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Article

7-Chloroquinoline-1,2,3-triazoyl Carboxylates: Organocatalytic Synthesis and Antioxidant Properties

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We describe herein our results on the synthesis and antioxidant properties of 7-chloroquinoline-1,2,3-triazoyl-4-carboxylates. This class of compounds have been synthesized in moderated to excellent yields by the reaction of 4-azido-7-chloroquinoline with a range of β-ketoesters in the presence of a catalytic amount of pyrrolidine (10 mol%). The synthesized compounds ethyl 1-(7-chloroquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate and ethyl 1-(7-chloroquinolin-4-yl)-5-phenyl-1*H*-1,2,3-triazole-4-carboxylate were screened for their *in vitro* antioxidant activity and the results demonstrated that the first compound reduces the lipid peroxidation levels induced by sodium nitroprusside in liver of mice, while the second compound shown nitric oxide scavenging activity. This is an efficient method to produce new heterocyclic compounds with potential antioxidant activities.

Keywords: quinolines, 1,2,3-triazoles, organocatalysis, cycloaddition, antioxidant

Introduction

Quinolines[1] are an important class of heterocyclic compounds and their structural unit is widespread in alkaloids, therapeutics and synthetic analogues with interesting biological activities.[2] A great range of quinoline derivatives have been used as antiviral, anticancer, antibacterial, antifungal, antiobesity and anti-inflammatory agents (Figure 1).[3] Specially, 7-chloroquinoline derivatives are biologically active entities and display a broad range of pharmacological activities, including antimalarial and antitubercular properties.[4] Because of its importance as a substructure in a wide variety of synthetic and natural products, considerable efforts have been directed to the design and the synthesis of new molecules based on 7-chloroquinoline.

On the other hand, 1,2,3-triazoles[5] are a class of nitrogen-heterocycles commonly used in the discovery and modulation of drug candidates[6] and several methodologies based on the 1,3-dipolar cycloaddition of azides with alkynes have been already reported to access this class of compounds.[7,8] In particular, the selective construction of both 1,2,3-triazole geometrical isomers has conventionally been accomplished through a metal-mediated catalysis, such as copper or ruthenium.[8] However, the use of metallic catalysts has restricted the application of such methodologies in chemical biology.[9] Aiming to overcome this drawback, organocatalytic approaches involving enamide-azide cycloaddition have been described.[10] For example, Ramachary *et al.*[11] described a practical and environmentally friendly amino acid catalyzed cascade process for the synthesis of highly substituted 1,2,3-triazoles through the cascade [3+2]-cycloaddition/hydrolysis of Hagemann's esters with *p*-toluenesulfonyl azide (TsN_3) using proline as a catalyst.

Therefore, it remains the necessity for studies on the combinations of different substrates and reaction conditions for the synthesis of highly functionalized and complex heterocyclic structures, such as quinolines and 1,2,3-triazole derivatives. The synthesis of molecules containing these two heterocyclic units has extensive importance since their combine the well-known biological activities of the quinoline[2-4] unit with those of 1,2,3-triazole moiety.[5,6]

In this context, Savini *et al.*[12] described the synthesis of bifunctional hybrids containing 1,2,3-triazoyl-carboxylates and 7-chloroquinoline by the cycloaddition reaction of azidoquinolines with activated methylene compounds.[12] The obtained molecules presented anti-inflammatory and analgesic activities; however, the respective compounds were synthesized using equivalent

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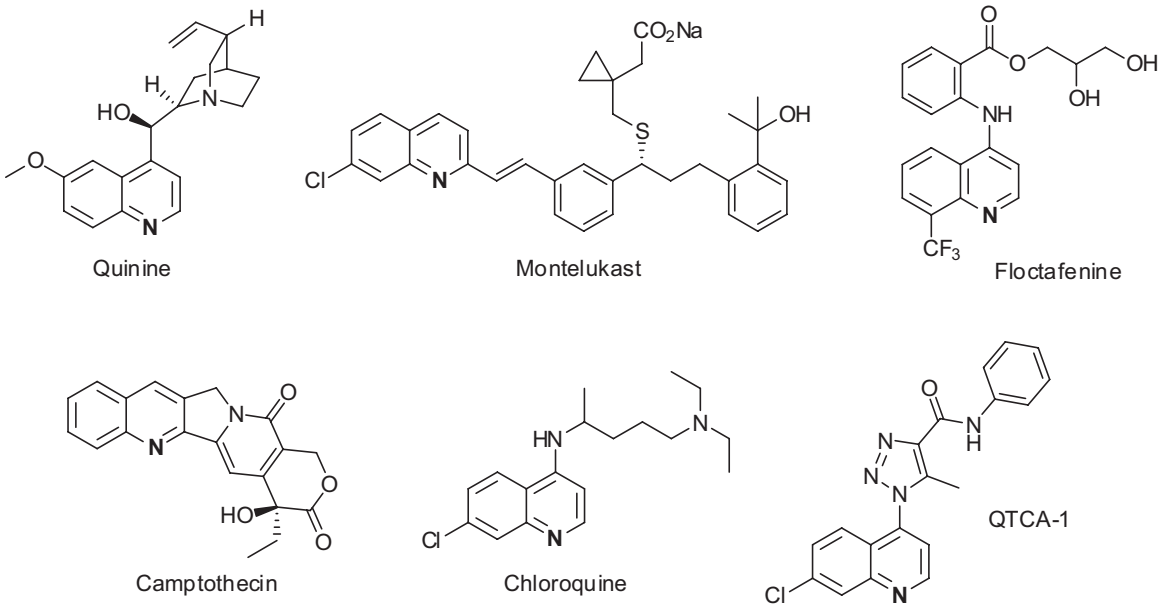


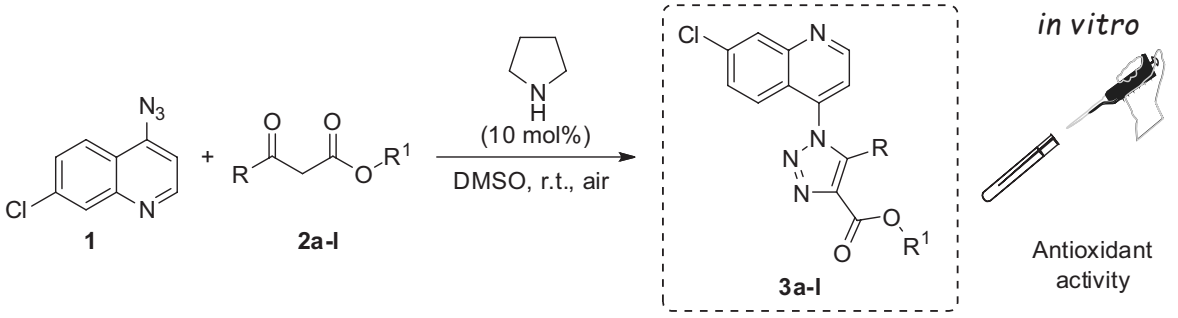
Figure 1. Biologically important quinolines.

amounts of a strong base (EtONa). Recently, Kumar and co-workers[13] described the synthesis, docking and *in vitro* antimalarial evaluation of bifunctional hybrids containing 1,2,3-triazoles and 7-chloroquinoline derivatives. More recently, our research group described the synthesis and pharmacological properties of 7-chloroquinoline-1,2,3-triazoyl carboxamides.[14] One of synthesized compounds (**QTCA-1**, Figure 1) was screened for anticonvulsant, antinociceptive and anti-inflammatory activities *in vivo* and it was effective in decreasing the appearance of seizures induced by pilocarpine and pentylenetetrazole. **QTCA-1** has an effect on the central pain modulation, presenting antinociceptive and anti-inflammatory properties to combat acute pain.[14]

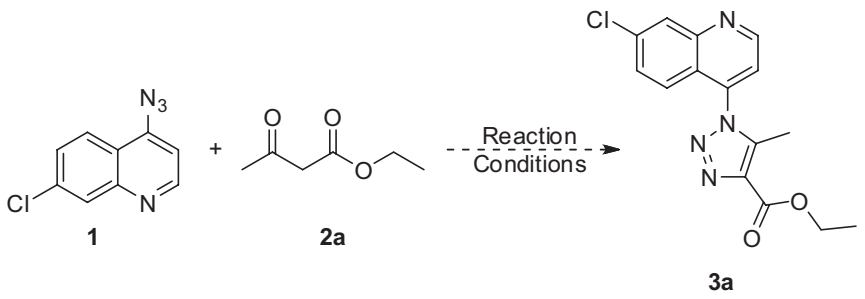
However, to the best of our knowledge, an organocatalytic approach to synthesize bifunctional hybrids containing 1,2,3-triazoyl-carboxylates and 7-chloroquinoline have not been explored. In this sense, and due to our interest correlated to the preparation of nitrogen-functionalized heterocycles,[14,15] we describe herein the efficient synthesis of 7-chloroquinoline-1,2,3-triazoyl carboxylates **3** by the reaction of 4-azido-7-chloroquinoline **1** with a range of β-keto-esters **2** in the presence of an organocatalyst (Scheme 1). Additionally, the obtained compounds **3a** and **3k**, derivative from commercial β-keto-esters **1a** (R = CH_3; R^1 = C_2H_5) and **1k** (R= C_6H_5; R^1 = C_2H_5), were screened for their *in vitro* antioxidant activity.

Results and Discussion

To found the more suitable reaction conditions for the synthesis of the desired 7-chloroquinoline-1,2,3-triazoyl carboxylates **3** in high yields, a set of experiments was performed using the 4-azido-7-chloroquinoline **1** and β-keto-ester **2a** as standard substrates (Scheme 2 and Table 1). We started the reaction conditions screening by reacting 4-azido-7-chloroquinoline **1** (0.3 mmol) with ethyl acetoacetate **2a** (0.3 mmol) in DMSO (0.3 mL) in the presence of 10 mol% of Et_2NH as the organocatalyst at 70 °C (Table 1, entry 1).



Scheme 1. General scheme of the reaction.



Scheme 2.

Table 1. Optimization of the reaction conditions[a]

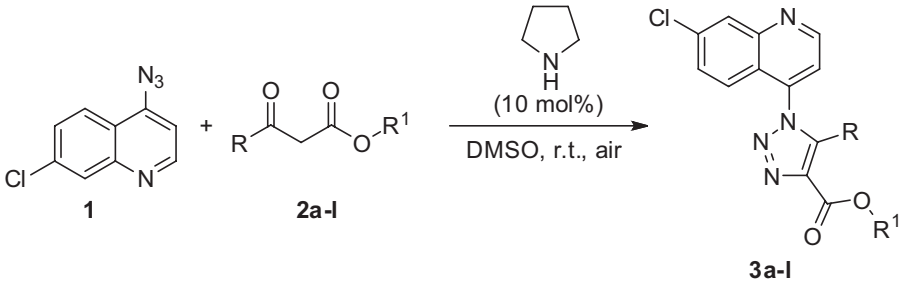
entry	Catalyst / mol%	Temperature / °C	Isolated yield of **3a**[b] / %
1	Et_2NH (10)	70	78
2	L-proline (10)	70	57
3	pyrrolidine (10)	70	93
4	piperidine (10)	70	57
5	Et_3N (10)	70	68
6[c]	–	70	18
7[d]	pyrrolidine (10)	70	89
8	pyrrolidine (10)	50	89
9	pyrrolidine (10)	r.t.	90
10	pyrrolidine (5)	r.t.	75
11[c]	pyrrolidine (1)	r.t.	35
12[e]	pyrrolidine (10)	r.t.	80
13[f]	pyrrolidine (10)	r.t.	57
14[g]	pyrrolidine (10)	r.t.	traces

[a]The reactions were performed using 4-azido-7-chloroquinoline **1** (0.3 mmol) and ethyl acetoacetate **2a** (0.3 mmol), using DMSO as solvent (0.3 mL) under air atmosphere for 24 h; [b]yields are given for isolated products; [c]the reactions were performed in 48 h; [d]the reaction was performed using 0.6 mL of DMSO; [e]the reaction was performed in PEG-400 (0.3 mL); [e]the reaction was performed in EtOH (0.3 mL); [e]the reaction was performed in glycerol (0.3 mL); r.t: room temperature.

Under this reaction conditions, the desired product **3a** was obtained in 78% yield after 24 h. Using the same conditions, however changing the organocatalyst to L-proline (10 mol%), a decrease in the yield of product **3a** was observed (Table 1, entry 2). To our satisfaction, a great increment in the chemical yield of **3a** was achieved changing the organocatalyst to pyrrolidine (10 mol%), with the product being isolated in 93% yield after 24 h at 70 °C.

When piperidine and Et_3N were used as organocatalysts, lower yields of product **3a** were obtained (Table 1, entries 4 and 5). In the absence of an organocatalyst, **3a** was isolated in only 18% yield, even after 48 h at 70 °C (Table 1, entry 6). Motivated by the result using pyrrolidine as organocatalyst, additional experiments were performed. Thus, the reaction using 10 mol% of pyrrolidine carried out at a diluted, 0.5 mol L^{-1} concentration (0.6 mL of DMSO was used) at 70 °C gave **3a** in 89% yield (Table 1, entry 7). When the concentrated (1.0 mol L^{-1}) reactions were conduced at 50 °C or at room temperature instead 70 °C, product **3a** was obtained in good yields (Table 1, entries 8-9). By decreasing the organocatalyst loading from 10 to 5 and 1 mol% in reactions using 0.3 mL of DMSO and at room temperature, caused a great decrease in the yields of **3a** (Table 1, entries 10 and 11). Reactions performed in PEG-400 and EtOH furnished 80 and 57% yield, respectively (Table 1, entries 12 and 13). When the reaction was carried out using glycerol, a range of by-products was observed and only traces of desired product were formed (Table 1, entry 14).

From the results shown in Table 1, it can be inferred that the best reaction conditions to obtain 7-chloroquinoline-1,2,3-triazoyl carboxylate **3a** is the stirring of a solution of 4-azido-7-chloroquinoline **1** (0.3 mmol), ethyl acetoacetate **2a** (0.3 mmol) and pyrrolidine (10 mol%) as organocatalyst in DMSO (0.3 mL) at room temperature under air atmosphere for 24 h (Table 1, entry 9). After that, we focused our efforts in expanding the scope of this methodology by reacting 4-azido-7-chloroquinoline **1** with a range of β-keto-esters **2** under the optimized reaction conditions (Scheme 3 and Table 2).



Scheme 3.

Table 2. Variability in the synthesis of 7-chloroquinoline-1,2,3-triazoyl-4-carboxilates **3**[a]

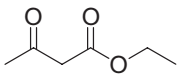
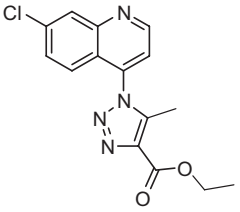
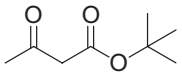
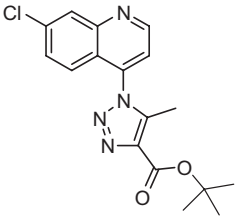
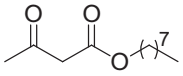
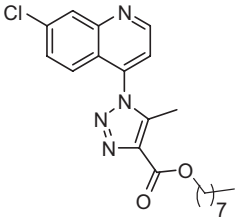
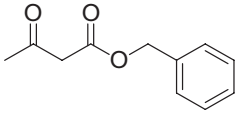
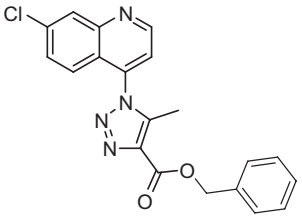
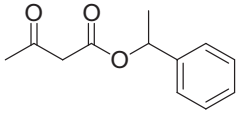
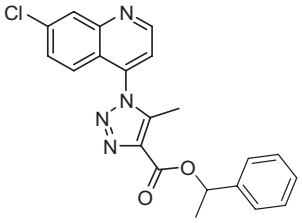
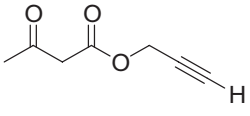
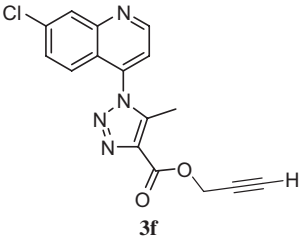
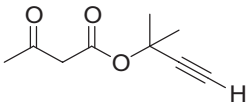
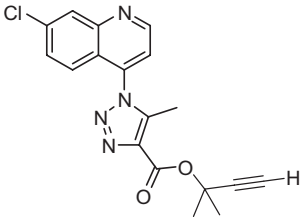
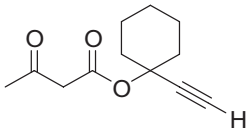
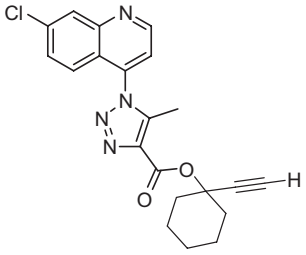
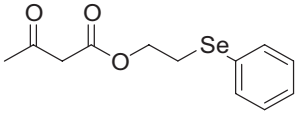
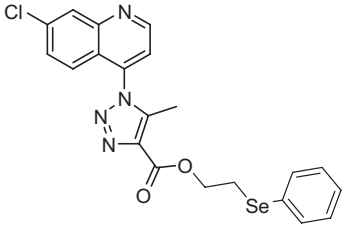
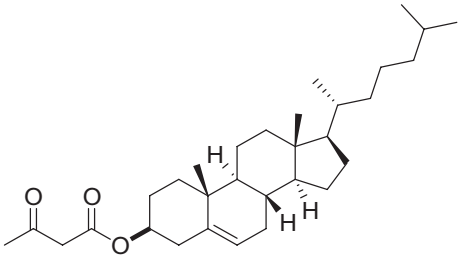
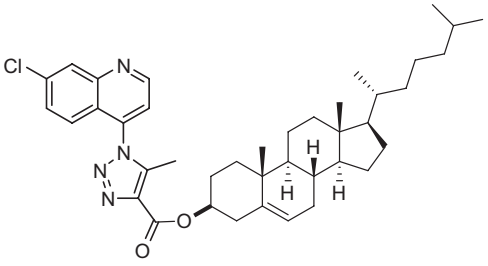
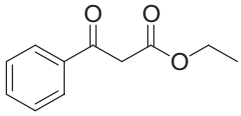
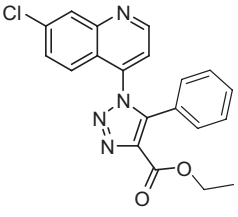
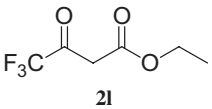
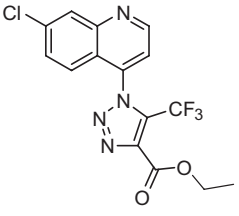
entry	β-Keto-ester	Product	Yield[b] / %
1	 **2a**	 **3a**	90
2	 **2b**	 **3b**	98
3	 **2c**	 **3c**	98
4	 **2d**	 **3d**	97
5	 **2e**	 **3e**	96
6	 **2f**	 **3f**	73

Table 2. Variability in the synthesis of 7-chloroquinoline-1,2,3-triazoyl-4-carboxilates **3**[a] (cont.)

entry	β-Keto-ester	Product	Yield[b] / %
7	 **2g**	 **3g**	97
8	 **2h**	 **3h**	41
9	 **2i**	 **3i**	63
10	 **2j**	 **3j**	48
11	 **2k**	 **3k**	85[c]
12	 **2l**	 **3l**	traces[d]

[a]Reactions were performed using 4-azido-7-chloroquinoline **1** (0.3 mmol), β-keto-esters **2a-l** (0.3 mmol) and pyrrolidine (10 mol%) in DMSO (0.3 mL) as solvent at room temperature for 24 hours under air atmosphere; [b]yields are given for isolated products; [c]obtained as a 10:1 mixture of regioisomers; [d]reactions were performed in 48 h.

The results depicted in Table 2 disclose that our protocol works well for a range of substituted β-keto-esters, affording high yields of the respective products **3**. For example, β-keto-esters **2b-c**, containing alkyl (*t*-Bu and Oct); **2d** containing benzyl and **2e**, containing phenethyl groups, afforded the expected products in excellent yields (Table 2, entries 2-5). Similarly, the reactions using alkynol derivatives **2f-h** yielded the corresponding quinoline-triazoyl carboxylates **3f-h** in high yields (Table 2, entries 6-8). Besides, 2-(phenylselanyl) ethyl 3-oxobutanoate **2i** reacted smoothly with 4-azido-7-chloroquinoline **1**, yielding the corresponding product **3i** in 63% yield (Table 2, entry 9). Additionally, β-keto-ester derived from cholesterol **2j** was efficiently reacted with 4-azido-7-chloroquinoline **1** affording satisfactory yield of product **3j** (Table 2, entry 10). Finally, when the reaction was performed using ethyl benzoylacetate **2k**, the corresponding product **3k** was obtained in 85% in a 10:1 mixture of regioisomers (Table 2, entry 11). Unfortunately, the reaction using ethyl 4,4,4-trifluoroacetoacetate **2l** gave only trace amounts of the desired product **3l**, even after 48 h (Table 2, entry 12). All the synthesized 7-chloroquinoline-1,2,3-triazoyl carboxylates (**3a-k**) were characterized by analysis of their mass, ^{1}H and ^{13}C NMR spectra and the spectral data support and confirm the formation of the target compounds.

The excessive production of reactive species by cellular respiration and other metabolic activities can cause damage to all cellular structures.[16] Oxidative stress is critical to the etiology of many chronic and degenerative diseases such as cancer, cardiovascular diseases, diabetes and obesity,[17] and the synthesis of compounds with antioxidant potential was increased in recent years.[18] Considering the necessity of discovery of new therapies to prevent or combat the damages caused by the oxidative stress and the pronounced biological activities, including antioxidant properties of quinoline derivatives, the synthesis of this class of compounds with antioxidant potential has received attention from researchers worldwide.[19] In this sense, after the synthesis and characterization of the 7-chloroquinoline-1,2,3-triazoyl-4-carboxilates **3**, we turned our attention to evaluate the antioxidant activity of compounds **3a** and **3k** using different *in vitro* assays, since that these compounds were synthesized in high yields and derived from commercial β-keto-esters **2a** and **2k**.

The thiobarbituric acid reactive species (TBARS) assay is often used to evaluate the ability of antioxidants in reducing the lipid peroxidation levels.[20] Compound **3a** reduced the lipid peroxidation levels in 24 and 41%, at the concentrations of 100 μmol L^{-1} and 500 μmol L^{-1}, respectively (Figure 2b). On the other hand, as demonstrated in Figure 2a, compound **3k** did not protect against lipid peroxidation induced by sodium nitroprusside (SNP).

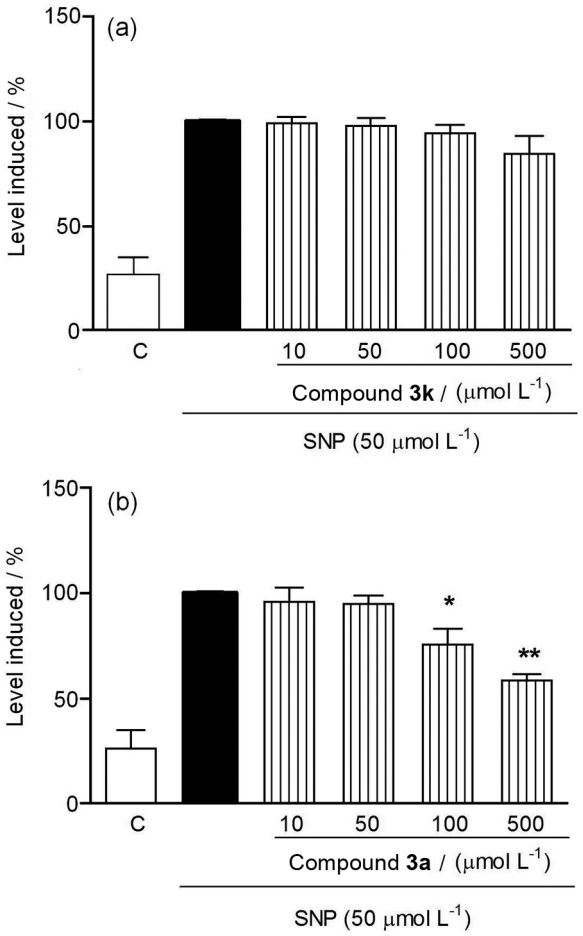


Figure 2. Effect of compounds **3a** and **3k** on lipid peroxidation levels induced by sodium nitroprusside (SNP) in rat liver. Data are reported as the mean (s) ± standard error of the mean (S.E.M.) of 3-4 independent experiments performed in duplicate and expressed as percentage (%) of induced. (*) denotes $p < 0.05$ and (**) denotes $p < 0.01$ as compared to induced (sample with inductor of oxidative damage - SNP) (One-way ANOVA / Newman-Keuls).

In this way, our results suggest a pharmacological potential of this class of compounds since the compound **3a** protects against the lipid peroxidation in TBARS assay. The lack of effect of the compound **3k**, however, does not rule out the possibility of it be exerting antioxidant action by other mechanisms. Thus, other assays were performed to verify if **3k** could act as an antioxidant *in vitro*.

It is important highlight that studies have demonstrated that products of lipid peroxidation contribute to the mutagenic and carcinogenic effects.[21] In fact, Shoeb *et al.*[22] reported that the formation of 4-hydroxy-2-nonenal protein adducts in renal and colon cancer tissues has been related to the growth and progression of kidney and colon cancers. Thus, strategies focusing on manipulating the reactive species generation, lipid peroxidation and production of

lipid electrophiles may be a viable approach for cancer prevention and treatment.

Free-radical scavenging is one of the known mechanisms by which several compounds act as an antioxidant. Thus, to extend the knowledge of the antioxidant potential of compounds **3a** and **3k**, their nitric oxide (NO),[23] 2,2-diphenyl-1-picrylhydrazyl (DPPH)[24] and 2,2-azinobis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS)[25] radicals scavenging abilities were evaluated.

As a result, the compound **3k**, at concentrations equal to or higher than 50 μmol L^{-1}, reduced the production of nitrite up to 41%, indicating its potential as a NO-scavenging agent. In contrast, analog compound **3a** did not present this effect (Figures 3a and 3b). NO has been associated with a variety of pathological process including neurodegenerative, inflammatory and cardiovascular diseases.[26] In this sense, the reduction of NO production has the potential to be beneficial as an approach to develop new therapies for these diseases.

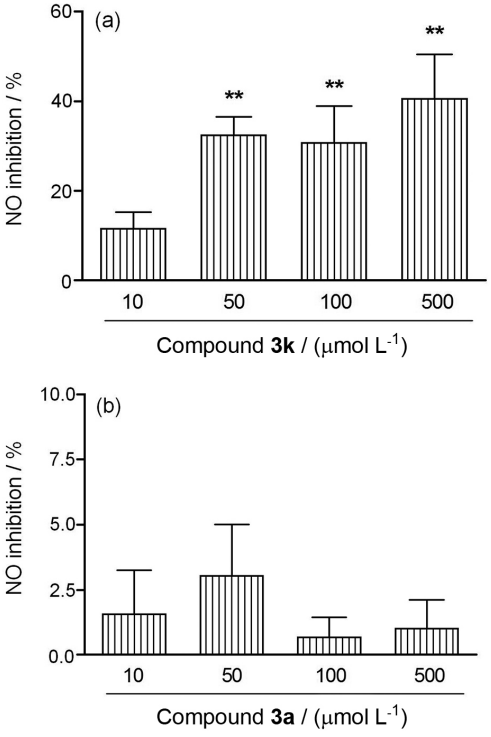


Figure 3. Effect of compounds **3a** and **3k** on nitric oxide (NO) radical scavenging assay. Data are reported as the mean (s) ± standard error of the mean (S.E.M.) of 3-4 independent experiments performed in duplicate and expressed as percentage (%) of inhibition. (**) denotes $p < 0.01$ as compared to induced (sample only with inductor of oxidative damage - SNP) (One-way ANOVA / Newman-Keuls).

The determination of DPPH and ABTS radicals scavenging activities are among the most common spectrophotometric methods used for the evaluation of *in vitro* antioxidant capacity.[27] As showed in Figures 4a and 4b, the compounds **3a** and **3k** did not present scavenger activity of these radicals, suggesting that the mechanism by which compounds **3a** and **3k** display antioxidant action cannot be evaluated by theses assays.

It is well established that the antioxidant activity could be correlated with the reducing power.[28] In this way, the ferric reducing antioxidant power (FRAP)[29] assay was used to determine the reducing power of the compounds **3a** and **3k**. As can be seen in Figure 4c, our results revealed that they have no reducing power at the tested concentrations.

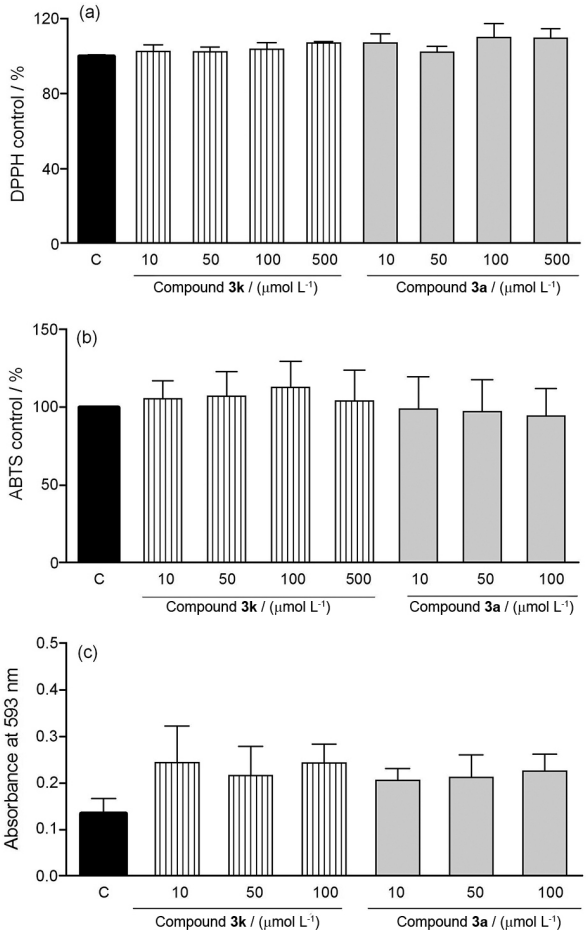


Figure 4. Effect of compounds **3a** and **3k** on (a) 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging; (b) 2,2-azinobis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radical scavenging and (c) ferric reducing antioxidant power (FRAP) assays. Data are reported as the mean (s) ± standard error of the mean (S.E.M.) of 3-4 independent experiments performed in duplicate and expressed as % of control (DPPH and ABTS) and absorbance at 593 nm (FRAP) (One-way ANOVA / Newman-Keuls).

Conclusions

In summary, we describe herein our results on the organocatalytic approach to synthesize bifunctional hybrids containing 1,2,3-triazoyl-carboxylates and 7-chloroquinoline units. This class of compounds was synthesized in moderated

to excellent yields by an enamide-azide cycloaddition reaction of 4-azido-7-chloroquinoline with a range of β-keto-esters in the presence of a catalytic amount of pyrrolidine (10 mol%). The preliminary biological assays shown that this class of compounds has the potential to act against the oxidative stress and our results corroborate with other studies in literature that revealed the antioxidant potential of other quinoline derivatives. Additional toxicological and pharmacological evaluations of these compounds are under studies in our laboratories.

Experimental

General remarks

Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 300 MHz on a Varian Inova 300 NMR spectrometer. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, with tetramethylsilane (TMS) used as the external reference. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (*J*) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 75.5 MHz on a Varian Inova 300 NMR spectrometer. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm in reference to the solvent peak of $CDCl_3$. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), qua (quartet), qui (quintet), dd (double doublet) and m (multiplet). Mass spectra (MS) were measured on a Shimadzu GCMS-QP2010 mass spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker Micro TOF-QII spectrometer 10416. Column chromatography was performed using a Merck silica gel (230-400 mesh). Thin layer chromatography (TLC) was performed using a 0.25 mm thick Merck silica sel GF_{254}. For visualization, TLC plates were either placed under ultraviolet light or stained with iodine vapor or acidic vanillin.

General procedure for the synthesis of 7-chloroquinoline-1,2,3-triazoyl carboxylates

To a solution of 4-azido-7-chloroquinoline **1** (0.3 mmol, 0.061 g) in DMSO (0.3 mL), was firstly added the β-ketoesters **2a-k** (0.3 mmol) and then the catalyst pyrrolidine (0.03 mmol. 0.021 g). The reaction mixture was stirred in an open vial at room temperature for 24 hours. After completion of the reaction, the crude product was purified by column chromatography on silica gel using a mixture of hexanes/ethyl acetate (5:1) as the eluent to afford the desired products **3a-k**.

Ethyl 1-(7-chloroquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (**3a**)

Yield: 0.085 g (90%); white solid; mp 128-130 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.15 (d, 1H, *J* 4.5 Hz, HetAr-H), 8.27 (d, 1H, *J* 1.9 Hz, HetAr-H), 7.60 (dd, 1H, *J* 9.0 and 1.9 Hz, HetAr-H), 7.48 (d, 1H, *J* 4.5 Hz, HetAr-H), 7.34 (d, 1H, *J* 9.0 Hz, HetAr-H), 4.50 (qua, 2H, *J* 7.1 Hz, OCH_2), 2.49 (s, 3H, CH_3), 1.47 (t, 3H, *J* 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.10, 151.28, 149.88, 140.20, 139.34, 137.00, 136.76, 129.67, 128.93, 123.58, 122.09, 118.75, 61.15, 14.18, 9.44; MS *m/z* (relative intensity): 316 (7), 259 (15), 243 (17), 231 (19), 217 (45), 215 (100), 214 (22), 205 (16), 203 (19), 189 (28), 181 (27), 179 (27), 164 (26), 162 (80), 137 (15), 135 (44), 127 (44), 126 (27), 100 (20), 99 (65), 83 (30), 75 (15), 74 (14), 43 (25); HRMS calcd. for $C_{15}H_{14}ClN_4O_2$ $[M + H]^+$: 317.0805; found: 317.0788.

tert-Butyl 1-(7-chloroquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (**3b**)

Yield: 0.101 g (98%); white solid; mp 133-135 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.15 (d, 1H, *J* 4.5 Hz, HetAr-H), 8.26 (d, 1H, *J* 1.8 Hz, HetAr-H), 7.58 (dd, 1H, *J* 9.0 and 1.8 Hz, HetAr-H), 7.47 (d, 1H, *J* 4.5 Hz, HetAr-H), 7.34 (d, 1H, *J* 9.0 Hz, HetAr-H), 2.47 (s, 3H, CH_3), 1.68 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.33, 151.30, 149.78, 139.61, 139.38, 137.80, 136.92, 129.61, 128.85, 123.67, 122.12, 118.77, 82.44, 28.13, 9.60; MS *m/z* (relative intensity): 344 (1), 215 (18), 163 (14), 57 (100), 41 (21); HRMS calcd. for $C_{17}H_{18}ClN_4O_2$ $[M + H]^+$: 345.1118; found: 345.1095.

Octyl 1-(7-chloroquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (**3c**)

Yield: 0.118 g (98%); yellow solid; mp: 70-72 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.15 (d, 1H, *J* 4.5 Hz, HetAr-H), 8.27 (d, 1H, *J* 2.0 Hz, HetAr-H), 7.58 (dd, 1H, *J* 9.0 and 2.0 Hz, HetAr-H), 7.48 (d, 1H, *J* 4.5 Hz, HetAr-H), 7.34 (d, 1H, *J* 9.0 Hz, HetAr-H), 4.43 (t, 2H, *J* 7.0 Hz, OCH_2), 2.49 (s, 3H, CH_3), 1.85 (qui, 2H, *J* 7.0 Hz, CH_2), 1.50-1.29 (m, 10H, $5CH_2$), 0.88 (t, 3H, *J* 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.22, 151.30, 149.84, 140.16, 139.31, 137.00, 136.78, 129.69, 128.93, 123.61, 122.07, 118.76, 65.35, 31.60, 29.06, 29.00, 28.55, 25.80, 22.46, 13.93, 9.53; MS *m/z* (relative intensity): 400 (2), 260 (25), 243 (21), 218 (23), 217 (30), 216 (64), 215 (37), 214 (20), 189 (23), 162 (30), 71 (26), 57 (62), 55 (23), 43 (100), 41 (46); HRMS calcd. for $C_{21}H_{26}ClN_4O_2$ $[M + H]^+$: 401.1744; found: 401.1687.

Benzyl 1-(7-chloroquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (**3d**)

Yield: 0.110 g (97%); yellow viscous liquid; ^{1}H NMR

($CDCl_3$, 300 MHz) δ 9.13 (d, 1H, *J* 4.5 Hz, HetAr-H), 8.25 (d, 1H, *J* 2.0 Hz, HetAr-H), 7.56 (dd, 1H, *J* 9.0 and 2.0 Hz, HetAr-H), 7.51 (dd, 2H, *J* 8.0 and 1.2 Hz, 2Ph-H), 7.46 (d, 1H, *J* 4.5 Hz, HetAr-H), 7.42-7.30 (m, 4H, 3Ph-H and HetAr-H), 5.46 (s, 2H, CH_2Ph), 2.46 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.82, 151.24, 149.70, 140.42, 139.13, 136.89, 136.39, 135.21, 129.61, 128.80, 128.39, 128.31, 128.24, 123.51, 121.93, 118.71, 66.67, 9.48; MS *m/z* (relative intensity): 377 (0.72), 202 (7), 162 (8), 91 (100), 92 (8), 65 (8); HRMS calcd. for $C_{20}H_{16}ClN_4O_2$ $[M + H]^+$: 379.0962; found: 379.0961.

1-Phenylethyl 1-(7-chloroquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (**3e**)

Yield: 0.113 g (96%); yellow solid; mp: 63-65 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.13 (d, 1H, *J* 4.5 Hz, HetAr-H), 8.26 (d, 1H, *J* 2.0 Hz, HetAr-H), 7.58-7.51 (m, 3H, 2HetAr-H and Ph-H), 7.43-7.29 (m, 5H, 4Ph-H and HetAr-H), 6.23 (qua, 1H, *J* 6.6 Hz, OCH), 2.45 (s, 3H, CH_3), 1.76 (d, 3H, *J* 6.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.52, 151.31, 149.85, 141.07, 140.40, 139.31, 137.06, 136.77, 129.74, 128.95, 128.50, 128.01, 126.15, 123.63, 122.09, 118.77, 73.47, 22.29, 9.60; MS *m/z* (relative intensity): 392 (0.53), 272 (10), 203 (11), 106 (9), 105 (100), 79 (9), 77 (8); HRMS calcd. for $C_{21}H_{18}ClN_4O_2$ $[M + H]^+$: 393.1118; found: 393.1139.

Prop-2-yn-1-yl 1-(7-chloroquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (**3f**)

Yield: 0.072 g (73%); white solid; mp: 97-99 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.16 (d, 1H, *J* 4.5 Hz, HetAr-H), 8.27 (d, 1H, *J* 2.0 Hz, HetAr-H), 7.60 (dd, 1H, *J* 9.0 and 2.0 Hz, HetAr-H), 7.50 (d, 1H, *J* 4.5 Hz, HetAr-H), 7.33 (d, 1H, *J* 9.0 Hz, HetAr-H), 5.03 (d, 2H, *J* 2.4 Hz, OCH_2), 2.60 (t, 1H, *J* 2.4 Hz, CH), 2.52 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.27, 151.33, 149.83, 140.91, 139.13, 137.06, 135.92, 129.78, 128.96, 123.52, 121.98, 118.79, 77.04, 75.49, 52.47, 9.58; MS *m/z* (relative intensity): 327 (7), 325 (23), 296 (21), 252 (21), 216 (38), 214 (93), 164 (33), 162 (100), 135 (51), 127 (43), 99 (59), 83 (33), 43 (36); HRMS calcd. for $C_{16}H_{12}ClN_4O_2$ $[M + H]^+$: 327.0649; found: 327.0625.

2-Methylbut-3-yn-2-yl 1-(7-chloroquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (**3g**)

Yield: 0.103 g (97%); white solid; mp: 61-63 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.16 (d, 1H, *J* 4.5 Hz, HetAr-H), 8.26 (d, 1H, *J* 2.0 Hz, HetAr-H), 7.58 (dd, 1H, *J* 9.0 and 2.0 Hz, HetAr-H), 7.48 (d, 1H, *J* 4.5 Hz, HetAr-H), 7.33 (d, 1H, *J* 9.0 Hz, HetAr-H), 2.70 (s, 1H, CH), 2.51 (s, 3H, CH_3), 1.91 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.52, 151.31, 149.78, 140.51, 139.24, 136.97, 136.81, 129.68, 128.88, 123.57, 122.03, 118.75, 84.07, 73.15, 28.97, 9.57; MS *m/z* (relative intensity): 354 (4), 216 (17), 215 (26), 205 (14), 203 (35), 163 (12), 162 (34), 135 (14), 127 (13), 99 (20), 83 (11), 67 (100), 65 (21), 57 (14), 43 (19), 41 (44); HRMS calcd. for $C_{18}H_{16}ClN_4O_2$ $[M + H]^+$: 355.0962; found: 364.0972.

1-Ethynylcyclohexyl 1-(7-chloroquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (**3h**)

Yield: 0.050 g (41%); white solid; mp: 68-70 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.15 (d, 1H, *J* 4.5 Hz, HetAr-H), 8.27 (d, 1H, *J* 2.0 Hz, HetAr-H), 7.58 (dd, 1H, *J* 9.0 and 2.0 Hz, HetAr-H), 7.45 (d, 1H, *J* 4.5 Hz, HetAr-H), 7.33 (d, 1H, *J* 9.0 Hz, HetAr-H), 2.75 (s, 1H, CH), 2.49 (s, 3H, CH_3), 2.40-2.33 (m, 2H, CH_2), 2.15-2.06 (m, 2H, CH_2), 1.84-1.70 (m, 6H, $3CH_2$), 1.64-1.56 (m, 1H, CH_2), 1.48-1.36 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.51, 151.34, 149.91, 140.53, 139.40, 137.12, 137.03, 129.78, 129.00, 123.69, 122.16, 118.78, 83.08, 76.96, 75.16, 37.06, 24.98, 22.51, 9.68; MS *m/z* (relative intensity): 394 (0.15), 203 (10), 105 (100), 97 (11), 95 (12), 83 (15), 81 (35), 77 (11), 71 (14), 69 (58), 57 (29), 55 (24), 43 (24), 41 (23); HRMS calcd. for $C_{21}H_{20}ClN_4O_2$ $[M + H]^+$: 395.1275; found: 395.1252.

2-(Phenylselanyl)ethyl 1-(7-chloroquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (**3i**)

Yield: 0.089 g (63%); yellow solid; mp: 139-141 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.15 (d, 1H, *J* 4.5 Hz, HetAr-H), 8.28 (d, 1H, *J* 1.9 Hz, HetAr-H), 7.60-7.56 (m, 3H, 2Ph-H and HetAr-H), 7.41 (d, 1H, *J* 4.5 Hz, HetAr-H), 7.32-7.26 (m, 4H, 3Ph-H and HetAr-H), 4.64 (t, 2H, *J* 7.4 Hz, OCH_2), 3.29 (t, 2H, *J* 7.4 Hz, $SeCH_2$), 2.45 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.95, 151.37, 150.10, 140.58, 139.46, 137.31, 136.61, 133.06, 129.93, 129.95, 129.19, 128.83, 127.42, 123.66, 122.22, 118.80, 64.41, 25.17, 9.65; MS *m/z* (relative intensity): 472 (0.03), 216 (15), 215 (17), 184 (9), 181 (8), 157 (28), 155 (16), 154 (10), 135 (5), 127 (5), 99 (8), 78 (13), 77 (28), 75 (5), 74 (7), 65 (4), 51 (14), 44 (21), 40 (100); HRMS calcd. for $C_{21}H_{18}ClN_4O_2Se$ $[M + H]^+$: 473.0284; found: 473.0279.

(3*S*, 8*S*, 9*S*, 10*R*, 13*R*, 14*S*, 17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl 1-(7-chloroquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (**3j**)

Yield: 0.094 g (48%); white solid; mp: 199-201 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.14 (d, 1H, *J* 4.5 Hz,

HetAr-H), 8.27 (d, 1H, *J* 2 Hz, HetAr-H), 7.58 (dd, 1H, *J* 8.9 and 2.0 Hz, HetAr-H), 7.46 (d, 1H, *J* 4.5 Hz, HetAr-H), 7.33 (d, 1H, *J* 8.9 Hz, HetAr-H), 5.45 (d, 1H, *J* 4.9 Hz, CH), 5.03-4.94 (m, 1H, OCH), 2.65-2.49 (m, 5H, CH_2 and CH_3), 2.06-1.81 (m, 6H, $3CH_2$), 1.62- 0.86 (m, 29H, $6CH_2$, 5CH and $4CH_3$), 0.70 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.66, 151.32, 149.86, 140.23, 139.37, 137.30, 137.08, 133.96, 129.76, 128.97, 123.65, 122.91, 122.13, 118.79, 75.15, 56.56, 56.01, 49.90, 42.18, 39.60, 39.39, 38.05, 36.92, 36.53, 36.06, 35.68, 31.81, 31.72, 28.13, 27.89, 27.72, 24.18, 23.72, 22.74, 22.47, 20.93, 19.24, 18.62, 11.76, 9.61; MS *m/z* (relative intensity): 371 (0,06), 288 (5), 147 (8), 145 (6), 107 (5), 105 (5), 95 (6), 93 (4), 69 (4), 66 (4), 55 (6), 44 (17), 39 (100); HRMS calcd. for $C_{40}H_{54}ClN_4O2$ $[M + H]^+$: 657.3935; found: 657.3877.

Ethyl 1-(7-chloroquinolin-4-yl)-5-phenyl-1*H*-1,2,3-triazole-4-carboxylate (**3k**)

Yield: 0.096 g (85%); pale white solid; mp: 124-126 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.92 (d, 1H, *J* 4.5 Hz, HetAr-H), 8.19 (d, 1H, *J* 2.0 Hz, HetAr-H), 7.54 (m, 2H, Ph-H), 7.35-7.16 (m, 6H, 3Ph-H and 3HetAr-H), 4.41 (q, 2H, *J* 7.1 Hz, OCH_2), 1.36 (t, 3H, *J* 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.49, 150.98, 149.79, 142.71, 139.76, 136.88, 130.36, 129.61, 129.55, 128.84, 128.39, 127.26, 124.42, 123.90, 122.13, 119.04, 61.44, 14.05; MS *m/z* (relative intensity): 377 (7), 304 (20), 293 (25), 292 (21), 278 (30), 277 (53), 276 (69), 275 (22), 264 (21), 242 (27), 241 (57), 240 (33), 204 (32), 161 (39), 145 (35), 135 (35), 118 (34), 105 (100), 99 (40), 89 (71), 77 (37); HRMS calcd. for $C_{20}H_{16}ClN_4O_2$ $[M + H]^+$: 379.0962; found: 379.0924.

Biological assays

Chemicals

DPPH and ABTS were purchased from Sigma (St. Louis, MO, USA). Compounds **3a** and **3k** were diluted in dimethyl sulfoxide (DMSO) and used at different concentrations (μmol L^{-1}). All other chemicals were of analytical grade and obtained from standard commercial suppliers.

Animals

Male adult Swiss mice (25-35 g) were used to lipid peroxidation levels determination. The animals were kept on a separate animal room, in a 12 h light/dark cycle, at a room temperature of 22 ± 2 °C, with free access to food (Guabi, RS, Brazil) and water. The animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources, Universidade Federal de Pelotas, Brazil.

Biochemical assays

Lipid peroxidation levels

Mice were euthanized and the liver tissue was rapidly dissected, weighed, placed on ice and homogenized in cold 50 mmol L^{-1} Tris-HCl, pH 7.4 (1/10, m/v). Homogenate freshly prepared was centrifuged at 2400 × g for 10 min to yield a pellet that was discarded and a low-speed supernatant (S_1). This assay was carried out to determine if compounds **3a** and **3k** protect against lipid peroxidation induced by SNP in mice liver homogenate. TBARS levels were used as a measure of lipid peroxidation. An aliquot of 200 μL of S_1 was added to the reaction: 50 μL of SNP (50 μmol L^{-1}), 10 μL of compounds **3a** or **3k** (10-500 μmol L^{-1}) and 30 μL of Tris-HCl (50 mmol L^{-1}). Afterward the mixture was pre-incubated at 37 °C for 1 h. The reaction product was determined using 500 μL thiobarbituric acid (TBA, 0.8%), 200 μL sodium dodecyl sulfate (SDS, 8.1%) and 500 μL acetic acid (pH 3.4) with subsequent incubation at 95 °C for 2 h. TBARS levels were spectrophotometrically determined at 532 nm as described by Ohkawa *et al.*,[20] using malondialdehyde (MDA, an end product of the peroxidation of lipids) as an external standard. Results were reported as percentage (%) of induced.

NO scavenging activity

NO scavenging activity of compounds **3a** and **3k** was measured according to the method of Marcocci *et al.*[23] The compound **3a** or **3k** (10 μL) at different concentrations (10-500 μmol L^{-1}) was mixed to 990 μL of SNP solution (25 mmol L^{-1}). The reaction mixture was allowed during 2 h under light at 37 °C. An aliquot (250 μL) of the sample was removed and diluted in 250 μL of Griess reagent. After 5 min, the absorbance of the chromophore (formed during the diazotiation of nitrite with sulfanilamide and its subsequent coupling with naphthylethylenediamine) was measured at 570 nm. Results were expressed as percentage (%) of inhibition. Control group exhibit 0% of inhibition.

DPPH radicals scavenging activity

The ability in scavenging DPPH radicals was evaluated to determine the possible mechanism by which the compounds **3a** and **3k** exhibit antioxidant property, according to the method described by Choi *et al.*[24] An aliquot of 10 μL of compound **3a** or **3k** at different concentrations (10-500 μmol L^{-1}) was mixed with 1 mL of a methanolic solution of DPPH radical, resulting in a final concentration of 85 μmol L^{-1} DPPH. The mixture was left to stand for 30 min at room temperature in the dark and the absorbance was measured at 517 nm. In the control tube was added an aliquot of 10 μL of vehicle. The values were expressed as percentage (%) of control.

ABTS radicals scavenging activity

The determination of the ABTS radical scavenging ability of compounds **3a** and **3k** was performed to a better understanding of the antioxidant property of compounds, according to the method of Re *et al.*[25] with some modifications. Primarily, the ABTS radical was generated by reacting 7 mmol L^{-1} ABTS solution in water with 140 mmol L^{-1} potassium persulfate in the dark for 12-16 h. In the day of the assay, the pre-formed ABTS radical solution was diluted in potassium phosphate buffer in a proportion of 1:88 (1 mL ABTS radical and 87 mL of 10 mmol L^{-1} potassium phosphate buffer, pH 7.0). Briefly, 1 mL of ABTS radical solution was added to tubes containing 10 µL of the compound **3a** or **3k** at different concentrations (10-500 µmol L^{-1}) or vehicle (control). The mixture was incubated at 25 °C for 30 min in dark. The decrease in absorbance was measured at 734 nm. Results were expressed as percentage (%) of the control.

Ferric reducing antioxidant power (FRAP)

The FRAP of compounds **3a** and **3k** was measured according to the method described by Stratil *et al.*[29] with slight modifications. The compounds **3a** or **3k** (10-500 µmol L^{-1}) and the FRAP reagent were added to each sample and the mixture was incubated at 37 °C for 40 min in dark. This assay determines the ability of compounds in reducing the ferric 2,4,6-tripyridyl-s-triazine complex $[Fe^{3+}\text{-}(TPTZ)_2]^{3+}$ to an intensely blue colored ferrous complex $[Fe^{2+}\text{-}(TPTZ)_2]^{2+}$ in acidic medium.[30] The absorbance of the resulting solution was measured spectrophotometrically at 593 nm. Results were expressed as absorbance.

Statistical analysis

Data were statistically analyzed by one-way analysis of variance (ANOVA), followed by the Newman-Keuls test when appropriate. Data are expressed as means ± standard error of mean (S.E.M.).

Supplementary Information

Supplementary Information (Experimental procedures, biological assays details, ^1H and ^{13}C NMR spectra) is available free of charge at http://jbcs.sbq.org.br.

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