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Synthesis and antioxidant properties of novel quinoline–chalcogenium compounds

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ABSTRACT

Herein we describe our results on the synthesis and antioxidant properties of 4-arylchalcogenyl-7-chloroquinolines. This new class of compounds has been synthesized in high yields by the reaction of 4,7-dichloroquinoline with diaryl dichalcogenides using KOH as base, DMSO as solvent at 100 °C under air atmosphere and tolerates a range of substituents in the arylchalcogenyl moiety. The obtained compounds **3a** and **3j** were screened for in vitro antioxidant activity and the results demonstrated that compound **3j** presented a potent antioxidant effect when compared to compound **3a**.

Organochalcogen compounds, especially containing selenium and tellurium, are attractive molecules because of their applicability in organic reactions[1,2] and interesting biological activities.[3,4] Applications in chemistry and biochemistry are well described in various books and reviews.[1–4] Among these organochalcogen compounds, those containing nitrogen atoms are a special class of molecules and they have been employed in various organic transformations, for instance, in asymmetric synthesis.[2e–g] In the last few years, the growth of interest in organochalcogen chemistry can be attributed to its specific properties and pharmaceutical applications.[1–4] Consequently, the search for new and efficient methodologies for the synthesis of novel nitrogen-functionalized organochalcogen compounds remain widely explored.

In the context of nitrogen-functionalized compounds, quinolines[5] are an important class of heterocyclic compounds and their structural unit widely existing in alkaloids, therapeutic agents, and synthetic analogues with interesting biological activities.[6] A range of quinoline derivatives have been used as antiviral, anticancer, antibacterial, antifungal, antiobesity, and anti-inflammatory agents.[7] Especially, 7-chloroquinoline derivatives are biological active units and display a broad range of pharmacological activity, including antimalarial and antitubercular properties.[8] Because of its importance as a substructure in a wide variety of synthetic and natural products, considerable efforts have been directed to the development of new structures based on 7-chloroquinoline.

In this regard, there are a large number of methodologies in the literature for the synthesis of chalcogenium-containing quinolines, especially selenium derivatives.[9] This class of compounds has great importance since they combine the well known applicability of the quinoline unit[6–8] with that of the selenium moieties[3,4] and their functions range from antioxidant, antifungal, and antibacterial agents, to selective DNA binding and photocleaving agents.[9a–g]

However, to the best of our knowledge, the synthesis of 7-chloroquinolines having an arylchalcogen moiety at the position 4 of quinoline ring is not described. In this sense, and due to our interest correlated to the preparation of nitrogen-functionalized organochalcogen compounds,[10] we describe herein the synthesis of 4-arylchalcogenyl-7-chloroquinolines by the reaction of 4,7-dichloroquinoline with diaryl dichalcogenides using KOH as base and DMSO as solvent at 100 °C under air atmosphere (Fig. 1). Additionally, the obtained 4-phenylselanyl-7-chloroquinoline **3a** and 4-phenyltellanyl-7-chloroquinoline **3j** were screened for their in vitro antioxidant activity.

Initially, our studies were focused on the synthesis of 7-chloro-4-(phenylselanyl)quinoline **3a**, and for this proposal, some experiments were performed. Recently, the copper-catalyzed cross-coupling reactions of diaryl diselenides with aryl halides have become a versatile tool for the synthesis of substituted aryl selenides.[11] For this reason, we started studying the reaction of 4,7-dichloroquinoline **1** (0.3 mmol) and diphenyl diselenide **2a** (0.15 mmol) in the presence of CuO nanoparticles (CuO NPs) (3 mol %), using DMSO as solvent at 100 °C in the open atmosphere (Scheme 1, condition A). Under this condition,[11c] the formation of

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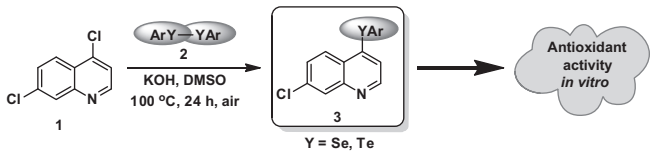
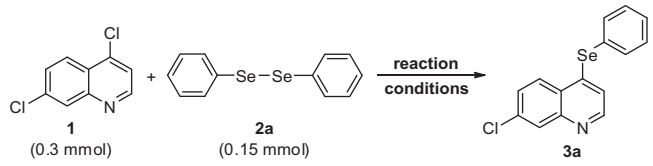


Figure 1. Synthesis of 4-arylchalcogenyl-7-chloroquinolines.



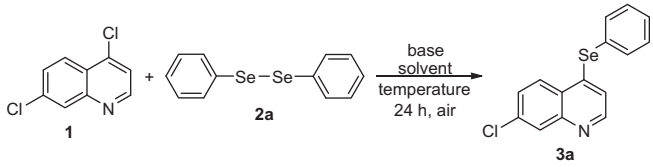
Condition A: CuONPs (3 mol%), DMSO, 24 h at 100 °C, air (no product)
Condition B: CuONPs (3 mol%), KOH (0.3 mmol), DMSO, 24 h at 100 °C, air (84%)

Scheme 1. Optimization of reaction conditions.

7-chloro-4-(phenylselanyl)quinoline **3a** was not observed and the starting materials were recovered. This reaction was also performed with the addition of KOH (0.3 mmol) as base and gratifyingly, the desired product **3a** was obtained in 84% after 24 h (Scheme 1, condition B).

To our delight, when we performed this reaction in the absence of copper catalyst, the desired product **3a** was obtained in similar yield after 24 h (Table 1, entry 1). This result was also observed in the reaction under nitrogen atmosphere (Table 1, entry 2). When the reaction of quinoline **1** and diselenide **2a** was performed using only DMSO as solvent and KOH as base at room temperature, only traces of product **3a** were detected (Table 1; entry 3). We observed that the nature of the base was critical for the success of the reaction. As shown in Table 1, reactions employing different bases, such as NaOH, Na_2CO_3, Cs_2CO_3, K_3PO_4, and Et_3N, gave a moderate

Table 1
Optimization of reaction conditions in the synthesis of 7-chloro-4-(phenylselanyl) quinoline **3a**[a]



Entry	Solvent	Base	Temperature (°C)	Isolated yield **3a** (%)
1	DMSO	KOH	100	89
2[b]	DMSO	KOH	100	89
3	DMSO	KOH	rt	traces
4	DMSO	NaOH	100	58
5	DMSO	Na_2CO_3	100	traces
6	DMSO	Cs_2CO_3	100	traces
7	DMSO	K_3PO_4	100	traces
8	DMSO	Et_3N	100	n.d.
9	DMSO	—	100	n.d.
10	toluene	KOH	100	n.d.
11	EtOH	KOH	reflux	n.d.
12	Glycerol	KOH	100	n.d.
13	DMF	KOH	100	n.d.
15[c]	DMSO	KOH	100	39
16[d]	DMSO	KOH	100	91

[a] Reactions are performed with 4,7-dichloroquinoline **1** (0.3 mmol), diphenyl diselenide **2a** (0.15 mmol), base (0.3 mmol), and at 100 °C under air atmosphere for 24 h.
[b] Reaction under nitrogen atmosphere.
[c] Reactions are performed with 0.15 mmol of KOH.
[d] Reactions are performed using 0.3 mmol of diphenyl diselenide **2a**.

or only a trace of product **3a** (Table 1, entries 4–8). Among the tested bases, the best result was obtained using KOH (0.3 mmol) which gave the product **3a** in good yield (Table 1, entry 1). Checking the Table 1, it is possible to verify that the reaction afforded the selenium–quinoline **3a** in high yield exclusively using DMSO as solvent. Using other solvents, such as, toluene, EtOH, glycerol, and DMF the formation of product **3a** was not detected (Table 1, entries 10–13). A great decrease in the yield of product **3a** was observed when the reaction was performed using 0.15 mmol of KOH (Table 1, entry 15). Finally, aiming to improve the yield of product **3a**, we used an excess of diphenyl diselenide **2a** (0.3 mmol) in the reaction, but no enhancement in the product yield was observed (Table 1; entry 16 vs 1). Analysis of the results showed in Table 1 indicated that the best reaction conditions[12] were the use of 4,7-dichloroquinoline **1** (0.3 mmol) and diphenyl diselenide **2a** (0.15 mmol), in the presence of KOH (0.3 mmol) using DMSO as solvent at 100 °C under air atmosphere for 24 h.

After that, the variability of our methodology reacting other diaryl diselenides **2b–i** with 4,7-dichloroquinoline **1** was evaluated (Table 2). The results showed in Table 2 reveal that the reaction worked well with a range of substituted diaryl diselenides, affording good yields of the products. The reactions are little sensitive to the electronic effect of the aromatic ring in diaryl diselenide. According to the results, diaryl diselenides containing electron-donating groups (OMe, Me) gave lower yields than the diaryl diselenides bearing electron-withdrawing groups (Cl, F, CF_3) (Table 2, entries 1–7). We observed that steric effects had no influence on the product formation and the reaction using dimesityl diselenide gave the desired product **3h** in 78% yield (Table 2; entry 8). When the reaction was performed with bis(2-thienyl) diselenide **2i**, the respective selenium–quinoline **3i** was obtained in 84% yield (Table 2; entry 9). In addition, under the optimized reaction conditions, the possibility of performing the reaction with diphenyl ditelluride was also investigated. Thus, 4,7-dichloroquinoline **1** was efficiently reacted with diphenyl ditelluride **2j**, affording the respective 7-chloro-4-(phenyltellanyl)quinoline **3j** in excellent yield (Table 2, entry 10).

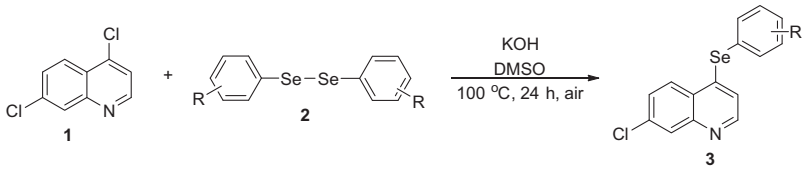
After these studies, we turned our attention to the antioxidant activity of compounds **3a** and **3j**. An antioxidant agent is defined as a molecule that protects a biological target against oxidative damage and it is this damage that causes many diseases. As a result, many diseases have been treated with antioxidants to prevent oxidative damage.[13] Synthetic radicals such as 2,2-azinobis-3-ethyl-benzothiazoline-6-sulfonic acid (ABTS) is often used to evaluate the ability of antioxidants to scavenge free radicals, which are known to be a major factor in the biological damage caused by oxidative stress.[14]

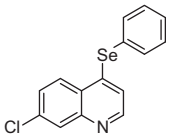
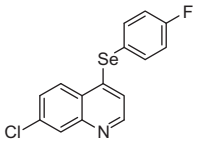
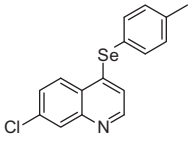
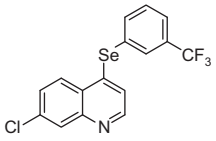
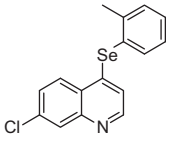
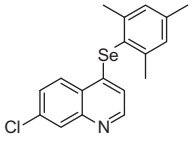
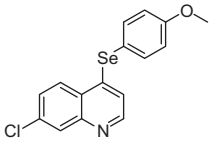
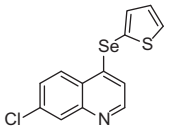
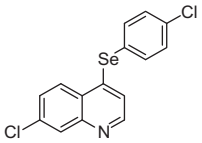
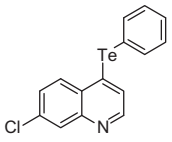
As shown in Table 3, compound **3j** in a concentration equal to or superior than 1 μM exhibited the antioxidant activity in the ABTS radical scavenging assay, whereas compound **3a** did not show the antioxidant effect in this test (data not shown). A potent radical scavenging antioxidant often acts as a potent reductant. The ferric ion reducing antioxidant power (FRAP) method is based on a redox reaction.[15] Thus the reducing capacity of a compound may serve as a significant indicator of its potential antioxidant activity (Table 4). In this assay, compound **3a** had an antioxidant potential at the starting concentration of 50 μM (Table 4), while **3j** did not show significant results in all concentrations tested.

As shown in Tables 3 and 4, compounds **3j** and **3a** were effective on linoleic acid peroxidation inhibition induced with Fe–Ascorbic acid, at a concentration equal or superior than 0.1 and 50 μM, respectively. In this assay, organotellurium compound **3j** was most effective than organoselenium compound **3a**, since in minor concentrations it presented antioxidant effect.

To determine the antioxidant effect of **3a** and **3j**, the sodium nitroprussate (SNP) assay was used as a classical inductor of lipid

Table 2
Variability in the synthesis of 4-arylchalcogenyl-7-chloroquinolines[a]



Entry	Product (Yield)	Entry	Product[b] (Yield)
1	 **3a** (89%)	6	 **3f** (89%)
2	 **3b** (81%)	7	 **3g** (87%)
3	 **3c** (79%)	8	 **3h** (78%)
4	 **3d** (78%)	9	 **3i** (84%)
5	 **3e** (88%)	10	 **3j** (90%)

[a] Reactions are performed with 4,7-dichloroquinoline **1** (0.3 mmol), diaryl dichalcogenide **2a–j** (0.15 mmol), and KOH (0.3 mmol) in DMSO (1 mL) at 100 °C under air atmosphere for 24 h.
[b] Yields are given for isolated products.

Table 3
Antioxidant activity of compound **3j** on ABTS, linoleic acid oxidation, and TBARS assays

(μM)	% Oxidation linoleic acid	% Scavenging ABTS	TBARS (% oxidation)		
			Hippocampus	Cortex	Cerebellum
0.1	53.65 ± 12.16***	1.72 ± 0.18	65.98 ± 10.91***	85.70 ± 2.95	81.55 ± 6.02
1	52.33 ± 7.89***	7.74 ± 0.18**	16.08 ± 2.69***	41.05 ± 14.36***	39.95 ± 16.73***
5	40.75 ± 6.89***	27.50 ± 4.72**	14.23 ± 5.1***	11.85 ± 1.38***	18.55 ± 2.17***
10	38.98 ± 4.95***	86.45 ± 1.2**	14.80 ± 1.23***	9.65 ± 1.95***	13.73 ± 2.51***
I_{max} (%)	61.02	86.45	85.2	90.35	86.27

Each value is expressed as mean ± standard error of the mean (S.E.M) ($n = 4$). (*) Denote $p < 0.05$; (**) $p < 0.01$; (***) $p < 0.001$ as compared to the respective control sample (one way ANOVA/Newman-Keuls). I_{max}: maximal inhibition (%). TBARS results are compared to the induced (SNP-100% of oxidation).

peroxidation.[16] The brain is susceptible to oxidative impairment, due to a high content of polyunsaturated fatty acids, abundance of redox-active transition metals. Moreover, some authors have shown that the cortex and the hippocampus are more susceptible to oxidative damage as compared to the cerebellum and thus have an increased risk of neurodegenerative disease.[17] Thus, based on the considerations above, we evaluated the effect of compounds **3a** and **3j** in the lipid peroxidation induced by SNP by the method of TBARS (substance reactive acid thiobarbituric-TBARS) in the cortex, the cerebellum and the hippocampus of mice (Table 3 and 5).

Table 4
Antioxidant activity of compound **3a** on FRAP and linoleic acid oxidation assays

(μM)	% Oxidation linoleic acid	(μM)	FRAP (abs)
50	77.71 ± 1.48***	10	0.089 ± 0.009
100	50.38 ± 4.97***	50	0.167 ± 0.027*
500	38.39 ± 3.48***	75	0.239 ± 0.029**
1000	32.48 ± 4.37***	100	0.305 ± 0.027**
I_{max} (%)	67.52		

Each value is expressed as mean ± S.E.M (n = 4). (*) Denote p <0.05; (**) p <0.01; (***) p <0.001 as compared to the respective control sample (one way ANOVA/Newman-Keuls). I_{max}: maximal inhibition (%). Abs = absorbance.

Table 5
Antioxidant activity of compound **3a** on TBARs induced by SNP in mice

TBARS (% oxidation)					
(μM)	Hippocampus	(μM)	Cortex	(μM)	Cerebellum
50	34.97 ± 19.16*	5	74.27 ± 1.57**	10	40.32 ± 6.9***
75	31.99 ± 15.12*	10	68.15 ± 3.69***	25	29.48 ± 9.49***
100	27.79 ± 13.07**	50	17.56 ± 3.00***	50	17.67 ± 1.46***
—	—	100	17.76 ± 5.75***	100	26.30 ± 12.75***
I_{max} (%)	72.21	I_{max} (%)	82.44	I_{max} (%)	82.33

Each value is expressed as mean ± S.E.M (n = 4). (*) Denote p <0.05; (**) p <0.01; (***) p <0.001 as compared to the induced (SNP-100% of oxidation) (one way ANOVA/Newman-Keuls). I_{max}: maximal inhibition (%).

As shown in Table 5, compound **3a** was effective in inhibiting the lipid peroxidation induced by SNP in the cortex, the cerebellum and the hippocampus of mice at a concentration equal to or higher than 5, 10, or 50 μM, respectively. The compound **3j** showed a significant inhibition of lipid peroxidation in the concentration equal or higher than 0.1 μM in the hippocampus, whereas in the cortex and the cerebellum starting from a concentration of 1 μM (Table 3). In fact, organotellurium compounds can protect against the pro-oxidant effects of peroxynitrite.[16]

Some studies have described that the toxicity of organoselenium and organotellurium compounds could be associated with the δ-aminolevulinate dehydratase (δ-ALA-D) inhibition. δ-ALA-D is a sulfhydryl containing enzyme which can be inhibited at different pro oxidant situations and this enzyme can be used as a marker of toxicity .[18–20] Thus, based on considerations above, we investigated whether compounds **3a** and **3j** can inhibit the δ-ALA activity. Our results showed that δ-ALA-D activity was not modified under the tested concentrations for organic compounds **3a** and **3j**.

In summary, we have demonstrated the efficient synthesis and antioxidant activity of a range of novel 4-arylchalcogenyl-7-chloroquinolines. This new class of compounds was synthesized in high yields by the reaction of 4,7-dichloroquinoline with diaryl dichalcogenides under simple reaction conditions and tolerates a range of substituents in the arylchalcogenyl moiety. The obtained results revealed that compounds **3a** and **3j** have antioxidant activity in vitro and the data demonstrated that **3j** exhibited a potent antioxidant effect when compared to **3a**. This protocol is an efficient method to produce new selenium–nitrogen compounds with antioxidant activity.

Acknowledgments

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12. *General procedure for the synthesis of 7-chloro-4-(arylselanyl)quinolines* ***3a–k:*** To a round-bottomed flask containing the appropriated diaryl dichalcogenide (0.15 mmol) and 4,7-dichloroquinoline (0.3 mmol), were added DMSO (1.0 mL) and KOH (0.3 mmol). The reaction mixture was allowed to stir at 100 °C for 24 h. After this time, the solution was cooled to room temperature, diluted with ethyl acetate (15 mL), and washed with water (3 × 15 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The obtained products were purified by flash chromatography on silica gel using a mixture of ethyl acetate/hexane (20:80) as the eluent. *Selected spectral and analytical data for: 7-chloro-4-(phenylselanyl)quinoline (**3a**):* Yield: 0.085 g (89%); pale yellow solid; mp 81–83 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.50 (d, J = 4.7 Hz, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.96 (d, J = 8.9 Hz, 1H), 7.63–7.61 (m, 2H), 7.49–7.37 (m, 4H), 6.97 (d, J = 4.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 150.38, 148.10, 145.86, 136.14, 135.56, 130.00, 129.36, 128.82, 127.50, 126.60, 126.23, 126.04, 121.93. MS (relative intensity) m/z: 321 (44), 320 (21), 319 (100), 317 (50), 284 (34), 282 (20), 241 (30), 239 (94), 204 (96), 162 (22), 142 (21), 135 (45), 127 (42), 99 (71), 77 (45), 75 (19), 51 (38). *7-Chloro-4-(phenyltellanyl)quinoline (**3j**):* Yield: 0.099 g (90%); pale yellow solid; mp 80–82 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.43 (d, J = 4.4 Hz, 1H), 8.05 (s, 1H), 7.85 (d, J = 7.6 Hz, 2H), 7.74 (d, J = 8.8 Hz, 1H), 7.50–7.43 (m, 2H), 7.35–7.31 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 150.27, 147.88, 140.50, 135.60, 132.94, 130.36, 130.19, 129.43, 129.39, 129.06, 128.66, 127.78, 111.81. MS (relative intensity) m/z: 371 (12), 369 (45), 367 (39), 365 (22), 241 (32), 239 (100), 204 (95), 162 (27), 135 (29), 127 (29), 99 (47), 77 (59), 51 (28).
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