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Synthesis of new 2- and 3-hydroxyquinoline-4-carboxylic acid derivatives as potential antioxidants

Abstract: A new series of 3-aryl-2-hydroxyquinoline-4-carboxylic acids **17a,b**, 2-aryl-3-hydroxyquinoline-4-carboxylic acids **12a–d** and their derivatives **13–16** and **18–21** were designed, synthesized and evaluated for their antioxidant activity using the ABTS assay method. Compounds **14** and **21a,b** showed good antioxidant activity, whereas the remaining compounds displayed mild to moderate activity. All compounds were characterized by physical and spectral data.

Keywords: ABTS assay; antioxidant; benzimidazole; quinoline-4-carboxylic acid; synthesis.

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Introduction

Quinoline derivatives are an important structural moiety in a number of chemotherapeutic agents and biologically active natural products. Several derivatives of cinchoninic acid (quinoline-4-carboxylic acid, **1**) are important quinoline derivatives, including the abandoned analgesic agent cinchophen (**2**) [1] and brequinar sodium (**3**) that has been discovered as an anticancer agent [2] and later found to have immunosuppressive activity [3]. 3-Hydroxy-2-phenylcinchoninic acid (HPC, **4**) has been reported to possess antirheumatic effects [4]. Other derivatives have been reported to show antipsychotic [5], antiallergic [6], antiarthritic [7] and anxiolytic activities [8]. In addition, a series of styrylquinoline derivatives that contain a COOH group at position 7 and an OH group at position 8 of the quinoline moiety have been discovered as antiviral agents. An example is (*E*)-8-hydroxy-2-[2-(3,4,5-trihydroxyphenyl) ethenyl]-7-quinolinecarboxylic acid (**5**) [9] (Figure 1). Furthermore, substituted quinolones/hydroxyquinolines have been investigated for their antioxidant activity. Among important derivatives are 7-chloro-4-hydroxyquinoline (**6**) and 7-fluoro-4-hydroxyquinoline (**7**), which have been characterized by their antioxidant effect against free radical initiated peroxidation [10]. Additional synthetic quinolone derivatives with effective antioxidant activity are TA 270 (**8**) [11] and quinoline-3-carbohydrazides (**9**) [12] (Figure 1). 2-Substituted benzimidazoles were recently reported to possess antioxidant activity [13]. Based on the previous data and literature review, new starting synthons were designed and synthesized: 3-aryl-2-hydroxyquinoline-4-carboxylic acids (**17a,b**) and 2-aryl-3-hydroxyquinoline-4-carboxylic acids (**12a-d**). Hybridization with several pharmacophoric moieties were achieved in order to explore the effect on enhancing the antioxidant activity. The following analogs were obtained: ester derivatives (**13a-d**, **15** and **18a,b**), *O*-acetyl derivatives (**16a-d**) and *O*-alkyl/aralkyl derivatives (**19a-d** and **20a,b**). In addition, a heterocyclic hybrid system, in which 2- or 3-hydroxyquinoline ring is hybridized at C4 with 2-benzimidazolyl ring (**14** and **21a,b**) was designed and synthesized. The effect of structural modification at C6 of the quinoline with two lipophilic groups one of which is electron donating and the other is electron withdrawing (-CH_3 and -Br respectively) were designed to discover their effect on potentiation of the antioxidant activity. The introduction of the latter group is useful where bromo-substituent as halogen bonding of the type R–X···Y–R′, where the halogen X acts as a Lewis acid and Y can be any electron donor moiety (electrostatic attraction) has been successfully harnessed for lead identification and optimization. In addition, halogenated aromatic systems are considered as common scaffolds in medicinal chemistry [14, 15]. As part of this work, a series of quinoline derivatives were synthesized and evaluated for their antioxidant activity using an improved ABTS decolorization assay [16]. ABTS is 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt.

Results and discussion

Chemistry

The structural core of quinoline has generally been synthesized by various conventional reactions such as

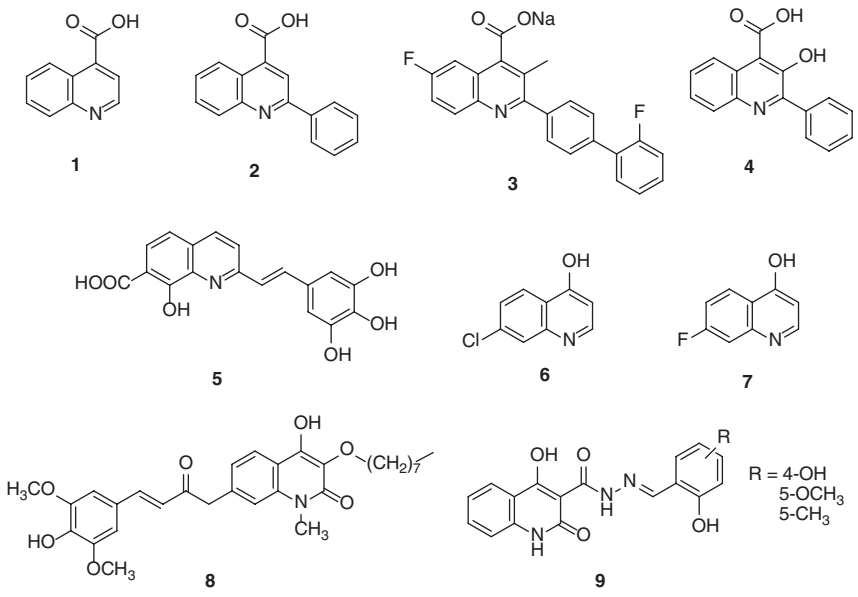
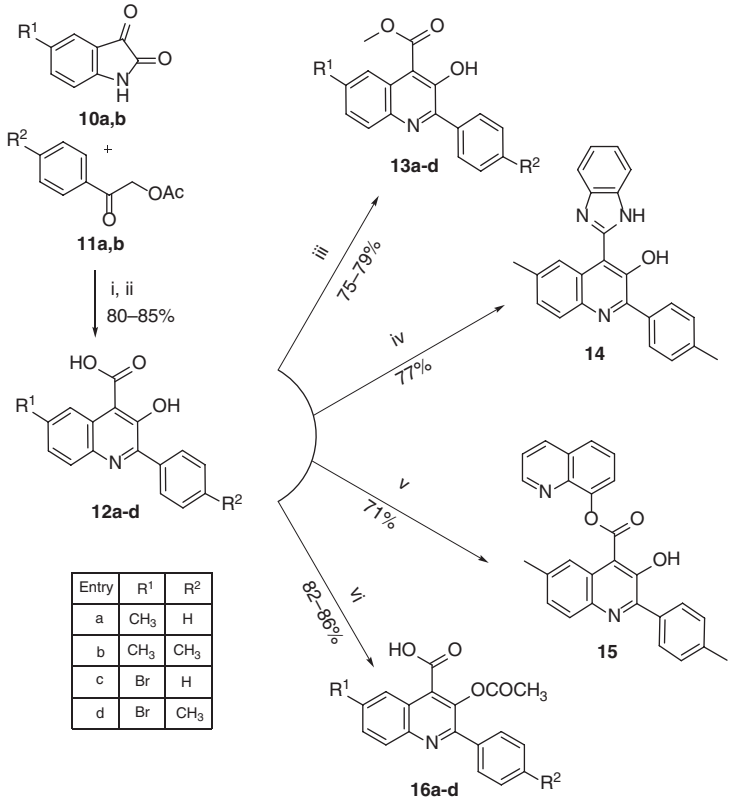


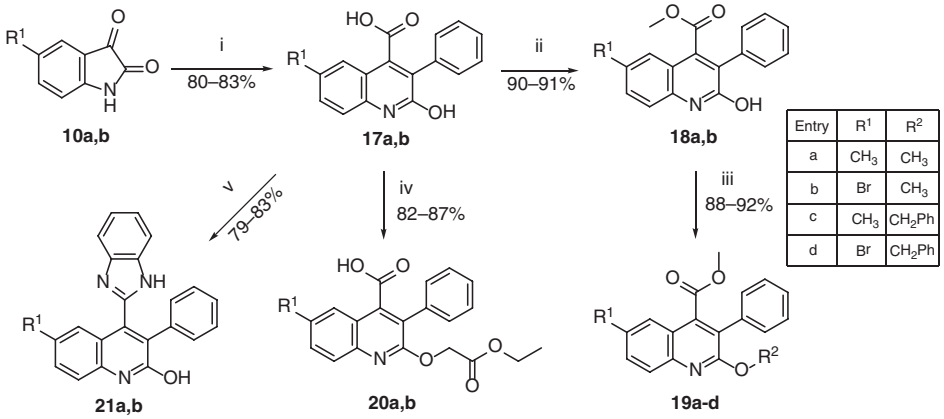
Figure 1 Biologically important hydroxyquinolines and quinolinecarboxylic acids.



Entry	R^1	R^2
a	CH_3	H
b	CH_3	CH_3
c	Br	H
d	Br	CH_3

Scheme 1 Reagents and conditions: (i) KOH, C_2H_5OH, H_2O, reflux, 24 h; (ii) HOAc; (iii) CH_3OH, H_2SO_4, reflux, 72 h; (iv) *o*-phenylenediamine, 140°C, 1–2 h; (v) 8-hydroxyquinoline, H_2SO_4, DMF, reflux, 72 h; (vi) HOAc/Ac_2O, reflux, 48 h.

Skraup, Doebner-Von Miller, Friedlander, Pfitzinger, Conrad-Limpach and Combes. These classical syntheses are well known and still used frequently for the preparation of quinoline backbone. However, these methods for quinoline synthesis often do not allow for adequate diversity and substitution on the quinoline ring system. Among the synthetic strategies which could be conceived for the synthesis of quinoline derivatives, the Pfitzinger



Scheme 2 Reagents and conditions: (i) phenylacetic acid, NaOAc, 200°C, 3 h; (ii) CH_3OH, H_2SO_4, reflux, 6 h; (iii) RX, CH_3CN, K_2CO_3, reflux, 24 h; (iv) $BrCH_2COOC_2H_5$, DMF, K_2CO_3, reflux, 24 h; (v) *o*-phenylenediamine, 140°C, 1–2 h.

reaction offers a very convenient synthetic entry to the quinoline-4-carboxylic acid derivatives from isatins and a ketone.

Synthesis of the substituted quinoline-4-carboxylic acid derivatives **12a–d**, which are the starting compounds of Scheme 1, was achieved through Pfitzinger reaction by heating isatins **10a,b** [17] with compounds **11a,b** [18] in an aqueous/alcoholic KOH solution. The conversion of compounds **12a–d** into their esters **13a–d** was accomplished by using Fischer esterification [19], that is, heating **12a-d** in methanol in the presence of sulfuric acid as a catalyst and a dehydrating agent. Benzimidazole derivative **14** was obtained by conventional condensation of **12b** with *o*-phenylenediamine under solvent-free condition. Esterification of **12b** with 8-hydroxyquinoline afforded the ester **15**. *O*-Acetylated compounds **16a–d** were obtained by heating of the respective substrates **12a–d** with a mixture of acetic anhydride and acetic acid (Scheme 1). Synthesis of 2-hydroxyquinoline-4-carboxylic acid derivatives **17a,b** was achieved through reaction of isatin derivatives **10a,b** and phenyl acetic acid via fusion in presence of sodium acetate as a catalyst (Scheme 2) [20]. The conversion of **17a,b** into their methyl esters **18a,b** was achieved through esterification following the same procedure already mentioned for the esters **13a–d**. Alkylation and aralkylation of compounds **18a,b** at the 2-hydroxy group affording **19a,b** was achieved through Williamson ether synthesis [21]. In a similar way, alkylation of the 2-hydroxyl group of compounds **17a,b** with ethyl bromoacetate in DMF using K_2CO_3 as a catalyst to afford esters **20a,b** [22, 23]. In addition, treatment of the carboxylic acids **17a,b** with *o*-phenylenediamine furnished the respective benzimidazoles **21a,b**

Table 1 Results of ABTS antioxidant assay.

Tested compound	Sample absorbance (mean)	% Inhibition	Tested compound	Sample absorbance (mean)	% Inhibition
Control	0.512	0.00	**16c**	0.473	7.20±0.29
Ascorbic acid	0.051	90.04±0.31	**16d**	0.466	8.97±0.41
12a	0.474	7.51±0.02	**17a**	0.504	1.65±0.19
12b	0.491	4.09±0.02	**17b**	0.490	4.29±0.24
12c	0.473	7.60±0.29	**18a**	0.491	4.19±0.13
12d	0.466	8.97±0.40	**18b**	0.436	14.82±0.29
13a	0.512	0.00±0.00	**19a**	0.446	12.87±0.39
13b	0.394	23.02±0.55	**19b**	0.458	10.63±0.35
13c	0.504	1.65±0.08	**19c**	0.290	43.41±0.24
13d	0.504	1.65±0.18	**19d**	0.335	34.53±0.47
14	0.048	96.00±0.52	**20a**	0.266	48.09±0.45
15	0.466	8.97±0.45	**20b**	0.114	77.65±0.87
16a	0.458	10.63±0.57	**21a**	0.050	93.00±0.64
16b	0.473	7.20±0.19	**21b**	0.049	94.00±0.55

Data are expressed as mean±SEM, n=3; SEM is standard error of the mean.

(Scheme 2). The synthesis of new target 2- or 3-hydroxyquinoline derivatives hybridized and conjugated with 1*H*-benzimidazol-2-yl moiety at C4 (**14** and **21a,b**) of the expected antioxidant activity is one of the unique points of this work. Compounds **14** and **21a,b** are the first examples of this class. The heterocyclic hybridized systems of non-hydroxylated quinolone derivatives have been previously obtained by using several synthetic methods [24–28].

ABTS antioxidant assay

The synthesized compounds were evaluated for their antioxidant activity using an improved ABTS decolorization assay [16]. The assay that uses ABTS, 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt, is a radical cation decolorization test. This spectrophotometric method is widely used for the assessment of antioxidant activity of various substances. The test is applicable for both lipophilic and hydrophilic compounds. The colored $ABTS^{\cdot+}$ radical cation, generated by oxidation of ABTS, is quantified spectrophotometrically. The results of the antioxidant screening are shown in Table 1.

Conclusions

The results summarized in Table 1 reveal that 2- or 3-hydroxyquinoline derivatives **14** and **21a,b** carrying benzimidazole moiety exhibit high antioxidant activity that is slightly higher than the antioxidant property of ascorbic acid. In addition, the esters **19c** and **20a,b** show mild antioxidant activity. The remaining compounds are weak antioxidants.

The exhibited promising antioxidant activity in compound **14** may be attributed to its behavior as a bidentate chelator (-OH at C3 and –NH of benzimidazole) for (Fe^{2+}, Cu^{2+}, Zn^{2+}), thus preventing metal oxidation catalysis, while the high antioxidant activity in **21a,b** may be potentiated by benzimidazole ring. However, those 2- or 3-hydroxyquinoline-benzimidazole hybrids may be regarded as lead compounds in combating oxidative stress. Further structural modification at C4 is needed for studying the effect of other functional groups on antioxidant activity.

Experimental

Chemistry

Melting points were recorded using a Fisher-Johns melting point apparatus and were uncorrected. ^{1}H NMR spectra (400 MHz) were obtained in DMSO-d_6 on a Bruker Avance 400 spectrometer at Georgia State University, Atlanta, GA, USA. Elemental analysis data were obtained at the Micro Analytical Center, Cairo University, Egypt. MS analyses were performed on a JOEL JMS-600H spectrometer in Cairo University. Reaction times were determined using a TLC technique on silica gel plates 60 F_{245} E. Merk, and the spots were visualized by UV irradiation at 366 nm or 245 nm. Synthesis of isatins **10a,b** and acetates of α-hydroxyketones **11a,b** is described elsewhere [17, 29]. 3-Hydroxy-6-methyl-2-phenylquinoline-4-carboxylic acid (**12a**) and 6-bromo-3-hydroxy-2-phenylquinoline-4-carboxylic acid (**12c**) were synthesized as previously reported [30].

Synthesis of 2-aryl-3-hydroxy-6-substituted quinoline-4-carboxylic acids (12a–d)

A mixture of acetoxy ketone **11a,b** (5 mmol), 5-substituted isatin **10a,b** (5 mmol) and KOH (1.28 g, 23 mmol) in 50% aqueous ethanol (20 mL) was heated under reflux for 24 h. Then, the reaction mixture was diluted with aqueous ethanol (20 mL, 30%) and neutralized with 50% acetic acid. The resultant precipitate was filtered, dried and crystallized from ethanol.

3-Hydroxy-6-methyl-2-(4-methylphenyl)quinoline-4-carboxylic acid (12b) Yellow crystals; mp 194–195°C; yield 82%; ^{1}H NMR: δ 2.31 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 7.33–7.40 (2H, m, Ar-H), 7.64 (d, J = 8 Hz, 1H, Quin-7-H), 8.05 (d, J = 8 Hz, 1H, Quin-8-H), 8.10–8.21 (m, 2H, Ar-H), 8.48 (s, 1H, Quin-5-H), 9.11 (s, 1H, OH, D_2O exchangeable), COOH proton seems to be exchanged by the solvent; MS: m/z 294 (M^++1, 10%), 293 (M^+, 43%). Anal. Calcd for $C_{18}H_{15}NO_3$ (293.32): C, 73.71; H, 5.15; N, 4.78. Found: C, 73.73; H, 5.10; N, 4.77.

6-Bromo-3-hydroxy-2-(4-methylphenyl)quinoline-4-carboxylic acid (12d) Yellow crystals; mp 180–182°C; yield 80%; ^{1}H NMR: δ 2.37 (s, 3H, CH_3), 7.30–7.42 (2H, m, Ar-H), 7.71 (d, J = 8 Hz, 1H, Ar-H Quin-7-H), 8.18–8.26 (m, 2H, Ar-H), 8.35 (d, J = 8 Hz, 1H, Quin-8-H), 8.56 (s, 1H, Quin-5-H), 9.65 (s, 1H, OH, D_2O exchangeable), COOH proton seems to be exchanged by the solvent; MS: m/z 360 (M^++2, 8%), 358 (M^+, 8%). Anal. Calcd for $C_{17}H_{12}BrNO_3$ (358.19): C, 57.00; H, 3.38; N, 3.91. Found: C, 57.03; H, 3.40; N, 3.92.

General procedure for synthesis of methyl 2-aryl-3-hydroxy-6-substituted quinoline-4-carboxylates (13a–d)

A few drops of concentrated sulfuric acid were added to a solution of compound **12a–d** in methanol (25 mL) and the reaction mixture was heated under reflux for 72 h. After cooling, the mixture was poured into ice water and the resultant solid was filtered, washed with water, dried and crystallized from ethanol.

Methyl 3-hydroxy-6-methyl-2-phenylquinoline-4-carboxylate (13a) White crystals; mp 118–120°C; yield 79%; ^{1}H NMR: δ 2.30 (s, 3H, Ar-CH_3), 3.40 (s, 3H, $COOCH_3$), 7.10–7.22 (m, 3H, Ar-H), 7.32–7.43 (m, 2H, Ar-H), 7.34 (d, J = 8 Hz, 1H, Quin-7-H), 7.90 (d, J = 8 Hz, 1H, Quin-8-H), 8.00 (s, 1H, Quin-5-H), 11.22 (s, 1H, OH, D_2O exchangeable); MS:

m/z 294 (M^++1, 9%), 293 (M^+, 40%). Anal. Calcd for $C_{18}H_{15}NO_3$ (293.32): C, 73.71; H, 5.15; N, 4.78. Found: C, 73.72; H, 5.12; N, 4.79.

Methyl 3-hydroxy-6-methyl-2-(4-methylphenyl)quinoline-4-carboxylate (13b) White crystals; mp 158–160°C; yield 77%; ^{1}H NMR: δ 2.31 (s, 3H, Ar-CH_3), 2.50 (s, 3H, Ar-CH_3), 4.23 (s, 3H, $COOCH_3$), 7.03–7.15 (m, 2H, Ar-H), 7.22 (d, *J* = 8 Hz, 1H, Quin-7-H), 7.52–8.62 (m, 2H, Ar-H), 7.87 (d, *J* = 8 Hz, 1H, Quin-8-H), 8.20 (s, 1H, Quin-5-H), 10.90 (s, 1H, OH, D_2O exchangeable); MS: m/z 308 (M^++1, 22%), 307 (M^+, 55%). Anal. Calcd for $C_{19}H_{17}NO_3$ (307.34): C, 74.25; H, 5.58; N, 4.56. Found: C, 74.28; H, 5.60; N, 4.58.

Methyl 6-bromo-3-hydroxy-2-phenylquinoline-4-carboxylate (13c) White crystals; mp 135–136°C; yield 79%; ^{1}H NMR: δ 4.32 (s, 3H, $COOCH_3$), 7.20–7.31 (m, 3H, Ar-H), 7.42–7.53 (m, 2H, Ar-H), 7.83 (d, *J* = 8 Hz, 1H, Quin-7-H), 8.20 (d, *J* = 8 Hz, 1H, Quin-8-H), 8.33 (s, 1H, Quin-5-H), 11.20 (s, 1H, OH, D_2O exchangeable); MS: m/z 360 (M^++2%), 358 (M^+, 24%). Anal. Calcd for $C_{17}H_{12}BrNO_3$ (358.19): C, 57.00; H, 3.38; N, 3.91. Found: C, 57.02; H, 3.39; N, 3.93.

Methyl 6-bromo-3-hydroxy-2-(4-methylphenyl)quinoline-4-carboxylate (13d) White crystals; mp 144–146°C; yield 75%; ^{1}H NMR: δ 2.42 (s, 3H, Ar-CH_3), 4.13 (s, 3H, $COOCH_3$), 7.22–7.30 (m, 2H, Ar-H), 7.88 (d, *J* = 8 Hz, 1H, Quin-7-H), 7.92–8.13 (m, 2H, Ar-H), 8.12 (d, *J* = 8 Hz, 1H, Quin-8-H), 8.23 (s, 1H, Quin-5-H), 11.20 (s, 1H, OH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.9, 53.1, 117.1, 121.3, 125.5, 125.6, 128.5, 129.4, 129.9, 131.5, 134.0, 138.8, 140.4, 149.0, 152.7, 167.1; MS: m/z 374 (M^++2, 18%), 372 (M^+, 19%). Anal. Calcd for $C_{18}H_{14}BrNO_3$ (372.21): C, 58.08; H, 3.79; N, 3.76. Found: C, 58.11; H, 3.81; N, 3.77.

Synthesis of 4-(1*H*-benz[*d*]imidazol-2-yl)-6-methyl-2-(4-methylphenyl)quinolin-3-ol (14)

A mixture of compound **12b** (2.93 g, 10 mmol) and *o*-phenylenediamine (1.08 g, 10 mmol) was thoroughly ground with a pestle in a mortar at room temperature in an open atmosphere until the overall mixture turned into a melt. The melted mixture was then heated in a sand bath at 140°C for 1–2 h. The progress of the reactions was monitored by TLC. After completion, the melt was cooled, poured over ice water, and the solid material was filtered, washed, dried and crystallized from dichloromethane: buff crystals; mp >300°C; yield 77%; ^{1}H NMR: δ 2.33 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.30–7.38 (2H, m, Ar-H), 7.60 (d, *J* = 8 Hz, 1H, Quin-7-H), 8.15 (d, *J* = 8 Hz, 1H, Quin-8-H), 8.19–8.25 (m, 2H, Ar-H), 8.28–8.35 (m, 4H, Ar-H), 8.50 (s, 1H, Quin-5-H), 8.98 (s, 1H, OH, D_2O exchangeable), NH proton seems to be exchanged by the solvent; MS: m/z 365 (M^+, 26%). Anal. Calcd for $C_{24}H_{19}N_3O$ (365.43): C, 78.88; H, 5.24; N, 11.50. Found: C, 78.90; H, 5.27; N: 11.54.

Synthesis of quinolin-8-yl 3-hydroxy-6-methyl-2-(4-methylphenyl)quinolin-4-carboxylate (15)

Sulfuric acid (1 mL) was added to a suspension of compound **12b** (2.93 g, 10 mmol) and 8-hydroxyquinoline (1.45 g, 10 mmol) in DMF (25 mL). The reaction mixture was heated under reflux for 6 h. After cooling, the precipitated solid was filtered, washed with ethanol, dried and crystallized from 95% ethanol: white crystals; mp 285–287°C; yield 71%; ^{1}H NMR: δ 2.32 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 7.10–7.25 (m, 3H, Ar-H), 7.33–7.64 (m, 3H, Ar-H), 8.05 (d, *J* = 8 Hz, 1H, Quin-7-H), 8.10–8.21 (m, 2H, Ar-H), 8.25–8.31 (m, 2H, Ar-H), 8.48 (s, 1H, Quin-5-H), 8.60 (d, *J* = 8 Hz, 1H, Quin-8-H), 9.00 (s, 1H, OH, D_2O exchangeable); MS: m/z 421 (M^++1, 0.1%), 420 (M^+, 0.03%). Anal. Calcd for $C_{27}H_{20}N_2O_3$ (420.46): C, 77.13; H, 4.79; N, 6.66. Found: C, 77.14; H, 4.81; N, 6.69.

Synthesis of 3-acetoxy-2-aryl-6-substituted-quinoline-4-carboxylic acids (16a–d)

A mixture of compound **12a–d** (10 mmol), glacial acetic acid (10 mL) and acetic anhydride (10 mL) was heated under reflux for 48 h. After cooling, the mixture was poured into ice water and the resultant solid was filtered, washed with water, dried and crystallized from dichloromethane.

3-Acetoxy-6-methyl-2-phenylquinoline-4-carboxylic acid (16a) White crystals; mp 206–208°C; yield 85%; ^{1}H NMR: δ 2.12 (s, 3H, Ar-CH_3), 2.65 (s, 3H, $OCOCH_3$), 7.41–7.52 (m, 3H, Ar-H), 7.54–7.66 (m, 2H, Ar-H), 7.71 (d, *J* = 8 Hz, 1H, Quin-7-H), 8.05 (d, *J* = 8 Hz, 1H, Quin-8-H), 8.37 (s, 1H, Quin-5-H), COOH proton seems to be exchanged by the solvent; MS: m/z 322 (M^++1, 10%), 321 (M^+, 41%). Anal. Calcd for $C_{19}H_{15}NO_4$ (321.33): C, 71.02; H, 4.71; N, 4.36. Found: C, 71.10; H, 4.73; N, 4.33.

3-Acetoxy-6-methyl-2-(4-methylphenyl)quinoline-4-carboxylic acid (16b) White crystals; mp 205–207°C; yield 82%; ^{1}H NMR: δ 2.11 (s, 3H, Ar-CH_3), 2.40 (s, 3H, Ar-CH_3), 2.63 (s, 3H, $OCOCH_3$), 7.22–7.34 (m, 2H, Ar-H), 7.50 (d, *J* = 8 Hz, 1H, Quin-7-H), 7.81–7.92 (m, 2H, Ar-H), 8.16 (d, *J* = 8 Hz, 1H, Quin-8-H), 8.32 (s, 1H, Quin-5-H), COOH proton seems to be exchanged by the solvent; MS: m/z 336 (M^++1, 14%), 335 (M^+, 45%). Anal. Calcd for $C_{20}H_{17}NO_4$ (335.35): C, 71.63; H, 5.11; N, 4.18. Found: C, 71.66; H, 5.16; N, 4.21.

3-Acetoxy-6-bromo-2-phenylquinoline-4-carboxylic acid (16c) White crystals; mp 195–197°C; yield 86%; ^{1}H NMR: δ 2.60 (s, 3H, CH_3), 7.05–7.18 (m, 3H, Ar-H), 7.22–7.34 (m, 2H, Ar-H), 7.84 (d, *J* = 8 Hz, 1H, Quin-7-H), 8.09 (d, *J* = 8 Hz, 1H, Quin-8-H), 8.25 (s, 1H, Quin-5-H), COOH proton seems to be exchanged by the solvent; MS: m/z 388 (M^++2, 22%), 386 (M^+, 23%). Anal. Calcd for $C_{18}H_{12}BrNO_4$ (386.20): C, 55.98; H, 3.13; N, 3.63. Found: C, 55.99; H, 3.16; N, 3.67.

3-Acetoxy-6-bromo-2-(4-methylphenyl)quinoline-4-carboxylic acid (16d) White crystals; mp 198–200°C; yield 85%; ^{1}H NMR: δ 2.12 (s, 3H, Ar-CH_3), 2.62 (s, 3H, $OCOCH_3$), 7.30–7.42 (m, 2H, Ar-H), 7.75 (d, *J* = 8 Hz, 1H, Quin-7-H), 7.88–7.97 (m, 2H, Ar-H), 8.10 (d, *J* = 8 Hz, 1H, Quin-8-H), 8.19 (s, 1H, Quin-5-H), COOH proton seems to be exchanged by the solvent; MS: m/z 402 (M^++2, 25%), 400 (M^+, 26%). Anal. Calcd for $C_{19}H_{14}BrNO_4$ (400.22): C, 57.02; H, 3.53; N, 3.50. Found: C, 57.05; H, 3.55; N, 3.53.

Synthesis of 2-hydroxy-3-phenyl-6-substituted quinoline-4-carboxylic acids (17a,b)

A mixture of 5-methyl or 5-bromoisatin (15 mmol), phenylacetic acid (3.57 g, 26.25 mmol) and sodium acetate (0.3 g) was heated at 200°C for 3 h. After cooling, sodium hydroxide solution (20 mL, 30%) was

added. The mixture was filtered and the filtrate was acidified with hydrochloric acid. The precipitated solid was filtered, washed with water, dried and crystallized from 95% ethanol.

2-Hydroxy-6-methyl-3-phenylquinoline-4-carboxylic acid (17a) White crystals; mp >300°C; yield 80%; ^{1}H NMR: δ 2.31 (s, 3H, CH_3), 7.25–7.34 (m, 3H, Ar-H),7.40–7.47 (m, 2H, Ar-H), 7.53 (d, *J* = 8 Hz, 1H, Quin-7-H), 7.66 (d, *J* = 8 Hz, 1H, Quin-8-H), 8.08 (s, 1H, Quin-5-H), 12.11 (s, 1H, OH, D_2O exchangeable), COOH proton seems to be exchanged by the solvent; MS: m/z 280 (M^++1, 20%), 279 (M^+, 75%). Anal. Calcd for $C_{17}H_{13}NO_3$ (279.29): C, 73.11; H, 4.69; N, 5.02. Found: C, 73.13; H, 4.72; N, 5.05.

6-Bromo-2-hydroxy-3-phenylquinoline-4-carboxylic acid (17b) White crystals; mp >300°C; yield 83%; ^{1}H NMR: δ 7.28–7.38 (m, 3H, Ar-H),7.40–7.52 (m, 2H, Ar-H), 7.70 (d, *J* = 8 Hz, 1H, Quin-7-H), 7.73 (d, *J* = 8 Hz, Quin-8-H), 8.11 (s, 1H, Quin-5-H), 12.31 (s, 1H, OH, D_2O exchangeable), COOH proton seems to be exchanged by the solvent; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 113.6, 117.1, 117.5, 126.9, 127.4, 127.9, 129.3, 130.0, 133.0, 133.9, 137.4, 140.63, 160.2, 166.6; MS: m/z 346 (M^++2, 16%), 344 (M^+, 16%). Anal. Calcd for $C_{16}H_{10}BrNO_3$ (344.16): C, 55.84; H, 2.93; N, 4.07. Found: C, 55.87; H, 2.95; N, 4.10.

Methyl 2-hydroxy-3-phenyl-6-substituted-quinoline-4-carboxylates (18a,b)

Concentrated H_2SO_4 (1 mL) was added to a suspension of compound **17a,b** (10 mmol) in methanol (25 mL). The reaction mixture was heated under reflux for 6 h. After cooling, the precipitated solid was filtered, washed with methanol, dried and crystallized from methanol.

Methyl 2-hydroxy-6-methyl-3-phenylquinoline-4-carboxylate (18a) White crystals; yield 90%; mp 263–265°C; ^{1}H NMR: δ 2.30 (s, 3H, Ar-CH_3), 3.31 (s, 3H, $COOCH_3$), 7.21–7.29 (m, 3H, Ar-H),7.33–7.42 (m, 2H, Ar-H), 7.98 (d, *J* = 8 Hz, 1H, Quin-7-H), 8.01 (d, *J* = 8 Hz, 1H, Quin-8-H), 8.20 (s, 1H, Quin-5-H), 12.12 (s, 1H, OH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.4, 52.4, 115.4, 124.5, 127.7, 128.1, 129.2, 130.1, 131.6, 132.2, 134.2, 135.1, 136.4, 140.2, 160.2, 166.5. MS: m/z 294 (M^++1, 9%), 293 (M^+, 43%). Anal. Calcd for $C_{18}H_{15}NO_3$ (293.32): C, 73.71; H, 5.15; N, 4.78. Found: C, 73.73; H, 5.13; N, 4.80.

Methyl 6-bromo-2-hydroxy-3-phenylquinoline-4-carboxylate (18b) White crystals; mp 247–248°C; yield 91%; ^{1}H NMR: δ 3.52 (s, 3H, CH_3), δ 3.52 (s, 3H, CH_3), 7.21–7.32 (m, 3H, Ar-H),7.30–7.42 (m, 2H, Ar-H), 7.59 (d, *J* = 8 Hz, 1H, Quin-7-H), 7.76 (d, *J* = 8 Hz, 1H, Quin-8-H), 8.00 (s, 1H, Quin-5-H), 12.31 (s, 1H, OH, D_2O exchangeable); MS: m/z 360 (M^++2, 40%), 358 (M^+, 41%). Anal. Calcd for $C_{17}H_{12}BrNO_3$ (358.19): C, 57.00; H, 3.38; N, 3.91. Found: C, 57.03; H, 3.41; N, 3.92.

Synthesis of methyl 2,6-disubstituted-3-phenylquinoline-4-carboxylates (19a–d)

A mixture of compound **18a,b** (10 mmol), alkyl or aralkyl halide (15 mmol) and K_2CO_3 (1.38 g, 10 mmol) in acetonitrile was heated under reflux for 24 h. After cooling, the solid product was filtered, washed with water, dried and crystallized from absolute ethanol.

Methyl 2-methoxy-6-methyl-3-phenylquinoline-4-carboxylate (19a) Yellow crystals; mp 262–264°C; yield 92%; ^{1}H NMR: δ 2.33 (s, 3H, CH_3), 3.40 (s, 3H, $COOCH_3$), 3.80 (s, 3H, OCH_3), 7.10–7.18 (m, 3H, Ar-H),7.28–7.36 (m, 2H, Ar-H), 7.60 (d, *J* = 8 Hz, 1H, Quin-7-H), 7.77 (d, *J* = 8 Hz, 1H, Quin-8-H), 7.92 (s, 1H, Quin-5-H); MS: m/z 308 (M^++1, 10%), 307 (M^+, 11%). Anal. Calcd for $C_{19}H_{17}NO_3$ (307.34): C, 74.25; H, 5.58; N, 4.56. Found: C, 74.28; H, 5.60; N, 4.59.

Methyl 6-bromo-2-methoxy-3-phenylquinoline-4-carboxylate (19b) Yellow crystals; mp 250–251°C; yield 90%; ^{1}H NMR: δ 3.43 (s, 3H, $COOCH_3$), 3.82 (s, 3H, OCH_3), 7.13–7.22 (m, 3H, Ar-H), 7.31–7.42 (m, 2H, Ar-H), 7.63 (d, *J* = 8 Hz, 1H, Quin-7-H), 7.84 (d, *J* = 8 Hz, 1H, Quin-8-H), 7.97 (s, 1H, Quin-5-H); MS: m/z 374 (M^++2, 29%), 372 (M^+, 30%). Anal. Calcd for $C_{18}H_{14}BrNO_3$ (372.21): C, 58.08; H, 3.79; N, 3.76. Found: C, 58.09; H, 3.81; N: 3.79.

Methyl 2-benzyloxy-6-methyl-3-phenylquinoline-4-carboxylate (19c) Yellow crystals; mp 270–272°C; yield 89%; ^{1}H NMR: δ 2.31 (s, 3H, CH_3), 3.31 (s, 3H, $COOCH_3$), 5.62 (s, 2H, CH_2), 7.26–7.57 (m, 10H, Ar-H), 7.93 (d, *J* = 8 Hz, 1H, Quin-7-H), 8.21 (d, *J* = 8 Hz, 1H, Quin-8-H), 8.30 (s, 1H, Quin-5-H); MS: m/z 384 (M^++1, 10%), 383 (M^+, 15%). Anal. Calcd for $C_{25}H_{21}NO_3$ (383.44): C, 78.31; H, 5.52; N, 3.65. Found: C, 78.33; H, 5.54; N, 3.68.

Methyl 2-benzyloxy-6-bromo-3-phenylquinoline-4-carboxylate (19d) Yellow crystals; mp 248–250°C; yield 88%; ^{1}H NMR: δ 3.33 (s, 3H, $COOCH_3$), 5.62 (s, 2H, CH_2), 7.27–7.45 (m, 10H, Ar-H), 7.67 (d, *J* = 8 Hz, 1H, Quin-7-H), 7.78 (d, *J* = 8 Hz, 1H, Quin-8-H), 8.25 (s, 1H, Quin-5-H); MS: m/z 450 (M^++2, 30%), 448 (M^+, 31%). Anal. Calcd for $C_{24}H_{18}BrNO_3$ (448.31): C, 64.30; H, 4.05; N, 3.12. Found: C, 64.32; H, 4.07; N, 3.15.

Synthesis of 6-substituted-2-{[(ethoxycarbonyl)methyl]oxy}-3-phenylquinoline-4-carboxylic acids (20a,b)

A mixture of compound **17a,b** (10 mmol), K_2CO_3 (1.38 g, 10 mmol) and ethyl bromoacetate (1.67 g, 10 mmol) in DMF (20 mL) was heated under reflux for 24 h. After cooling, the mixture was poured on ice water and the resultant solid was filtered, washed with water, dried and crystallized from water.

2-{[(Ethoxycarbonyl)methyl]oxy}-6-methyl-3-phenylquinoline-4-carboxylic acid (20a) Buff crystals; mp 210–211°C; yield 87%; ^{1}H NMR: δ 1.22 (t, 3H, CH_3), 2.34 (s, 3H, Ar-CH_3), 4.21 (q, 2H, CH_2), 4.72 (s, 2H, CH_2), 7.18–7.27 (m, 3H, Ar-H), 7.30–7.38 (m, 2H, Ar-H), 7.40 (d, *J* = 8 Hz, 1H, Quin-7-H), 8.43 (d, *J* = 8 Hz, 1H, Quin-8-H), 8.00 (s, 1H, Quin-5-H), COOH proton seems to be exchanged by the solvent; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 14.4, 21.0, 61.6, 62.1, 115.8, 116.0, 125.4, 128.3, 128.7, 129.8, 131.0, 132.0, 132.8, 134.4, 136.9, 139.8, 160.6, 166.2, 167.6; MS: m/z 366 (M^++1, 19%), 365 (M^+, 34%). Anal. Calcd for $C_{21}H_{19}NO_5$ (365.38): C, 69.03; H, 5.24; N, 3.83. Found: C, 69.05; H, 5.25; N, 3.85.

6-Bromo-2-{[(ethoxycarbonyl)methyl]oxy}-3-phenylquinoline-4-carboxylic acid (20b) Buff crystals; mp 191–192°C; yield 88%; ^{1}H NMR: δ 1.25 (t, 3H, CH_3), 4.24 (q, 2H, CH_2), 4.75 (s, 2H, CH_2), 7.19–7.24 (m, 3H, Ar-H), 7.33–7.40 (m, 2H, Ar-H), 7.45 (d, *J* = 8 Hz, 1H, Quin-7-H),

8.44 (d, J = 8 Hz, 1H, Quin-8-H), 8.12 (s, 1H, Quin-5-H), COOH proton seems to be exchanged by the solvent; MS: m/z 432 (M^++2, 32%), 430 (M^+, 32%). Anal. Calcd for $C_{20}H_{16}BrNO_5$ (430.25): C, 55.83; H, 3.75; N, 3.26. Found: C, 55.85; H, 3.77; N, 3.29.

Synthesis of 4-(1*H*-benz[*d*]imidazol-1-yl)-3-phenyl-6-substituted quinolin-2-ols (21a,b)

A mixture of **17a,b** (10 mmol) and *o*-phenylenediamine (1.08 g, 10 mmol) was thoroughly ground with a pestle in a mortar at room temperature in an open atmosphere until the overall mixture turned into a melt. The melted mixture was then heated in a sand bath at 140°C for 1–2 h. The progress of the reaction was monitored by TLC. After completion, the melt was cooled, poured over ice water, filtered, washed with water, dried and crystallized from water.

4-(1*H*-Benz[*d*]imidazol-1-yl)-6-methyl-3-phenylquinolin-2-ol (21a) White crystals; mp >300°C; yield 83%; ^{1}H NMR: δ 2.33 (s, 3H, CH_3), 7.30–7.38 (3H, m, Ar-H), 7.60 (d, J = 8 Hz, 1H, Quin-7-H), 8.15 (d, J = 8 Hz, 1H, Quin-8-H), 8.19–8.25 (m, 2H, Ar-H), 8.28–8.35 (m, 4H, Ar-H), 8.50 (s, 1H, Quin-5-H), 8.98 (s, 1H, OH, D_2O exchangeable), NH proton seems to be exchanged by the solvent; MS: m/z 352 (M^++1, 4%), 351 (M^+, 5%). Anal. Calcd for $C_{23}H_{17}N_3O$ (351.40): C, 78.61; H, 4.88; N, 11.96. Found: C, 78.63; H, 4.85; N, 11.99.

4-(1*H*-Benz[*d*]imidazol-1-yl)-6-bromo-3-phenylquinolin-2-ol (21b) White crystals; mp 209–211°C; yield 79%; ^{1}H NMR: δ 7.30–7.38 (3H, m, Ar-H), 7.60 (d, J = 8 Hz, 1H, Quin-7-H), 8.15 (d, J = 8 Hz, 1H, Quin-8-H), 8.19–8.25 (m, 2H, Ar-H), 8.28–8.35 (m, 4H, Ar-H), 8.50 (s, 1H, Quin-5-H), 8.98 (s, 1H, OH, D_2O exchangeable), NH seems to be exchanged by the solvent; MS: m/z 418 (M^++2, 1%), 416 (M^+, 1%). Anal. Calcd for $C_{22}H_{14}BrN_3O$ (416.27): C, 63.48; H, 3.39; N, 10.09. Found: C, 63.46; H, 3.38; N, 10.11.

ABTS antioxidant assay

The assay was conducted by using a previously published procedure [16] with the following modifications. The major change was the use of manganese dioxide instead of potassium persulfate. The ABTS solution was prepared in concentration of 0.1 g/100 mL. The amount of MnO_2 used was 25 mg/mL. All reagents were prepared in phosphate buffer (pH 7, 0.1 M), ABTS/MnO_2 = 2:3. The mixture was shaken, centrifuged and filtered to give and the green-blue ABTS×$^+$ radical solution, the color of which remained stable for more than 1 h. For measurements, the absorbance at 734 nm was adjusted to approximately 0.2. The control 2% solution of antioxidant ascorbic acid was used. The concentration of each test sample was 0.01 mg/mL in methanol/phosphate buffer (1:1). The following function was used: the percent inhibition of superoxide production=[(control absorbance – test absorbance)/control absorbance]×100.

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