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Synthesis and investigation of antibacterial and antioxidants properties of some new 5-subsituted-8-hydroxyquinoline derivatives

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Abstract

A new series of 5-alkoxymethyl-8-hydroxyquinoline, 5-alkyaminomethyl-8-hydroxy-quinoline, 5-alkylthio-methyl-8-hydroxyquinoline were synthesized starting from 5-chloromethyl-8-hydroxyquinoline and identified using spectral analysis IR, ^{1}H NMR and ^{13}C NMR. The newly synthesized compounds were evaluated and screened "*in vitro*" for antibacterial activities against Gram-positive and Gram-negative bacterial strains; the preliminary screening results showed that the series of the alkylthiomethyl-8-hydroxyquinoline present a significant antibacterial activity when compared to the standard antibiotic, Nitroxoline. Furthermore, the synthesized compounds demonstrated moderate antioxidant activities at a low compared with to the ascorbic acid by free radical scavenging method with 2,2-diphenyl-1-picrylhydrazyl (DPPH).

1. Introduction

Some bacteria have become resistant to commonly used antibiotics; produce increasingly an important public health's problem. It was estimated that the resistance to antibiotics had caused thousands of deaths, and also causing an economical point of view of billion dollars every year, hence the necessity to find out new antibacterial agents in structural classes distinct to the existing antibiotic.

The quinoline scaffold exists in numerous natural products and synthetically prepared compounds; it has a great importance to humanity due to their wide spectrum of biological activities, many quinoline derivatives have been used as antibiotic [1], anticancer [2-4], antituberculosis [5], and antimalarial drugs [6], therefore, many synthetic routes have been put in evidence for the preparation of quinoline derivatives. The introductions of some heterocyclic substituents having different physico-chemical properties on the quinoline nucleus keep and enhance the antibacterial profile [7-8].

In particular, 8-hydroxyquinoline and its derivatives have been known for a long time due to their widespread application in the field of analytical chemistry and separation techniques [9-10].It plays a very important role for extraction of metal ions; they are coordinated with various transition metal ions forming complexes those were reported to be active against certain bacteria, fungi and its potency proportional with its ion chelation due to their lipid solubility [11-12]. However, some derivatives have also been reported to act as organic inhibitors of corrosion [13], as potential HIV-1 integrase inhibitors [14]. They have also been used as potent agents for neuroprotection against Alzheimer, Parkinson, and other neurodegenerative diseases [15]. Furthermore, research showed that the modification of an 8-hydroxyquinoline moiety by changing its substituents at 2-position, 5-position and 7-position, have also attracted considerable interest in bioorganic and medicinal chemistry. Dardari

et al. [16] designed and synthesized 7-[5′-(3′-phenylisoxazolino)-methyl]-8-hydroxyquinoline, which inhibited the multiplication *in vitro* of *Leishmania tropica*, *Leishmania major* and *Leishmania infantum* (Antileishmanial activity) at micromolar concentrations. Another research [17] showed that, 8-hydroxy-2-quinolinecarbaldehyde has showed the best *in vitro* cytotoxicity against the human cancer cell lines. Also, the substitution at the position 5 of 8-hydroxyquinoline have been the subject of several research due to their unique chemical properties. For example, in a previous work, we have synthesized a series of 5-((4-alkylpiperazin-1-yl) methyl) quinoline-8-ol derivatives and studied their antibacterial activity. Three of them exhibit significant antibacterial activity compared to standard antibiotics [18]. Madonna *et al*. [19] reported the synthesis of 5,5'-(3,5-Bis(trifluoromethyl)benzylazanediyl)bis(methylene)diquinaldine-8-ol and their antiproliferative effect on a large panel of cancer cell lines. On the other hand, phenolic compounds and the aromatic rings bearing N–H bond functions are reported in the literature as good antioxidants [20], but no work has been reported in literature concerning the application of 8-hydroxquinoline derivatives as antioxidants.

The aim of the present work is to synthesize series of some 5-alkylthiomethyl, 5-alkoxymethyl- and 5-aminomethyl-substituted 8-hydroxyquinoline. The synthesized compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy and tested against Gram-positive and Gram-negative bacteria, and the antioxidant effect of some compounds has been evaluated using DPPH radical scavenging.

2. Experimental section

2.1. General Information

All used solvents and chemicals products of departures used were purchased from Aldrich (France or Spain). NMR spectra were recorded on a Bruker Avance model (300 MHz) for solutions in Me_2SO-d_6; Chemical shifts are given as δ values with reference to tetramethylsilane (TMS) as internal standard. The progress of the reaction was followed by Thin-Layer Chromatography (TLC) using silica gel 60 F254 (E. Merck) plates with visualization by UV light (254 nm). Silica gel with 0.040–0.063 mm particle size was used as a support in every flash chromatography purification procedure; Melting points were determined on an automatic electrothermal IA 9200 digital melting point apparatus in capillary tubes and are uncorrected.

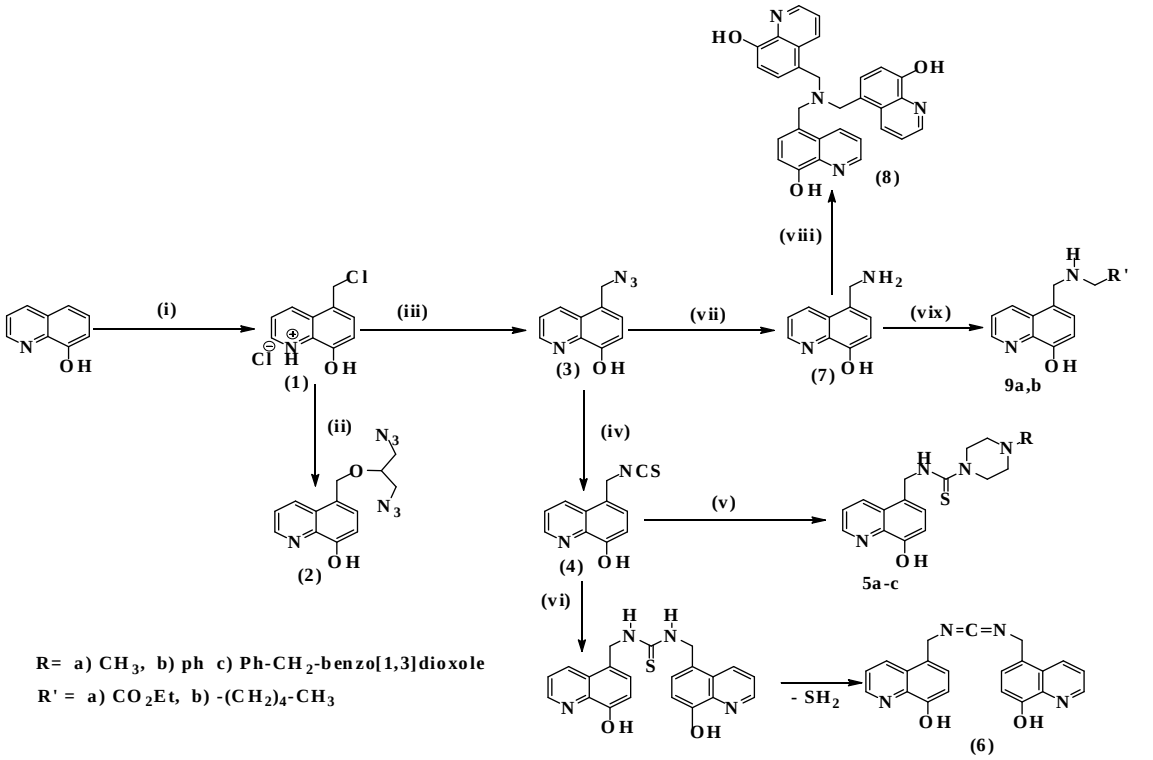
2.2. Chemical synthesis and characterization

The 8-hydroxyquinoline has been transformed on 5-chloromethyl-8-hydroxyquinoline hydrochloride **(1)** according to a modified method described before [24], the crude product was washed with concentrated hydrochloric acid and acetone to obtain a high purity of 5-chloromethyl-8-hydroxyquinoline hydrochloride and in order to eliminate the 8-hydroxyquinoline remain. The *O*-alkylation of product **(1)** with 1,3-diazidopropan-2-ol was realized in acetone at 60 °C in the presence of triethylamine used as a base. In other works according to the literature, the use of inorganic bases, such as sodium hydroxide, potassium bicarbonate, sodium hydrogencarbonate, leads to undesirable side products as 5-hydroxymethyl-8-hydroxyquinoline [25]. The product **(1)** reacted with sodium azide to give the 5-azidomethyl-8-hydroxyquinoline **(3)** in excellent yield under mild conditions. As a first step, **(3)** was transformed to the 5-isothiocyanatomethyl-8-hydroxyquinoline **(4)** under the action of carbon disulfide and triphenylphosphine at room temperature in good yield. The condensation of **(4)** with appropriate piperazine derivatives in the presence of triethylamine gave the corresponding 5-substituted products **(5a-c)**. The isothiocyanate **(4)** was reacted with 5-aminomethyl-8-hydroxquinoline for only one example because the product **(6)** was only obtained in a moderate yield (35 %); similar difficulties were obtained by Hankovszky *et al.* [26]. Secondly and according to Staudinger reaction, the 5-azidomethy-8-hydroxyquinoline **(3)** was converted to the corresponding 5-aminomethyl-8-hydrioxquinoline **(7)** through the action of triphenylphosphine [27]. Next, the compound **(7)** was reacted with an excess of compound **(1)** led to the formation of the bis-8-hydroxyquinoline **(8)** in moderate yield (39 %). The last step consists of adding alkyl bromides to the product (7) in order to obtain the compounds (9a-b) in good yields. The synthetic route used to prepare all the compounds is outlined in scheme 1.

2.3. Synthesis methods

*2.3.1. Synthesis of 5-chloromethyl-8-quinolinol **(1)***

5-Chloromethyl-8-hydroxyquinoline hydrochloride **(1)** was prepared according to the method reported in the literature [18,21].



Scheme 1. Synthetic route used for the preparation of the compounds **2-9**

*2.3.2. Synthesis of 1,3-diazidopropan-2-ol **(2)***

1,3-diazidopropan-2-ol which is prepared according to the method reported in the literature [22].To a suspension of 5-chloromethyl-8-quinolinol hydrochloride **(1)** (1 g, 4.35mmol),1,3-diazidopropan-2-ol (0.63 g, 4.35 mmol) and sodium bicarbonate (0.36 g, 4.35 mmol) in pure ethyl acetate. The mixture was refluxed under stirring for 12 h. The progress of the reaction was monitored by TLC using hexane-acetone (4:6, v/v) as the mobile phase. The reaction mixture was made basic with 5 % of ammonium hydroxide solution and separated organic layer was dried over anhydrous magnesium sulfate. After removal of the solvent under vacuum, the obtained residue was purified by column chromatography on silica gel with hexane/CH_2Cl_2 (9:1 to 3:7, v/v), to give the compound **(2)** as a white solid.

Table 1. Yields and physicochemical characteristics of the synthesized compounds

Compound	Yield (%)	M.p. (°C)	Data spectral
5-(((1,3-Diazidopropan-2-yl)-oxy)-methyl)-quinolin-8-ol **(2)**	64	68	^{1}H NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 6.70-8.85 (m, 5 H, quinoline), 4.72 (s, 2H, quinoline-CH_2-O), 3.83 (m, 1H, O-CH-), 1.08 (t, 2H,-CH_2-N_3) ^{13}C NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 53.98 (-CH_2-N_3); 65.12 (quinoline-CH_2-O); 69.93 (O-CH-); 110.45, 122.23, 124.91, 133.59, 148.35 (CH-quinoline); 127.84, 128.75, 139.17, 153.74 (C-quinoline).
5-Azidomethyl-8-hydroxyquinoline **(3)**	95	112	^{1}H NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 7.04-8.90(m, 4H, quinoline), 4.80 (s, 2H, aromatic-CH_2-N_3). ^{13}C NMR (300 MHz, DMSO-d_6), δ_{ppm} = 51.37, 110.47, 122.69, 127.55, 130.02, 133.167, 139.29, 148.72, 154.54.
5-Isothiocyanato-methyl-8-hydroxy-quinoline **(4)**	85	200	^{1}H NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 6.43-8.89 (m, 5H, quinoline), 8.74 (s, 2H, -NH_2), 4.61 (s, 2H, quinoline-CH_2-NCS).

			^{13}C NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 55.89 (quinoline-$\underline{C}H_2$-NCS), 116.82, 122.09, 124.69, 126.57, 136.81, 148.22 ($\underline{C}$H-quinoline); 128.09, 139.04, 132.14, 153.22 ($\underline{C}$-quinoline); 130.14 (-N=$\underline{C}$=S).
N-((8-Hydroxyquinolin-5-yl)-methyl)-4-methyl-piperazine-1-carbothio-amide **(5a)**	73	110	^{1}H NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 6.94-8.84 (m, 5H, quinoline), 7.26 (s, 1H, -NH-CS), 4.64-4.69 (s, 2H, quinoline-CH_2-N), 2.70 (s, 3H, -CH_3), 3.25 (t, 4H, piperazine), 2.37 (t, 4H, piperazine). ^{13}C NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 46.84 (-CH_3), 51.57 (-CH_2- of piperazine), 53.07 (-CH_2- of piperazine), 49.22 (quinoline-$\underline{\mathbf{C}}H_2$-NH), 116.52, 121.46, 128.62, 132.18, 147.60 (CH-quinoline); 127.94, 129.01, 138.60, 151.91 (C-quinoline); 188,93 (-C=S).
N-((8-Hydroxyquinolin-5-yl)-methyl)-4-phenyl-piperazine-1-carbothio-amide **(5b)**	60	182	^{1}H NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 6.65-8.82 (m, 10H, quinoline and phenyl), 4.66 (s, 2H, quinoline-CH_2-N), 3.28 (t, 4H, piperazine), 3.69 (t, 4H, piperazine). ^{13}C NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 51.43 (-CH_2- of piperazine), 54.43 (-CH_2- of piperazine), 46.02 (quinoline-CH_2-NH), 110.71, 121.143, 122.65, 124.50, 126.40, 128.84, 133.16, 134.21, 136.25, 148.67 (CH-quinoline and phenyl); 127.54, 129.08, 139.28, 152.65, 154.46 (C-quinoline and phenyl); 195.21 (-C=S).
4-(Benzo[d][1,3]-dioxol-5-ylmethyl)-*N*-((8-hydroxy-quinolin-5-yl)-methyl)-piperazine-1-carbothio-amide **(5c)**	56	136	^{1}H NMR (300 MHz, Me_2SO-d_6), δ_{ppm} =6.72-8.76 (m, 8H, quinoline & benzo-[1.3]-dioxole), 8.81 (s, 1H, quinoline -OH), 4.50 (s, 2H, quinoline-CH_2-N), 3.41 (s, 2H, piperazine-CH_2-benzo-[1.3]-dioxole l), 2.44-2.50 (s, 4H,-CH_2-piperazine), 3.79 (s, 4H, -CH_2-piperazine), 5.91(s, 2H, O-CH_2-O) ^{13}C NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 48.67 (quinoline-CH_2-N), 100.90, 107.87, 108.80, 109.64, 121.39, 124.56, 127.94, 132.18, 147.63 (CH-quinoline and benzo-[1.3]-dioxole); 128.45, 131.55, 134.09, 138.71, 146.68, 147.52, 151.88 (C-quinoline and benzo-[1.3]-dioxole); 171,17 (-C=S), 62.61 (piperazine-CH_2-(benzo-[1.3]-dioxole), 52.87-52.91 (-CH_2-of piperazine), 60.47 (-CH_2-of piperazine).
5,5'-((Methanediylidene-bis-(azanylylidene))-bis-(methylene))-bis-(quinolin-8-ol) **(6)**	35	86	^{1}H NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 6.89-8.87 (m, 5H, quinoline), 4.64 (s, 2H, quinoline-CH_2-N). ^{13}C NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 55.84 (quinoline-CH_2-N), 110.65, 120.81, 124.68, 129.15, 148.17 (CH-quinoline); 126.19, 127.85, 138.88, 153.52 (C-quinoline); 139.27 (N=C=N).
5-Aminomethyl-8-hydroxyquinoline **(7)**	92	98	IR (KBr, cm^{-1}): 3453 (quinoline-OH, N-H), 1502-1461 (C=C aromatic), 1270 (aromatic C-N), 1065-1274 (C-N), 1366 (quinoline C=N-). ^{1}H NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 6.99-8.49 (m, 5H, quinoline), 4.05 (s, 2H, quinoline-CH_2-N). ^{13}C NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 50.24 (quinoline-$\underline{C}H_2$-NH_2), 110.44, 120.71, 127.42, 129.30, 139.24 (CH-quinoline); 121.44, 126.54, 128.15, 133.73, 148.07 (C-quinoline).

Compound	**Yield (%)**	**M.P. (°C)**	**Data spectral data**
5,5',5''-(Nitrilotris-(methylene))-tris-(quinolin-8-ol) **(8)**	39	130	^{1}H NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 6.92-6.99 (m, 3H, quinoline), 7.50-7.55 (m, 6H, quinoline), 8.41-8.44 (m, 3H, quinoline), 8.83-8.85 (m, 3H, quinoline), 4.66 (s, 6H, quinoline-CH_2-N). ^{13}C NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 61.26 (quinoline-CH_2-N); 110.74, 122.14, 126.91, 127.75, 130.74, 148.73 (CH of quinoline); 124.91, 128.26, 139.31, 152.36 (C of quinoline).
Ethyl-2-(((8-ethyl-2-(((8-hydroxyquinolin-5-yl)-methyl)-amino)-acetate **(9a)**	86	135	^{1}H NMR (300 MHz, Me_2SO-d_6), δppm = 6.94-9.02 (m, 5 H, quinoline), 3.99 (s, 2 H, quinoline-CH_2-N), 4.04 (d, 2H, O-CH_2-ester function), 3.55 (s, 2H,-CH_2-COO), 1.13 (d, 3H, -CH_3), 4.02 (s, 1H, NH) ^{13}C NMR (300 MHz, Me_2SO-d_6), δ_{ppm} = 14.50 (CH_3), 60.39 (O-CH_2-), 52.21 (quinoline-CH_2-N), 54.50 (N-CH_2-COO), 110.35, 121.96, 124.24, 132.00, 134.68, 148.37 (CH-quinoline); 129.13, 128.49, 139.26, 153.66 (C-quinoline); 171.17 (-C=O).

5-((Pentylamino)-methyl)-quinolin-8-ol **(9b)**	79	168	^{1}H NMR (300 MHz, Me_2SO-d6), δ_{ppm} = 6.99-8.32 (m, 5H, quinoline), 3.06 (s, 2H, quinoline-CH_2-N), 4.58 (s, 1H, -NH), 2.18 (t, 2H, N-CH2-(chain aliphatic)), 1.83 (m, 2H, -CH_2-chain aliphatic), 1.48 (m, 2H, -CH_2- chain aliphatic), 1.17 (m, 2H, -CH_2-chain aliphatic), 0.83 (t, 3H,-CH_3 (chain aliphatic)). ^{13}C NMR (300 MHz, Me_2SO-d6), δ_{ppm} = 14.20 (-CH_3, chain aliphatic), 22.44 (-CH_2-chain aliphatic), 29.06 (-CH_2-chain aliphatic), 30.00 (-CH_2-chain aliphatic), 46.20 (-CH_2-chain aliphatic), 56.31 (quinoline-CH_2-N), 110.45, 122.05, 132.41, 132.00, 150.32 (CH-quinoline); 128.014, 129.204, 133.085, 152.976 (C-quinoline).

*2.3.3. Synthesis of 5-azidomethyl-8-hydroxyquinoline **(3)***

To a mixture of 5-choromethyl-8-hydroxyquinoline **(1)** (1.00 g, 4.35 mmol) and NaN_3 (0.41 g, 6.525 mmol) in absolute acetone was stirred for 12 h at room temperature. Then, the solvent was removed under vacuum. The obtained residue was hydrolyzed and extracted with CH_2Cl_2 (3 x 20 mL), the organic layers were combined, washed thrice with 20 mL of water, dried over anhydrous magnesium sulfate and evaporated under vacuum. The crude product was purified by recrystallization from ethanol to afford the compound **(2)** as a white crystal.

*2.3.4. Synthesis of 5-isothiocyanatomethyl-8-hydroxyquinoline **(4)***

Carbon disulfide (0.38 g, 5 mmol) was added drop wise to a solution of the compound **(3)** (1 g, 5 mmol) and triphenylphosphine (1.58 g, 6 mmol) in absolute THF (20 mL). The reaction mixture was stirred for 6 h at room temperature. The formed solid was filtered and recrystallized from ethanol to afford the desired compound (**4)** as a white solid.

*2.3.5. Synthesis of compounds **(5a-c)***

To a stirred solution of 5-thiocyantomethyl-8-hydroxyquinoline **(4)** (1.23g, 5.74 mmol) and triethylamine (0.6 mL, 8.5 mmol) in absolute THF (20 mL), the appropriate piperazine (5.74 mmol) was added and the resulting mixture was heated at 80 °C for 12 h. The reaction was monitored by thin (layer chromatography TLC). After completion and cooling to room temperature, water (50 mL) was subsequently added and the aqueous layer was *extracted* with *ethyl acetate* (3 × *50 mL*). The combined organic layers were combined, dried over anhydrous magnesium sulfate, filtered and the solvent was removed by rotary evaporation. The crude product was purified by column chromatography on silica gel using hexane/CH_2Cl_2 (9:1 to 4:6) to afford the products **(5a-c)** as white solids.

*2.3.6. Synthesis of 5,5'-((methanediylidene-bis-(azanylylidene))bis-(methylene))bis-(quinolin-8-ol) **(6)***

To a solution of 5-thiocyantomethyl-8-hydroxyquinoline **(4)** (1.23 g, 5.74 mmol), 5-aminomethyl-8-hydroxyquinoline (**7)** (1.00 g, 5.74 mmol) and triethylamine (1 mL, 6.88 mmol) refluxed in absolute dioxane (20 mL) for 24 h. After removal of the solvent under reduced pressure, the obtained residue was diluted with dichloromethane, washed with brine and the organic layer was dried over anhydrous magnesium sulfate. After the evaporation of the solvent under vacuum, the residue obtained was purified by column chromatography on silica gel with a mixture of hexane/CH_2Cl_2 (9:1 to 2:8) to give the compound **(6)** as a white solid.

*2.3.7. Synthesis of 5-aminomethyl-8-hydroxyquinoline **(7)***

A mixture of compound (**3)** (1 g, 5 mmol) and triphenylphosphine (1.57 g, 6 mmol) in abs. THF, the mixture was stirred for 12 hours at room temperature. Then we add some water (1 mL, 55.5 mmol) and another portion of PPh_3 (0.144 g, 55 mmol) and the resulting mixture was then stirred for a further 12 h. The yellow solid obtained was collected by filtration washed by THF and dried to give 5-aminomethyl-8-hydroxyquinoline **(7)** as a yellow solid.

*2.3.8. Synthesis of 5,5',5''-(nitrilotris(methylene))-tris-(quinolin-8-ol) **(8)***

To a suspension of 5-chloromethyl-8-quinolinol **(1)** (2.64 g, 1.15 mmol), 5-aminomethyl-8-hydroxyquinoline (**7)** (1 g, 5.7 mmol) and (0.96 g, 0.0115 mol) of $NaHCO_3$ in absolute acetone (40 mL) was refluxed for 24 h. After cooling, the reaction mixture was filtered and washed with cold acetone (15 mL). The filtrate was concentrated under vacuum and diluted in diethyl ether (15 mL). The formed solid was filtered, washed twice with diethyl

ether and purified by column chromatography on silica gel using hexane/acetone (7:3 to 2:8) as a mobile phase to give the compound (**8**) as a white solid.

*2.3.9. Synthesis of compounds **(9a,b)***

The mixture of 5-aminomethyl-8-hydroxyquinoline (**7)** (1.00 g, 5.75 mmol), alkyl bromide (4.3 mmol) and triethylamine (0.83 mL, 5.75 mmol) in abs. dioxane was refluxed for 6 h. After cooling to room temperature, the mixture reaction was concentrated under vacuum; the obtained residue was diluted with CH_2Cl_2, washed successively with H_2O and brine. The separated organic layer was dried over anhydrous magnesium sulfate and evaporated under vacuum. The crude product was purified by column chromatography on silica gel using hexane/CH_2Cl_2 (9:1 to 4:5) as an eluent to give compounds (**9a,b)** as white solids.

3. Pharmacological screening

3.1. Antibacterial activity

All the synthesized compounds were tested for their microbiological screening against Gram-negative bacteria (*Escherichia coli*, *Enterobacter ludwigii*), and gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*), by using serial dilution method. Muller Hinton was employed as a culture medium for bacterial growth; the antimicrobial activity was realized by disc diffusion method by measuring zone of inhibition in mm after incubation for 24 h at adequate temperature for the development of the germ concerned. For evaluation, the chosen test concentrations are 200 and 500 µg /mL in dimethylsulfoxyde as solvent. Standard Antibiotic Nitroxoline was used under similar conditions against these organisms as a reference. Sterile filter paper discs (6 mm of whatman filter paper) were soaked in different concentrations of the test solution of the newly synthesized compounds and placed on culture medium. All microorganisms were supplied by laboratory of nutrition, health and environment.

3.2. Antioxidant Activity

The biologically active compounds against the studied bacteria were screened for their antioxidant using the DPPH radical scavenging activity, according to the method describe by Sanchez-Moreno with some modifications [23]. The concentrations of the synthesis compounds and standard (ascorbic acid) compound were prepared in DMSO and mixed with 150 µl of DPPH radical in ethanol, and allowed to stand for 30 minutes in dark. After the incubation period at room temperature, the absorbance measured at 517 nm, the free radical scavenging activity was determined by measuring the decrease in absorption at 517 nm in a UV-visible spectrophotometer. For a given concentration of antioxidant, antioxidant activity, AA (%) was calculated from the following formula:

$$AA\% = \frac{(A_c - A_s)}{A_c} \times 100$$

where A_c and A_s are the absorbance values without and with tested synthesized compound.

IC50 (Inhibitory concentration 50 %) value indicates the concentration required to reduce 50 % of the $DPPH^*$ free radicals, and was determined from the graph of AA % against compound concentrations by linear regression.

4. Results and discussion

The results of the measured inhibition zone (in millimeters) for the 5-substituted 8-hydroxyquinoline derivatives against the various bacteria used are shown in Table 2. On the other hand, for all the compounds tested, the pH is between 7.5 and 8.0. However, the choice of Nitroxoline as reference is based on the fact that the its chemical structure very close to that of the studied molecules.

Many of the studied compounds possessed moderate to very good inhibitory activity against all the strains, concerning antimicrobial activity data in table 2**,** the inhibition against microbial strains increases with the increase in the newly synthesized compounds concentration, it was observed that the 5-isothiocyanatomethyl-8-hydroxyquinoline exhibited best activity against all the pathogenic bacterial strains, following the addition of the piperazine substituted **(5a)** and 5-aminomethyl-8-hydroxyquinoline **(6)** groups on the isothiocyanate dramatically reduces activity, this could be attributed to the increase in the size of substituent at the amino group.

Comparing compounds (**6-9c)**, it seems that the insertion of different alkyl substituents in 5-aminomethyl-8 hydroxyquinoline **(7)** has enhanced the activity inhibitor, and **(8)** present better efficacy than **(9a-c)** may be due to presence of the electron donating substituents. So, it's clear that the nature of the substituent at the 5-*N* position of

the 5-aminomethyl-8-quinoline ring system has strong influence on the spectrum and extent of antibacterial activity, this finding is also concomitant with the earlier work [28]. On the other hand, the compounds (**2-3)**, showed moderate and low growth inhibition against all tested bacteria, in comparison to the reference Nitroxoline drug.

Table 2. The inhibition zone (mm) of the synthesized compounds and standard Nitroxoline against bacteria

Compound	Conc. [µg/ml]	Inhibition zone diameter (mm)				
		Gram positive bacteria		Gram negative bacteria		
		S. aureus	*B. subtilis*	*E. coli*	*Xanthosomas fragariae DW*	*Pseudomonas aeruginosa*
2	500	6	13	11	-	12
	200	-	-	-	-	9
3	500	-	-	9	-	7
	200	-	-	-	-	1
4	500	30	26	55	35	45
	200	25	25	30	25	20
5a	500	25	12	24	29	20
	200	8	10	9	24	11
5b	500	15	14	18.5	26	19
	200	10	8	-	12	6
5c	500	7	-	12	17	13
	200	-	-	-	6	-
6	500	10	14	10	17	11
	200	-	-	-	5	-
7	500	-	-	7	-	-
	200	-	-	-	--	-
8	500	15	12	21	12	16
	200	-	6	10	7	8
9a	500	-	-	-	1	2
	200	-	-	-	-	-
9b	500	10	14	10	6	9
	200	-	7	2	-	-
Nitroxoline	200	-	4	10	5	7

(- : no inhibition zone)

Concerning the compounds **(5a-c)**, they differ only by substituent at 4-position of the piperazine moiety, and based on the zone of inhibition produced against the tested bacteria, these analogues exhibited good antibacterial activity against both gram-positive and gram-negative organisms, the compound (**5a)** was found the most active among them.

Concerning DPPH radical scavenging assay, some of the synthesized compounds were able to reduce the stable radical DPPH to the yellow colored diphenylpicrylhydrazine; their principle is laid on the reduction of alcoholic DPPH solution in the presence of a compound capable of donating H-atoms or electrons. Antioxidant activity of studied compounds is presented in figure 1. The IC50 and correlation coefficient (R^2) values are given in table 3. The data shown in table 3 reveal that the IC50 values of the newly synthesized compounds in this test were in the range of 0.8 to 2.4 mg/mL with a best correlation coefficient (0.99), the obtained IC50 values are less than that with the standard (ascorbic acid).

The compound (**8)** demonstrated a higher inhibition compared with the other compounds followed by the compound (**6)** with IC50 values 0.8 and 1.2 mg/mL, respectively. This could be explained by the presence of three hydroxyl group (electron donating group) bearing on the quinoline ring in the compound (**8)**, and the compound (**6)** contains two hydroxyl group, whereas while the rest of organic molecules incorporating only one

hydroxyl group. This was confirmed that the radical scavenging and antioxidant activities of the studied antioxidants were absolutely clear in relationship with the number of phenolic hydroxyl groups [29]. Thus, the insertion of electron donating group in phenol enhances the antiradical effect; this is the case with compound (**5a)**.

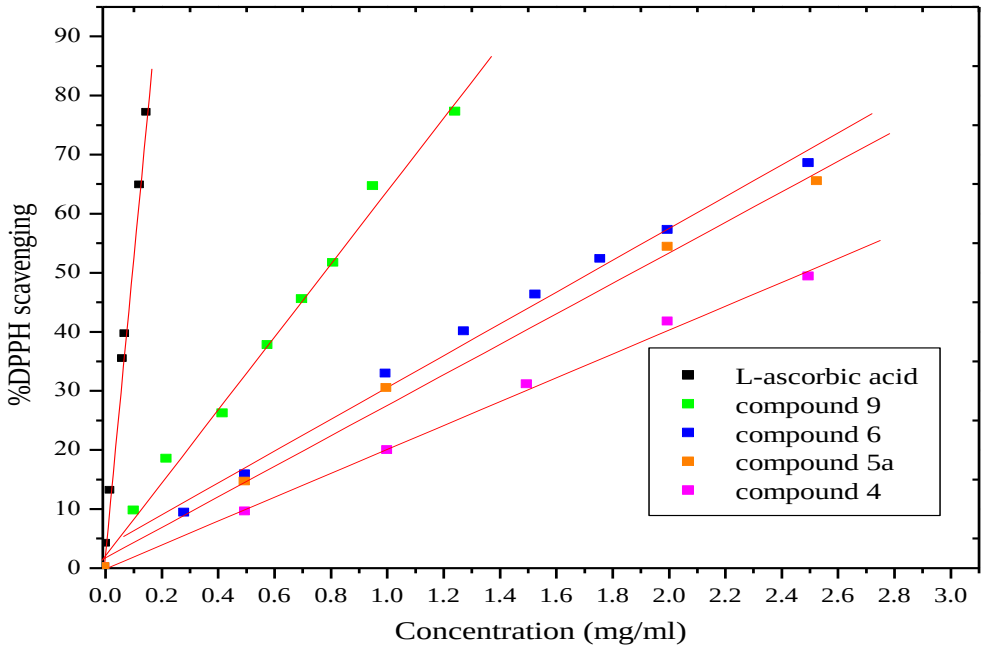


Figure 3. Antioxidant activity of studied compounds and L-ascorbic acid at different concentrations measured by DPPH radical scavenging assay at 298 **K**.

Table 3. IC50 values of the some tested compounds

Compound	IC50	R^2
4	2.49	0.994
5a	1.80	0.997
5b	1.74	0.995
6	1.20	0.997
8	0.80	0.994
l-Ascorbic acid	0.10	0.999

Conclusion

In summary, we have described the preparation and characterization a series of novel 5-alkylthiomethyl-, 5-alkoxymethyl-, and 5-aminomethyl-substituted 8-hydroxyquinoline. These new compounds are obtained according to the simple operating procedures in satisfactory yields. Biological tests showed that the studied series have moderate to strong activity against microbial strains. The family of 5-alkylthiomethyl-8-hydroxyquinoline have strong activity compared to others class; particularly the product appointed as 5-isothiocyanatomethyl-8-hydroxyquinoline (compound **6**) and their activity decreases when we modify the isothiocyanate function. Some of reported compounds demonstrate mild to good DPPH radical-scavenging activity, among those, compound **8** shows the best activity, which is due to the presence of aromatic rings bearing three hydroxyl substituents.

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