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# Organoselenium group is critical for antioxidant activity of 7-chloro-4-phenylselenyl-quinoline

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ABSTRACT

The quinolone compounds have been reported for many biological properties, especially as potent antioxidants. This study investigated the antioxidant effect of 7-chloro-4-phenylselenyl-quinoline (PSQ), a quinolone derivative with organoselenium group, against oxidative stress induced by sodium nitroprusside (SNP) in brains of mice. A second objective was to verify the importance of phenylselenyl group presents at position 4 of the quinoline structure to antioxidant effect of compound. So, it was compared the antioxidant effect of PSQ with a quinoline without organoseleniun group (7-chloroquinoline [QN]). Swiss mice were used and received SNP (0.335 μmol/site, intracerebroventricular) 30 min after treatment with PSQ or QN, at the doses of 50 mg/kg (intragastrically). After 1 h, animals were sacrificed and the brains were removed to biochemistry analysis. Thiobarbituric acid reactive species (TBARS), protein carbonyl (PC) and non-protein thiol (NPSH) levels, as well as catalase (CAT), glutathione S transferase (GST) and δ -aminolevulinic acid (δ-ALA-D) activities were determined. SNP increased TBARS and PC levels, and reduced the enzymatic (CAT and GST activity) and non-enzymatic (NPSH levels) antioxidant defenses and inhibited the δ-ALA-D activity. PSQ avoided the increase in the lipid peroxidation and PC levels, as well as the decrease in the NPSH levels, CAT, GST and δ-ALA-D activities QN partially avoided the increase in lipid peroxidation, but it not protected against alterations induced by SNP. In conclusion, phenylselenyl group present in quinoline structure is critical for antioxidant activity of PSQ.

## 1. Introduction

Selenium is an essential mineral, which has important biological functions for health of human body [1]. In this sense, organoselenium compounds have attracted special attention, given that this class of compounds has presented several pharmacological properties, such as antioxidant [2,3], anti-inflammatory [4,5], neuroprotective [6], anxiolytic-like [7], antihyperglycemic [8], among others.

In addition, quinoline compounds have promising biological activities, being found in natural products pharmacologically active [9,10], and extensively used in the clinic [10,11]. Among them, it can highlight Bedaquiline used for the treatment of multidrug resistant tuberculosis, and Irinotecan used for the treatment of colorectal cancer. In this context, quinolone ring has attracted great attention in the field of drug development and advances have been made in order to synthesize new quinoline compounds. In this way, studies have shown that this class of heterocyclic compounds have several pharmacological properties, such as antibiotic [12], anticancer [13], anti-inflammatory [14,15], antimicrobial [16,17], anticonvulsant [18], anxiolytic-like [19], as well as antioxidant [15,20–22].

Based on important pharmacological properties of quinoline compounds and selenium, our research group has devoted special attention

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to the synthesis and evaluation of pharmacological effects of quinoline compounds containing selenium [15,19,21,22]. 7-chloro-4-phenylselenyl-quinoline (PSQ), a quinolone derivative with organoselenium substituent, has demonstrated a significant number of pharmacological properties. This compound showed antioxidant action *in vitro* [21] and absence of toxicity [19]. Moreover, recently our research group demonstrated that PSQ presented antinociceptive and anti-inflammatory properties in mice nociception models [15,23], as well as anxiolytic-like action [19]. However, the antioxidant effect of this compound in the cerebral oxidative stress was not studied until this moment. Indeed, oxidative stress is presented in several neurodegenerative diseases, such as Parkinson's, Alzheimer's and Huntington [24–27]. Therefore, the interest in the treatment of diseases related to cerebral oxidative stress with antioxidants molecules has increased in the last years [28–30].

Based on the above considerations, the aim of this study was to investigate the antioxidant effect of PSQ, a quinoline derivative with organoseleniun substituent, against oxidative stress induced by sodium nitroprusside (SNP) in brains of mice. Another major objective was to verify the importance of phenylselenyl group, an organoselenium substituent, in quinoline structure to antioxidant effect of compound.

## 2. Material and methods

### 2.1. Chemicals and reagents

Quinoline compounds with organoselenium substituent (PSQ) and without organoselenium substituent, 7-chloro-quinoline (QN), are presented in the Fig. 1A and B, respectively. PSQ and QN were prepared and characterized by methods previously described [21,31]. Analysis of the $^{1}H$ NMR and $^{13}C$ NMR spectra showed analytical and spectroscopic data in full agreement with their assigned structures. Quinoline compounds were dissolved in canola oil, while SNP was dissolved in 0.9% saline solution. All other chemicals were of analytical grade and obtained from standard commercial suppliers.

### 2.2. Animals

Male adult Swiss mice (25–35 g) from a local breeding colony were used. The animals were kept on a separate room, on a 12 h light/dark cycle, at a temperature of 22 ± 2 °C, with free access to food and water. The present experimental study was approved by the Ethical Research Committee of the Federal University of Pelotas, affiliated to the National Council for the Control of Animal Experimentation, and registered under number 1287–2016.

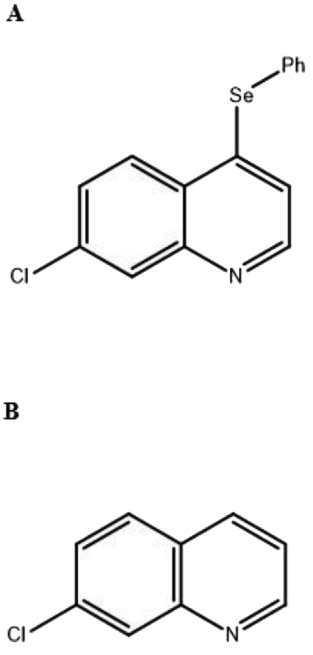


**Fig. 1.** Chemical structures of (A) 7-chloro-4-(phenylselenyl)quinoline (PSQ) and (B) 7-chloro-quinoline (QN).

### 2.3. Protocol of exposure

Mice were divided into six groups of seven animals each. Animals belonging to groups I and IV received canola oil (10 ml/kg), used as vehicle. Mice belonging to groups II and V were treated with PSQ (50 mg/kg), while animals belonging to groups III and VI received QN (50 mg/kg). Canola oil or quinoline derivatives were administered by intragastric (i.g.) route, via gavage. Thirty minutes after these treatments, mice of groups IV, V and VI received SNP (0.335 µmol/site, 2 µl, intracerebroventricular (i.c.v.)), while groups I, II and III received saline solution (NaCl 0.9%) (i.c.v., 2 µl). The time for treatment and dosage of quinoline-based compounds were based on a previous study of [19]. The dosage of SNP was based on a previous study of [29]. I. c.v. injections were given as described by Haley and McCormick [32] and modified by Laursen and Belknap [33] with the bregma fissure as a reference point.

### 2.4. Tissue preparation

One hour after administration of SNP or saline, the mice were sacrificed by isoflurane inhalation anesthesia. Brains were removed and immediately homogenized in cold 50 mM Tris–HCl, pH 7.4 (1/5, weight/volume), centrifuged at 900 × g at 4 °C for 10 min and supernatants were used for biochemical assays. Protein carbonyl content was assayed using the homogenate (without centrifugation).

### 2.5. Thiobarbituric acid reactive species (TBARS) levels

TBARS levels were determined as described by Ohkawa et al. [34] and used as lipid peroxidation measure. An aliquot of supernatant was added to the reaction mixture containing: 8.1% sodium dodecyl sulfate (SDS), 0.8% thiobarbituric acid and acetic acid buffer (pH 3.4). The system was incubated at 95 °C for 2 h. Absorbance was measured at 532 nm in a spectrophotometer. Results were reported as nmol malondialdehyde (MDA)/mg protein.

### 2.6. Protein carbonyl content

An increase of carbonyl content is found in oxidatively-modified proteins [35]. An aliquot of a homogenate diluted (Tris–HCl buffer, pH 7.4, in a proportion of 1:8 (vol/vol)) was mixed with 10 mM dinitrophenylhydrazine (DNPH) or 2 M HCl [36]. After 1 h of incubation at room temperature in dark, denaturing buffer 150 mM sodium phosphate buffer, pH 6.8, containing 3% SDS), heptane (99.5%) and ethanol (99.8%) were added. The tubes were shaken with a vortex mixer for 40 s and centrifuged at 900 × g for 15 min. Following, the pellet (protein isolated) was washed twice with ethyl acetate/ethanol 1:1 (vol/vol) and suspended in denaturing buffer. Absorbance was measured at 370 nm in a spectrophotometer. Total carbonylation was calculated using a molar extinction coefficient of 22000 $M^{-1}$/cm. Results were expressed as nmol carbonyl content/mg protein.

### 2.7. Non-protein thiols (NPSH) levels

NPSH levels were determined by the method of Ellman [37]. This method is used to evaluate the levels of non-enzymatic antioxidant defenses. Supernatant was mixed (1:1, vol/vol) with 10% trichloroacetic acid (TCA). Tubes were centrifuged at 900 × g for 10 min. After, the protein pellet was discarded and free-thiol (SH) groups were determined in the clear supernatant. An aliquot of supernatant was