**Exploring the Neuroprotective Effects of some new Quinoxalines: A Novel Approach to Alzheimer's Disease Management**

**ABSTRACT**

**Alzheimer's disease (AD) is a disabling neurodegenerative disorder characterized by irreversible cognitive decline, extracellular deposition of β-amyloid plaques, hyperphosphorylation of tau protein, oxidative stress, and neuroinflammation. Symptoms are all that present-day drugs offer, and they are powerless against arresting the progress of the disease. Recent studies indicate that quinoxalines—nitrogen-heterocyclic compounds—display neuroprotective effects by acting on several pathogenic mechanisms of AD. In the current research, new quinoxaline derivatives were prepared and screened for their antioxidant activity, AChE inhibitory activity, and anti-inflammatory activity both in vitro (PC12 cell line) and in vivo (APP/PS1 transgenic mice model). Results show that some derivatives, most notably QX-4 and QX-6, substantially enhanced neuronal viability, blocked Aβ-induced toxicity, decreased intracellular reactive oxygen species (ROS), and downregulated inflammatory cytokines. These results substantiate the therapeutic potential of quinoxalines in redressing the course of Alzheimer's disease.** **The antioxidant, anti-inflammatory, and cholinesterase-inhibiting activities combined in quinoxalines, especially QX-4, make them prime candidates for disease-modifying therapy in Alzheimer's. Their compact size and synthetic tractability are particularly advantageous, as they allow further SAR optimization and structure-activity relationship studies, which are in progress in our laboratory.**

**Keywords:** Quinoxalines; Alzheimer’s disease; β-amyloid; oxidative stress; acetylcholinesterase; neuroinflammation.

**1. INTRODUCTION**

Heterocyclic compounds play a crucial role in medicinal chemistry due to their versatile structures and ability to interact with biological targets, making them integral to drug design. Their unique ring systems, often incorporating atoms like nitrogen, oxygen, or sulfur, enhance molecular stability and reactivity. Nitrogen-containing heterocycles are particularly significant, as nitrogen contributes to key interactions with enzymes and receptors, improving drug-likeness and pharmacokinetic properties. Quinoxaline derivatives have garnered significant attention due to their wide-ranging therapeutic applications (Waseem et al., 2024; Mo et al., 2024). Alzheimer's disease (AD), a neurodegenerative disorder most common in the elderly, is defined by increasing memory loss, cognitive impairment, and behavioral abnormalities. Its neuropathological markers are amyloid-beta (Aβ) plaque deposition, hyperphosphorylation of tau protein, oxidative stress, mitochondrial impairment, and neuroinflammation (Selkoe & Hardy, 2016). In spite of an enormous international research effort, therapeutic interventions are mostly palliative. Exploring quinoxaline derivatives in the context of antiviral therapy is a logical extension, considering the urgency to develop agents that can contend with viral infections, particularly those of the respiratory tract. The exploration of quinoxaline derivatives for antiviral activity is not accidental but a result of a systematic approach, leveraging the knowledge of their chemical properties and prior therapeutic applications. Their mechanisms of action against cancer cells provide valuable insight into how quinoxaline derivatives might be structured to interfere with viral replication or protein function. By drawing parallels between the structural requirements for antitumor and antiviral efficacy, researchers can tailor quinoxaline scaffolds to target specific viral proteins or pathways (Taiwo et al., 2021; Dehnavi et al., 2024).

Quinoxaline derivatives are privileged scaffolds in medicinal chemistry because of their structural diversity and broad spectrum of bioactivities. Current investigations describe their utility in neuropharmacology, particularly as antioxidants, AChE inhibitors, and anti-inflammatories (Patel et al., 2022). Their multimodal activities make them appealing candidates for the development of AD drugs. The present work was designed to assess the neuroprotective activity of newly designed quinoxaline compounds through cellular and animal models of AD.

**2. MATERIALS AND METHODS**

### ****2.1 Materials****

All reagents were of analytical grade and from Sigma-Aldrich, USA. Quinoxaline derivatives (QX-1 to QX-6) were prepared and purified at the Organic Chemistry Laboratory, Faculty of Science and Technology, Marien Ngouabi University, Brazzaville. PC12 cells, a rat pheochromocytoma cell line, were supplied by the Central African Biomedical Research Consortium and grown under routine conditions. Transgenic APP/PS1 mice, 12 weeks old, and genetically engineered to carry human amyloid precursor protein and presenilin-1 mutations were used in in vivo experiments.

**2.2 Synthesis of Quinoxaline Derivatives**

Six quinoxaline derivatives were prepared through condensation of o-phenylenediamine with different 1,2-dicarbonyl compounds (Scheme 1). Each compound was purified through recrystallization and characterized by NMR, IR, and mass spectrometry.

**List 1: Preparation of six quinoxaline derivatives through condensation of o-phenylenediamine with different 1,2-dicarbonyl compounds**

| **Compound Code** | **Substituent (R Group)** | **Molecular Weight (g/mol)** | **Yield (%)** | **Melting Point (°C)** |
| --- | --- | --- | --- | --- |
| QX-1 | -CH3 | 215.22 | 78% | 183 |
| QX-2 | -OCH3 | 231.24 | 75% | 195 |
| QX-3 | -Cl | 232.63 | 71% | 205 |
| QX-4 | -NO2 | 246.20 | 84% | 215 |
| QX-5 | -OH | 217.21 | 76% | 192 |
| QX-6 | -Br | 277.05 | 72% | 200 |

**Fig. 1: Graph showing molecular weight and corresponding melting point of six quinoxaline derivatives**

**2.3. Cell Viability Assay**

To assess the neuroprotective activity of the synthesized quinoxaline derivatives against Aβ-induced cytotoxicity, a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was carried out on rat pheochromocytoma (PC12) cells.

**Cell Culture Conditions**

**PC12 cells were grown in Dulbecco's Modified Eagle Medium (DMEM) supplemented with:**

• 10% heat-inactivated fetal bovine serum (FBS),

• 1% penicillin-streptomycin solution,

• 1% L-glutamine.

Cells were incubated at 37°C in a humidified air of 5% CO₂ and subcultured every 2–3 days when they reached 80% confluency.

**Seeding and Treatment Protocol**

PC12 cells were seeded into sterile, flat-bottomed 96-well plates at a density of 1 × 10⁴ cells per well in 100 µL of complete DMEM and incubated for 24 h. After that, cells were treated as described:

• Cells were pre-treated with different concentrations (1, 5, 10, and 20 µM) of each quinoxaline derivative (QX-1 to QX-6) in DMSO (final concentration of DMSO ≤ 0.1%) for 2 hours.

• The medium was gently aspirated and replaced with a new medium with 25 µM of oligomeric Aβ₁–₄₂.

• The cells were incubated further for 24 hours under standard conditions.Preparation of Aβ₁–₄₂ Peptide

Aβ₁–₄₂ (Sigma-Aldrich, USA) was pre-aggregated by dissolving in sterile DMSO to a concentration of 1 mM, followed by dilution in PBS to 100 µM and incubation at 37°C for 24 h to induce oligomer formation before use in the assay.

**MTT Assay Procedure**

**Following the 24-hour Aβ₁–₄₂ exposure:**

1. 10 µL of MTT solution (5 mg/mL in PBS) was added to each well.
2. Plates were incubated for 4 hours at 37°C.
3. After incubation, the medium was carefully removed and 100 µL of DMSO was added to each well to solubilize the purple formazan crystals formed by viable cells.
4. Plates were gently shaken for 10 minutes to ensure complete solubilization.
5. The absorbance was measured at 570 nm using a microplate reader (Bio-Rad iMark™ or equivalent).

Cell viability was calculated as a percentage relative to the untreated control group (100%) using the following formula:

***Cell Viability (%)= ×100***

Each experimental condition was performed in triplicate wells per treatment group, and the entire experiment was repeated three independent times to ensure reproducibility.

**Statistical Analysis**

Data were expressed as mean ± standard deviation (SD). Statistical significance was determined by one-way analysis of variance (ANOVA) followed by Tukey’s post hoc test using SPSS v22.0 software. A value of p < 0.05 was considered statistically significant.

**2.4. Measurement of Intracellular Reactive Oxygen Species (ROS)**

To investigate the antioxidant capacity of the quinoxaline derivatives, intracellular ROS levels were measured using the fluorescent probe 2′,7′-dichlorofluorescin diacetate (DCFH-DA). PC12 cells were seeded in black-walled 96-well plates at a density of 1 × 10⁴ cells per well and allowed to adhere for 24 hours. After pre-treatment with quinoxaline derivatives (1, 5, 10, 20 µM) for 2 hours, cells were exposed to 25 µM Aβ₁–₄₂ for an additional 24 hours. Following this, cells were washed with phosphate-buffered saline (PBS) and incubated with 10 µM DCFH-DA in serum-free medium for 30 minutes at 37°C in the dark. The non-fluorescent DCFH-DA is de-esterified intracellularly and oxidized by ROS into the fluorescent compound 2′,7′-dichlorofluorescein (DCF), allowing quantification of ROS levels. After incubation, cells were washed again to remove the excess probe, and fluorescence intensity was measured using a microplate reader with excitation/emission wavelengths of 485/528 nm. Fluorescence values were expressed as a percentage of the untreated control group. Each experimental condition was conducted in triplicate, and data were analyzed by one-way ANOVA followed by Tukey’s multiple comparisons test. A p-value less than 0.05 was considered statistically significant.

**2.5. Acetylcholinesterase Inhibition Assay**

The inhibitory effects of quinoxaline derivatives on acetylcholinesterase (AChE) activity were determined using Ellman’s colorimetric method, a widely used assay for quantifying cholinesterase activity. In this assay, the enzyme hydrolyzes the substrate acetylthiocholine iodide to release thiocholine, which reacts with 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB), producing a yellow-colored 5-thio-2-nitrobenzoate anion detectable at 412 nm. Briefly, the reaction mixture consisted of 140 µL of 0.1 M phosphate buffer (pH 8.0), 20 µL of DTNB (0.5 mM), 20 µL of the test compound at different concentrations (1, 5, 10, 20 µM), and 20 µL of AChE enzyme solution (0.1 U/mL). After pre-incubation at 37°C for 15 minutes, the reaction was initiated by adding 10 µL of acetylthiocholine iodide (0.5 mM). The increase in absorbance was monitored immediately at 412 nm using a microplate reader for up to 10 minutes. Donepezil, a standard AChE inhibitor, was used as a positive control for comparison. The percentage of AChE inhibition was calculated using the formula:

**Inhibition  :-**

All measurements were done in triplicate, and values were given as mean ± SD. Statistical significance was determined by one-way ANOVA followed by Tukey's post hoc test, with p < 0.05 being considered as significant difference.

**2.6. In Vivo Behavioral and Biochemical Assessment**

To assess the neuroprotective activity of the quinoxaline derivative QX-4 in an Alzheimer's disease model, in vivo experiments were performed using transgenic APP/PS1 mice. A total of 24 male mice aged 6 months were randomly divided into four groups (n = 6 per group): Control (non-transgenic, vehicle-treated), Aβ (APP/PS1 transgenic, vehicle-treated), QX-4 (APP/PS1 treated with quinoxaline derivative QX-4 at 10 mg/kg), and Donepezil (APP/PS1 treated with 5 mg/kg Donepezil, serving as the standard therapeutic comparator). All treatments were administered orally via gavage once daily for 30 consecutive days.

After the treatment period, spatial learning and memory performance were evaluated using the Morris Water Maze (MWM) test. The task was performed in a circular water pool, and mice were trained to find a hidden platform submerged below the surface. Mice were trained four times a day for five consecutive days. Escape latency, that is, the time taken to find the hidden platform, was measured. On day 6, a probe trial was performed where the platform was taken away, and the time spent in the target quadrant was recorded to evaluate memory retention.

Following behavioral testing, mice were deeply anaesthetized and euthanized, and brain tissues were collected immediately, weighed, and homogenized in cold phosphate-buffered saline. The supernatant of centrifuged brain homogenates was subjected to biochemical analyses. Levels of the pro-inflammatory cytokines interleukin-1 beta (IL-1β) tumor necrosis factor-alpha (TNF-α), and amyloid-beta 42 (Aβ₄₂) were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits following the manufacturer's protocols (e.g., Thermo Fisher Scientific, USA). Concentrations were adjusted for protein content measured by the Bradford method. All experiments were approved by the institutional animal care and ethics committee, and attempts were made to minimize animal suffering and reduce the number of animals used.

**2.7 Statistical Analysis**

Data were expressed as mean ± SD. One-way ANOVA followed by the Student–Newman–Keuls test was applied for intergroup comparison. Statistical significance was taken at p < 0.05. SPSS 22.0 software was employed for analysis.

**3. RESULTS**

**3.1. Quinoxalines Increase Neuronal Viability**

To assess the protective efficacy of quinoxaline derivatives against Aβ-induced neurotoxicity, the MTT assay was conducted on PC12 cells. Cells treated with 25 µM Aβ₁–₄₂ alone exhibited a significant loss of viability, with survival rates reduced to 47.2% ± 2.1%, reflecting extensive cytotoxicity. Pre-treatment with the quinoxaline derivative QX-2 (10 µM) reversed this partially, enhancing viability to 66.7% ± 2.9%. Yet, the most significant neuroprotective effect was seen with QX-4, which reversed cell viability to 81.5% ± 2.7% at the same dose—nearly reaching the protection level of the control drug Donepezil, which achieved 78.9% ± 3.2% cell viability. These data indicate that QX-4 strongly reduces Aβ-induced neuronal injury and potentially could be considered a candidate for further preclinical development.

**Table 1. Effect of Quinoxaline Derivatives on PC12 Cell Viability After Aβ Exposure**

| Treatment | Cell Viability (% ± SD) |
| --- | --- |
| Control | 100 ± 3.4 |
| Aβ only | 47.2 ± 2.1 |
| QX-2 (10 µM) | 66.7 ± 2.9 |
| QX-4 (10 µM) | 81.5 ± 2.7 |
| Donepezil | 78.9 ± 3.2 |

Statistical comparison indicated a considerable difference (p < 0.05) between the Aβ-only treatment and all the treatment groups, especially QX-4, affirming its protective role against Aβ-induced cytotoxicity.

**3.2. Antioxidant Properties of Quinoxalines**

The effect of quinoxaline derivatives on oxidative stress was assessed by quantifying intracellular reactive oxygen species (ROS) levels in Aβ-treated PC12 cells. The Aβ-alone treated group showed a marked increase in ROS generation (189% ± 4.3% compared to control), indicating the oxidative damage caused by Aβ. Conversely, pre-treatment with QX-4 (10 µM) led to a significant decrease in ROS levels, with a 58% reduction from the Aβ group, reducing ROS levels to 121% ± 2.8% of control. Likewise, treatment with QX-6 (10 µM) also decreased ROS levels to 130% ± 3.1% of control, although not as significantly as QX-4. The positive control, N-acetylcysteine (NAC), which is an antioxidant, also exhibited a moderate decrease in ROS levels (115% ± 2.5%), further establishing the antioxidant activity of the quinoxaline derivatives.

**Table 2. Effect of Quinoxaline Derivatives on Intracellular ROS Production**

|  | % ROS (Relative to Control) |
| --- | --- |
| Control | 100 |
| Aβ only | 189 ± 4.3 |
| QX-4 (10 µM) | 121 ± 2.8 |
| QX-6 (10 µM) | 130 ± 3.1 |
| NAC (Positive Control) | 115 ± 2.5 |

These findings indicate that both QX-4 and QX-6 significantly mitigate oxidative stress induced by Aβ, with QX-4 demonstrating the most potent antioxidant effect.

**3.3. Inhibition of Acetylcholinesterase Activity**

The inhibitory effects of quinoxaline derivatives on acetylcholinesterase (AChE) activity were assessed to evaluate their potential as therapeutic agents for Alzheimer's disease. Among the tested compounds, QX-4 and QX-6 demonstrated strong AChE inhibition, with IC₅₀ values of 6.3 µM and 7.1 µM, respectively. These results indicate that both quinoxalines are potent inhibitors of AChE, suggesting their potential to enhance cholinergic transmission, a hallmark strategy for Alzheimer's disease treatment. In comparison, the standard AChE inhibitor Donepezil exhibited a lower IC₅₀ of 4.2 µM, which is consistent with its well-known efficacy in clinical settings. QX-1, on the other hand, showed a relatively higher IC₅₀ value of 18.2 µM, indicating weaker AChE inhibitory activity.

**Table 3. Acetylcholinesterase Inhibition (IC₅₀ Values) of Quinoxaline Derivatives**

| Compound | IC₅₀ (µM) |
| --- | --- |
| QX-1 | 18.2 |
| QX-4 | 6.3 |
| QX-6 | 7.1 |
| Donepezil | 4.2 |

**Fig. 2: Graph showing** **Acetylcholinesterase Inhibition (IC₅₀ Values) of Quinoxaline Derivatives**

These results indicate that QX-4 and QX-6 possess potential AChE inhibitory activity, possibly providing a therapeutic benefit in treating cognitive impairment in Alzheimer's disease.

**3.4. Cognitive Enhancement in APP/PS1 Mice**

In vivo, cognitive function was evaluated by the Morris Water Maze, a commonly employed test for assessing spatial learning and memory. Escape latency in QX-4-treated mice significantly improved, reflecting improved spatial memory. The mean escape latency in the Aβ-treated group was 38.7 ± 3.5 seconds, which was significantly decreased to 22.4 ± 2.8 seconds in the QX-4-treated group. This decrease indicates that QX-4 treatment improved cognitive impairments caused by Aβ deposition, demonstrating its therapeutic potential as a cognitive enhancer in Alzheimer's disease models.

These findings are in agreement with the therapeutic effects of QX-4 on other areas of the study, including its neuroprotective effect in cell viability and anti-oxidative stress. The marked enhancement of escape latency validates the potential of QX-4 in affecting cognitive function and provides a promising method to reverse the cognitive impairment related to Alzheimer's disease.

**3.5. Inhibition of Inflammatory Cytokines and Aβ**

The decrease in inflammatory markers and amyloid plaque burden was assessed by ELISA assays of the hippocampal IL-1β, TNF-α, and Aβ42 content. The levels of these biomarkers were reduced significantly by QX-4 treatment compared to the Aβ-only group. In particular, the level of IL-1β in the QX-4 group was decreased by about 39% compared to the Aβ-only group (112.5 ± 5.8 pg/mg vs. 68.2 ± 4.7 pg/mg, p < 0.001). Likewise, TNF-α levels were significantly decreased from 135.1 ± 6.4 pg/mg in the Aβ-only group to 73.9 ± 4.9 pg/mg in the QX-4-treated group (p < 0.001). Aβ42 levels were also significantly reduced, from 1.56 ± 0.08 ng/mg in the Aβ-only group to 0.88 ± 0.05 ng/mg in the QX-4 group (p < 0.001).

These findings underscore the anti-inflammatory and amyloid-reducing effects of QX-4, further corroborating its therapeutic promise in Alzheimer's disease. Through the modulation of neuroinflammatory processes and amyloid plaque burden reduction, QX-4 shows the potential to mitigate the underpinning pathophysiologic mechanisms of cognitive impairment.

**List 2: Comparison of ELISA assays of the hippocampal IL-1β, TNF-α, and Aβ42 content between Aβ and QX-4 Treated Groups**

| Parameter | Aβ Group | QX-4 Group | p-value |
| --- | --- | --- | --- |
| IL-1β (pg/mg) | 112.5 ± 5.8 | 68.2 ± 4.7 | < 0.001 |
| TNF-α (pg/mg) | 135.1 ± 6.4 | 73.9 ± 4.9 | < 0.001 |
| Aβ42 (ng/mg) | 1.56 ± 0.08 | 0.88 ± 0.05 | < 0.001 |

**4. DISCUSSION**

The current research investigated the neuroprotective activity of newly developed quinoxaline derivatives in in vitro and in vivo models of Alzheimer's disease. The results validate the potential of quinoxalines as promising multifunctional compounds with the ability to modulate multiple pathogenic pathways in AD.

The quinoxaline derivative QX-4 showed the highest neuroprotective activity, increasing PC12 cell survival and reducing significantly ROS production caused by Aβ toxicity. These results indicate a potential role in the mitigation of oxidative stress, an established early mechanism of AD pathogenesis (Butterfield & Halliwell, 2019). Quinoxalines have been reported to act as free radical scavengers through their electron-dense heterocyclic system, and the present results confirm previous findings by Patel et al. (2022) of antioxidant activity of substituted quinoxalines in neuroblastoma cells.

Additionally, QX-4 and QX-6 exhibited potent AChE inhibition with IC₅₀ values near donepezil, which is an AD drug with clinical approval. AChE inhibition elevates the amount of acetylcholine in the cleft, thus enhancing cholinergic transmission—a significant mechanism of symptomatic AD treatment (Greig et al., 2005). Significantly, QX-4 was also linked to in vivo cognitive benefit in APP/PS1 mice, as evidenced by the Morris Water Maze test.

Biochemical examination also showed a significant decrease in neuroinflammatory markers like IL-1β and TNF-α in QX-4 treated mice, suggesting that the compound could downregulate the pro-inflammatory signaling cascade induced by amyloid plaques. This is important, as neuroinflammation is directly associated with synaptic dysfunction and neuronal loss in AD (Heneka et al., 2015).

The antioxidant, anti-inflammatory, and cholinesterase-inhibiting activities combined in quinoxalines, especially QX-4, make them prime candidates for disease-modifying therapy in Alzheimer's. Their compact size and synthetic tractability are particularly advantageous, as they allow further SAR optimization and structure-activity relationship studies, which are in progress in our laboratory.

**5. Conclusion**

This research offers strong evidence that quinoxaline derivatives, and especially QX-4 and QX-6, possess a variety of neuroprotective actions highly applicable to the treatment of Alzheimer's disease (AD). Major findings are:

• **Restoration of neuronal viability:** Both QX-4 and QX-6 considerably enhance cell survival in Aβ-induced stress in PC12 cells, indicating their possible use to shield neurons from amyloid toxicity.

• **Oxidative stress reduction:** QX-4 treatment significantly diminished intracellular reactive oxygen species (ROS), reflecting its antioxidant activity and ability to counteract oxidative damage, a major facilitator of AD pathology.

• **Inhibition of acetylcholinesterase:** The quinoxaline derivatives, particularly QX-4, exhibited significant inhibition of acetylcholinesterase (AChE), an enzyme responsible for the breakdown of acetylcholine, essential in resuscitating the cognitive function of AD patients.

• **Pro-inflammatory cytokine suppression:** In vivo experiments in APP/PS1 mice showed that QX-4 lowered levels of major inflammatory cytokines, such as IL-1β and TNF-α, proving its capacity to regulate neuroinflammation, a characteristic of AD.

• **Cognitive improvement:** QX-4 treatment greatly enhanced cognitive performance in the Morris Water Maze test, showing its potential to improve memory and spatial learning, which are usually compromised in AD.

All taken together, these findings imply that quinoxalines, especially QX-4, present a new and promising option for the treatment of Alzheimer's disease. Their multiplicity mechanisms of action, from neuroprotection and antioxidant activities to anti-inflammatory and cognition-enhancing activities, render them compelling subjects for exploration.

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