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ORIGINAL PAPER

Synthesis, regioselectivity, and DFT analysis of new antioxidant pyrazolo[4,3-*c*]quinoline-3,4-diones

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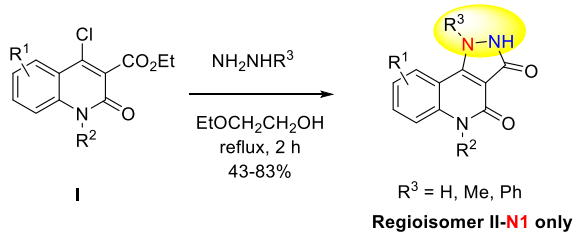
Abstract The condensation of hydrazine, *N*-methylhydrazine, and *N*-phenylhydrazine with ethyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate derivatives has been investigated. As a result, 12 new antioxidant pyrazolo[4,3-*c*]quinolin-3,4-diones were obtained with good to high yields. When two cross-products could be possible, only one isomer bearing the methyl or the phenyl group at the N1 position is isolated and unequivocally characterized using 1D and 2D NMR techniques, FT-IR, and combustion analyses. DFT analysis of the reaction mechanism was carried out in the Pearson's hard soft acid base framework, confirming the assigned structure to the observed pyrazolo[4,3-*c*]quinolin-3,4-diones. These calculations indicate a favored kinetic control for the synthesized pyrazolo[4,3-*c*]quinolin-3,4-diones compared to its possible regioisomer.

Graphical abstract



Keywords Isomers · Kinetic control · Pyrazoloquinolines · Density functional theory · Antioxidants

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Introduction

Over the past two decades, functionalized pyrazoloquinolines have attracted much attention due to their considerable biological and pharmacological activities [1, 2]. Particularly, the pyrazolo[4,3-*c*]quinoline heterocyclic ring system is a very attractive scaffold in medicinal chemistry which has been incorporated in high-affinity benzodiazepine receptor ligands [3, 4], interleukin inhibitors [5], selective cyclooxygenase-2 (COX-2) inhibitors [6], phosphodiesterase 4 (PDE4) inhibitors [7], as well as anticancer [8] and anti-inflammatory agents [9]. Accordingly, several synthetic approaches have been reported, based on the annulation of the pyrazole ring onto a quinoline motif [10–12] or the quinoline ring onto a pyrazole scaffold [13–19].

Recently, Moyano et al. reported a new synthetic approach toward 2-aryl-2*H*-pyrazolo[4,3-*c*]quinolin-3-ones. They found that the reaction of arylhydrazines with

ethyl 4-chloroquinolin-3-carboxylates in DMF at 130–140 °C, furnished only the N2 isomer of the corresponding pyrazolo[4,3-*c*]quinolin-3-one adduct, but when the condensation was carried out with benzylhydrazine, in the presence of sodium methoxide, a mixture of the N1 and N2 regioisomers was detected and conveniently characterized (Scheme 1; Eq. (1)) [20].

Based on this report and the recent synthetic developments using the related, diversely substituted ethyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate derivatives **I** [21–24], we describe in this paper the results we have obtained in the condensation of compounds of type **I** with hydrazine, *N*-methylhydrazine, and *N*-phenylhydrazine (Scheme 1; Eq. (2)). As a result, we have synthesized and characterized 12 pyrazolo[4,3-*c*]quinolin-3,4-diones **7a**–**7l**, whose antioxidant properties are reported herein. In addition, in-depth NMR studies and mechanistic DFT-analysis have been carried out in order to shed light into the mechanism of this reaction, to justify the regioselective formation of the N1-substituted pyrazolo[4,3-*c*]quinolin-3,4-diones (isomer **II-N1**) versus the N2-substituted pyrazolo[4,3-*c*]quinolin-3,4-diones (isomer **II-N2**) (Scheme 1; Eq. (2)) in the reaction of ethyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate derivatives with *N*-methylhydrazine and *N*-phenylhydrazine.

Results and discussion

Chemistry

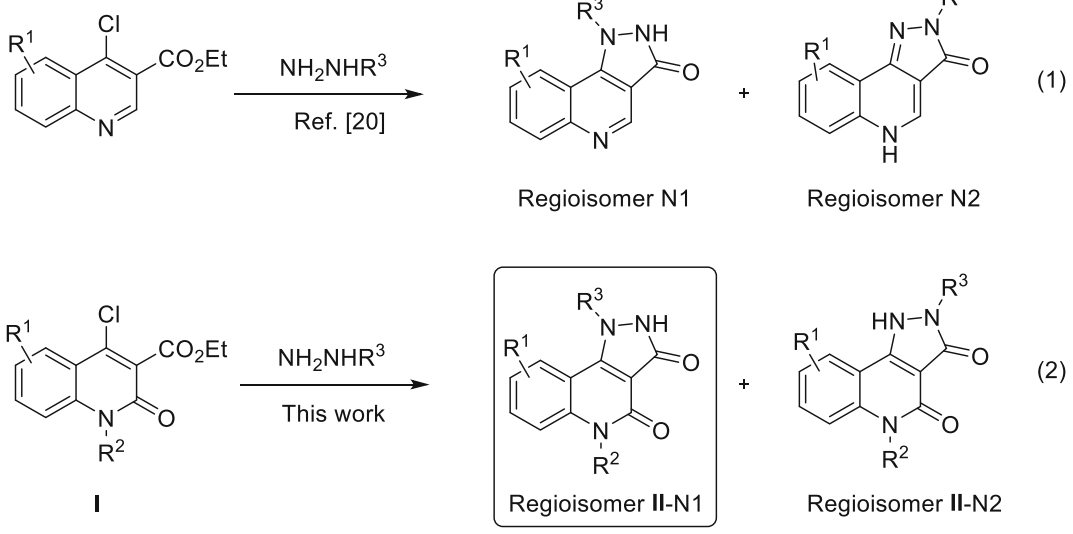
The key 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate intermediates **6** have been prepared as shown in Schemes 2 and 3. The first step in the synthetic sequence was the preparation of the two isatoic anhydrides **3** bearing a hydrogen atom or a chlorine atom at C5. Accordingly, while isatoic anhydride (**3a**) is commercially available, compound **3b** was obtained from the corresponding 2-amino-6-chlorobenzoic acid (**1**) after reaction with triphosgene in dioxane at 0 °C [25].

Next, compound **3a** was submitted to *N*-alkylation with benzyl bromide in the presence of di-*iso*-propylethylamine (DIPEA) as a base, in dimethylacetamide (DMA) as a solvent, to provide the benzylated isatoic anhydride **4a** (Scheme 2) [26]. *N*-Methylisatoic anhydride (**4b**, Scheme 2) is commercially available, and used as received. In the next steps, these two intermediates were submitted to the same synthetic sequence starting the reaction with diethyl malonate in the presence of NaH in DMA, a process that afforded the expected quinolones **5a**, **5b** [21–24, 27] whose reaction with $POCl_3$ provided the required chloride derivatives **6a**, **6b** (Scheme 2). Similarly, the reaction with diethyl malonate followed by treatment with $POCl_3$ applied to precursor **3a**, provided the required chloride **6c** via compound **5c** (Scheme 2).

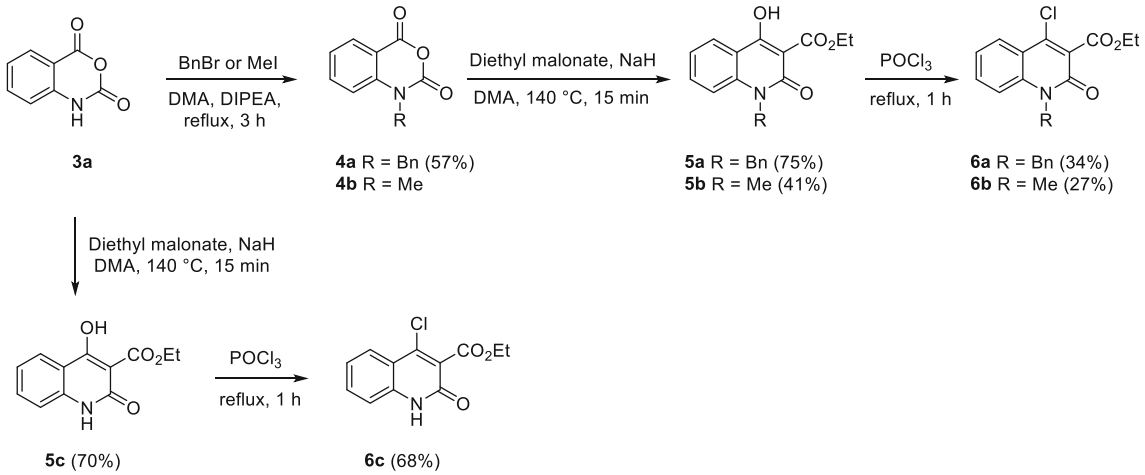
Afterward, the isatoic anhydride **3b** was submitted to the same synthetic procedures as shown for compound **3a**, which afforded the expected key intermediates **6d**–**6f** via anhydrides **4c**, **4d** and hydroxy-derivatives **5d**–**5f** (Scheme 3) [21–24, 28]. All new compounds gave analytical and spectroscopic data in full agreement with their structures (see "Experimental" section).

Finally, the tricyclic pyrazolo[3,4-*c*]quinolin-3,4-diones **7a**–**7l** were obtained by treatment of chlorides **6a**–**6f** with hydrazine, *N*-methylhydrazine, and *N*-phenylhydrazine (Scheme 4), in yields ranging between 44 and 83 % (Table 1). As shown, only the N1-substituted (Me

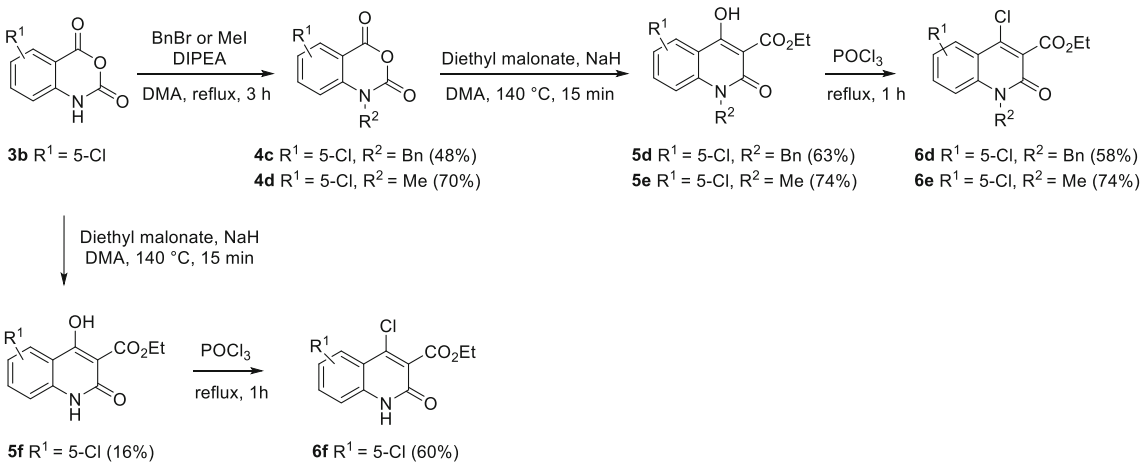
Scheme 1



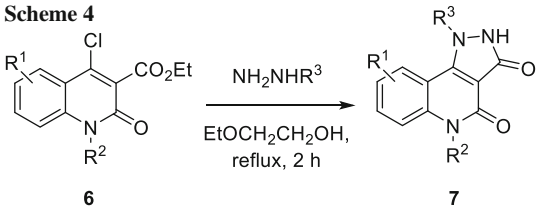
Scheme 2



Scheme 3



Scheme 4



or Ph) pyrazolo[3,4-*c*]quinolin-3,4-dione regioisomers were isolated.

A complete elucidation of the structures was achieved by HMBC and ROESY 2D NMR experiments (Fig. 1). HMBC analysis of compound **7e** showed correlations between hydrogen of methyl group of hydrazide and the C-9b at 138.74 ppm and three correlations between hydrogen of the *N*-methyl group of the quinoline ring (3.57 ppm), the carbonylic carbon signal (157.22 ppm) at the position 4, carbon C-5a (139.18 ppm), and carbon C-6 (115.86 ppm). In the ROESY experiment, two significant signals corresponding to interactions through space between protons of the methyl group of the hydrazide (4.13 ppm) and proton H-9 (8.17 ppm) were observed: the second interaction shows correlation between hydrogen of the *N*-methyl group (3.57 ppm) of the quinoline ring and proton H-6 (7.55 ppm). These findings allowed us to confirm the structure of compound **7e** and the conclusion was also extended to the other derivatives **7**.

Computational studies and reaction mechanism

Since the total electronic energy of isomers **II-N1** is less negative than the other possible regioisomer **II-N2**, the

Table 1 Synthesis of compounds **7a–7l**

Compound	R^1	R^2	R^3	Yield/ %
7a	H	H	H	79
7b	H	H	Me	46
7c	H	H	Ph	72
7d	H	Me	H	66
7e	H	Me	Me	77
7f	H	Me	Ph	78
7g	H	Bn	H	83
7h	H	Bn	Me	44
7i	H	Bn	Ph	52
7j	9-Cl	H	Me	71
7k	9-Cl	Me	Me	61
7l	9-Cl	Bn	Me	51

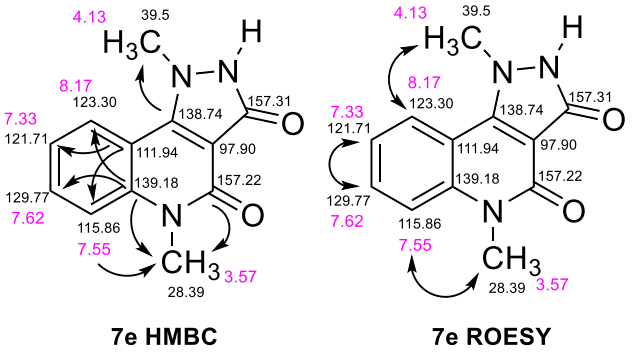


Fig. 1 HMBC and ROESY (500 MHz, 298 K, DMSO-d_6) correlations for compound **7e**

elucidation of their regioselectivity cannot be studied on the basis of this global descriptor. In the HSAB framework, local descriptors such as Fukui functions $f(r)$ and local chemical softness $s(r)$ and electrophilicity (ω) are more appropriate and considered as the reactivity index. In this context, successful prediction criteria have been proposed on rigorous theoretical basis [29–31]. When applied to our molecules, all these elements provide a better understanding for the formation of a single product between the quinolinones **6** and hydrazine or derivatives.

The regioselectivity and reactivity of compounds **6** with hydrazine and its derivatives have been studied by calculating the local Fukui functions and then the corresponding softnesses and electrophilicity indexes of electrophilic and nucleophilic centers (f^+ and f^-, then s^+ and s^- respectively and ω^+ and ω^-). In addition to these chemical indicators, the effect of solvent (i.e. ethoxyethanol) as a polarized continuum was taken into consideration since error can rise from reactivity difference of molecules in gas and liquid phases (Table 2).

By applying the site selectivity criteria to the reaction between compound **6b** and methylhydrazine and between the four centers, there are two possible pathways Δ_I and Δ_{II}:

$$\Delta_I = \left(s^+_{(\text{unsubstituted } N)} - s^-_{(C \text{ ester})}\right)^2 + \left(s^+_{(\text{substituted} N)} - s^-_{(C \text{ of } C-Cl)}\right)^2$$

$$\Delta_{II} = \left(s^+_{(\text{substituted } N)} - s^-_{(C \text{ ester})}\right)^2 + \left(s^+_{(\text{unsubstituted} N)} - s^-_{(C \text{ of } C-Cl)}\right)^2$$

These calculations indicate a preferable mechanism Δ_I ($\Delta_I < \Delta_{II}$) leading to the unique product **7b** and further confirmed experimentally by HMBC and ROESY 2D NMR experiments. According to the DFT-based descriptors, the bond formation between the atoms concerns the ester carbon (from quinolinone) with the non-substituted nitrogen atom (from methylhydrazine) having antibonding molecular orbitals (MOs) and the carbon atom bonded to the chlorine atom (from quinolinone) with the substituted nitrogen atom (from methylhydrazine) having bonding MOs [32]. Moreover, the charges carried by these atoms show that the two nitrogen centers act as nucleophilic site and on the contrary, the two carbon atoms (from quinolinone) involved in the reaction are electrophilic sites. Therefore, a larger orbital overlap occurs explaining a single major product as confirmed experimentally.

The reaction path calculations allowed us to verify the connection between the reactant and the product via the transition structures. The resulting potential energy profile of the reaction is illustrated by Fig. 2. The energy profile for the synthesized pyrazolo[4,3-*c*]quinolin-3,4-diones **7a–7l** compared to its possible regioisomer underlines a kinetic control of the reaction between selected quinolinone and hydrazine (and derivatives) since the more energetically stable isomer **II-N2** is not obtained.

The preferable mechanism of the reaction between quinolone and hydrazine derivatives (Scheme 5) consists in the approach of hydrazine towards **6b** near the ester function; this constitutes a transition state leading to an energy barrier. Then, a rearrangement occurs with the departure of ethanol (step 2) and finally a nucleophilic attack of the substituted nitrogen atom on the halogenated carbon atom (step 3). This step corresponds to a second energy transition state in gas phase which is found to disappear in 2-ethoxyethanol explaining why the solvent can affect the kinetic or thermodynamic control of the reaction. The departure of hydrochloric acid causes the reaction to evolve towards the final product (step 4).

Antioxidant activity study

Free radical scavenging is considered to be one of the major mechanisms by which antioxidants halt lipid peroxidation, thus mitigating any damages caused to the cell membrane lipids and mitochondrial machinery. In our

Table 2 Condensed Fukui functions, local softnesses for C and N centers of molecules solvated in 2-ethoxyethanol and electrophilicity indexes

	f^+	f^-	s^+	s^-	ω^+	ω^-
6b						
Carbon atom of C–Cl	0.11374	0.03329	0.01825	0.00534	0.222	0.065
Carbon atom of ester	0.00961	−0.00589	0.00154	−0.00094	0.019	−0.011
Methyl hydrazine						
Non-substituted nitrogen atom	−0.10075	0.24100	−0.02532	0.06057	−0.030	0.072
Substituted nitrogen atom	−0.07652	0.24967	−0.01923	0.06274	−0.023	0.075

The global softnesses calculated from the neutral molecules are S(quinolinone **6b**) = 0.16041 (a.m.u.) and S(methylhydrazine) = 0.25131 (a.m.u.). ω(**6b**) = 1.952 eV and ω(methylhydrazine) = 0.300 eV

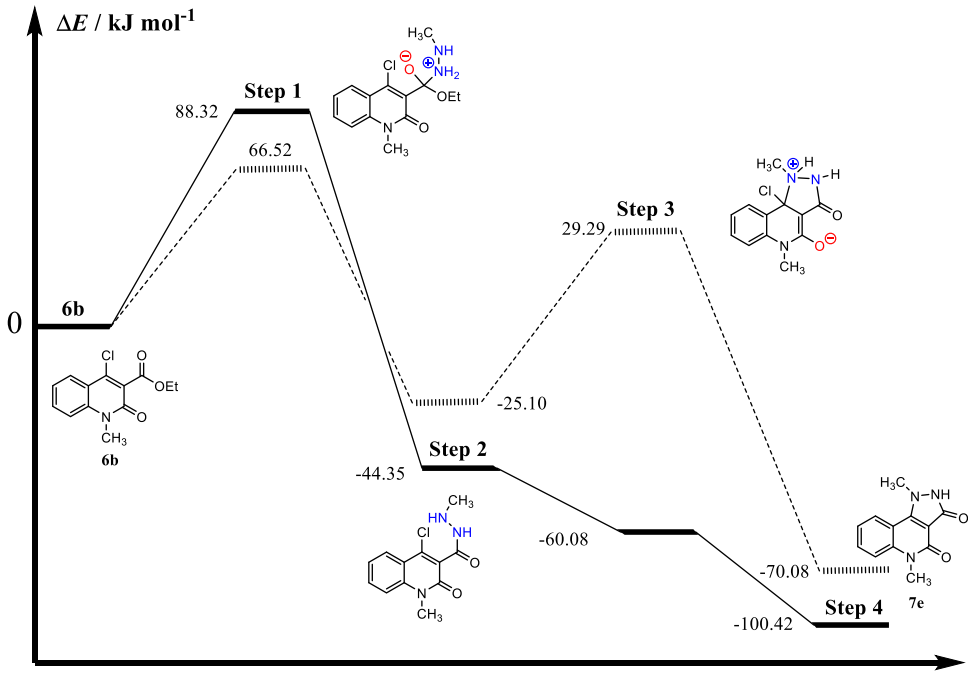
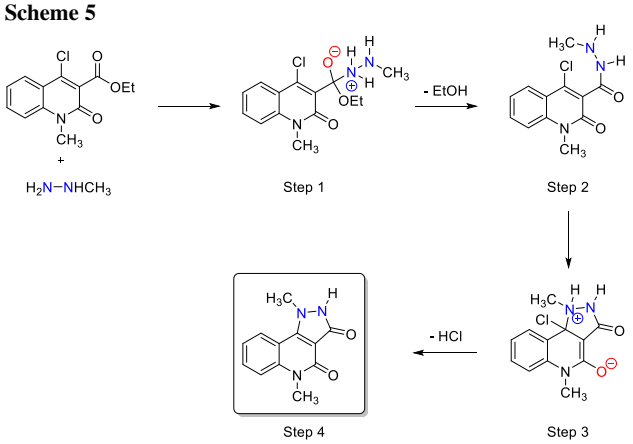


Fig. 2 Energy profile ΔE (in kJ/mol) of the reaction between compound **6b** and methylhydrazine versus the reaction coordinates. *Dash line* molecules in vacuum; *solid line* molecules solvated in 2-ethoxyethanol

Scheme 5



quest to find potent antioxidants, we were then interested in assessing the antioxidant power of pyrazolo[4,3-*c*]quinolin-3,4-diones **7a–7l** using the well-known 2,2-diphenyl-1-picryl-hydrazyl (DPPH) and hydroxyl radicals (standard assays) as probes to determine the radical scavenging activity (RSA) of the aforementioned compounds.

DPPH radical scavenging

In a methanolic solution, the DPPH radical displays a deep purple color with a maximum absorption at 517 nm. This color vanishes gradually in the presence of various concentration of antioxidant in the medium (see Scheme 6). Thus, the DPPH radical can be quenched by the capture of a labile hydrogen atom or by electron donation from the antioxidant, probably via a free-radical attack on the DPPH molecule. This process provides then a blanched solution [33, 34]. RSA DPPH values of compound **7a–7l** (Table 3) correspond to a percentage of the ratio of the decrease in optical density at 517 nm over the absorbance of a DPPH control solution which does not contain the compounds **7a–7l**.

Scheme 6

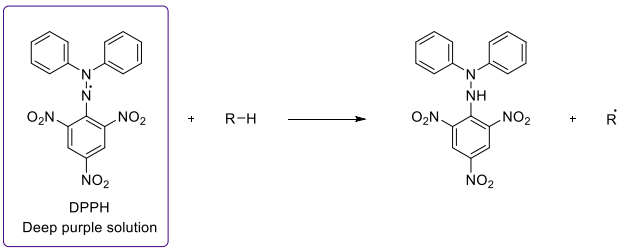


Table 3 Decreasing DPPH absorbance and decreasing fluorescence at 50 μmol/dm^3 of compounds **7a–7l**

Compound	Decreasing absorbance DPPH/%	Decreasing fluorescence/%
7a	15.2	66.7
7b	13.8	65.8
7c	10.8	53.3
7d	6.9	68.2
7e	5.7	69.2
7f	7.3	67.8
7g	6.4	64.3
7h	6.9	71.6
7i	7.6	73.9
7j	10.1	72.7
7k	5.0	72.4
7l	5.9	73.1
Ascorbic acid	75.9	–
Quercetol	–	88.9

From the results gathered in Table 3, we can say that the pyrazolo[4,3-*c*]quinolin-3,4-diones **7a–7l** scavenging effect on DPPH radicals increase was suitable for compounds **7a–7c** (10.8–15.2 % at 50 μmol/dm^3), but lower than RSA DPPH value found for ascorbic acid (37.9 % at 50 μmol/dm^3) used as a reference. *N*-Substituted derivatives **7d–7g**, **7i**, and **7k** have shown moderate activity while derivatives **7h** and **7l** presented the poorest activity compared to the standard one. Thus, in order to display a good antioxidant activity, the pyrazolo[4,3-*c*]quinolin-3,4-dione scaffold may embed the N–H moiety in the quinolone or pyrazole ring. Accordingly, compound **7a** behaves as a better antioxidant with three N–H moieties in its structure.

Hydroxyl radical scavenging

The capacity of our compounds to scavenge the hydroxyl radical was evaluated using the benzoic acid method [35]. In brief, the benzoic acid is converted to salicylic acid or 4-hydroxybenzoic acid in the presence of the hydroxyl radical generated during the Fenton reaction. The fluorescence emission, measured at 407 nm with excitation wavelength set at 305 nm, decreases if there is any antioxidant in the medium. Potent antioxidant product impedes the hydroxylation of benzoic acid by providing hydrogen atom. The hydroxyl RSAs of the adducts **7a–7l** are summarized in Table 3. We can conclude that all the products presented at 50 μmol/dm^3 good hydroxyl radical scavenging activities ranging between 53.3 and 73.9 % compared to quercetol at 50 μmol/dm^3 (88.9 %), used here as reference compound.

Conclusions

The spectroscopic (1D NMR ^{1}H/^{13}C and 2D NMR HMBC and ROESY) and the computational analyses (DFT) confirms that the reaction between ethyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate derivatives and the selected hydrazine derivatives yields a unique product, kinetically favored but disadvantaged in comparison to other possible regioisomers. Compared to conventional frontier molecular orbital description, any of the DFT-based descriptors predicted the correct regioselectivity in favor of the **N1-II** isomer. Our results showed also the important role played by 2-ethoxyethanol during this type of condensation. All new compounds gave interesting hydroxyl radical scavenging activities and slight capacity to inhibit DPPH radical. Based on these outcomes, compound **7a** bearing three NH moieties was found to be the most balanced antioxidant. Further synthetic studies are underway to enhance the antioxidant potency of the pyrazolo[4,3-*c*]quinolin-3,4-dione backbone.

Experimental

All reactions were controlled by TLC using precoated silica gel aluminum plates (Macherey–Nagel) and revealed by UV light at 254 nm. Melting points were determined on a Köfler bench. Infrared spectra were recorded on a Shimadzu FTIR-8201 PC spectrometer in KBr ($\overline{\nu}$ in cm^{-1}). NMR spectra were recorded on Bruker AC 300, AC 250 spectrometers or on a Varian System-500 spectrometer. $CDCl_3$ and DMSO-d_6 were used as deuterated solvents. Chemical shifts are reported in parts per millions relative to tetramethylsilane (TMS) signal and coupling constants (*J*) are given in Hertz (Hz). The following abbreviations are employed: s, singlet; br s, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quadruplet; m, multiplet. Microanalyses were performed at Service Central

d'Analyses (CNRS, Vernaison, France). All reagents are of analytical grade pure and used without further purification. Isatoic anhydride (**3a**) and *N*-methylisatoic anhydride (**4b**) are commercially available. The compounds 5-chloroisatoic anhydride (**3b**) [25], *N*-benzylisatoic anhydride (**4a**) [26], 5-chloro-*N*-methylisatoic anhydride (**4d**) [21], ethyl 1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (**5a**) [27], ethyl 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**5b**) [21], ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (**5c**) [21], ethyl 5-chloro-4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**5e**) [22], ethyl 5-chloro-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (**5f**) [21], ethyl 1-benzyl-4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate (**6a**) [23], ethyl 4-chloro-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**6b**) [21], and ethyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate (**6c**) [28] had been previously described.

N-Benzyl-5-chloroisatoic anhydride (**4c**, $C_{15}H_{10}ClNO_3$)
5-Chloroisatoic anhydride (**3b**, 1 g, 5.06 mmol) was suspended in 10 cm^3 DMA with 0.654 g DIPEA (5.06 mmol). The solution was stirred 10 min and then, 1.09 g benzyl bromide (6.07 mmol) was added and the mixture was heated for 3 h. After cooling to room temperature, 10 cm^3 water was added and the solution was vigorously stirred for 30 min; the precipitate was filtered, washed with water and diethyl ether to give white product **4c** (0.70 g, 48 %). M.p.: 115 °C; IR (KBr): $\overline{\nu} = 1768, 1700, 1590\ cm^{-1}$; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.87$ (m, 2H), 7.44 (d, $J = 8.2$ Hz, 1H), 7.25–7.35 (m, 5H), 4.80 (s, 2H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 156.15$ (CO), 151.20 (CO), 139.42 (C8-a), 130.88 (C, benzyl), 129.11 (C5), 128.14 (C7), 126.13 (2CH, benzyl), 124.13 (2CH, benzyl), 123.77 (CH, benzyl), 123.28 (C6), 121.21 (C4-a), 112.44 (C8), 43.52 (CH_2, benzyl) ppm.

Ethyl 1-benzyl-5-chloro-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (**5d**, $C_{19}H_{16}ClNO_4$)
To a solution of 1 g 5-chloro-*N*-benzylisatoic anhydride (**4c**, 3.47 mmol) in 10 cm^3 DMF at 0 °C were added slowly 0.17 g sodium hydride (7.0 mmol) and 2.78 g diethyl malonate (17.6 mmol). The reaction was heated at 85 °C for 5 h. After cooling, water was added and the mixture obtained was acidified with conc. HCl. The resultant solid was filtered, washed with water, and dried to afford a yellow product **5d** (0.78 g, 63 %). M.p.: 124 °C; IR (KBr): $\overline{\nu} = 1672, 1630, 1570\ cm^{-1}$; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 12.9$ (s, 1H, OH), 7.53 (d, $J = 7.3$ Hz, 1H), 7.15–7.28 (m, 7H), 5.02 (s, 2 H), 4.16 (q, $J = 7.0$ Hz, 2H), 1.30 (t, $J = 7.0$ Hz, 3 H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 162.45$ (CO), 161.22 (CO), 139.45 (C8-a), 138.67 (C4), 135.67 (C, benzyl), 130.32 (C5), 127.14 (CH, benzyl), 126.68 (2×CH, benzyl), 126.32 (2×CH, benzyl), 124.33 (C7), 123.63 (C4-a), 123.27 (C6), 112.46 (C8), 102.33 (C3), 61.13 (CH_2, ester), 46.28 (CH_2, benzyl), 15.63 (CH_3) ppm.

General procedure for preparation of 6d **and** 6e

The corresponding quinolines **5d**, **5e** suspended in $POCl_3$ (2–6 cm^3) were heated at 100 °C for 1 h. Then, the mixture was cooled to 0 °C and neutralized with water and NaOH (10 N). The resulting solid was filtered and dried.

Ethyl 1-benzyl-4,5-dichloro-2-oxo-1,2-dihydroquinoline-3-carboxylate (**6d**, $C_{19}H_{15}Cl_2NO_3$)
Following the general procedure, 0.50 g compound **5d** (1.40 mmol) and 2 cm^3 $POCl_3$ gave white solid **6d** (0.31 g, 58 %). M.p.: 115 °C; IR (KBr): $\overline{\nu} = 1715, 1656, 1550\ cm^{-1}$; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.40$–7.24 (m, 6H), 7.23 (d, $J = 7.5$ Hz, 2H), 5.57 (s, 2H), 4.53 (q, $J = 7.1$ Hz, 2H), 1.46 (t, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 164.25$ (CO), 158.10 (CO), 141.52 (C8-a), 140.24 (C, benzyl), 135.51 (C5), 134.18 (C4), 132.04 (CH, benzyl), 130.13 (C4-a), 129.47 (2×CH, benzyl), 128.16 (C7), 128.02 (C6), 126.94 (2×CH, benzyl), 116.23 (C3), 115.44 (C8), 62.92 (CH_2, ester), 47.82 (CH_2, benzyl), 14.54 (CH_3) ppm.

Ethyl 4,5-dichloro-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**6e**, $C_{13}H_{11}Cl_2NO_3$)
Following the general procedure, 1 g compound **5e** (3.74 mmol) was suspended in 3 cm^3 $POCl_3$ and gave white product **6e** (0.43 g, 40 %). M.p.: 106 °C; IR (KBr): $\overline{\nu} = 1710, 1660, 1573\ cm^{-1}$; ^{1}H NMR (DMSO-$d_6$, 500 MHz): $\delta = 7.70$ (m, 2H), 7.51 (dd, $J = 6.6, 2.1$ Hz, 1H), 4.36 (q, $J = 7.0$ Hz, 2H), 1.31 (t, $J = 7.0$ Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): $\delta = 163.18$ (CO), 156.34 (CO), 141.51 (C8-a), 137.14 (C5), 132.50 (C7), 131.41 (C4), 129.13 (C4-a), 127.17 (C6), 115.71 (C8), 113.90 (C3), 61.81 (CH_2), 30.74 (N-CH_3) 13.80 (CH_3 ester) ppm.

Ethyl 4,5-dichloro-2-oxo-1,2-dihydroquinoline-3-carboxylate (**6f**, $C_{12}H_9Cl_2NO_3$)
Compound **5f** (0.8 g, 3 mmol) and 2 cm^3 $POCl_3$ were stirred at 110 °C for 6 h. After cooling, the solvent was concentrated. The residue was dissolved in a small amount of AcOEt and the mixture was poured into ice water followed by extraction with AcOEt. The extract was washed with 1 M NaOH, water, and brine, dried over $MgSO_4$, and concentrated in vacuum. This mixture was then stirred with 0.27 g AcONa (3.3 mmol) in 2 cm^3 AcOH at 120 °C for 20 h. The reaction mixture was then added to water, the precipitated solid was collected and washed with water to give the product **6f** (0.52 g, 60 %) as a white solid. M.p.: 102–104 °C; IR (KBr): $\overline{\nu} = 2995,$

1735, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 12.74$ (s, 1H), 7.59 (t, $J = 8.1$ Hz, 1H), 7.46 (dd, $J = 8.3$, 0.8 Hz, 1H), 7.59 (dd, $J = 7.8$, 1.0 Hz, 1H), 4.34 (q, $J = 7.1$ Hz, 2H), 1.30 (t, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): $\delta = 163.28$ (CO), 156.69 (CO), 140.73 (C8-a), 138.42 (C5), 130.73 (C4), 132.45 (C7), 124.26 (C4-a), 126.27 (C6), 112.95 (C3), 116.27 (C8), 61.83 (CH_2), 13.89 (CH_3) ppm.

General procedure for preparation of compounds 7a–7l

The 4-choroquinolines were added to a solution of the corresponding hydrazine (5–7 equiv) in 5–25 cm^3 ethoxyethanol. The solution was heated for 2–6 h and allowed cool to rt. The precipitate obtained was filtered, washed with diethyl ether, and dried to yield the desired compound.

1,2-Dihydro-3H-pyrazolo[4,3-c]quinoline-3,4(5H)-dione (**7a**, $C_{10}H_7N_3O_2$)

Following the general procedure, the reaction of 0.3 g compound **6c** (1.19 mmol) and 0.6 cm^3 hydrazine monohydrate (8.33 mmol) in 10 cm^3 ethoxyethanol gave off-white compound **7a** (0.19 g, 79 %). M.p.: >260 °C; IR (KBr): $\overline{\nu} = 3320$, 2990, 1651, 1585 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 10.52$ (br s, 1H, NH), 7.87 (d, $J = 6.2$ Hz, 1H), 7.09–7.32 (m, 3H) ppm; ^{13}C NMR (DMSO-d_6, 62.5 MHz): $\delta = 161.53$ (CO), 160.36 (CO), 144.72 (C, C5-a), 138.49 (C, C9-b), 128.84 (CH, C7), 121.67 (CH, C9), 121.44 (CH, C8), 115.96 (2C, C6, C9-a), 95.22 (C, C3-a) ppm.

1-Methyl-1,2-dihydro-3H-pyrazolo[4,3-c]quinoline-3,4(5H)-dione (**7b**, $C_{11}H_9N_3O_2$)

Following the general procedure, the reaction of 0.3 g compound **6c** (1.19 mmol) and 0.44 cm^3 methylhydrazine (9.45 mmol) in 10 cm^3 ethoxyethanol gave off-white compound **7b** (0.12 g, 46 %). M.p.: >260 °C; IR (KBr): $\overline{\nu} = 3330$, 2995, 1675, 1590 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 11.11$ (br s, 1H, NH), 10.58 (br s, 1H, NH), 8.10 (d, $J = 7.8$ Hz, 1H), 7.48 (t, $J = 7.4$ Hz, 1H), 7.37 (m, 1H), 7.22 (d, $J = 7.3$ Hz, 1H), 4.11 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 158.41$ (CO), 157.69 (CO), 140.41 (C5-a), 139.02 (C9-b), 129.94 (C7), 123.44 (C9), 122.07 (C8), 116.63 (C6), 111.40 (C9-a), 98.89 (C3-a), 39.5 (CH_3, overlapped with DMSO) ppm.

1-Phenyl-1,2-dihydro-3H-pyrazolo[4,3-c]quinoline-3,4(5H)-dione (**7c**, $C_{16}H_{11}N_3O_2$)

Following the general procedure, the reaction of 0.3 g compound **6c** (1.19 mmol) and 0.82 cm^3 phenylhydrazine (8.33 mmol) in 10 cm^3 ethoxyethanol gave light brown compound **7c** (0.24 g, 72 %). M.p.: >260 °C; IR (KBr): $\overline{\nu} = 3327$, 3015, 1666, 1588 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 10.61$ (br s, 1H, NH), 7.95–7.97 (m, 3H), 7.47 (m, 2H), 7.39 (m, 1H), 7.23 (m, 2H), 7.12 (m, 1H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 161.44$ (CO), 160.18 (CO), 147.32 (C, C5-a), 139.32 (C9-b), 135.12 (C, phenyl), 129.80 (C7), 129.22 (2×CH, phenyl), 122.21 (C9), 121.76 (C8), 121.47 (CH, phenyl), 121.39 (2×CH, phenyl), 116.21 (C6), 116.18 (C9-a), 107.09 (C3-a) ppm.

5-Methyl-1,2-dihydro-3H-pyrazolo[4,3-c]quinoline-3,4(5H)-dione (**7d**, $C_{11}H_9N_3O_2$)

Following the general procedure, the reaction of 0.3 g compound **6b** (1.13 mmol) and 0.3 cm^3 hydrazine (9.45 mmol) in 25 cm^3 ethoxyethanol gave yellow compound **7d** (0.16 g, 66 %). M.p.: >260 °C; IR (KBr): $\overline{\nu} = 3328$, 1651, 1585, 1554 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.95$ (dd, $J = 1.5$ Hz, 7.7 Hz, 1H), 7.45 (t, $J = 7.0$ Hz, 1H), 7.36 (d, $J = 8.1$ Hz, 1H), 7.18 (t, $J = 7.2$ Hz, 1H), 3.50 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 161.18$ (CO), 159.35 (CO), 143.57 (C, C5-a), 139.49 (C, C9-b), 129.49 (CH, C7), 122.16 (CH, C9), 121.81 (CH, C8), 115.79 (C, C6), 114.89 (CH, C9-a), 94.76 (C, C3-a), 28.48 (CH_3) ppm.

1,5-Dimethyl-1,2-dihydro-3H-pyrazolo[4,3-c]quinoline-3,4(5H)-dione (**7e**, $C_{12}H_{11}N_3O_2$)

Following the general procedure, the reaction of 0.5 g compound **6b** (1.88 mmol) and 0.5 cm^3 methylhydrazine (9.55 mmol) in 20 cm^3 ethoxyethanol gave yellow compound **7e** (0.33 g, 77 %). M.p.: >260 °C; IR (KBr): $\overline{\nu} = 3256$, 1647, 1596, 1542 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): $\delta = 8.17$ (d, $J = 8.0$ Hz, 1H), 7.62 (t, $J = 7.9$ Hz, 1H) 7.55 (d, $J = 8.5$ Hz, 1H), 7.33 (t, $J = 7.6$ Hz, 1H), 4.13 (s, 3H), 3.57 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): $\delta = 157.31$ (CO), 157.22 (CO), 139.18 (C5-a), 138.74 (C9-b), 129.77 (C7), 123.30 (C9), 121.71 (C8), 115.86 (C6), 111.94 (C9-a), 97.90 (C3-a), 39.5 (CH_3, overlapped with DMSO), 28.39 (CH_3) ppm.

5-Methyl-1-phenyl-1,2-dihydro-3H-pyrazolo[4,3-c]quinoline-3,4(5H)-dione (**7f**, $C_{17}H_{13}N_3O_2$)

Following the general procedure, the reaction of 0.5 g compound **6b** (1.88 mmol) and 1 cm^3 phenylhydrazine (10.1 mmol) in 20 cm^3 ethoxyethanol gave light brown compound **7f** (0.094 g, 78 %). M.p.: 189 °C; IR (KBr): $\overline{\nu} = 1627$, 1593, 1569, 1542 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 8.10$ (d, $J = 7.5$ Hz, 1H), 7.83 (d, $J = 7.8$ Hz, 2H), 7.62–7.48 (m, 4H), 7.31 (m, 1H), 7.29 (t, $J = 7.5$ Hz, 1H), 3.57 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 158.19$ (2xCO), 146.53 (C, C5-a), 140.13 (C9-b), 138.10 (C, phenyl), 130.97 (C7), 129.53 (2×CH, phenyl), 127.29 (CH, phenyl), 122.91 (2×CH, phenyl), 122.74 (C9), 122.48 (C8), 116.23 (C6, C9-a), 96.30 (C3-a), 28.11 (CH_3) ppm.

5-Benzyl-1,2-dihydro-3H-pyrazolo[4,3-c]quinoline-3,4(5H)-dione (**7g**, $C_{17}H_{13}N_3O_2$)
Following the general procedure, the reaction of 0.05 g compound **6a** (0.15 mmol) and 25 mm^3 hydrazine (0.78 mmol) in 5 cm^3 ethoxyethanol gave yellow compound **7g** (0.038 g, 83 %). M.p.: >260 °C; IR (KBr): $\overline{\nu} = 1643$, 1554 cm^{-1}; ^{1}H NMR (DMSO-d_6, 250 MHz): $\delta = 13.00$ (br s, 1H, NH), 8.06 (d, $J = 7.0$ Hz, 1H), 7.43 (t, $J = 7.1$ Hz, 1H), 7.10–7.33 (m, 7H), 5.49 (s, 2H) ppm; ^{13}C NMR (DMSO-d_6, 62.5 MHz): $\delta = 159.53$ (CO), 158.43 (CO), 141.97 (C5-a), 138.47 (C9-b), 137.95 (C, benzyl), 130.32 (CH, benzyl), 128.99 (2×CH, benzyl), 127.28 (C7), 126.79 (2×CH, benzyl), 122.80 (C9), 122.34 (C8), 116.73 (C6), 112.31 (C9-a), 96.73 (C3-a), 44.14 (CH_2, benzyl) ppm.

5-Benzyl-1-methyl-1,2-dihydro-3H-pyrazolo[4,3-c]-quinoline-3,4(5H)-dione (**7h**, $C_{18}H_{15}N_3O_2$)
Following the general procedure, the reaction of 0.05 g compound **6a** (0.15 mmol) and 39 mm^3 methylhydrazine (0.75 mmol) in 5 cm^3 ethoxyethanol gave yellow compound **7h** (0.021 g, 44 %). M.p.: >260 °C; IR (KBr): $\overline{\nu} = 3355$, 1651, 1573 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 12.55$ (s, 1H, NH), 8.18 (d, $J = 8.1$ Hz, 1H), 7.47 (t, $J = 7.5$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.26–7.21 (m, 3H), 7.21–7.21 (m, 3H), 5.51 (s, 2H), 4.16 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 158.04$ (2xCO), 139.42 (C5-a), 138.75 (C9-b), 137.77 (C, benzyl), 130.21 (CH, benzyl), 129.06 (2×CH, benzyl), 127.35 (C7), 126.78 (2×CH, benzyl), 124.12 (C9), 122.41 (C8), 116.95 (C6), 112.83 (C9-a), 98.16 (C3-a), 44.26 (CH_2, benzyl), 39.5 (CH_3, overlapped with DMSO) ppm.

5-Benzyl-1-phenyl-1,2-dihydro-3H-pyrazolo[4,3-c]quinoline-3,4(5H)-dione (**7i**, $C_{23}H_{17}N_3O_2$)
Following the general procedure, the reaction of 0.05 g compound **6a** (0.15 mmol) and 74 mm^3 phenylhydrazine (0.75 mmol) in 5 cm^3 ethoxyethanol gave light brown compound **7i** (0.030 g, 52 %). M.p.: >260 °C; IR (KBr): $\overline{\nu} = 3200$, 1667, 1580 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 8.10$ (d, $J = 7.4$ Hz, 1H), 7.96 (d, $J = 7.8$ Hz, 2H), 7.61–7.40 (m, 3H), 7.40–7.15 (m, 8H), 7.18–7.20 (m, 5H), 5.48 (s, 2H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 160.09$ (CO), 159.97 (CO), 146.22 (C5-a), 139.07 (C9-b), 138.07 (C, benzyl), 130.28 (C, phenyl), 129.43 (2×CH, benzyl), 129.33 (C7), 129.02 (2×CH, phenyl), 127.31 (CH, benzyl), 126.89 (2×CH, benzyl), 122.72 (CH, phenyl), 122.53 (2×CH, phenyl), 121.90 (C9), 121.85 (C8), 121.79 (C6), 116.73 (C9-a), 95.20 (C3-a), 43.95 (CH_2, benzyl) ppm.

9-Chloro-1-methyl-1,2-dihydro-3H-pyrazolo[4,3-c]quinoline-3,4(5H)-dione (**7j**, $C_{11}H_8ClN_3O_2$)
Following the general procedure, the reaction of 0.05 g compound **6f** (0.17 mmol) and 45 mm^3 methylhydrazine (0.87 mmol) in 5 cm^3 ethoxyethanol gave yellow compound **7j** (0.031 g, 71 %). M.p.: >260 °C; IR (KBr): $\overline{\nu} = 3002$, 1680, 1590 cm^{-1}; ^{1}H NMR (DMSO-d_6, 250 MHz): $\delta = 11.29$ (br s, 1H), 7.46 (m, 1H), 7.33–7.26 (m, 2H + 1NH), 3.96 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 62.5 MHz): $\delta = 158.94$ (CO), 158.00 (CO), 141.71 (C5-a), 141.29 (C9-b), 130.82 (C9), 127.99 (C7), 124.24 (C9-a), 115.58 (C8), 110.42 (C6), 100.84 (C3-a), 44.07 (CH_3) ppm.

9-Chloro-1,5-dimethyl-1,2-dihydro-3H-pyrazolo[4,3-c]-quinoline-3,4(5H)-dione (**7k**, $C_{12}H_{10}ClN_3O_2$)
Following the general procedure, the reaction of 0.5 g compound **6e** (0.17 mmol) and 45 mm^3 methylhydrazine (0.87 mmol) in 5 cm^3 ethoxyethanol gave yellow compound **7k** (0.027 g, 61 %). M.p.: >260 °C; IR (KBr): $\overline{\nu} = 3290$, 1667, 1610 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 10.80$ (br s, 1H), 7.63–7.44 (m, 2H), 7.42 (d, $J = 7.5$ Hz, 1H), 3.93 (s, 3H), 3.55 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 159.21$ (CO), 157.52 (CO), 141.86 (C5-a), 140.84 (C9-b), 131.09 (C9), 128.55 (C7), 124.49 (C9-a), 115.27 (C8), 111.39 (C6), 100.41 (C3-a), 43.78 (CH_3), 29.68 (CH_3) ppm.

5-Benzyl-9-chloro-1-methyl-1,2-dihydro-3H-pyrazolo[4,3-c]quinoline-3,4(5H)-dione (**7l**, $C_{18}H_{14}ClN_3O_2$)
Following the general procedure, the reaction of 0.05 g compound **6d** (0.14 mmol) and 36 mm^3 methylhydrazine (0.70 mmol) in 5 cm^3 ethoxyethanol gave yellow compound **7l** (0.023 g, 51 %). M.p.: >260 °C; IR (KBr): $\overline{\nu}n = 3300$, 1675, 1580 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.31$–7.24 (m, 8H), 5.40 (s, 2H), 3.53 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 161.27$ (2xCO), 142.31 (C5-a), 140.36 (C9-b), 137.90 (C, benzyl), 129.90 (C9), 128.92 (CH, benzyl), 127.29 (2×CH, benzyl), 126.88 (2×CH, benzyl), 124.67 (C7), 123.96 (C9-a), 115.50 (C8), 114.88 (C6), 104.01 (C3-a), 44.32 (CH_2, benzyl), 32.57 (CH_3) ppm.

Computational studies

DFT calculations at the B3LYP level of theory using 6-311G** basis set were performed with the Gaussian09 package. Full geometry optimizations of reactants and products (in gas and liquid phases) were done at 298 K, for ground state as well as for transition state searches including vibrational analysis to locate stationary point and zero point energy (zpe). The effect of solvation in 2-ethoxyethanol as included in the code was carried out using PCM method [36, 37]. Transition state (TS) structures were determined by searching the synchronous transit-guided quasi-Newton (STQN) method (QST2 keyword) for first-order saddle points on the potential energy

surface (PES) via frequency calculations. The Fukui function and local softness were computed from anionic and cationic forms of reactants with the same geometry as the neutral one using gross electronic population [38].

Hydroxyl radical scavenging activity assay

In a screw-capped test tube, 0.2 cm^3 sodium benzoate (10 mmol), 0.2 cm^3 $FeSO_4 \cdot 7H_2O$ (10 mmol), and EDTA (10 mmol) were added. Then a phosphate buffer (pH 7.4, 0.1 mol) was added to give a total volume of 1.8 cm^3. A H_2O_2 solution (0.2 cm^3, 10 mmol) was added, and the mixture was then incubated at 37 °C for 2 h. The fluorescence was measured at 407 nm emission and excitation 305 nm. RSA OH°% = Absorbance in the presence of sample divided by the absorbance in the absence of sample $\times$ 100. Mean values from three independent samples were calculated and showed for each compound a standard deviations less than 5 %. Quercetol was used as a positive control.

DPPH radical scavenging activity assay

For this assay the method of Hatano et al. [39] was used to evaluate the capacity of compounds to scavenge the "stable" free radical DPPH. Different concentrations of methanolic solutions (0.3 cm^3) of the compounds were mixed with a DPPH methanolic solution (1.5×10^{-4} mol/dm^3, 2.7 cm^3). The solution was mixed vigorously and kept for 2 h in the dark, until stable absorption values were obtained. The quenching of the DPPH radical was determined by measuring the absorption at 517 nm. The RSA was calculated as a percentage of disappearance of DPPH purple color using the equation $\%\ \mathrm{RSA} = [(A_{\mathrm{DPPH}} - A_{\mathrm{S}})/A_{\mathrm{DPPH}}] \times 100$, where A_{DPPH} is the absorbance of the DPPH solution and A_{S} is the absorbance of the solution when the compound has been added at a given concentration. Mean values from three independent samples were calculated and showed for each compound a standard deviations less than 5 %. Ascorbic acid was used as a positive control.

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