total locomotor activity in mice is almost the same for all the compounds except compound 14 which exhibited maximal inhibition at 40 mg/kg, i.p.

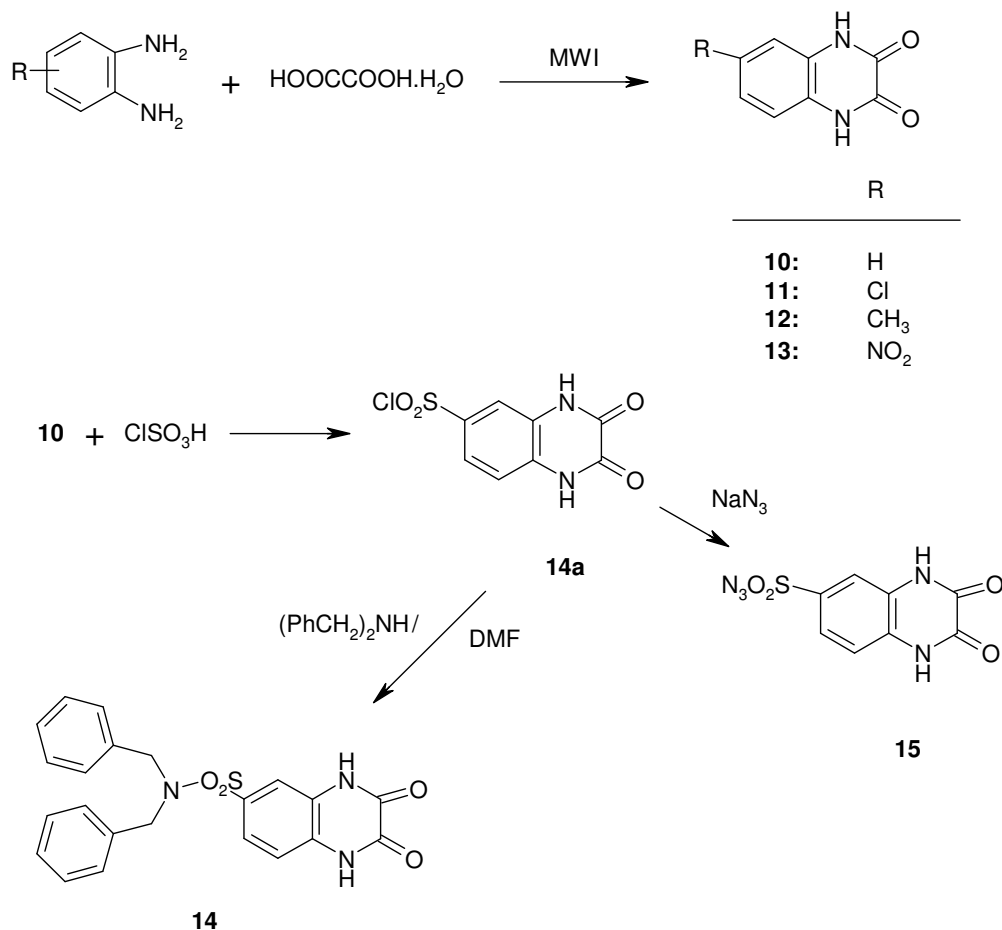


Figure 3. Synthesis of 2,3-quinoxalinediones derivatives.

Anticonvulsant activity in mice

The result of the anticonvulsant test of the synthesized compounds is as shown in Table 3. Compound 14 protected the mice against both 1,5-pentamethylene-tetrazol and strychnine-induced convulsions, and the effect was superior to the protection offered by 20 mg/kg i.p. phenobarbitone sodium employed as the standard anticonvulsant drug (100% Vs 90%, respectively). Compound 11 protected mice from the convulsive action of 1,5-pentamethylenetetrazol only and not from the convulsion induced by strychnine and the protection was comparable to that produced by phenobarbitone (20 mg/kg, i.p.). The other compounds (10, 12, 13, 15, 16 and 17) did not show any anticonvulsant effect against the two convulsive agents.

Anxiolytic effect in mice

Only compounds 10, 13, and 14 exhibited anxiolytic effect by inducing low index of open arm avoidance in mice in an elevated plus maze model of anxiety (Table 2). Compounds 13 and 14 showed anxiolytic effect in

mice that was superior to the effect produced by diazepam (1 mg/kg, i.p.) while compound 10 exhibited anxiolytic effect comparable to diazepam. The other compounds (11, 12, 15, 16 and 17) did not show any anxiolytic property.

Analgesic and antidopaminergic effects

Experiments with amphetamine and apomorphine-induced stereotyped behaviour in mice, pain threshold (hot plate, 51°C) in mice and pain threshold (paw pressure) in rats were all negative for the entire compounds (10-17).

DISCUSSION

All the quinoxalinone derivatives (10-17) have been found to have varying degrees of acute toxicity in mice. The order of acute toxicity of the quinoxalinone derivatives (14>>10~11~13~15~16~17>12) indicates that compound 14 is the most toxic and 12 the least toxic. The only struc-

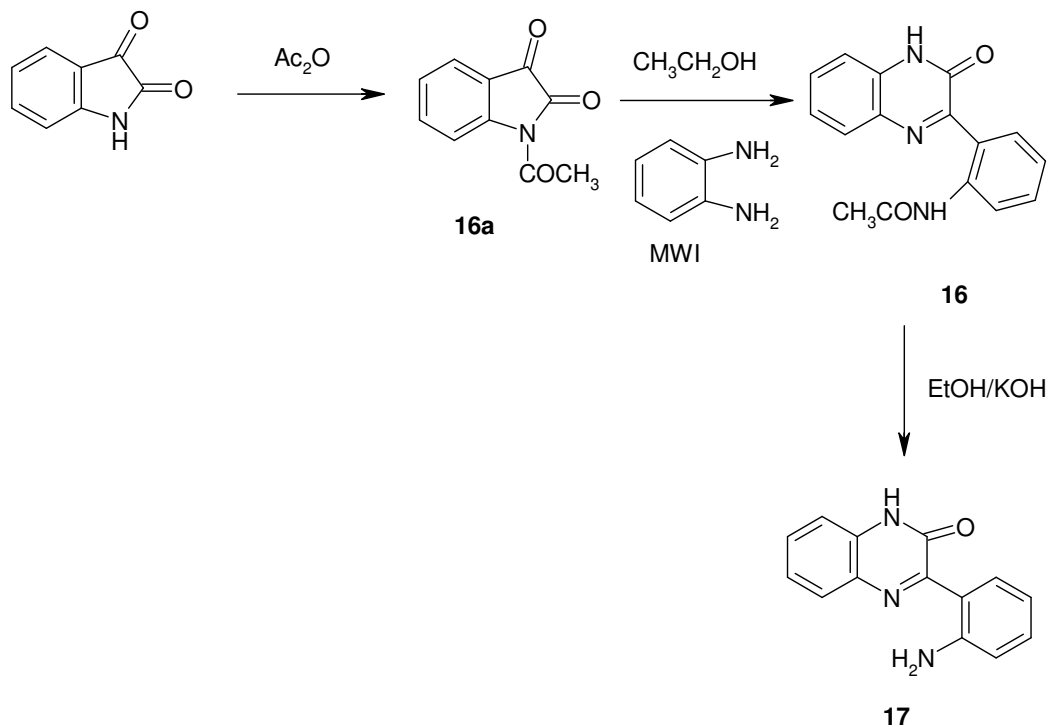


Figure 4. Synthesis route to 2-quinoxalinones **16** and **17**.

Table 1. Effect of compounds (**10-17**) on total locomotor activity in mice and the LD₅₀ values of the compounds.

Treatment Dose→ Drug↓	Total locomotor activity (n=5)				LD ₅₀
	20 mg/kg,i.p.	40 mg/kg,i.p.	80 mg/kg,i.p.	100 mg/kg,i.p.	
Normal saline (10 ml/kg, i.p.)	120±5.0				
10	111±4.7	82±3.7*	60±1.5*	53±4.0*	144
11	98±4.0*	85±2.0*	79±2.5*	39±3.5*	150
12	100±4.0*	80±1.5*	66±1.8*	30±3.3*	160
13	118±6.3	65±2.6*	61±1.6*	54±3.0*	154
15	110±5.0	85±3.0*	71±1.8*	65±3.2*	150
16	123±6.0	85±3.6*	41±4.8*	26±3.8*	152
17	105±4.2*	66±5.1*	23±3.0*	16±2.0*	149
14	5 mg/kg,i.p. 81±3.6*	10 mg/kg,i.p. 49±2.6*	20 mg/kg,i.p. 21±1.5*	40 mg/kg,i.p. 5±1.0*	74

*indicates significant difference from the normal saline control treatment ($p < 0.001$; Student-Newman-Keul post hoc test).

Note the difference in effective doses for compound **14** (in bold).

Number of mice per treatment dose was 5, while number of mice for the determination of LD₅₀ was 10 for each dose level.

tural difference between the most toxic and the least toxic being that compound 12 has an electron-donating methyl group (CH₃) at position 6, while 14 has an electron-withdrawing N,N-dibenzylsulfonamido group ((PhCH₂)₂NSO₂-) at position 6.

From the total locomotor activity test, all the quinoxalino derivatives (10-17) have been found to have strong

sedative effect in mice, in the order (14>17>16>12>11>10>15). Compound 14 exhibited the most sedative effect (~ 5 at 40 mg/kg,i.p.), indicating that a dibenzylsulfonamido group ((PhCH₂)₂NSO₂-) at position 6 is beneficial in exhibiting sedative property. This can be inferred, for example, when compound 14 is compared with 15 which carries an azidosulfonyl group (N₃SO₂-) at

Table 2. Effect of compounds (10-17) on the frequency of arm entries and time spent in the arms of an elevated plus maze in mice.

Treatment	Number of entries into arms		Time spent in each arm		% Time spent in open arm	% Entry into open arm	Index of open arm avoidance
	Open	Close	Open	Close			
Normal saline (10 ml/kg, i.p.)	5±1.0	16±3.1	50±4.0	221±7.0	22.6	23	77.2
10 (25 mg/kg, i.p.)	13±3.2	5.0±1.0	189±8.2	100±6.2	63.0	72.2	32.4*
11 (10mg/kg, i.p.)	4±1.1	12±2.1	22±3.1	265±7.0	7.3	25.0	83.9
12 (10 mg/kg, i.p.)	3±1.0	12±3.0	505±4.0	238±11.0	16.8	20.0	81.6
13 (30 mg/kg, i.p.)	15±2.0	3±1.0	171±9.0	119±5.0	57.0	83.3	29.9*
14 (2.5 mg/kg, i.p.)	17±3.0	4±2.0	202±8.0	94±7.3	67.3	81.0	25.9*
15 (30 mg/kg, i.p.)	5±2.1	14±3.0	55±3.6	225±8.2	18.3	26.3	77.7
16 (30 mg/kg, i.p.)	6±1.1	15±2.0	25±5.2	254±9.0	8.3	28.6	81.6
17 (10 mg/kg, i.p.)	4±1.2	15±3.0	59±7.1	230±6.2	19.7	21.1	79.6
Diazepam (1 mg/kg i.p.)	14±2.0	3±1.0	160±5.0	110±4.0	53.3	82.4	32.2*

* indicates significant difference from the normal saline control treatment ($p < 0.05$; SNK post hoc test). Number of mice per treatment was 5. Note that anxiolytic doses are lower than sedative doses to avoid affecting motor coordination in the animals. Test compounds are coded as 10-17 in bold.

Table 3. Anticonvulsant screening of synthesized compounds.

Drug treatment	Dose mg/kg I.P.	Protection (%) at 60 min after	
		Leptazol 80 mg/kg i.p.	Strychnine 2.0 mg/kg i.p.
Control (saline)	10 mg/kg	0	0
10	100	0	0
11	100	100	0
12	100	0	0
13	100	0	0
14	25	100	100
15	100	0	0
16	100	0	0
17	100	0	0
Phenobarbitone sodium	20	90	90

position 6 but showed only a locomotor activity of ~65 (at maximum dose of 100mg/kg,i.p). In addition, compounds 16 and 17 exhibited high sedative effects suggesting that a 2-aminophenyl group at position 3 of a quinoxalinone ring is also beneficial for such activity.

Only compounds 11 and 14 possessed anticonvulsant activity. While compound 11 was effective against 1,5-pentamethylenetetrazol, compound 14 was effective against both 1,5-pentamethylenetetrazol and strychnine. This suggests that while compound 11 is acting on the GABAergic system to offer neuroprotection against the induced convulsion, compound 14 appeared to possess both GABAergic and glycinergic effect due to its protection of the animals from strychnine induced convulsion (Olayiwola, 2005). It is interesting to note that other compounds (10, 12, 13, 15-17) did not protect the mice against the induced convulsion, showing that only

the chloro (Cl) functional group at position 6 and the N-N-dibenzylsulfonamido group are essential for neuroprotection against the induced seizures. In addition, the observed good activity of the dibenzylsulfonamidoquinoxalinedione 14 is in agreement with the binding site hypothesis of Dimmock (Dimmock and Baker, 1994) and Pandeya (Pandeya et al, 2000), in some aryl semicarbazones, in which (a) an aryl hydrophobic binding site (AH), (b) hydrogen-bonding site (HBD) and (c) an electron donor site (D) are required for anticonvulsant activity. In our series of compounds, the active compound 14 possess all the essential requirements for anticonvulsant activity as proposed by Dimmock and other workers (Figure 5). The clinically available anticonvulsant compounds-diazepam (18) and phenobarbital (19) have two or three of these characteristics, respectively, that promote their anticonvulsant effects (Figure 6).

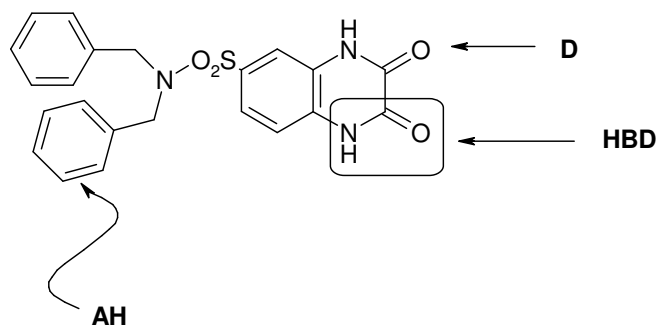


Figure 5. Structure of **14** showing the locations considered to be hydrophobic binding area (AH), hydrogen bonding site (HBD) and electron donor group (D).

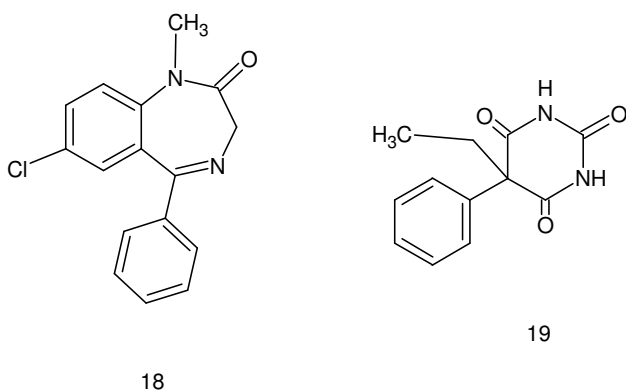


Figure 6. Clinically available anticonvulsant compounds, diazepam (**18**) and phenobarbital (**19**).

Furthermore, AMPA receptors agonists, such as compound **3**, have been implicated in seizures induced in experimental animal. (Loscher, 1998; Rogawski and Donevan, 1999). Compounds **4-9** have high affinity and selectivity for the AMPA receptors as antagonists and accordingly exhibited anticonvulsant effect (Loscher and Honack, 1994; Nordholm et al., 1997; Kodama et al., 1999; Loscher et al., 1999). Compounds **11** and **14** which are quinoxalinone derivatives, just like compounds **4-8**, showed anticonvulsant activity. The strong anticonvulsant effect of **14** may reside in its large hydrophobic group which confers strong ability to cross the blood-brain barrier, and the electron donating action of the chloro group on **11** might be responsible for the anticonvulsant effect observed in **11**. It is therefore interesting to note that the anticonvulsant effect of **14** might be due to stimulation of a repertoire of receptors which include GABA, GABA-benzodiazepine, glycine and antagonism of AMPA receptors, while the anticonvulsant effect of **11** might be due to combination of glycine receptors stimulation and AMPA receptors antagonism.

Anxiolytic effects were observed in compounds **10**, **13**

and **14**, at the doses selected (which were generally lower than the sedative doses of the compounds to prevent motor incoordination in the mice). It is interesting that while the anxiolytic effect induced by compound **10** was comparable to that of diazepam, those due to compounds **13** and **14** were superior to the anxiolytic effect of diazepam (Table 2). The functional groups present in **11**, **12**, **15**, **16** and **17** were not able to confer anxiolytic effect, even though they all showed sedative effects. This observation suggests that anxiolytic effect of compounds with sedative property should not be assumed.

REFERENCES

- Abdel-Barry JA, Al-Hakein MHH (2000). Acute intra-peritoneal and oral toxicity of the leaf glycosidic extract of *Trigonella foenum-graecum* in mice. *J. Ethnopharmacol.* 70: 65–68.
- Ajayi AA, Ukponmwam OE (1994). Evidence of angiotensin II and endogenous opioid modulation of novelty-induced rearing in the rat. *Afr. J. Med. Med. Sci.* 23: 287–290.
- Ali MM, Ismail MMF, El-Gaby MSA, Zahran MA, Ammar YA (2000). Synthesis and antimicrobial activities of some novel quinoxalinone derivatives. *Molecules* 5: 864–873.
- Badran MM, Abouzid KAM, Hussein MHM (2003). Synthesis of certain substituted quinoxalines as anti-microbial agents, Part II. *Arch. Pharm. Res.* 26: 107–113.
- Brown RE, Corey S, Moore AK (1999). Differences in measures of exploration and fear in MHC-Congenic C57BL/6J and B6-H-2K mice. *Behavior Genetics.* 26: 263–271.
- Carta A, Sanna P, Gherardini, Usai D, Zanetti S. (2001). Novel functionalized pyrido[2,3-*g*]quinoxalinones as antibacterial, antifungal and anticancer agents. *Il Farmaco* 56: 933–938.
- Chimirri A, Gitto R, Zappala M (1999). AMPA receptor Antagonists. *Expert Opinion on Therapeutic Patents.* 9: 557–570.
- Crowther AF, Curd FHS, Davey DG, Stacey GJ. (1949). Synthetic antimalarials. Part XXXIX. Dialkylaminoalkyl-aminoquinoxalines. *J. Chem. Soc.* pp. 1260–1262.
- Dimmock JR, Baker GB (1994). Anticonvulsant activities of 4-bromobenzaldehyde semicarbazone. *Epilepsia* 35: 648–655.
- El-Gendy AA, El-Meligie S, El-Ansary A, Ahmedy AM (1995). Synthesis of some quinoxaline derivatives containing indoline-2,3-dione or thiazolidine residue as potential antimicrobial agents. *Arch. Pharm. Res.* 18: 44–47.
- El-Hawash SA, Habib NS, Fanaki NH (1999). Quinoxaline derivatives Part II: Synthesis and antimicrobial testing of 1,2,4-triazolo[4,3-*a*]quinoxalines, 1,2,4-triazino[4,3-*a*]quinoxalines and 2-pyrazolylquinoxalines. *Pharmazie* 54: 808–815.
- Glantz AS (1992). *Primer of Biostatistics* (Version 3.02). McGraw-Hill Inc.
- Haefely W (1984). The biological basis of the psychotropic action of drugs. In: Poldinger W (ed). *Compendium of Psychopharmacotherapy*. Editiones Roche, Basle, Switzerland, pp. 19–47.
- Handley SL, Mithani S (1984). Effects of α -adrenoceptor agonists and antagonists in a maze-exploration model of 'fear'-motivated behaviour. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 327: 1–5.
- Hayes WA (1989). *Principles and Methods of Toxicology* 2nd Edition. New York. Raven Press Ltd. pp. 221–226.
- Jaso A, Zarranz B, Aldana I, Monge A (2003). Synthesis of new 2-acetyl and 2-benzoylquinoxaline 1,4-di-N-oxide derivatives as anti-*Mycobacterium tuberculosis* agents. *Eur. J. Med. Chem.* 38: 791–800.
- Kodama M, Yamada N, Sato K, Kitamura Y, Koyama F, Sato T, Morimoto K, Kuroda S (1999). Effects of YM90K, a selective AMPA receptor antagonist, on amygdalal-kindling and long-term hippocampal potentiation in the rat. *Eur. J. Pharmacol.* 374: 11–19.
- Kurasawa Y, Muramatsu M, Yamazaki K, Tajima S, Okamoto Y, Takada A (1986b). A facile synthesis of 1-aryl-3-heteroaryl-1H-pyrazolo[3,4-

- 6]quinoxalines and related compounds with antifungal activity [1]. *J. Heterocyclic Chem.* 23: 1391–1394.
- Le Bars D, Gozariu M, Cadden SW (2001). Animal models of nociception. *Pharmacological Reviews* 53: 598–643.
- Lister RG (1987). The use of a plus-maze to measure anxiety in the mouse. *Psychopharmacology*, 111: 323–331.
- Lister RG (1990). Ethologically-based animal models of anxiety disorders. *Pharmacological Theory* 46: 321–340.
- Locke D (1983). A new approach to practical acute toxicology. *Arch. Toxicol.* 54: 275–287.
- Loscher W (1998). New visions in the pharmacology of anticonvulsion. *Eur. J. Pharmacol.* 342: 1–13.
- Loscher W, Honack D (1994). Effects of the non-NMDA antagonists NBQX and the 2,3-benzodiazepine GYKI 52466 on different seizure types in mice: comparison with diazepam and interactions with flumazenil. *Br. J. Pharmacol.* 113: 1349–1357.
- Loscher W, Lehmann H, Behl B, Seeman D, Teschendorf HJ, Hofmann HP, Lubisch W, Hoger T, Lemaire HG, Gross G (1999). A new pyrrolyl-quinoxalinedione series of non-NMDA glutamate receptor antagonists: pharmacological characterization and comparison with NBQX and valproate in the kindling model epilepsy. *Eur. J. NeuroSci.* 11: 250–262.
- Monge A, Martinez-Crespo FJ, Cerain AL, Palop JA, Narro S, Senador V, Marin A, Sainz Y, Gonzalez M, Hamilton E, Barker AJ (1995). Hypoxia-selective agents derived from 2-quinoxaline carbonitrile 1,2-di-N-oxides. *J. Med. Chem.* 38: 4488–4494.
- Nasr MNA (2002). Synthesis and antibacterial activity of fused 1,2,4-triazolo[4,3-a]quinoxaline and oxopyrimido[2,1':5,1]-1,2,4-triazolo[4,3-a]-quinoxaline derivatives. *Arch. Pharm. Med. Chem.* 8: 389–394.
- Nordholm L, Sheardown SD, Honore T (1997). In: *Excitatory amino acids – clinical results with antagonists*. Herrling, PL (Ed.). Academic Press, London, pp. 89–97.
- Obafemi CA, Akinpelu DA (2005). Synthesis and antimicrobial activity of some 2(1H)-quinoxalinone-6-sulfonyl derivatives. *Phosphorus, Sulfur, Silicon Relat. Elem.* 180: 1795–1807.
- Obafemi CA, Pfeleiderer W (1994). Permanganate oxidation of quinoxaline and its derivatives. *Helv. Chim. Acta* 77: 1549–1556.
- Olayiwola G (2005). Neuropharmacological properties of *Stachytarpheta cayennensis* leaves (L.C. Rich) vahl (Verbenaceae). Ph.D Thesis, Obafemi Awolowo University, Nigeria.
- Pandeya SN, Yogeewari P, Stables JP (2000). Synthesis and anticonvulsant activity of 4-bromophenyl substituted aryl semicarbazones. *Eur. J. Med. Chem.* 35: 879–886.
- Pellow S, Chopin Ph, File SE, Briley M (1985). Validation of open-closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. *J. Neurosci. Meth.* 14: 149–167.
- Randall LO, Selitto JJ (1957). A method for measurement of analgesic activity on inflamed tissue. *Arch. Int. Pharmacodyn.* 111: 409–419.
- Rangisetty JB, Gupta CNVHB, Prasad AL, Srinivas P, Sridhar N, Parimoo P, Veeranjanyulu A (2001). Synthesis of new arylaminoquinoxalines and their antimalarial activity in mice. *J. Pharmacy and Pharmacology* 53: 1409–1413.
- Reddy DS, Kulkarni SK (1997). Differential anxiolytic effects of neurosteroids in the mirrored chamber behaviour test in mice. *Brain Research.* 752: 61–71.
- Refaat HM, Moneer AA, Khalil OM (2004). Synthesis and antimicrobial activity of certain novel quinoxalines. *Arch. Phram. Res.* 27: 1093–1098.
- Ries UJ, Priekpe HW, Havel NH, Handschuh S, Mihm G, Stassen JM, Wiene W, Nar H (2003). Heterocyclic thrombin inhibitors. Part 2: quinoxalinone derivatives as novel, potent antithrombotic agents. *Bioorg. Med. Chem. Lett.* 13: 2297–2302.
- Rogawski MA, Donevan SD (1999). AMPA receptors in epilepsy and as targets for antiepileptic drugs. *Adv. Neurol.* 79: 947 – 963.
- Sanna P, Carta A, Loriga M, Zanetti S, Sechi L (1999). Synthesis of 3,6,7-substituted-quinoxalin-2-ones for evaluation of antimicrobial and anticancer activity. Part 2: *Il Farmaco* 54: 161–168.
- Sanna P, Carta A, Loriga M, Zanetti S, Sechi L (1999). Preparation and biological evaluation of 6/7-trifluoromethyl(nitro) – 6,7-difluoro-3-alkyl(aryl)-substituted-quinoxalin-2-ones. Part 3: *Il Farmaco* 54: 169–1177.
- Sarges R, Howard HR, Browne RG, Lebel LA, Seymour PA, Koe Bk (1990). 4-Amino[1,2,4]triazolo[4,3-a]quinoxalines. A novel class of potent adenosine receptor antagonists and potential rapid-onset antidepressants. *J. Med. Chem.* 33: 2240–2254.
- Siqueira IR, Lara DR, Silva D, Gaiessi FS, Nunes DS, Elisabetsky E (1998). Psychopharmacological properties of *Ptochopetalum olacoides* Bentham (Oleaceae). *Pharm. Biol.* 36: 327–334.
- Su D-S, Bock MG (2005). 2-Quinoxalinone derivatives as bradykinin antagonists and novel compounds. *US Patent Appl.* (20050020591).
- Trullas R, Skolnick P (1993). Differences in fear motivated behaviour among in-bred mouse strains. *Psychopharmacology* 111:323 – 331.
- Ukponmwan OE, Ruprecht J, Dzolijic M (1986). An analgesic effect of enkephalinase inhibition is modulated by monoamine oxidase-B and REM sleep deprivations. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 332: 376–379.
- United States Environmental Protection Agency (USEPA) (2004). Probit analysis program for the determination of LC/EC values, Version 1.5 (Web resource www.usepa.gov).
- Vogel GH (2002). Pharmacology Core Battery Tests. In: *Drugs Discovery and Evaluation*, 2nd Edition, Springer Publishers, Berlin, pp. 385–544.
- Wafai ZA, Mehta VL (1986). Some neuropharmacological actions of 3-methyl-5-phenyl-(4-methyl)-quinolenodiazepine. *Indian J. Pharmacol.* 18: 89–94.
- Warner PL, Lubner EJ (1979). 1-(2-Acylamino-phenyl)imidazoles. U.S. Patent, 4,172,647[Chem. Abstr. 1980, 92:58785a]
- Wendt GR, Ledig KW (1969). 6,7-Dihydroxy-1H-pyrazolo[3,4-6]quinoxaline-5,8-diones. U.S. Patent, 3,431,262 [Chem. Abstr. 1969. 70: 106512].
- Wiedermannova I, Slouka J, Hlavac J (2000). Oxoderivatives of quinoxaline II. The study of reactivity of 2-(2-oxo-1,2-dihydroquinoxaline-3-yl)benzenyl cation. *Acta Universitatis Palackianae Olomucensis, Facultas Perum Naturalium* 39: 69–74.