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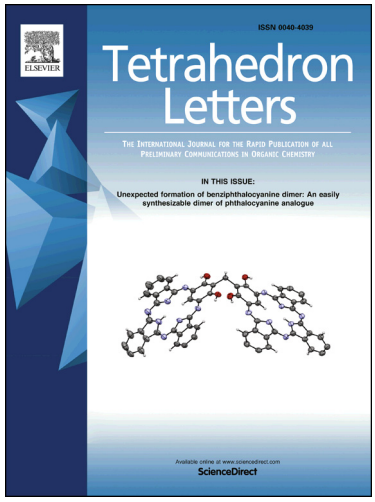

A simple method for the synthesis of 4-arylselanyl-7-chloroquinolines used as *in vitro* acetylcholinesterase inhibitors and *in vivo* memory improvement

Luis Fernando B. Duarte, Eduardo S. Barbosa, Renata L. Oliveira, Mikaela P. Pinz, Benhur Godoi, Ricardo F. Schumacher, Cristiane Luchese, Ethel A. Wilhelm, Diego Alves

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Graphical Abstract

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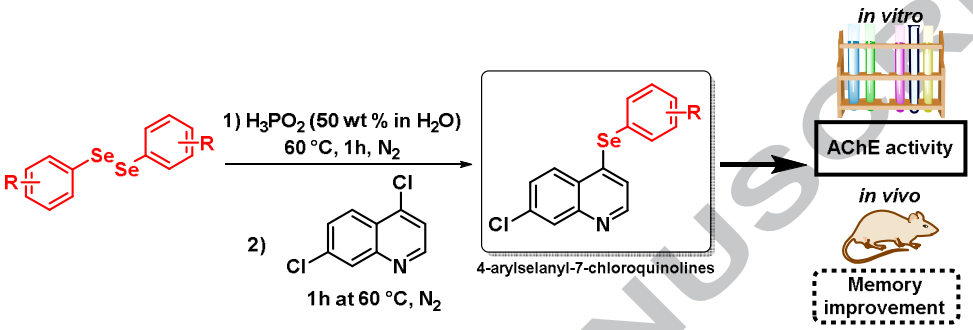

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A simple method for the synthesis of 4-arylselanyl-7-chloroquinolines used as *in vitro* acetylcholinesterase inhibitors and *in vivo* memory improvement

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ABSTRACT

We described here an alternative method for the synthesis of 4-arylselanyl-7-chloroquinolines through reactions of 4,7-dichloroquinoline with organylselenols, generated *in situ* by the reaction of diorganyl diselenides with H_3PO_2 (50 wt% in H_2O). These reactions proceeded efficiently at 60 °C under N_2 atmosphere and are suitable to a range of diorganyl diselenides containing electron-donating and electron-withdrawing groups, affording the corresponding 4-aryl-7-chloroquinolines in high yields. The synthesized compounds were screened for their *in vitro* acetylcholinesterase (AChE) activity and our results demonstrated that the 7-chloro-4-[(4-fluorophenyl)selanyl]quinoline inhibited the AChE activity and improved memory in mice, making this compound is a potential therapeutic agent for the treatment of Alzheimer disease and other neurodegenerative disorders.

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Quinolines are an important class of heterocyclic compounds and their structural entities are common in therapeutics, alkaloids and synthetic analogues with interesting biological activities.[1] A great variety of quinoline derivatives have been used as antiviral, anticancer, antibacterial, antifungal, antiplatelet, antiobesity and anti-inflammatory agents (Figure 1).[2] Particularly, molecules containing the nucleus 7-chloroquinoline are biologically active units and display a wide range of pharmacological properties, such as antimalarial and antitubercular properties.[3] Because of their presence in a wide diversity of synthetic and natural products, significant efforts have been dedicated to the design and the synthesis of new molecules containing quinoline nucleus.

In this context, there are a large number of methodologies in the literature for the synthesis of chalcogen-containing quinolines, especially selenium derivatives.[4] Organoselenium compounds are valuable scaffolds in organic synthesis because their pharmacological activities,[5] and also as versatile building blocks participating in regio-, chemio-, and stereoselective reactions.[6] Thus, the synthesis of selenium-containing quinolines have great significance and their applicability range from antioxidant, antifungal, and antibacterial agents, to selective DNA binding and photocleaving agents.[4]

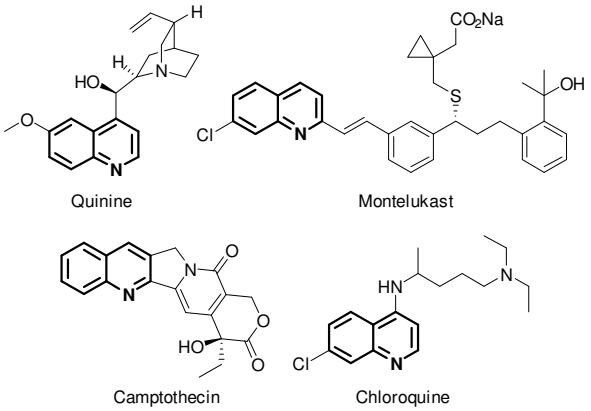

Figure 1. Selected examples of bioactive quinolines.

Recently, a significant increase in the number of alternative procedures for the synthesis of organoselenium compounds has appeared, especially involving the use of non-volatile and renewable solvents, and alternative energy sources.[7] In this sense, the use of aqueous solution of hypophosphorous acid (H_3PO_2) have been described as an efficient and cheap way to synthesize organoselenium compounds.[8] This acid is air-stable and can be used efficiently in aqueous solution while the expected organylselenol is easily generated *in situ* after cleavage of diorganyl diselenide under nitrogen atmosphere, avoiding the bad smell of this selenating agent, and the incompatibility of boron

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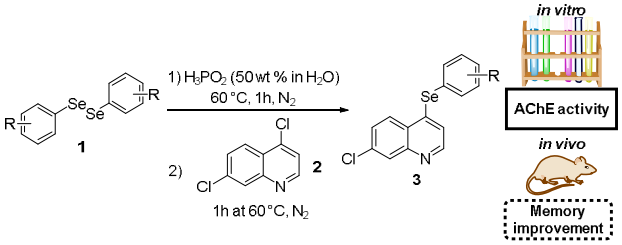
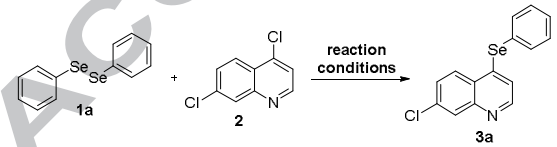
hidrides or alkali metals with sensitive groups. In recent years, our group published some methodologies using H_3PO_2 to the generation of organylselenols *in situ* from diorganyl diselenides, with application in the synthesis of mono- or bis-selanyl alkenes, benzoselenazoles or benzoselenazolines, unsymmetrical diaryl selenides, organylselanyl pyridines and selanylesters.[8d-h]

In continuation to our efforts devoted to the development of new efficient protocols correlated to the nitrogen-functionalized organoselenium compounds, we report an alternative method for the synthesis of 4-arylselanyl-7-chloroquinolines. This method involves reactions of 4,7-dichloroquinoline with organylselenols, generated *in situ* by the reaction of diorganyl diselenides with H_3PO_2 (50 wt% in H_2O). In addition, the obtained products were screened for their *in vitro* acetylcholinesterase (AChE) activity, and the best inhibitor was assessed on the *in vivo* memory improvement (Scheme 1).



Scheme 1. General scheme of the present work.

Initially, we choose diphenyl diselenide **1a** (0.25 mmol) and 4,7-dichloroquinoline **2** (0.5 mmol) as model substrates to establish the best conditions for the reaction using H_3PO_2 (50 wt% in H_2O) as the reducing agent and some experiments were performed to synthesize the 7-chloro-4-(phenylselanyl)quinoline **3a** (Scheme 2). All the reactions were carried out in a Schlenk tube and monitored by TLC until total disappearance of starting materials. Thus, a mixture of diphenyl diselenide **1a** (0.25 mmol) and H_3PO_2 (50 wt% in H_2O, 0.5 mL) was stirred at 90 °C under N_2 atmosphere for 1 h. Then, 4,7-dicloroquinoline **2** (0.5 mmol) was added and the mixture was stirred for additional 1 h at 90 °C.[8h] Under these reaction conditions, the estimated product **3a** was obtained in 69% yield (Condition A, Scheme 2). Interestingly, the yield of 7-chloro-4-(phenylselanyl)quinoline **3a** was increased to 93% and 97% when the reaction temperature was maintained at 60 °C after the addition of 4,7-dicloroquinoline **2** (Conditions B and C, Scheme 2). Unfortunately, when the reaction temperature was maintained at room temperature after the addition of substrate **2**, a decrease in the yield of product **3a** was observed, even after 24 h (Condition D, Scheme 2).



Condition A: 1) H_3PO_2 (50 wt % in H_2O), 90 °C, 1h, N_2. 2) **2**, 90 °C, 1h, N_2 (69%).
Condition B: 1) H_3PO_2 (50 wt % in H_2O), 90 °C, 1h, N_2. 2) **2**, 60 °C, 1h, N_2 (93%).
Condition C: 1) H_3PO_2 (50 wt % in H_2O), 60 °C, 1h, N_2. 2) **2**, 60 °C, 1h, N_2 (97%).
Condition D: 1) H_3PO_2 (50 wt % in H_2O), 60 °C, 1h, N_2. 2) **2**, r.t., 24h, N_2 (57%).

Scheme 2. Optimization of the reaction.

Analyzing the results shown in Scheme 2, we judged that the best reaction conditions to afford 7-chloro-4-(phenylselanyl)quinoline **3a** are those in Condition C. This condition involves the preliminary reaction of diphenyl diselenide **1a** (0.25 mmol) with H_3PO_2 50 wt% in H_2O (0.5 mL) at 60 °C under N_2 for 1 h (for the formation *in situ* of benzeneselenol, followed by the addition of 4,7-dichloroquinoline **2** (0.5 mmol) and stirring for additional 1 h at 60 °C. Our results indicates that this reaction of diphenyl diselenide **1a** with H_3PO_2 (50 wt% in H_2O) produce *in situ* two portions of benzeneselenol, and subsequent reaction with 4,7-dichloroquinoline **2** is able to use both benzeneselenol groups, highlighting the atom economy of this process.

Once defined the ideal reaction parameters, we have focused on the study of the generality and limitations of the synthetic method. Therefore, several experiments were carried out by employing the 4,7-dichloroquinoline **2** and diaryl diselenides **1a-h** bearing different substituents bonded to the aromatic rings, as substrates (Table 1). The reaction system showed to be no sensitive to electronic effects from donating and electron-withdrawing groups present in the structure of the diaryl diselenides affording the desired 4-arylselanyl-7-chloro-quinolines **3a-g** in good to excellent yields (Table 1, entries 1-7). In order to test the influence of steric effects in the efficiency of the synthetic approach, the substrate **2** was submitted to the reaction conditions in the presence of the sterically hindered dimesityl diselenide **1h**. Through this reaction the expected 4-arylselanyl-quinoline derivative **3h** was isolated in 86% yield (Table 1, entry 8). It is important to note that the synthetic methodology proved to be highly regioselective once all experiments furnished the desired quinolines **3** only by replacement of chlorine atom at C-4 position of the heterocyclic nucleus. These results must be highlighted since the preservation of the chlorine atom at C-7 position enables the further functionalization of the heterocyclic unit.

After these studies, we turned our attention to the *in vitro* AChE activity and *in vivo* memory improvement of the synthesized compounds. Progressive loss of memory is a major feature of Alzheimer's disease. In recent years, therapy of Alzheimer's disease using AChE inhibitors has been extensively studied.[9] Nowadays, the Food and Drug Administration (FDA) approved five drugs for the treatment of Alzheimer's disease, including four AChE inhibitors (tacrine, donepezil, galanthamine and rivastigmine). Unfortunately, these drugs have low bioavailability and undesirable side effects, such as hepatotoxicity. Indeed, no new treatment has been approved for the Alzheimer's disease since 2003 and several new candidates have not succeeded in clinical trials. Therefore, in a first step, we investigated the inhibitory effect of synthesized quinolines **3** on the cerebral AChE activity *in vitro*.

AChE is an enzyme that presents a key role in cholinergic neurotransmission by hydrolyzing the acetylcholine to acetate and choline in the synaptic cleft.[10] Acetylcholine is the major neurotransmitter involved in learning and memory, and in the regulation of cognitive functions.[11] Consequently, AChE inhibitors, which enhance the availability of acetylcholine in the synaptic cleft, are a potential treatment strategy to enhance the cholinergic function.[12] Thus, this study reported inhibitory effect of quinoline derivatives **3a**, **3b**, **3c**, **3e** and **3g** on cerebral AChE activity, since cholinergic system is important to cognitive process. Compounds **3d**, **3f** and **3h** were not used in the assay because of their low solubility in DMSO.

Table 2 shows the effect of 4-arylselanyl-7-chloroquinolines **3a**, **3b**, **3c**, **3e** and **3g** on AChE activity in cerebral cortex of mice. Compound **3e** significantly inhibited the cerebral cortex AChE activity at concentrations equal to or greater than 1 μM, being that the I_{max} was 36.5%. 7-Chloroquinoline derivatives **3a**, **3b**, **3c** and **3g** had no effect in inhibiting AChE activity in cerebral cortex of mice.

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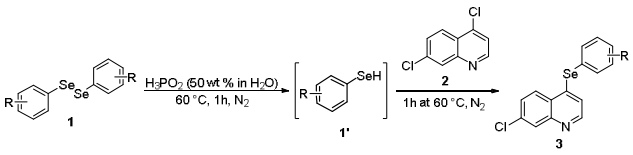
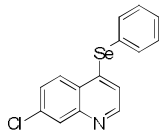
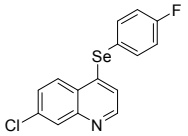
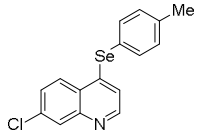
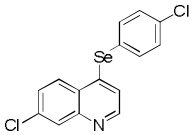
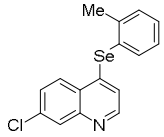
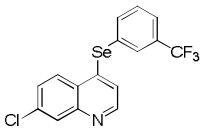
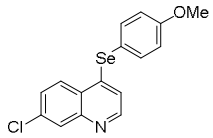
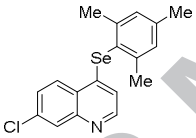
Table 1. Variability in the synthesis of 4-arylselanyl-7-chloroquinolines.[a]



Entry	Product (Yield)[b]	Entry	Product (Yield)[b]
1	 **3a** (97%)[c]	5	 **3e** (67%)
2	 **3b** (87%)	6	 **3f** (75%)
3	 **3c** (81%)	7	 **3g** (75%)
4	 **3d** (71%)	8	 **3h** (86%)

[a] Reactions are performed using diorganyl diselenide **1a-h** (0.25 mmol), 0.5 mL of H_3PO_2 (50 wt% in H_2O) at 60 °C under N_2 atmosphere for 1 hour. After the generation of the organylselenol, 4,7-dichloroquinoline **2a** (0.5 mmol) was added and the mixture was stirred at 60 °C for additional 1 hour. [b] Yields are given for isolated products. [c] One reaction was performed using diphenyl diselenide **1a** (5 mmol), 5 mL of H_3PO_2 (50 wt% in H_2O) and 2-chloropyridine **2a** (10 mmol) and the desired product **3a** was obtained in 87% yield.

Therefore, it can suggest that the fluorine in the chemical structure of quinoline derivative **3e** contributes to the inhibitory effect on cerebral AChE activity. In accordance, Liu and co-workers demonstrated that insertion of fluorine atom markedly influenced the activity and the selectivity of chalcone derivatives in inhibiting AChE.[13] Moreover, so far hundreds of fluorine-containing drugs had been applied in clinical practice, such as Fluoxetine (antidepressant), Ofloxacin (antibacterial), 5-Fluorouracil (anti-cancer agent), among others.

Table 2 - Effect of 4-arylselanyl-7-chloroquinolines **3a**, **3b**, **3c**, **3e** and **3g** on AChE activity in cerebral cortex of mice.

	4-arylselanyl-7-chloroquinolines				
	3a	**3b**	**3c**	**3e**	**3g**
Vehicle	9.6 ± 0.5	9.6 ± 0.5	9.6 ± 0.5	9.6 ± 0.5	9.6 ± 0.5
1 µM	10.2 ± 3.9	10.2 ± 0.9	8.5 ± 0.8	6.9 ± 1.6*	8.2 ± 1.7
10 µM	9.1 ± 1.2	9.4 ± 0.7	8.3 ± 2.6	6.0 ± 0.7*	8.4 ± 2.2
100 µM	7.6 ± 1.7	8.1 ± 1.6	8.5 ± 1.7	6.2 ± 1.9*	7.4 ± 1.7
200 µM	7.8 ± 1.5	8.7 ± 1.6	9.4 ± 1.9	6.1 ± 0.7*	9.0 ± 1.2

Data are reported as mean ± S.D. of 3 independent experiments. AChE activity was expressed as µmol acetylthiocholine/h/mg protein. * $p < 0.05$ as compared with the vehicle group (one-way ANOVA/Newman-Keuls).

Considering the results obtained *in vitro*, we extend our studies to investigate the effect of the best inhibitor on the three stages of memory, acquisition, consolidation and retrieval, in mice. Memory can be defined as the record of information representation acquired through experiences, and it is a process that has several stages.[14] Moreover, there are multiple mechanisms and neurotransmitters involved in the memory, but cholinergic system has a key function in this process.[11] Thus, based on *in vitro* results of quinoline derivatives on the AChE activity, compound **3e** was used to investigate its effect in improving memory in mice.

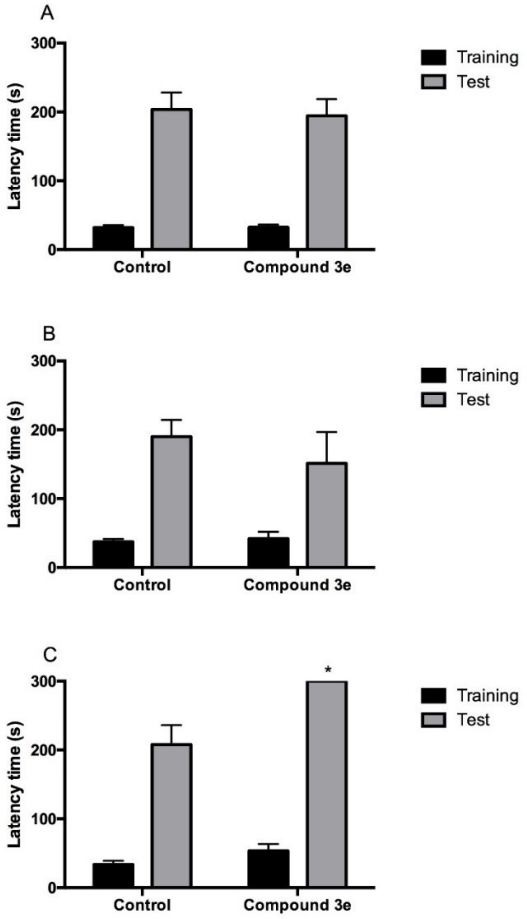


Figure 2. Effect of compound **3e** on the step-down inhibitory avoidance task in mice. Compound, at the dose of 10 mg/kg, was administered, intragastrically, 30 min before training session (acquisition) (A), immediately post-training (consolidation) (B) and 30 min before test (retrieval) (C). Each column represents mean ± S.E.M. for 7 to 8 animals per group. Data were analyzed using a non-paired t-test. (*) $p < 0.05$ when compared to the control group.

Figure 2 shows the effect of quinoline derivative **3e** on the step-down inhibitory avoidance task in mice. During the training session in the step-down inhibitory avoidance task, there was no difference in the step-through latency time among groups. Administration of compound **3e** 30 min before the training (acquisition) and immediately after the training session (consolidation) did not alter the step-through latency time in these stages of memory (Figures 2A and 2B, respectively).

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However, administration of the compound **3e** 30 min before the test session (retrieval) increased (around 44 %) the step-through latency in comparison to the control group (Figure 2C). Acquisition, consolidation and retrieval are stages of memory.[14] The present study established a cognitive enhancement in the memory phase of retrieval after administration of quinoline derivative **3e** in the step-down inhibitory avoidance task.

Administration of compound **3e** pre-training, immediately post-training and before test did not change the number of crossings and rearing in the open-field test in mice (data not shown). Therefore, compound **3e** did not cause impairment in the locomotor activity and exploratory behavior of mice assessed by the open-field test.

In summary, we have developed an alternative methodology for the synthesis of 4-aryl-7-chloroquinolines. This method involves the reaction of 4,7-dichloroquinoline with organylselenols, generated *in situ* by the reaction of diorganyl diselenides with aqueous H_3PO_2. Reactions are suitable to a range of diorganyl diselenides and proceeded efficiently at 60 °C under N_2 atmosphere. In addition, the synthesized compounds were screened for their *in vitro* AChE activity. Our results demonstrated that quinoline derivative **3e** inhibited AChE activity *in vitro*. Moreover, this quinoline derivative administrated in mice caused cognitive enhancement in the memory phase of retrieval in the step-down inhibitory avoidance task in mice. Given that quinoline derivative **3e** inhibited the AChE activity and improved cognitive enhancement, this compound is a potential therapeutic agent for the treatment of Alzheimer disease and other neurodegenerative disorders.

Acknowledgments

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- Arylselenation of quinolines using aqueous solution of hypophosphorous acid.
- Selenium-functionalized 7-chloroquinolines in good to excellent yields.
- Synthetized compounds are a potential therapeutic agents for the Alzheimer disease.

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