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**Research Article**

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# Synthesis and *in vitro* antioxidant activity of some 8-hydoxyquinoline derivatives

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**ABSTRACT**

*A series of 8-hydroxyquinoline derivatives **3a-c**, were prepared by the reaction of 5-Cyanomethyl-8-hydroxyquinoline **2a** and 5-Azidomethyl-8-hydroxyquinoline**2b** with different secondary amines under the conditions of the Mannich reaction in refluxing ethanol. The synthesized compounds were screened for the antioxidant activity by DPPH (2,2- diphenyl-1-picrylhydrazyl) method. Ascorbic acid was used as standard. All the compounds showed DPPH radical scavenging activity, where compound **3b** was the best radical scavenger.*

**Keywords:** 8-Hydroxyquinoline, Synthesis, Antioxidant Activity, DPPH.

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## INTRODUCTION

The importance of researches on the roles of free radical species in biological systems has been significantly increased in the last decades. The production of these species in naturally occurring biological reactions is an inevitable phenomenon in aerobic metabolic processes. The presence of a singlet electron in free radicals renders them extreme reactivity which may cause severe oxidative damages to the biomolecules such as lipids, proteins and DNA [1].

Various disorders such as cancer, atherosclerosis, diabetes, alzehimer, parkinson and disease related to aging process are long term manifestations of these damages [2]. Since this kind of damages can exert irreversible adverse effects on cells, there are some antioxidant mechanisms and compounds with endogenous and exogenous origin to deactivate or neutralize these reactive species.Substances, which can chelate iron cations potentially, suppress oxidative reactions to alleviate the destroying effects of free radicals. The 8-hydroxyquinoline and its derivatives havereceived in the recent years considerable attention for their biological activity because of its metal chelating properties [3-10]. The 5 and 7-substituted derivatives of oxime are particularly synthesized and tested [11-16].This study is the continuity of our work searches concerning the synthesis of new organic compounds and the study of their chelating and biological properties [17-19].

Here, we report on the synthesis of some and in vitro antioxidant activity of some novel derivatives 5 and 5, 7-substituted of 8-hydroxyquinoline.

## EXPERIMENTAL SECTION

Melting points were measured with a Buchi 510 apparatus and are uncorrected. NMR spectra were recorded in DMSO-$d_6$ using a Bruker AC200 spectrometer operating at 300 MHz for $^1$H. Assignments of the various protons were supported by successive irradiations. IR spectra were recorded on a Perkin Elmer 577 spectrometer, solid products being palletized in KBr. Elemental analysis were carried out by the 'Service de Microanalyse' of the 'Institut de Chimie des Substances Naturelles' in Gif-sur-Yvette, France. ESI$^+$-HRMS were performed on a QTOF micro Waters MS-spectrometer at the University Blaise Pascal in Clermont Ferrand, France and MS-IE$^+$ on a Polaris thermo-electron MS-spectrometer at the UATRS/CNRS in Rabat, Morocco.

**Chemistry**

The preparation and synthesis of products **2a-b** and **3a-c** (Scheme 1) were previously done in a reported work [20].

***5-Cyanomethyl-8-hydroxyquinoline (2a)****:* 5-Chloromethyl-8-hydroxyquinoline, HCl (**1)** [21] (4.60 g, 20 mmoles) were carefully added over 15 min into a solution of KCN (3.9 g, 3.0 eq) in dry DMSO (50 mL) at 90°C under Ar under an efficient fume board. The mixture was stirred under 95°C for 1 hour, allowed to cool to room temperature, poured onto 100 mL of chilled water. The precipitate was filtered on a sintered glass and thoroughly washed with cold water, dried *in vacuo* to yield the nitrile **2a** (3.12 g, 84%) as a brown solid used without further purification for the Mannich reaction; mp 179-180°C; IR: 2260 cm$^{-1}$; $^1$H-NMR (300 MHz, DMSO-d$_6$, δ(ppm))δ:4.35 (s, $CH_2$-$R_1$, 2H), 7.15 (d , H-7, 1H), 7.54 (d, H-6, 1H), 7.65 (m, H-3, 1H), 8.43 (d, H-4, 1H), 8.92 (d, H-2, 1H). EI$^+$-MS: m/z 184.06 (44) $[M]^{\cdot+}$.

***5-Azidomethyl-8-hydroxyquinoline (2b)****:* A mixture of 5-chloromethyl-8-hydroxyquinoline, HCl (**1)** (4.60 g, 20 mmoles) and $NaN_3$ (7.84 g, 3 eq) in abs. acetone (100 mL) was refluxed for 20 hours under controlled atmosphere ($N_2$). After cooling, the solvent was evaporated under reduced pressure and the residue partitioned between $CHCl_3$/$H_2O$ (150 mL, 1:1). The organic phase was isolated, washed with water (3×20 mL), dried ($Na_2SO_4$), and finally concentrated *in vacuo* to yield the azide (**2b)** as a grey solid (3.12 g, 90%) used without further purification for the Mannich reaction; mp110°C; IR: 2090 cm$^{-1}$; $^1$H-NMR (300 MHz, DMSO-d$_6$, δ(ppm))δ:8.95 (d, H-2, 1H), 7.66 (m, H-3,1H), 8.53 (d, H-4,1H), 7.51 (d, H-6,1H), 7, 18 (d, H-7, 1H), 4.84 (s, $CH_2$-$R_1$, 2H) . EI$^+$-MS: m/z 200.97 (14) $[M+H]^+$.

***General procedure for the Mannich reaction****:*An equimolar mixture of the substrate (**2a** or **2b**), paraformaldehyde, and the sec. amine in abs. EtOH (30 mL) was refluxed for 4 hours under controlled atmosphere ($N_2$). After cooling, the solvent was evaporated under reduced pressure and the resulting solid isolated on a sintered glass, washed with cold ether (*ca.* 30 mL), and finally dried *in vacuo*. Analytical samples were obtained by crystallization from hot EtOH.

***5-Cyanomethyl-7-piperidinomethyl-8-hydroxyquinoline(3a):***was obtained as a brown solid in78% yield (620 mg from 2.7 mmoles of **2a**); mp150°C; IR: 2270 cm$^{-1}$ (C≡Nstretching); $^1$H-NMR (300 MHz, DMSO-d$_6$, δ(ppm))δ:1.39 (s, H-c, 2H), 1.48 (s, H-b, 4H), 2.42 (s, H-a, 4H), 3.72 (s, $CH_2$-$R_1$, 2H), 4.43 (s, $CH_2$-$R_2$, 2H), 7.56 (dd, H-3, $J_{3-4}$=8.7 Hz), 8.97 (dd, H-2, $J_{2-3}$=4.3 Hz), 8.38 (dd, H-4, $J_{2-4}$=1.4 Hz), 7.49 (s, H-6, 1H); Anal. Calcd. $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81. N, 14.94. Found: C, 72.53; H, 6.71; N, 14.87. ESI$^+$-HRMS: m/z 282.1609 (13) $[M+H]^+$.

***5-Cyanomethyl-7-morpholinomethyl-8-hydroxyquinoline(3b):***was obtained as a beige solid in77% yield (590 mg from 2.7 mmoles of **2b**); mp138°C; IR: 2307 cm$^{-1}$ (C≡Nstretching); $^1$H-NMR (300 MHz, DMSO-d$_6$, δ(ppm))δ:2.47 (s, H-b, 4H), 3.61 (s, H-a, 4H), 3.72 (s, $CH_2$, 2H), 4.48 (s, $CH_2$, 2H), 7.56 (s, H-6, 1H), 8.45 (dd, $J_{2-4}$=1.6 Hz), 7.58 (dd, $J_{3-4}$ =8.9 Hz), 8.94 (dd, $J_{2-3}$=4.5 Hz); Anal.Calcd. $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.75; H, 5.99; N, 14.77;EI$^+$-MS: m/z 283.93(26) $[M+H]^+$.

***5-Azidomethyl-7-morpholinomethyl-8-hydroxyquinoline (3c):***was obtained as a yellow solid in40% yield (300 mg from 2.5 mmoles of **2b**); mp134°C; IR: 2097 cm$^{-1}$ ($N_3$stretching); $^1$H-NMR (300 MHz, DMSO-d$_6$, δ(ppm))δ:2.63 (s, 4H), 3.77 (s, 4H), 3.88 (s, 2H), 4.63 (s, 2H), 7.34 (s, 1H), 7.49 (dd, $J_{3-4}$=8.7 Hz), 8.35 (dd, $J_{2-4}$=1.4 Hz) 8.94 (dd, $J_{2-3}$=4.3 Hz). Anal.Calcd.$C_{15}H_{17}N_5O_2$: C, 60.19; H, 5.72, N, 23.40. Found: C, 60.14; H, 5.68, N, 23.26. EI$^+$-MS: m/z257.1 (27) $[M-N_3]^{\cdot+}$.

**Antioxidant activity**

*DPPH Free radical scavenging activity*

The radical-scavenging activity of each synthesized compounds was evaluated on the basis of its activity in scavenging the stable DPPH radical, according to the method described by Li [22]. In this procedure, 2 ml of a 4 % solution of DPPH radical in methanol (w/v) was mixed with 500 µl of sample solutions at different concentrations.

The scavenging capacity was determined spectrophotometrically after 30 min of incubation by monitoring the decrease of the absorbance at 517 nm. Lower absorbance of the reaction mixture indicates higher free radical-scavenging activity. Ascorbic acid was used as standard. The percent DPPH scavenging effect was calculated using the following equation:

% RSA = [(Ac - At)/Ac] x100

Where *Ac* is the absorbance of the control sample (DPPH solution without test sample) and *At*is the absorbance of the test sample (DPPH solution + test compound). Test was performed in triplicate, and the results were averaged.

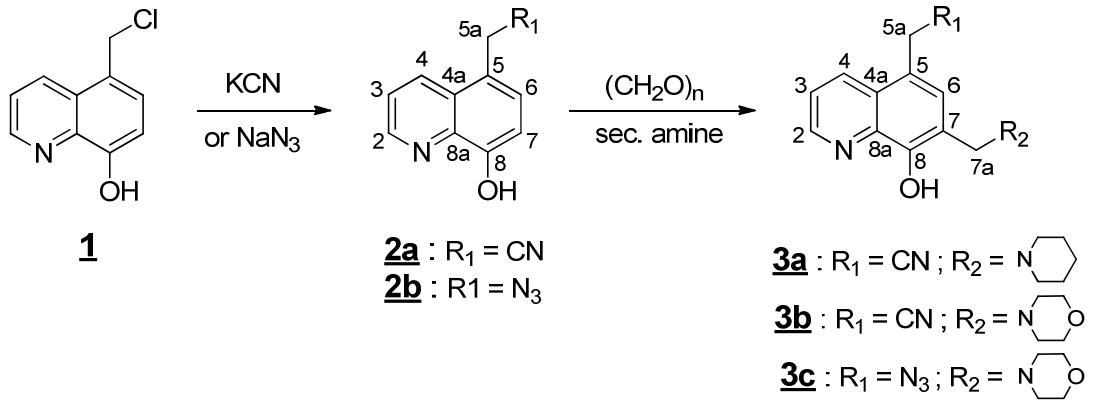
## RESULTS AND DISCUSSION

### Chemistry

5-Cyanomethyl-8-hydroxyquinoline **2a** was synthesized according to the method reported[20]. 5-Chloromethyl-8-hydroxyquinoline hydrochloride **1**[21] underwent rapid and exothermic nucleophilic displacement by an excess of potassium cyanide in dimethylsulfoxide (DMSO) at 90°C to give **2a** in good yield. The IR-spectra of the purified product exhibits the characteristic C≡N stretching vibration at 2260 $cm^{-1}$. The $^1$H-NMR spectrum displays a characteristic singlet at 4.35 ppm integrating for the two benzylic protons, two signals at 7.15 and 7.6 ppm for H-6 and H-7 respectively, and a broad signal around 10 ppm attributed to the phenolic proton.

5-Azidomethyl-8-hydroxyquinoline **2b** was isolated in good yield from **1**via a classical azide displacement in refluxing acetone [23]. The IR-spectra of **2b** exhibits the intense characteristic $N_3$-stretching vibration at 2090 $cm^{-1}$ and the $^1$H-NMR spectrum displays the expected singlet integrating for two benzylic protons at 4.8 ppm and 2 signals at 7.1 and 7.5 ppm for H-6 and H-7 respectively. Their pharmaceutical activities following oral administration in mice were recently evaluated [18].

As outlined in Scheme 1, the reaction of **2a** and **2b** with different secondary amines under the conditions of the Mannich reaction in refluxing ethanol yields tree new products **3a-c**. The structure of these solely ortho-substituted products isolated in medium to fair yield was established on the basis of their spectroscopic data. All IR-spectra display the expected set of characteristic bands in the region 2800-2980 $cm^{-1}$ corresponding to the C-*H* valence stretching vibrations of the benzylic protons on C-5a and C-7a, and those of the amine. The H-7 doublet around 7.1 ppm in the precursors **2**and**3**disappeared whereas the H-6 doublet turned into a singlet around 7.4 ppm on all $^1$H NMR spectra of the products




**Scheme 1: General procedure for the synthesis of 8-hydroxyquinoline derivatives**

### Antioxidantactivity

The synthesized compounds **2a-b** and **3a-c** were tested for their antioxidant properties by using the free stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH). This assay was used to test the capacity of the antioxidant compounds as proton radical scavengers or hydrogen donors. The DPPH radical reacts with suitable reducing agents; then, electrons become paired off, and the solution loses color, observed by the decrease in absorbance at 517 nm, and the results were compared with that of standard antioxidant Ascorbic acid. All compounds showed excellent activity with inhibition values in the range of 49.66 – 73.71% at 1000 µg.$ml^{-1}$. In fact, the compound **3b** exhibited excellent radical scavenging activity when compared with the standard Ascorbic acid. Results of the DPPH assay are shown in Table 1.

**Table 1 Antioxidant activity of the synthesized compounds**

| Compounds | DPPH scavengingactivity (%) | | | | |
|---|---|---|---|---|---|
| | **60 (µg/ml)** | **125 (µg/ml)** | **250 (µg/ml)** | **500 (µg/ml)** | **1000 (µg/ml)** |
| 2a | 11,75 ± 0,97 | 10,27 ± 0,21 | 20,56 ± 0,03 | 36,18 ± 0,00 | 52,6 ± 1,25 |
| 2b | 37,06 ± 0,10 | 35.79 ± 1,69 | 46.85 ± 2,74 | 52,11 ± 0,18 | 61,27 ± 0,48 |
| 3a | 11,49 ± 1,74 | 21,79 ± 1,18 | 35,27 ± 0,07 | 47,49 ± 0,98 | 50,19 ± 1,35 |
| 3b | 3,63 ± 0,17 | 12,97 ± 1,21 | 23,31 ± 1,48 | 50,22 ± 1,50 | 73,71 ± 0,16 |
| 3c | 13,76 ± 1,18 | 19,94 ± 1,34 | 26,47 ± 1,15 | 37,6 ± 1,32 | 49,66 ± 1,19 |
| Ascorbicacid | 95,69 ± 0,10 | 96,30 ± 0,08 | 96,34 ± 0,03 | 96,37 ± 0,12 | 96,5 ± 0,65 |

Ascorbic acid (reference antioxidant compounds) was used as a standard. The scavenging capacities were represented as percentage inhibition and values were the means of three replicates (mean ± SD, n = 3)

## CONCLUSION

In conclusion, a series of new 8-hydroxyquinoline derivatives **2a-b**and **3a-c**were synthesizedin good yield, characterized by different spectral studies and their antioxidant activity has beenevaluated. All the compounds showed DPPH radical scavenging activity, where compound **3b** wasthe best radical scavenger.

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